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Patents, Public-Private Partnerships or Prizes: How should we support pharmaceutical innovation?

Paul Grootendorst

SEDAP Research Paper No. 250

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Patents, Public-Private Partnerships or Prizes: How should we support pharmaceutical innovation?

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Abstract:

The question as to how society should support pharmaceutical ('pharma') innovation is both pertinent and timely: Pharma drugs are an integral component of modern health care and hold the promise to treat more effectively various debilitating health problems. The productivity of the pharma R&D enterprise, however, has declined since the 1980s. Many observers question whether the patent system is conducive to pharma innovation and point to several promising alternative mechanisms. These mechanisms include both 'push' programs – subsidies directed towards the cost of pharma R&D – and 'pull' programs – lumpsum and royalty-based rewards for the outputs of pharma R&D, that is, new drugs. I review evidence why our current system of pharma patents is defective and outline the various alternative mechanisms that may spur pharma innovation more effectively.

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A manuscript based on an earlier version of this paper is forthcoming in *Expert Review of Pharmacoeconomics and Outcomes Research*.

Résumé:

La question de savoir comment la société devrait promouvoir l’innovation dans le domaine des produits pharmaceutiques tombe à point nommé pour plusieurs raisons: les produits pharmaceutiques font partie intégrante des systèmes de santé modernes et tiennent la promesse de traiter plus efficacement un certain nombre de problèmes de santé débilitants. Cependant, la productivité des compagnies pharmaceutiques est en baisse depuis les années 80. Beaucoup d'observateurs se demandent aujourd’hui si le système d’attribution des brevets existant est en mesure de générer les incitations nécessaires en faveur de l'innovation et proposent des solutions remplacement alternatives. Ces solutions comprennent des programmes de subventions des coûts de R & D dans le domaine pharmaceutique (push programs) et l'allocation de primes suite à la création des produits pharmaceutiques issus de la R & D, par exemple, de nouveaux médicaments. Je passe en revue les éléments de preuves qui démontrent dans quelle mesure le système de brevets pharmaceutiques actuellement en place est déficient et présente des solutions de remplacements qui pourraient stimuler l'innovation pharmaceutique de manière plus efficace.

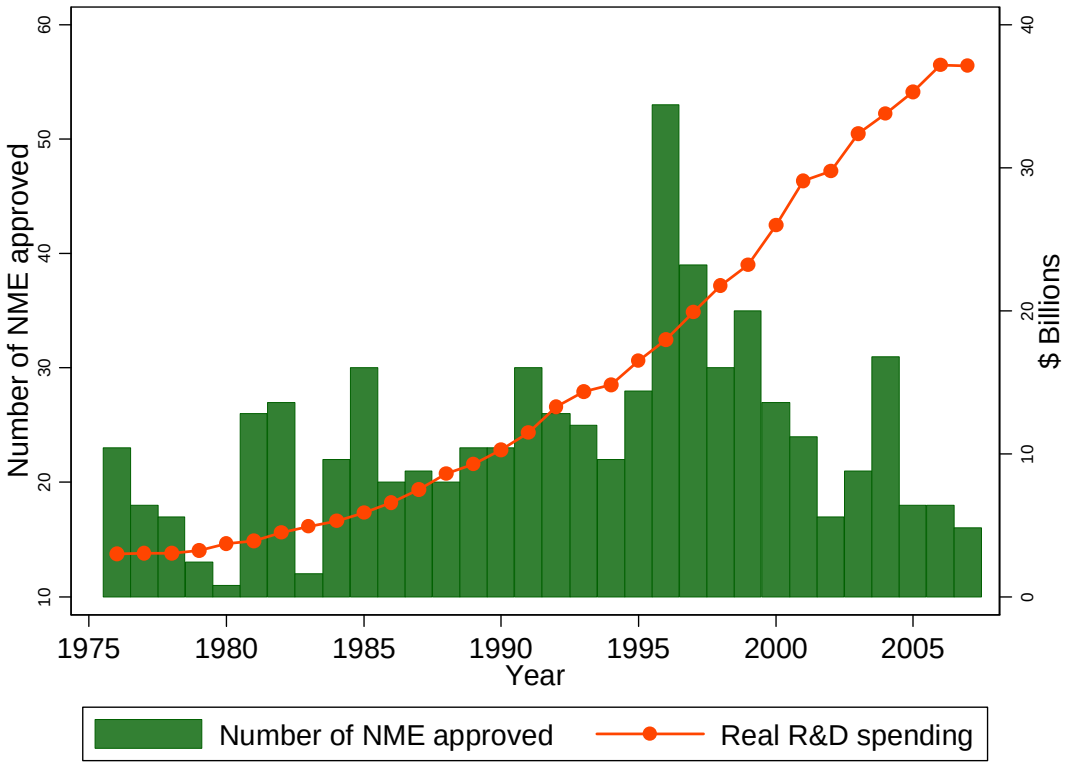
JEL Classification: I18, O34

Key Words: Pharmaceuticals, R&D, patents, prizes, innovation

1. Introduction

The development of new pharmaceutical ('pharma') drugs, coupled with advances in disease management, has undoubtedly contributed to the impressive growth in the length and quality of life observed in most developed countries since the second world war (Cutler, Deaton and Lleras-Muney 2006; Cutler et al 2007; Lichtenberg 2008). In the last three decades, however, the productivity of the pharma R&D enterprise – the number of therapeutically important new molecules brought to market per dollar spent on R&D – has declined markedly (Figure1; FDA 2004, Baker 2007, Garnier 2008). This productivity slowdown has occurred despite the advent of genomic technologies, structure-guided methods, combinatorial chemistry approaches, knock-out mice and other technologies that held the promise to boost output (Edwards 2008).

Figure 1 Number of new molecular entities (NMEs) approved in the US, and real US pharma industry R&D spending, by year: 1976-2008



Data Source: **NME**: U.S. Food and Drug Administration Centre for Drug Evaluation Research. *New Molecular Entity Drug and New Biologic Approvals in Calendar Year*. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NMEDrugandNewBiologicApprovals/default.htm. **R&D**: Pharmaceutical Research and Manufacturers of America (PhRMA), Annual survey report, Washington, D.C., various years. http://www.phrma.org. **GDP deflator** (used to convert

nominal R&D spending into real): US Bureau Economic Analysis, National Economic Accounts, National Income and Product Accounts Table 1.1.4. Price Indexes for Gross Domestic Product.

This productivity slowdown raises questions about how pharma innovation should be encouraged. To many observers, but especially those in the pharma industry, there is no question – the development of important new drugs requires stronger patent protection. There is a growing body of evidence, however, that patents provide only weak incentives for innovative activity in general, and the development of new drugs in particular. At worst, patents can actually stifle innovation (Baker 2007, Bessen and Meurer 2008, Boldrin and Levine 2008, Boyle 2008, Gold 2008, Heller 2008, Jaffe and Lerner 2006, Lipinski 2006, Palombi 2009).

The question as to how society should support pharma innovation is both pertinent and timely. Pharma drugs are an integral component of medicine. They are routinely used to manage chronic conditions, prevent infectious disease, and hold the promise to treat more effectively Alzheimer's disease, schizophrenia, arthritis and various other debilitating health problems. Pharma firms, private foundations and governments spend large sums on pharma R&D, both directly (e.g., intra-mural programs, research grants, R&D tax credits) and indirectly (prescription drug subsidies and tax subsidies of employer-provided drug insurance). Providing the appropriate incentives and economic environment for drug discovery is therefore crucial.

Several different mechanisms to support pharma R&D have been proposed. These include both 'push' programs – subsidies directed towards the cost of pharma R&D, including biomedical research and clinical trials – and 'pull' programs – lumpsum rewards and royalty based schemes for new drugs. In other words, the alternatives can be broadly distinguished by whether they subsidize the inputs or the outputs of the pharma R&D process. In this paper, I outline the argument against patents and review how these alternative mechanisms might yield more important new drugs per dollar spent on R&D.

2. Description and rationale for patents

Pharma patents allow developers a time-limited period of market exclusivity, or monopoly, over the sale of the drug. During this time, innovators can charge a price well above marginal drug production and distribution costs (MC) without fear of being undercut by competitors. This margin between price and MC, or 'profit', earned on each unit of the drug sold can be used to recover sunk R&D costs. Indeed, this is the pharma industry's mantra: high margins fuel drug innovation.

