Patents and Other Incentives for Pharmaceutical Innovation

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Synopsis:

The public sector helps finance the drug discovery enterprise through a variety of mechanisms. These include grants for biomedical research conducted in public sector labs, tax subsidies for private drug plans, and the extension of intellectual property privileges to drug developers. The cost of bringing new drugs to market has increased markedly during the last two decades. This has raised questions about whether existing forms of public sector support is optimal, and, in particular, if alternative forms of public support would result in more therapeutically valuable drugs per dollar spent. This chapter reviews the advantages and deficiencies of existing forms of government support for drug R&D, and the features of the alternative arrangements that their proponents suggest will improve upon the current system. We review both "push" programs – schemes that make private investment in pharmaceutical R&D more profitable by reducing the private cost of the R&D – and "pull" programs – schemes that increase the revenues accruing to companies that manage to bring new drugs to market. We conclude with an assessment of the issues that need to be resolved for these alternative forms of support to be actually implemented.

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1. Introduction

Innovation – the discovery of ways to get more value from limited resources – is critically important for society's health and material standard of living.[1] Despite the salience of innovation, there is no consensus on how much investment in innovation there should be, or how to ensure that the optimal investments are made, or how much the public sector should pay. These issues are particularly contentious in the pharmaceutical industry, given the high cost of drug development and the extraordinary importance of pharmaceuticals for human health.

Pharmaceutical research and development (R&D) takes place within both not-for-profit and for-profit organizations. The not-for-profit sector – comprising both academic and public sector labs – tends to focus on basic research, while for-profit drug companies exploit this basic research, as well as their own research, to develop, test and market new drugs. Public support of basic research is usually by way of grants, administered by charitable foundations and public agencies, such as the Wellcome Trust in the UK and the National Institutes of Health in the US. Government support for the subsequent steps in the drug development process is composed of three core approaches: (1) tax subsidies for clinical trials and other R&D costs; (2) patents and other forms of intellectual property (IP) protection that enable the innovator to enjoy an exclusivity period in sales of newly developed products; and (3) prescription drug subsidies (often extended to seniors and those with high drug costs relative to income). These policies increase the profits to firms that undertake R&D, either by decreasing R&D costs (in the case of tax subsidies) or increasing revenues earned on the sale of new drugs (prescription drug subsidies, IP protection). Policies that decrease firms' costs of drug development are commonly referred to as "push" incentives, while policies that increase the revenues accruing to firms that manage to bring new drugs to market are termed "pull" incentives.

During the last decade or so, there has been considerable interest by academics, activists, politicians, and others in the manner in which governments support pharmaceutical R&D undertaken by for-profit firms. Of particular concern is the declining productivity of the pharmaceutical R&D sector. Recent academic studies place the capitalized cost of drug development to be between $1.5[2] and $1.8 billion.[3] Other estimates are even higher. [4] Different types of push and pull incentives, it is argued, would yield more therapeutically novel drugs per dollar of public support. But while there is agreement that reform is needed, there is less agreement over what should be done to improve matters.

This chapter reviews the contours of the academic debate, focusing on the advantages and deficiencies of existing forms of government support for drug R&D, and the features of the alternative arrangements that their proponents suggest will improve upon the current system.

2. Intellectual Property: Advantages and Disadvantages

Much of the analysis of the defects of current arrangements focus on the system of IP protection afforded to new drugs. This is not surprising, considering that IP privileges constitute one of the most expensive of all the forms of public support extended to the pharmaceutical sector.

There are two distinct kinds of IP currently available for pharmaceuticals: patents and data exclusivity.[5] A patent provides its owner with a 20-year period of exclusive use of the invention disclosed in the patent. Typically, drugs will be protected by a number of patents, each of which may have a number of claims disclosing distinct inventions. Since the innovation process is long, some of the relevant patents are filed many years before the drug comes to market. The result is that the average period of exclusivity owing to patents is roughly 10 years.

Data exclusivity is another important IP tool. The patent protects the invention, and can therefore protect the drug if it embodies the invention and there is no way of circumventing the patent. Data exclusivity protects the data produced by the innovator for the purpose of obtaining regulatory approval. Regulators such as the US Food and Drug Administration (FDA) require extensive testing of drugs, and running the clinical trials to obtain data that will demonstrate safety and effectiveness is extremely costly – typically around half of the total cost of drug development.[6] During the term of data exclusivity, which begins after the drug receives regulatory approval and varies by country from five to ten years, no generic drug is approvable based on a reference to the clinical trial data of the innovator's drug.