Most national governments agree that patents are necessary for innovation. For instance, the United States Patent and Trademark Office (USPTO) asserts: "The strength and vitality of the U.S. economy depends directly on effective mechanisms that protect new ideas and investments in innovation and creativity. The continued demand for patents and trademarks underscores the ingenuity of American inventors and

entrepreneurs. The USPTO is at the cutting edge of the Nation's technological progress and achievement."[1]

The Canadian Intellectual Property Office (CIPO) claims "Patents fuel progress". It states: "By giving inventors monopolies on their creations for a specific time period, patents protect investments and allow inventors to profit financially from their creativity. This in turn provides an attractive incentive for research and development, ultimately benefiting all Canadians. Without the possibility of patent protection, many people might not take the risk of investing the time or money necessary to create or perfect new products, without which our economy would suffer."[2]

Most national governments offer patent protection to creative endeavors and liken the property rights afforded these endeavors to the property rights afforded physical property. The CIPO website, for instance, states: "You can receive legal recognition for these endeavours in much the same way as you receive title to a piece of land."[3] As Boldrin and Levine (2008) note, however, patents give the owner of 'intellectual property' (IP) a stronger form of exclusivity than the owner of physical property. The owner of a plot of farmland has exclusive rights to use the land, but cannot prevent other farmers from competing with him/her. IP owners naturally retain the right to use their IP but, in addition, can exclude others, including those who have purchased this IP, from competing with the IP owner.

3. Why pharmaceutical patents may be counterproductive

3a. Inefficiency

Economists recognize that monopoly incurs an efficiency cost, but most contend that this is the price of progress. This inefficiency, known as 'deadweight loss' (DWL), pertains to the non-realized sales of the drug to 'price sensitive' consumers – those who are unable or unwilling to pay the monopoly price but who are willing and able to pay the MC. These sales are valued at more than their resource cost, so society gains if these sales take place. But they don't because a monopolist would lose money by doing so. Why? To make these sales, it would need to reduce its price and, by so doing, it would lose more revenues on its 'price insensitive' customers – those who are willing to pay the monopoly price – than it earns on its price sensitive customers. It *would* be profitable to sell at a lower price just to its price sensitive consumers if it could prevent resale of the product to price insensitive customers. But it is costly to prevent resale, as is clear from the controversies over pharma companies' initial reluctance to sell at discounted prices AIDS drugs in low income countries.

There is growing evidence that the DWL of pharma patents constitutes a large social cost. Guell and Fischbaum (1997) estimate DWL in the US market to be in the order of 60 percent of sales revenues. As Hollis (2005) notes, DWL, not to mention the attendant human suffering, are likely much higher in resource poor countries. These DWLs are in addition to the cost to the health care system of drug cost related

[1] http://www.uspto.gov/web/menu/intro.html

[2] http://www.cipo.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr01090.html#sec5

[3] http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr00010.html

medication non-compliance (Tamblyn et al 2001; Schoen et al 2001; Lexchin and Grootendorst 2004; Gibson et al 2005, 2006; Goldman, Joyce and Karaca-Mandic 2006) and the contribution of drug costs to personal bankruptcies (Himmelstein et al 2009).

3b. Profit expropriation

The DWL of pharma patents is widely recognized. Perhaps less well recognized is the fact that some of the potential profits conferred by patent protection are simply lost and hence unavailable to the innovator. The reason is simple: Patents create high margins and high margins attract, for lack of a better word, 'raiders' – those who want to expropriate these margins. (Economists use the more cumbersome term 'rent seekers'.) The potential profits from patent protection therefore decline, both by the profits actually expropriated and by the resources expended by the innovator to fend off the raiders. Hence the threat posed by raiders dulls the financial incentive to conduct R&D in the first place.

Profit raiders include drug resellers (those who engage in what is variously known as 'arbitrage', 'parallel trade' or 'drug re-importation': buying drugs in low price jurisdictions and selling them in high price jurisdictions), counterfeiters (who infiltrate drug distribution channels with bogus copies of a patented drug), competing firms that develop therapeutically similar 'me-too' drugs (which are sufficiently differentiated to avoid patent infringement), generic drug firms (that challenge the validity of patents perceived as being weak), government price regulators, and, finally, drug insurers (which impose various reimbursement controls, and also impose a substantial money and time cost for applying for formulary listing). It is difficult to quantify precisely the resources drawn into the battle over control of the pharma innovator's profits, but the following should convey the scale of the problem.

3b1. Counterfeiters. High margins and low transport costs make patented drugs an attractive target for counterfeiters. Historically, pharma firms ignored the problem given that most contraband was sold in resource poor countries where potential profits were low. This has changed. Advances in counterfeit technology, the entry of organized crime syndicates into the counterfeit industry, and the introduction of patent protection (and hence higher drug prices) in several emerging markets following the 1994 ratification of the Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreement (World Trade Organization 2009), resulted in large increases in counterfeit sales (Lybecker 2008). This counterfeit is increasingly difficult to distinguish from the genuine product and is infiltrating developed country markets. Pharma firms have responded by changing the design of their pills, tablets and packaging to make imitation more costly; they have also invested in radio-frequency identification and other technologies to secure their distribution channels from infiltration (Wertheimer 2008; Lybecker 2008). Despite these efforts, losses from counterfeiting are estimated to be in the order of $45 billion (US) annually (Lybecker 2008). Lybecker (2007) reports that counterfeiting remains a pervasive problem "impacting nations of every size and income level and drugs of every description."

3b2. Price regulators. Government price regulation is another threat to pharma R&D; Lichtenberg (2007) estimates that a 10% decline in drug prices would likely cause a 5–

6% decline in US pharma R&D outlays. Abbott and Vernon (2007) estimate even larger R&D disincentive effects of price reduction. Not surprisingly, the pharma industry employs a cadre of lobbyists to prevent price regulation. Despite this lobbying, most OECD countries have instituted some form of drug price control (US Department of Commerce 2004, Sood et al 2009). Even the US federal government, arguably the most sympathetic to the pharma industry, has used price controls in its various drug plans (Hollis 2004).

3b3. Drug re-sellers. International differences in price regulation regimes and national income, as well as exchange rate fluctuations and other factors result in differences in the maximum price that a multinational pharma firm can charge in different markets (Hollis and Ibbott 2006). These variations present pharma firms with a dilemma. On the one hand, profit maximization requires that they charge as much as each market will bear, so that, for instance, poorer countries will pay less towards the cost of R&D than richer countries. But drug resellers are quick to exploit price differences. Moreover, price regulators in Canada and elsewhere mandate that they pay no more than what is paid in a set of comparator countries. So listing at a low price in one country might cannibalize profits elsewhere. Faced with this choice, a pharma firm might sacrifice profits in a country with limited willingness to pay (by delaying listing or listing at a higher than optimal price) to preserve more substantial profits in a country with greater willingness to pay (Grootendorst 2004, 2006).

Nevertheless, it is difficult to eliminate all arbitrage opportunities. For instance, Bart (2008) presents estimates of the value of the drugs resold in the EU as being in the order of EUR 5 to 6 billion in 2006. Other threats loom on the horizon: according to Bate (2009), the US federal government is considering relaxing regulatory constraints on the importation of low cost prescription drugs.

3b4. Drug insurers. In most markets, firms sell their products directly to consumers. The pharma market is different. Most consumers in developed countries have insurance that covers some or all of the cost of prescribed drugs, so pharma firms effectively sell to drug plans. Many drug plans wield substantial bargaining power on account of their large size[4] and increasingly exploit this power to extract price concessions from pharma firms who wish to have their products listed on the drug plan formulary (Sood et al 2009). These price concessions directly reduce the margins that are ostensibly there to recoup R&D costs.

The price concessions are sometimes directly negotiated with drug plans. For instance, the executive director of the public drug plan operating in the province of Ontario, Canada extracts confidential discounts off of branded drug list prices. (The confidential aspect allows pharma firms to price discriminate.) Other plans adopt a maximum price that they are willing to pay, not for tablets or pills, but for units of health generated by use of a new drug. These health units are usually denominated in ‘quality adjusted life

[4] France, UK and Australia, for instance, operate national drug plans that account for the majority of drug sales. Federal states without national drug plans typically have large-scale plans operated by regional governments. The Ontario government drug plan, for instance, accounts for over 40% of prescribed drug sales in the province (CIHI 2009). Public drug plans in smaller Canadian provinces are currently forming consortia to gain additional bargaining power.

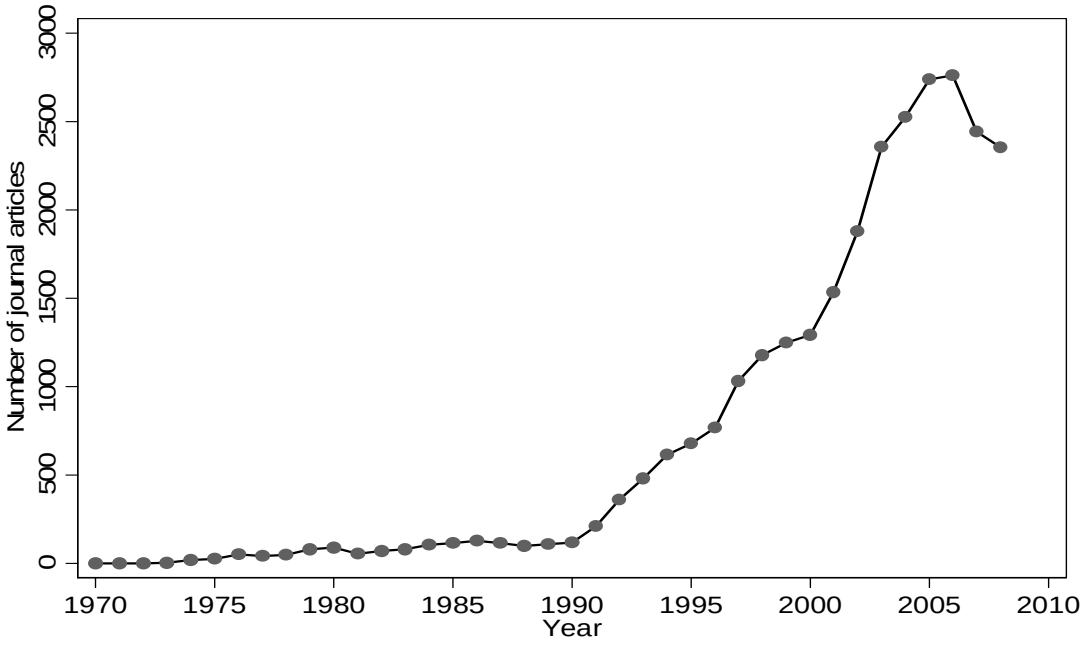
years' (or 'QALYs') – which measure both survival and quality of life gains. Typically, drug plans' willingness to pay for a QALY are well below consumers' willingness to pay. The UK National Institute for Health and Clinical Excellence (NICE), for instance, uses a threshold of £20 000 to £30 000 per QALY. Consensus estimates of consumers' valuation of a life year in normal health are closer to $100 thousand (US) (Murphy and Topel 2006, Jena and Philipson 2007).

The use of QALY assessments reflects a growing tendency on the part of drug plans to assess value for money when considering whether, and under what conditions, they will reimburse a drug. Whereas drug plans used to cover almost all new drugs that received regulatory approval, drug plans, as a whole, are becoming much more selective consumers. This has reduced innovators' margins in ways that are less obvious than for price discounts. First, innovators face substantial costs in applying for drug plan reimbursement. In particular, they are often required to submit budget impact assessments and provide estimates of their drugs' value for money to be considered. These requirements reduce margins both directly (due to the cost of hiring 'market access specialists', contract research organizations and academics to carry out the studies) and indirectly (the time required for the evidence to be compiled and reviewed by drug plans reduces patent life). Second, if drug plans do reimburse a costly new drug, they increasingly will cover it only if the prescriber provides written documentation demonstrating that lower cost options are not effective. This prior authorization requirement effectively curtails demand given the time and hassle required to complete the paperwork. Third, most employer-provided drug plans in the US provide financial incentives (such as reduced co-payments) to beneficiaries who use lower cost pharmaceuticals (Blumenthal 2006). A variant of this approach used primarily outside of the US, reference pricing, limits drug plan reimbursement of all drugs in a group of therapeutically similar drugs to the lowest price drug in the group.

An innovator, of course, can elect to forgo formulary listing; consumers always have the option of paying cash for drugs that are not insured. But if the drug plan has a large market share, then exclusion from the formulary will markedly reduce sales. The reason is that non-formulary drugs tend not to be used, perhaps because physicians are not accustomed to prescribing them (Wang, Pauly and Lin 2003, Wang and Pauly 2005).

In summary, patents afford innovators some market power, but more and more drug plans are exercising countervailing market power and, by so doing, are reducing innovators' margins and hence the incentive to conduct R&D. Many payers now require innovators to demonstrate that their new drugs provide sufficient value for money as a condition for reimbursement. This has reduced margins both directly (by using low willingness to pay thresholds) and indirectly (by requiring firms to incur the time and expense of conducting economic appraisal studies). The amount of resources drawn into the economic appraisal industry is evidenced by a review of the published literature. There are now in the order of 2,500 economic evaluations of pharmaceutical drugs published annually (Figure 2).

Figure 2 Number of economic appraisals of pharmaceutical drugs published annually, 1070-2008.



Data Source: Scopus search for the number of journal articles published annually containing key words ("cost effectiveness" OR "cost utility" OR "cost benefit") AND (pharmaceutical OR drug OR medicine OR medication)

3b5. Brand and generic competitors. The innovator will also engage rival drug firms, both generic and brand, in costly battles over market share. Generic firms have an obvious financial incentive to enter large markets as soon as possible and will mount legal challenges to patents perceived as being weak. Grabowski (2004) indicates that many of the top selling brand drugs in the US have been subject to these legal challenges. He suggests that a generic firm might profitably challenge a portfolio of top selling drugs given that the payoff from prevailing in just one case would more than cover total litigation costs. Brand firms defend against generic entry by applying for multiple, overlapping patents on top selling drugs, increasing the number of patents that a generic must successfully challenge to order to launch a product. Frank (2007) notes that branded drug firms in the US now carry an average of 10 patents for each drug — as compared with an average of 2 a decade ago. If generic entry is imminent, some brand firms will launch a generic version of its branded drug product – a so-called 'authorized generic' – to compete with independent generics in the price-sensitive part of the market.

Battles with prospective me-too drugs are also sometimes fought in the courts. For instance, Pfizer attempted to block the market introduction of two competitors to Viagra, the first drug for male erectile dysfunction, claiming that they infringed on a patented physiologic mechanism of action. More commonly, however, the innovator will concede entry to the me-too but promote its drug to physicians and patients to defend market

share. A recent study (Gagnon and Lexchin 2008) suggests that industry outlays on pharma promotion in the US are almost double the amount it spends on pharma R&D. Despite these promotional expenditures, innovators can expect to lose substantial revenues to me-toos. Lichtenberg and Philipson (2002) estimate that the reduction in the present discounted value of sales revenues from me-too competition is four times as large as the reduction in revenues due to competition from generic drugs after patent expiry.

The moniker 'me-too' is pejorative. (Indeed, some prefer the term 'follow-on' drugs.) If patients respond idiosyncratically to any one in a group of similar drugs, it is no doubt useful having alternatives. Indeed, some me-too drugs are therapeutically superior to the pioneer. The issue is that patents create the high margins that attract more me-too drugs than would otherwise be the case. These me-too drugs, each of which incurs its own development and clinical testing costs, engage in costly battles with the pioneer over market share that dull the incentive to develop first-in-class drugs.

3c. Patent extension

Note that not all of pharma promotional spending is made to defend market share from me-toos. Even if it faced no competition, economic theory predicts that the lure of high margins would cause a pharma firm to promote its patented drug to expand unit sales (Dorfman and Steiner, 1954). Hence patents will induce more outlays on promotion than would exist in their absence. The lure of high margins also provides incentives to extend patent life. A pharma firm can use a variety of tactics to do so. First, it might attempt to block or discourage generic entry by using any one of the strategies outlined in Hollis (2009) and European Commission (2008). Second, the innovator might repackage its molecule in a new dosage form or bundle its molecule with other drugs; in either case, it may gain additional patent life. Third, it might develop a new molecule – perhaps a metabolite or isomer – derived from the original molecule; this new molecule is in effect a 'me-too' version of its original product (Angell 2004). The issue here is that the resources expended to help extend patent protection are socially wasteful; to the extent that these tactics are successful, they create additional DWL.