IP allows the innovator to earn more sales revenue than would be possible without exclusivity. The variable costs of production and distribution for drugs are typically only a small fraction of the brand drug price, ranging from approximately 5% to 25%. After covering other costs, such as marketing and administration, the remainder (often called the mark-up or the margin) can be paid as dividends or reinvested into R&D.[7] IP thus creates very powerful incentives to develop therapeutically novel drugs (among other innovations). The chief appeal of this system of market exclusivity is that it automatically generates a relationship between the reward to the innovator (the mark-up times the volume of sales) and the value of the innovation to society, as Adam Smith himself noted.[8] More therapeutically valuable drugs are expected to earn greater sales revenues. IP, however, also has some drawbacks, five of which we focus on below.

2.1 Drug R&D Costs

The first drawback is that the IP system can increase the cost of drug R&D, for two reasons. Basic research conducted in academic or public sector labs will occasionally identify cellular proteins, known as "targets", implicated in disease pathways. Multiple companies will then attempt to develop drugs that act on these targets. But drug development is very difficult because human biology is very complicated. As a result, many drugs simply do not work as expected and many of those that successfully disrupt the disease pathway either show no therapeutic benefit or do so only at doses that are toxic. It is also difficult to

deliver an agent to its target in sufficient concentration and for an appropriate duration to achieve the desired therapeutic effect.

Often the viability (or otherwise) of a drug candidate or a disease mechanism becomes apparent only after much time and money has been spent. Ideally, drug companies would share this information. Sharing would reduce duplication of R&D costs, would eliminate unnecessary experimentation on human subjects, and would advance the understanding of human pathophysiology and pharmacology. But commercial drug R&D has historically been conducted in a culture of secrecy. Some of this secrecy, no doubt, is due to normal competitive behavior, present to varying degrees in all technology-intensive industries. But pharmaceutical companies are hesitant to share information, at least prior to patent filing, owing to the risk that this information may be used by a competitor that is developing patents in the same area. Such a competitor may pre-emptively patent a class of molecules with therapeutic promise, or worse, attempt to patent the target or pathway itself.[9]

Of course, patents, once filed, publicly disclose the claimed inventions, so they do help to disseminate knowledge. Also the "first to file" rule for patents gives incentives to patent, and therefore disclose, early. And companies routinely report scientific and clinical progress at academic and medical meetings. But the information that is disclosed in patents or at meetings is typically incomplete, and certainly does not prevent multiple drug companies pursuing leads that are known by other competitors to be dead ends. [10]

IP can hinder drug development in another way. Many research inputs, such as disease-linked human genes and techniques to manipulate DNA and proteins, are patented. Innovating firms must therefore conduct R&D cognizant of the landscape of existing patents.[11] [12] [13][14] One way is to conduct R&D in ways that do not infringe on existing patents. But if it is not possible (or prohibitively costly) to use a circuitous technique, the firm 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 strike a mutually beneficial deal with possibly numerous patent holders. Another approach is to 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. Each of these strategies can increase the costs of research substantially.

2.2 "Follow-on" drugs

A successful new "first-in-class" drug will often face competition from a series of "me-too" or "follow-on" drugs that are therapeutically similar to the first-in-class drug. Often, follow-on drugs are simply the natural outcome of simultaneous research programs into the same therapeutic target.[15] In other cases, they are the result of an intentionally imitative research program.[16] The angiotensin converting enzyme (ACE) inhibitors, a class of drugs routinely used to manage

high blood pressure, is illustrative. The first ACE inhibitor, captopril, was introduced in the US in 1981. Since then, over 10 ACE inhibitors have been launched, the last one in the mid 1990s. It appears that some of these later arriving ACE inhibitors were launched to capitalize on the commercial success (and clinically proven mechanism of action) of the earlier ACE inhibitors.

The proliferation of follow-on drugs is the subject of some debate. Proponents note that some follow-on drugs are therapeutically superior to the pioneer. Indeed, this appears to be the case for the ACE inhibitors.[17] Moreover, if patients respond idiosyncratically to any one in a group of similar drugs, it is very useful to have alternatives.[18] But the threat of imitative drug development also reduces the incentive for firms to develop first-in-class drugs. The reason is that follow-on drugs decrease the expected sales revenues and increase the costs of the pioneer.[19] Lichtenberg and Philipson[20] show that competition from follow-on drugs decreases the pioneer drug's revenues more than the competition from generics after patent expiry, in large part because the competition from follow-on drugs occurs early in the life of the pioneer drug. Costs increase because the pioneer firm typically spends on marketing and promotion to defend market share from capture by competitive products. Follow-on drugs may therefore dull the incentive to develop first-in-class drugs. As evidence of this, critics point to the protein kinases; these cellular proteins represent among the most common targets for drug discovery. However, although there are 518 protein kinases in the human genome, more than half the current drug discovery programs focus on the handful of kinases for which there is already an existing drug.[21]