3d. Increased R&D costs

Patents also increase R&D costs when innovation is sequential, that is, when new products build upon patented discoveries or use patented techniques. Consider, for instance, the challenges of developing new internet commerce software in the US. As Lessig (1999) notes, large swaths of computer code that enable such software enjoy patent protection: "Patent No. 5,715,314, for example, gives the holder a monopoly over "network-based sales systems" - we call that e-commerce. Patent No. 5,797,127 forms the basis for Priceline.com and effectively blocks any competitor. Patent No. 4,949,257 covers the purchase of software over a network." Widely diffused ownership over productive inputs makes it costly for innovators to develop new products, for two reasons. First, bargaining costs are obviously higher, the greater the number of patentees that hold IP rights over inputs. Second, any one patentee can attempt to extract the bulk of the profits associated with the sale of the new product by threatening to withhold consent to use its IP. Hence ownership of 'upstream' research results can impede 'downstream' research. This is what economists call the 'hold-up' problem.

How susceptible is pharma innovation to this problem? Historically, drug development was not sequential. Scientists capitalized on chance discoveries made by assessing the therapeutic properties of very large numbers of synthetic molecules or naturally occurring substances. But this hit-and-miss approach is being supplanted by a new paradigm of drug discovery that exploits an increasingly sophisticated understanding of human physiology, including therapeutic proteins, raw genomic DNA sequences, and cell receptors (Edwards 2008). Many of the extant discoveries in these areas, however, have received patents and this increases the cost of conducting R&D (Heller and Eisenberg 1998; Merz and Cho 2005; Stix 2006; Boldrin and Levine 2008; Boyle 2008; Palombi 2009). Why? Firms contemplating introducing new products into such markets must anticipate the threat of legal action by patent holders. One way to deal with such threats is to pay licensing fees, assuming that the entrant can make a mutually beneficial deal with possibly numerous patent holders. Another is to simply wait until relevant patents have expired. The potential entrant might also mount a legal challenge to the validity of patents perceived as being weak. Yet another tactic is to amass a portfolio of patents so that the firm can credibly threat to counter-sue for infringement of some of its own patents.

It is unclear to what extent promising avenues of research have been compromised or abandoned on account of this problem. But there are telling anecdotes. For instance, in 2006 a Boston jury ruled that two drugs marketed by Eli Lilly infringed on patents licensed by Ariad Pharmaceuticals (Garber 2006). Lilly's drugs were found to have infringed on a patented mechanism of action (the 'NF-kB pathway') that targets inflammation. Since inflammation is prevalent in numerous diseases, this ruling will likely affect pharma R&D in a variety of therapeutic areas (and also encourage others to patent higher and higher up the mechanism pathways). Heller and Eisenberg (1998) and Heller (2008) provide other anecdotal reports of research conducted by for-profit firms abandoned on account of hold up. A survey conducted by Walsh, Cho and Cohen (2005) suggests that basic biomedical research conducted in academic and other not-for-profit institutions has not been adversely affected. (Many academics, evidently, simply ignore IP rights.) However, there is little systematic inquiry into the issue.

3e. Distortion of research directions

Some promising drug compounds are not patentable, perhaps because they were previously disclosed or rendered obvious by scientific advances (Roin 2009). The non-patentability of such compounds, in turn, will discourage pharma firms from investing the considerable resources required to develop, test and shepherd them through the regulatory review process. Likewise, drugs that been genericized could have potentially important, and patentable new uses. But there may be sufficient R&D into new uses of off-patent drugs given the difficulty of enforcing patents on therapeutic indications. Hence, unlike some other forms of aid for pharma R&D, the patent system affects the choice of compounds to develop. According to Roin (2009), the distortion caused by non-patentability is significant: "Untold numbers of other drugs have been screened out of development by pharmaceutical companies for reasons related to their patentability, perhaps including drugs for HIV, cancer, heart disease, stroke, diabetes, malaria, tuberculosis, and diarrhea—conditions that afflict and kill millions of people each year. Losing an effective treatment for any one of those conditions would be a tragedy, even if

it offered only minor improvements in health outcomes."

3f. Administrative costs of the patent system

Finally, I note that the patent system is costly to administer. Patent applications must be assembled and examined for novelty, usefulness and non-obviousness. Application preparation costs vary tremendously; however an application handled by a patent agent or attorney can cost in excess of $10,000. A more substantive cost is incurred when the patent examiner makes an error, by either denying a meritorious application or approving an undeserving one. The former error leads to worthwhile drugs being abandoned; the latter error precipitates legal disputes and contributes to hold-up and the other problems discussed earlier. Jaffe and Lerner (2004) suggest that the error rate has increased in the last two decades on account of the exponential growth in the number of patent applications (about 1,000 applications are submitted to the US Patent Office daily); the difficulty in attracting and retaining examiners who possess content expertise; the difficulty of delineating contributions to the body of prior art in biotechnology, software, and other rapidly evolving areas; and the legal presumption in the US that an application is valid unless proven otherwise. The result, they state is "a decline in the standards for granting patents, and the emergence of broad, apparently invalid, patents in particular industries undergoing rapid technological change."

There is growing evidence, then, that the pharma patent system is not serving the interests of either the pharma industry or consumers. Whatever incentives it creates to conduct R&D into socially valuable new drugs is mitigated by DWL, the value of resources drawn into the battle over an innovator's margins, the value of resources used by an innovator to expand its market and extend its patents, the increased costs of pharma R&D when innovation is sequential, distorted research directions and administrative costs. The resources spent by raiders to usurp innovators' margins are also socially unproductive.

One remaining, putative advantage of the patent system is that they make public technological innovations. Hence even if they do not fuel R&D, pharma patents may serve a valuable disclosure role. But even this advantage is unclear. Specifically, some claim that pharma patents are written in ways that effectively disguise the essential innovation so as to protect the innovation from challenges by generic drug firms and others (Edwards 2008). In any event, given advances in methods of reverse engineering, a product patent disclosure is not necessary to learn about the chemical composition of a new drug.

4. What are the alternatives to patents?

4a. No intervention

It is worth noting at the outset that government intervention (such as the provision of patent privileges or direct subsidies) is not always necessary for innovation. In many markets, firms have sufficient incentive to incur substantial R&D costs without any assistance. Boldrin and Levine (2008) describe the mechanisms, which include trade secrecy, first mover advantages (e.g. the innovator often enjoys an enduring reputational advantage, or failing that, can earn profits until competitors' sales drive the

market price down to MC), learning curve advantages (i.e. the innovator is more familiar with the underlying technology than are imitators), capacity constraints and other entry barriers (e.g. if each competitor needs to invest in productive capacity then there are limits to the number of firms that will enter the market), and the sale of complementary services (e.g. open source software developers earn profits on the sale of product support).

What would pharma innovation look like without patents or any other form of government intervention? Given the relatively low barriers to entry, removal of patents would hasten generic competition, decreasing profits and the amount of R&D spending. But profits would not decline to zero, as some commentators imply. One reason is that pharma R&D costs would be lower: Abolishing patents on upstream research would decrease the cost of conducting downstream research.

Sales revenues could also be substantial in a world without patents. The reduction in margins following generic competition would reduce the number of me-too drugs entering the market, and lessen other forms of profit competition as well. Moreover, generic competition would not be instantaneous. Before 1987, the Canadian *Patent Act* permitted compulsory licensing of pharma drugs; generic firms could launch their own versions of a patented drug in exchange for a very modest royalty. Even during this time, many branded drugs did not face any generic competition. Of those that did, most enjoyed several years of exclusivity (Table 1). When they eventually faced generic competition, innovators retained a sizeable market share owing to the habit persistence of physician prescribing (McRae and Tapon 1985). Of course, this all occurred at time when drug plans were much less cost conscious than they are today. Now, generics gain a much larger market share following entry owing to the reimbursement policies of major drug plans. Nevertheless, one could imagine that should patents be eliminated, and should drug plans relax their rules concerning generic substitution, then innovators could earn substantial revenues.

Table 1 Fraction of brand drugs that faced generic drug competition, and distribution of years of market exclusivity of these drugs, by brand launch year, Canada, 1980-1986.

Year	# branded drugs launched	Fraction of these genericized	Distribution of years of market exclusivity of those facing generic competition		
			min	median	max
1980	13	61.5%	2.0	15.8	27.9
1981	16	50.0%	1.0	9.0	22.5
1982	11	36.4%	5.0	6.0	13.0
1983	13	46.2%	7.0	10.0	21.3
1984	18	50.0%	5.0	12.0	20.3
1985	15	40.0%	6.0	10.6	19.3
1986	11	90.9%	3.0	9.5	14.5

Data Source: Health Canada Drug Products Database. http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp Retrieved June 5, 2009. Data reflect oral solid medications (tablets and

capsules) exclusively. In some cases, launch dates were ascertained from the date that the drug received regulatory approval.

The profitability of drug companies in a world without patents should not be overstated, however. According to Scherer (2000), most *patented* drugs are commercial failures – they fail to recoup their development costs; the development costs of these drugs are essentially subsidized by sales on patented 'blockbusters'. But blockbusters would attract the most generic competitors and this would reduce the sales revenues used to finance the development of failures. Expanding the amount of pharma R&D relative to amount of R&D that would exist in the 'no assistance' world therefore requires a pull or push program.

4b. Pull programs based on the existing patent system

Although there are many variants, all pull programs provide greater rewards to drugs judged to be more valuable. One type is the current patent system: drugs that the market deems to be more valuable earn greater profits. But the patent system creates DWL, wasteful profit competition and the other social costs previously discussed. Moreover, the market's measure of value – willingness to pay – is a noisy measure of a drug's value. In most markets, consumers assess whether a good or service is worth the price; consumer willingness to pay in such markets is a reasonable estimate of social value. But, as Hollis (2005) notes, pharmaceutical markets are extraordinary because the consumer neither chooses the medicine (the physician does) nor pays for it (the insurer does). Physicians are delegated prescribing rights because they typically have much better knowledge about pharmacotherapy than do consumers. Physicians' knowledge, however, is still incomplete. Physicians' medication choices are sometimes deleterious to consumer health (Tamblyn et al 1994, Anderson et al 2008) or wasteful in the sense that expensive therapies are used in preference to equally effective, but less costly alternatives (Morgan et al 2005).

Despite these problems, some commentators recommend that the patents system continue, but be modified or supplemented to correct some of its limitations and defects. Some proposals target problems in the patent office. Jaffe and Lerner (2004), for instance, outline a program of reforms to reduce examiner errors. These reforms include the institution of pre-grant opposition, whereby outside parties could provide information on prior art to the examiners before a patent is issued. Bessen and Meurer (2008) would require patent applicants, especially those attempting to patent more abstract innovations common in the areas of software and biotechnology, to more precisely define the claimed innovation. This would avoid the granting of overly broad patents, and hence reduce hold-up.

Other proposals deal explicitly with pharma patents. Danzon and Towse (2003), for instance, propose that multinational drug companies maintain uniform prices across different countries, thereby stymieing drug resellers, but offer to drug plans confidential rebates that are sufficiently large to induce them to purchase the drug. Some proposals would help ameliorate DWL. DiMasi and Grabowski (2007) recommend public drug coverage be extended to the uninsured. Goldman et al (2008) target the related problem of medication non-compliance among those with partial insurance. Currently,

most drug plans and their beneficiaries share the cost of each prescription filled. Beneficiary cost sharing, in turn, leads to some prescriptions not being filled. An alternative is for the drug plan to charge a lumpsum fee that would entitle beneficiaries to a medically optimal number of prescriptions over the course of a year. (The fee is chosen so that the total beneficiary contribution remains unchanged.) Because the per-prescription cost is much lower under this scheme, compliance should improve.

Various other proposals have been advanced to spur R&D into therapeutic areas where drug development costs exceed potential drug sales revenues. These include diseases affecting only small numbers of individuals in rich countries (such as Paget's disease, nephroblastoma, Creutzfeldt-Jakob Syndrome and other rare diseases, or pediatric uses of drugs that treat diseases common among adults) and diseases affecting large numbers of individuals in low income countries (such as drug resistant TB, malaria, schistosomiasis and other tropical diseases). Stiglitz (2006), for instance, proposes that lump-sum rewards be used to promote R&D into therapies for malaria and other tropical disease. Other proposals guarantee drug developers a subsidy on a fixed quantity of a drug or vaccine that meets pre-specified technical requirements. This is the basis of Kremer's (2002) Advanced Market Commitment (AMC). Roin (2009) would grant non-patentable drugs that receive regulatory approval a lengthy period of market exclusivity to help recoup development and testing costs.

4c. Other Pull Programs

The patent system allows innovators to recover sunk R&D costs by granting them exclusive control over use of a patented drug. This control allows the innovator to restrict sales to those with the greatest willingness to pay. The alternate pull mechanisms reward innovators via publicly financed lump-sum payments or royalties paid to the innovator by all other firms selling the drug. The alternatives, therefore, do not artificially restrict unit sales. Assuming imitation costs are sufficiently low, this should result in more firms selling the drug, which should lower both drug prices and margins. The reduction in margins, in turn, would reduce DWL as well as parallel trade, counterfeiting, me-too drug proliferation, and other forms of profit competition. It would also dull the incentives for innovators to expand unit sales via promotion or extend its patents. Moreover, in some of the proposed schemes, all drugs – even those that would not have been patentable – are eligible for rewards.

The alternative pull programs have yet one more advantage over patents. To avoid pre-emption by competitors, firms apply for patents early in the drug development process, well before the drug is marketed. Regulations that delay market entry, such as heightened safety and efficacy standards, reduce effective patent life and hence profits. The patent system therefore distorts a pharma firm's optimal launch date for a new drug. The alternative push programs do not create these distortions.

Placing new drugs in the public domain may, or may not, deal with the hold-up problems created by the proprietary ownership of therapeutic proteins, raw genomic DNA sequences, and the other 'building blocks' of drug discovery. This depends on whether the building blocks come 'bundled with' the new drug or whether they are separate. If they are bundled together, then placing the new drug in the public domain will automatically place the building blocks in the public domain. If not, then the hold-up

problem will remain.

The prize/reward proposals can be categorized along several dimensions.

4c1. Agency discretion. First, they can be distinguished by the amount of discretion afforded the prize agency in setting research directions and monetary rewards. Some would grant the agency much discretion. Sanders' (2007) Medical Innovation Prize Fund Act, for instance, would allow the agency to decide on reward amounts and identify priority disease areas. The agency would be bound only by various guidelines, such as the guideline that more effective drugs should earn larger rewards. Other proposals would see the agency reward all comers in proportion to the extent they meet some predefined social objective. Hollis (2005) and Hollis and Pogge (2008) would reward a new drug in proportion to its measured impact on population health, while Grinols and Henderson (2007) would base rewards on consumer's surplus (defined as estimates of drug plans' maximum willingness to pay, less drug prices). Others would assess social value by using firms' assessments of the profitability of the new drug, either with the privilege of market exclusivity (Guell and Fischbaum 1995, Kremer 1998) or without this privilege (Levine 2009).

DiMasi and Grabowski (2007) would appear to favor a formulaic over a discretionary reward system. They express concern that under a discretionary system, 'political rent seeking' and lobbying may distort research directions. Moreover, they suggest that for-profit drug developers are best able to identify and pursue the scientific opportunities that will lead to socially valuable products.

4c2. Division of social surplus. The proposed reward programs also differ in the division of the social surplus of the new drug between consumers and the innovator. (The social surplus is the dollar value of the health gains created by the drug less the costs of developing, producing, marketing and distributing the new drug.) Some would set the reward amount at a level that makes both consumers and the innovator better off relative to the current system. In other words, the reward amount would exceed the patentee's monopoly profits, but would be smaller than the social value of the innovation. Hollis and Pogge (2008), for instance, propose a scheme whereby developers can elect to exercise their patent privilege or relinquish this privilege in exchange for a series of payments. By making the scheme optional, developers can earn at least their monopoly profits. Guell and Fischbaum (1995) and Kremer (1998) propose schemes whereby innovators would receive the present discounted value of their anticipated monopoly profits; the former would estimate monopoly profits by selling the new drug for a limited time in a test market, the latter would use an auction format.

Other formulae provide developers with rewards that are less than their monopoly profits but greater than their opportunity costs. In particular, Levine (2009) proposes that firms bid for the rights to drug candidates (these are promising compounds that have yet to subjected to large scale clinical trials). Bids consist of royalty rates that would accrue to the winner from all firms selling the drug, should the drug clear all the clinical trials and gain regulatory approval. The lowest bidder earns royalty income but is responsible for covering trial costs.

Levine's proposal is akin to the compulsory licensing schemes that have been used in Canada and elsewhere, but with one major difference. Historically, regulators set

compulsory license royalty rates at some arbitrary amount (Canada 1984), whereas Levine would let firms bid on the royalty rate. A firm's bid would depend on its ability to operate clinical trials and its expectations re: the likelihood that the drug will clear regulatory hurdles, the therapeutic value of the drug (vis-à-vis current therapies), the anticipated market size, and the number of competing firms.

4c3. Setting rewards for a new drug. Levine (2009) is one of two proposals that advocate an auction format to set rewards accruing to new drugs. Kremer (1998) is the other. He proposes that patent rights to a new drug be put for auction; the winning bid sets the reward amount. Kremer's auction is unusual, however, in that the winning bidder does not automatically receive the patent. Instead, this depends on the outcome of a coin toss. If it comes up heads, the highest bidder pays the innovator his bid and gets the patent. If the coin comes up tails, the agency pays the innovator the highest bid and places the discovery in the public domain. A defect of this scheme is that half of all new drugs remain under patent. However, as Landsburg (2007) notes, this problem can be easily mitigated. One merely throws "a biased coin that comes up tails, say, 90 percent of the time. Then 90 percent of all patents end up in the public domain, which is not as good as 100 percent but far better than none at all. We do have to give the private bidders some hope of winning so they'll take their bidding seriously." The Kremer auction also has provisions to help avoid bid rigging.

The auction mechanism is widely used to elicit private information on value. But Grinols and Henderson (2007) question the utility of the auction formats proposed by Kremer (and presumably by Levine as well) given the substantial uncertainty over the profitability of a new drug. They argue that it is difficult to forecast profits owing to the introduction of competing drugs, and changes in disease prevalence and severity.

The mechanisms proposed by Grinols and Henderson (2007) and Hollis and Pogge (2008) do not require profit forecasts. Instead, the timing of reward payments is tied to the timing of the social benefits produced by the new drug. Under both mechanisms, the social benefits produced by a drug depend on the total unit sales of the drug and the social benefit per unit sold. The mechanisms take different approaches to benefit measurement. Grinols and Henderson use willingness to pay (presumably by drug plans and cash paying consumers) in excess of MC. Hollis and Pogge, conversely, use the health gain produced per unit of the drug. The two measures are obviously related – presumably, willingness to pay should increase with health benefit – but there is an important difference. Drug plans' willingness to pay depends on at least two factors besides the drug's effectiveness – the ability to pay of drug plan sponsors and the plans' bargaining power. Hollis and Pogge's scheme relies exclusively on assessment of effectiveness.

Firms participating in the Hollis and Pogge scheme would be required to sell their drug worldwide at a regulated price near the average cost of production and distribution. In exchange, following market approval, an agency called the Health Impact Fund (HIF) would issue the firm a series of 10 annual payments. Each payment represents a share of a reward fund; the reward fund share for drug x in a given year is equal to drug x's share of the global health produced by all participating drugs in that year. Health impacts would be measured using many of the same methods of health technology assessment currently used by drug plans when deciding whether or not to reimburse a

new drug (Claxton et al 2008; Brazier et al 2007). For example, if all participating drugs were estimated to have saved twenty million QALYs in a given year, and if drug x had saved two million of these QALYs, then it would receive ten percent of the fund. This proposal therefore rewards drugs to the extent that they realize their raison d'être, that is, improving health.

Although all new drugs could participate in the HIF, it would likely attract those drugs whose potential health impact is large relative to the sales revenue it could earn should the developer elect to exercise its patents. In other words, it would likely attract drugs for tropical disease, drugs that confer large positive externalities, such as new antibiotics and vaccines, and drugs that are inherently unpatentable. The HIF might also attract me-too drugs that elect to compete with existing patented drugs on the basis of price.

4c4. Valuing me-too/follow-on drugs. Several schemes offer greater rewards to first-in-class or breakthrough drugs, recognizing that they are generally more expensive and risky to develop than me-too drugs. Hollis (2005) would measure a drug's value, not in terms of its share of the total QALYs produced by participating drugs (as in Hollis and Pogge (2008)), but as the difference between the QALYs produced by a unit of the drug relative to the QALYs produced by a unit of the existing standard therapy. Breakthrough therapies would thus earn a larger reward per QALY produced than me-too drugs. However, monetary rewards also depend on the total QALYs produced so that should a me-too drug supplant a breakthrough drug, perhaps by virtue of an improved side effect profile, or greater efficacy, the me-too could earn a substantial reward. The total reward accruing to the developer of the breakthrough drug would therefore depend on how quickly follow on drugs are launched and capture sales of the breakthrough product.

Sanders (2007) would grant the reward agency some latitude in rewarding breakthrough drugs. He writes: "In cases where a new invention is based upon an earlier invention, [the proposal] allows for sharing of rewards, so that a follow-on invention may completely replace an existing medicine, but the earlier product could still receive prize money, even with a zero market share, if the second product was based upon its technology. The aim is to give the correct incentives for products that are both first- and second-movers, since both are important." The proposals advanced by Levine, Kremer and Guell and Fischbaum would treat breakthrough and me-too drugs symmetrically.

4c5. Financing rewards. All proposals, except Levine (2009), would finance rewards using public funds. Public finance has both pros and cons. On the one hand, because the technology to produce a new drug is a classic public good, prices should ideally be close to MC. With publicly financed rewards, drug prices would be closer to MC than in reward schemes financed by royalties from imitators to innovators. Public finance could also simultaneously address distributional goals. A publicly financed reward scheme would distribute the financial burden of pharma R&D across taxpayers. In a privately financed scheme, this burden is distributed across drug users. The difference in drug prices would likely not be large for high volume drugs, but they could be for low volume drugs (including drugs used to treat rare disorders). Moreover, like the patents system, a privately financed rewards scheme would not induce innovation into therapeutic areas in which R&D costs exceed potential sales revenue. Hence a rewards scheme that is

entirely privately financed would not serve the needs of those suffering from rare diseases, or those suffering from diseases prevalent in resource poor countries.

Both the existing patents system and the proposed publicly financed rewards systems rely on contributions by different jurisdictions to finance pharma R&D. One important advantage of a publicly financed reward system is that each jurisdiction's contribution to the rewards fund would be transparent, making it easier to ensure that financial commitments are being honored. International contributions to pharma R&D in the existing patents system, by contrast, are opaque. The reason is that the agreement that governs patents and hence contributions to pharma R&D – the TRIPS agreement – regulates only minimum nominal patent terms. Signatories to TRIPS can reduce their pharma R&D contribution using a variety of tactics. First, they can increase the time required for review of a new drug's safety, effectiveness and cost-effectiveness. (To preempt competitors, firms apply for patents early in the development process. Thus regulatory review reduces effective patent life.) Second, they can set a high standard for patentability. Third, they can exercise their prerogative to compulsory license the drug. Fourth, public and private plans operating in the jurisdiction can impose reimbursement controls. These policies reduce the monopoly rents that are ostensibly there to recoup R&D costs.

Publicly financed rewards would also better align incentives. Presently, national governments are responsible for pharma patent policy, but do not bear the full burden of higher drug prices; these costs are often borne by regional government drug plans or private plans. These plans do not receive any political kudos for supporting innovation, and, indeed, are rewarded by plan sponsors for reducing prices. Plan sponsors presumably care about innovation but the impact of price controls on pharma innovation is at best indirect and occurs only after a considerable lag. There is also a strong temptation to free ride. As a result these plans tend to focus myopically on cost control. A national government, conversely, could benefit politically from financing a pharma innovation fund: it would create lower drug prices, no doubt popular with constituents, and it would support pharma innovation in a very direct, visible way.

A rewards based scheme has yet one more advantage over the patents system, at least for those living outside the US. According to Civan and Maloney (2006), global pharma R&D is almost exclusively focused on ameliorating the burden of diseases prevalent in the US, even though the US constitutes less than half the global market.[5] They write: "The transmission mechanism of this perverse effect is cross-country importation policies and the pricing formulas of some countries that are based on the lowest price at which the drug is sold worldwide. These policies make it unprofitable to develop drugs to treat diseases where most sales will be in low-price countries." So, while many developed countries pay proportionately less than the US for pharma R&D, they benefit only in so far as their disease burden coincides with that in the US. These countries' 'free-riding' comes at a cost of a paucity of research on diseases that are most important to them. A publicly financed rewards system, conversely, could more closely align R&D to local disease priorities.

[5] Civan and Maloney note that pharma sales revenues in the US for the year ending May 2004 was $168 billion while the combined sales in Canada, Germany, France, Italy, UK, Spain, Japan, Australia, New Zealand, Mexico, Argentina and Brazil was $162 billion.

Public finance also has various challenges. Presumably, funds would be collected and prizes would be disbursed by a quasi-governmental, likely international, agency. For this agency to carry out its mandate, it would require a mechanism to: i) set criteria for prizes (i.e. a formulaic or discretionary rewards system); ii) set the size of the prize fund at levels that encourage participation by innovators; iii) divide costs amongst the various sponsoring jurisdictions; and iv) establish ways to enforce compliance among sponsors. Clearly, innovators will not commit resources or support such programs if they suspect that the agency will renege on its promise to pay or if rewards are set too low.

Some commentators (Farlow 2007; DiMasi and Grabowski 2007) are pessimistic about the prospects for such an agency owing to the difficulties of achieving consensus on both (i) which diseases will be the focus of R&D activities and (ii) a reward mechanism among sponsoring jurisdictions; Wei (2007) argues that achieving consensus among stakeholders even within a jurisdiction would be very difficult.

Another drawback of public finance is the DWL of the taxes required to raise the prize funds. This problem, however, might not be as daunting as it first appears. The total public outlays under a rewards scheme might be of the same magnitude as current outlays on prescription drugs, estimated to be $750 billion globally in 2009 (IMS 2009). Most spending in developed countries is already publicly funded, either directly or through tax subsidies for private drug insurance. Under a rewards scheme, drug prices would drop markedly – likely by a larger percentage than the percentage increase in unit volume. Publicly funded drug spending should therefore decrease, and the savings could be directed towards the reward fund.

4d. Push Programs

The pull programs reviewed above provide rewards for the end products of the R&D process – new drugs. Push programs, conversely, aim to reduce the cost to pharma firms of conducting R&D. They include both general R&D subsidies, such as the R&D tax credits provided by the US Orphan Drug Act (Yin 2008), and programs that reduce firms' cost of the three stages of the pharma R&D process, i.e., basic science, pre-clinical research and clinical research. These stages are described below.

Basic Science. Drug discovery begins with the basic science needed to understand the biological mechanisms and pathways pertaining to the disease state of interest.

Pre-clinical research. Scientists then develop drug candidates that exploit, to varying degrees, an understanding of these mechanisms. Typically, this understanding is incomplete (Edwards et al 2009); drug discovery is thus still largely a hit and miss operation. Indeed, the search for promising compounds typically proceeds by assessing the functional attributes of a very large number of candidates whose composition is guided by at best a tenuous (or at worst incorrect) understanding of disease mechanisms. Candidates are first screened en masse for their efficacy (i.e., is the drug sufficiently potent?), toxicity (i.e., are there unwanted side effects?), and specificity (i.e., does it affect mechanisms other than its intended target?). This procedure involves introducing the drug into cultured human cells contained in separate compartments or 'wells' that are arranged in a rectangular grid. After exposure to the drug candidate, the vital status and the signaling behaviour of cells are monitored to assess toxicity and efficacy. This process is called 'high throughput screening'. Once

the high potency compounds have been identified from high throughput screening, they will be further tested in animal models to confirm in vivo activity. At the same time, these lead compounds will be evaluated by a Discovery Support group to ensure that they exhibit physicochemical properties acceptable for developing into drug products. Based on these pre-clinical results, the best candidate compound will then be recommended for further development. Once the compound is pushed into the development pipeline, formulators will then develop suitable dosage forms (capsules, tablets or suspensions) for the first human studies. To ensure these dosage forms are bioavailable, animal experiments are conducted to test the extent of absorption and bioavailability of the prototype dosage forms.

Clinical research. Drug candidates that emerge from this pre-clinical research are then tested in humans. Testing begins first on a small number of healthy subjects to assess the drug's toxicity at different dosage levels and dosing frequencies (in what are called Phase I trials), and, if successful at this stage, on up to 500 subjects with the disease to assess its therapeutic properties, sometimes at various stages of disease progression (Phase II trials). The safety and efficacy of drugs that clear these hurdles are then tested in clinical trials involving many subjects with the disease (Phase III trials). It is at this stage that investigators occasionally realize that the hypothesized disease mechanisms that guided the design of drug candidates turned out to be incorrect. Candidates that are abandoned at this stage can be enormously costly. A recent high profile example was the failure of Pfizer's drug torcetrapib in phase III trials in 2006. Evidently, this cost the company $1 billion.[6] The increasing rates of attrition, especially in late stage clinical trials (Mervis 2005), have dramatically increased the cost of bringing a new drug to market.

4d1. Push programs targeting pre-clinical research

Several commentators have proposed ways to address this problem. Edwards (2008) presents a compelling case for the creation of large-scale, not-for-profit, public-private consortia that conduct the basic research necessary to design viable drug candidates and reduce the high rate of attrition of drug candidates as they progress through clinical trials.

Edwards proposes that: i) to spread risk, the costs of this research be shared by all stakeholders (pharma industry, private charitable foundations, non-profit research institutions and governments); ii) the research findings be placed in the public domain to disseminate findings rapidly and widely so as to avoid duplication of effort, and to conserve the time and energy that is required to define and resolve IP rights over basic scientific discoveries; and iii) the research be conducted in partnership between academic and industrial scientists, so as to capitalize on their respective skill sets and promote collective learning.

Several such initiatives have already begun. The first such program was the Single Nucleotide Polymorphism (SNP) Consortium, founded in 1999. This initiative has discovered more than 1.8 million SNPs, which are the primary building blocks of the

[6] Pfizer shares hit by drug failure [Internet]. BBC. 2006 Dec 4;[cited 2009 Jun 18] Available from: http://news.bbc.co.uk/2/hi/business/6205528.stm

human genome. This collaborative involves academic and industrial scientists working at four academic institutions: (Sanger Centre, Stanford University, Washington University (St. Louis) and Whitehead Institute). Another initiative, the Structural Genomics Consortium (SGC), founded in 2003, has purified over 1,500 human proteins and has determined the structures of over 500 new human proteins, accounting for about 20% of all the human protein structures over the past 4 years (all on a budget of only $25M per year). More recently, the Toxicogenomics Research Consortium was established to characterize the effects of drugs and toxins found in the environment on gene expression. The Centre for Microbial Chemical Biology, launched in May 2009, seeks to understand how bacteria infect the human organism and how these attacks can be repelled using antibiotics.

DiMasi and Grabowski (2007) express concern with public subsidy of pharma R&D, arguing, among other things, "because it is difficult to gauge the effectiveness of R&D activities, some shirking may occur from reduced efforts or from the pursuit of what is of purely scientific interest. Attempts to deal with this problem by constructing contracts with a high degree of specificity can have their own adverse consequences, because they can stifle innovative approaches to problem solving." The success of these public private partnerships suggests that this concern is unfounded, at least for the conduct of basic research. Indeed, it appears that industrial and academic scientists can collaborate in ways that satisfy both the goals of academic scientists and the goals of the project sponsors. Pharma firms benefit because they can influence research priorities into directions that may yield commercially successful products and are kept abreast of developments in basic research. Placing results into the public domain also reduces holdup and transactions costs for downstream research. Likewise, academics profit from their access to the resources required to execute their research programmes.

These collaborations have proved to be successful for the production of very basic scientific knowledge, such as the kind pursued by the SNP and SGC initiatives, but additional knowledge is needed to overcome the hurdles to drug development. In particular, more needs to be known about the behaviour of cellular proteins (known in the industry as 'targets') that are implicated in disease pathways and how the activity of these protein targets can be altered pharmacologically in ways that ameliorate disease. There are about 3000 targets in the human genome that are potentially susceptible to a drug (Russ and Lampel 2005). But according to Whitty and Kumaravel (2005), thus far, only a few hundred targets have been fully validated in the sense that they have been shown to be therapeutically useful and modifiable by metabolically accessible, non-toxic drugs.

Much more work is needed to validate the remaining targets. Rai et al (2008) and Edwards et al (2009) concur that this work requires the expertise and resources of both the academic and industrial pharma sectors, and therein lies the problem. Academic researchers collectively have superior knowledge of the therapeutic relevance of targets than do individual pharma firms. Pharma firms possess the high throughput screeners and other specialized equipment required for the exercise. They also hold two other key inputs for validation: i) proprietary collections of small molecules (known in the industry as 'chemical probes') which are needed to assess the functional attributes of proteins, and ii) the expertise of medicinal chemists to produce new ones.

To accelerate the process of target validation, Rai et al (2008) proposes that a trusted agency provide a sort of match making service between academics and pharma firms. The agency would assess targets advanced by academics using the small molecule libraries owned by pharma firms and notify both parties if a match occurred. If both parties wanted to deal, the agency would help broker an IP agreement. Edwards et al (2009) suggest that target validation is best conducted using the open access, not-for-profit collaborative model that has proved successful for the production of very basic research. Their view is that pharma firms that contribute their screening equipment, molecular libraries and the expertise of their medicinal chemists and other scientists will gain more from the collaboration (by way to generating viable drug candidates) than they lose from divulging their molecular libraries to potential competitors. To prevent free riding, they propose that membership should be restricted to organizations that make a meaningful, and agreed-upon, contribution.

4d2. Push programs targeting clinical research

Other pull programs proposals have focused on Phase III clinical trials. Several commentators, including Lewis, Reichman and So (2007), Baker (2008), and Jayadev and Stiglitz (2009), have advocated for the public funding of Phase III clinical trials. Public funding of clinical trials does have much to recommend it.

First, they can produce information that is more useful than the industry-funded trials mandated by regulators. These latter trials are often placebo-controlled, typically focus on surrogate endpoints, enroll relatively healthy individuals, and are conducted for a relatively short period of time; moreover trial results are proprietary (Morgan et al 2000, Angell 2004, Baker 2008, Avorn 2006). (This is not intended to be a criticism of the industry. Indeed, this is rational economic behaviour given regulatory requirements, the behaviour of competing firms, and the time-limited nature of patent terms.) Publicly funded trials, conversely, could disclose publicly the evidence on comparative drug effectiveness needed by prescribers to make informed choices. Indeed, publicly funded trials are an extremely cost effective health care investment (Detsky 1989, 1990; Phelps and Parente 1990) that would otherwise be underprovided. The US National Institutes of Health have run some landmark clinical trials, including the ALLHAT study of the efficacy of different anti-hypertensive drugs[7] and WHI study of postmenopausal hormone therapy.[8] The latter trial has transformed prescribing in the area.

Second, public spending on clinical trials could also be relatively modest, for several reasons: 1) Public funding may temper the tendency of regulators to impose additional rules and conditions on the conduct of clinical trials (Yusuf 2004, Califf 2006); regulators would face the full cost of the administrative burden that they impose. 2) Governments likely face a cost of capital less than that faced by the pharma industry. According to Grabowski, Vernon and DiMasi (2002), the pharma industry's cost of capital is 11%. Moreover, drug R&D expenses are incurred up to 12 years prior to regulatory approval, so that capital costs account for about half the $802 million cost of drug development estimated by DiMasi, Hansen and Grabowski (2003). 3) Pharma firms rely on hospitals, physicians, and other health care providers to recruit patients into clinical trials and

[7] http://www.nhlbi.nih.gov/health/allhat/facts.htm

[8] http://www.nhlbi.nih.gov/whi/

execute trial protocols. Payments to providers and institutions constitute a large and growing cost, especially if patients with the disease under study are few in number (Silversides 2009). A centralized purchaser of these services might be able to negotiate better rates than individual pharma firms.

A final justification for public funding of clinical trials is that it would relieve pharma firms of the single largest cost of drug R&D. Clinical trials account for about 55% of the cost of drug development (Adams and Brantner 2006); public funding would therefore address the industry's standard justification for patent protection.

One drawback of public trial funding, echoing concerns raised by DiMasi and Grabowski (2007) of prize-based schemes, is that the public agency responsible for the trials may not be well informed of the most promising drug candidates. The agency's choice of drugs whose trial costs are eligible for public subsidy may also be subject to undue political interference.

4e. Alternatives to the patent system: Push-pull Hybrids

Another option is to combine push and pull programs to at once lower the costs of drug discovery and give developers incentives to bring therapeutically important new drugs to market. Recall that the high cost of pharma R&D is ultimately due to a limited understanding of disease mechanisms in humans. Many drug candidates are developed and advance to late stage clinical trials on the basis of speculative, and ultimately incorrect hypotheses about disease mechanisms. An obvious remedy is to support the basic research needed to design viable drug candidates. Edwards (2008, 2009) argues that this support should take the form of open access, not-for-profit collaboration between academic and industrial scientists, supported by both the public and private sectors. In principle, one could expand the scope of such collaborations to include early stage pre-clinical research on drug candidates. This activity would yield families of molecules, with promising therapeutic potential and which are not encumbered by IP. Next, pharma firms could use their expertise to shepherd promising drug candidates through the stages of mid and late stage pre-clinical research. The mechanism proposed by Levine (2009) could then be used to finance the cost of clinical trials of candidates that emerge from this pre-clinical research. Recall that rights to these candidate drugs would be auctioned. The firm that bids the lowest royalty rate covers the trial costs but receives the royalty from all firms selling the drug, should the drug receive regulatory approval.

This hybrid approach has much to recommend it. First, the use of open source public private partnerships capitalizes on collective learning and the synergistic combination of the expertise and resources of the academic and industrial sectors needed to produce viable drug candidates. By reducing the rate of attrition of candidates in late stage clinical trials, the creation of such consortia hold the promise to dramatically decrease the cost of pharma R&D. Second, the mechanism capitalizes on the expertise of the pharma industry in identifying promising drug candidates, coordinating clinical trials and marketing and distributing drugs. Indeed, the auction format would favor the firm that is most efficient in running the trial. Third, the use of royalty based rewards in lieu of patents should enhance competition in the final dosage form drug market, reducing margins and hence DWL, wasteful profit competition and the other social costs

identified earlier. Fourth, because public subsidies are limited to the cost of basic, and early stage pre-clinical research, there is perhaps less scope for political interference than if applied research and clinical trials were publicly funded. That being said, a public agency could in principle specify the parameters of the trial (e.g. comparators, endpoints, duration) so that the information generated could be useful to clinicians. Finally, unlike a patents-based reward scheme where longer trials directly reduce patent life, royalty payments would accrue indefinitely so that innovators would not face the same degree of pressure to minimize trial durations.

5. Conclusion

Many commentators take it as self evident that the patent system is the best way to support the development of new pharma drugs. A growing body of evidence suggests otherwise. Patents confer temporary monopoly power which innovators can use to earn profits on the sale of patented drug. The DWL of monopoly power is widely recognized, but there are other social costs that are perhaps less well recognized. These include: 1) the costs to the healthcare system of medication non-compliance due to higher drug prices; 2) the resources consumed in the battle over the innovator's profits; 3) the resources spent by the innovator to expand unit sales and extend patents; 4) the increased costs of pharma R&D when this R&D builds on patented upstream discoveries; 5) the distortions in research direction caused by non-patentability of certain compounds; and 6) the administrative costs of the patent system.

Some of these costs, specifically 2) and 5) and to a lesser extent 6), directly reduce the payoff to conducting R&D into therapeutically important drugs. The costs associated with item 2) appear to be particularly large. The innovator will need to spend resources fending off counterfeiters, resellers, competing drug companies (both generic and branded me-toos), and negotiating with and lobbying price regulators and drug insurers that appear to be myopically focused on cost containment. Given the critical importance of the pharma sector in improving health, these disincentives to conducting R&D are simply unacceptable.

There are alternatives to the patent system that avoid some or all of its downsides. These include public subsidy of the cost of pharma R&D, publicly financed lumpsum rewards for new drugs, and royalty payments paid by imitator to innovator firms. All of these schemes would lower drug margins and hence reduce the cost associated with DWL, profit competition, as well as market and patent expansion. Some argue against public finance, owing to problems of political interference, and informational problems. On this basis, a royalty-based scheme seems attractive.

Although much more work is needed to operationalize and compare the merits of these alternative approaches, my sense is that they hold the promise to increase the productivity of the pharma R&D enterprise and decrease social costs and therefore deserve serious consideration.

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