A related criticism concerns the large outlays on the marketing and promotion of branded pharmaceutical drugs, more generally. Estimates of promotional expenditures are somewhat uncertain, but data compiled by Gagnon and Lexchin[22] suggests that in 2004 the US pharmaceutical industry spent at least as much on promotion as it did on R&D.* Economic theory predicts that firms will continue to spend on promotion as long as the last dollar spent results in a compensatory increase in unit sales and gross profits. Thus IP, to the extent that it increases the margins earned on unit sales, encourages promotion.

No doubt some, perhaps the majority, of this promotion is socially valuable, alerting consumers to the availability of effective therapies for an untreated health condition, or providing prescribers with information on the properties of new drugs. However, critics charge that a significant portion is more persuasive than informative, and in some cases is misleading. This kind of advertising is socially wasteful, as it represents a zero-sum competition between firms for market share; in the worst cases it might lead to worse health outcomes if clinicians are persuaded to prescribe drugs that are unnecessary or inferior to other therapies.

* Gagnon and Lexchin's estimate includes two particularly notable components of promotional cost. First, they include samples (representing 27.7% of total promotional dollar value) and estimated "unmonitored" expenditures (representing 25%). The samples are valued at the retail prices, which are probably on average at least 10 times the cost of manufacture; and the estimate of unmonitored expenditure is highly uncertain. Removing these components reduces promotional expenditures to an amount closer to the amount spent on R&D.

2.3 Drug pricing

In most markets, consumer willingness and ability to pay is an important constraint on the price charged. Pharmaceutical markets are different. Most consumers in developed countries have insurance that covers some or all of the cost of prescribed drugs. If consumers do not pay for their drugs, what constrains prices? The answer, of course, is that insurers set limits on what they will pay. Indeed, many drug plans wield substantial bargaining power on account of their large size. 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. These plans increasingly exploit their negotiating power to extract price concessions from drug companies who wish to have their products listed on the drug plan formulary.[23] These price concessions directly reduce the margins that are ostensibly there to recoup R&D costs.† Negotiation costs and costs of applying for formulary listing can also be substantial; Cohen[24] reports that drug manufacturers often need to contract with hundreds of different drug plans in the US.

The price concessions are sometimes directly negotiated with insurers. For instance, the public drug plan operating in the province of Ontario, Canada extracts confidential discounts off list prices. Other insurers set a maximum price that they are willing to pay, not for tablets or pills, but for expected units of health generated by use of a new drug. These health units are usually denominated in 'quality adjusted life years' (or 'QALYs') – which measure both survival and quality of life gains.[25] Typically, insurers' willingness to pay for a QALY are well below consumers' expressed 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 in the US are closer to $100 thousand (~£65 000).[26,27] One reason that public insurers are willing to pay less than consumers is that public healthcare budgets are constrained. The relevant consideration for NICE is its opportunity cost: if the threshold payment per QALY is too high, it will displace other, more cost-effective non-pharmaceutical interventions.[28] A relatively low willingness to pay for drugs is thus appropriate if the public health authority wishes to maximize health given a constrained budget, although this raises questions about the adequacy of the health budget.

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† A notable exception is Medicare Part D – the drug program extended to US Medicare beneficiaries in 2006. The enabling legislation (the Medicare Modernization Act) explicitly prohibits the government from using its buying power to reduce drug prices. Private sector participants in this system may, however, achieve substantial discounts that indirectly benefit the government.

‡ The UK's NICE is perhaps the most well known national health technology assessment body, but it is not the only such initiative. Others countries that have created such agencies include Australia (Pharmaceutical Benefits Advisory Committee), Canada (Common Drug Review), Scotland (Scottish Medicines Consortium), Sweden (TLV), and Germany (IQWiG). Although the US has no national level body, Cohen [24] notes that many insurers informally consider cost effectiveness when making formulary decisions.

The use of QALY assessments reflects a growing tendency on the part of insurers to assess value for money when considering whether, and under what conditions, they will reimburse a drug. The insurers that used to cover almost all new drugs that received regulatory approval are now becoming much more selective consumers. An innovator, of course, can elect to forgo formulary listing in a given insurance plan; beneficiaries always have the option of paying cash for drugs that are not insured. But if the insurer has a large market share (as is typical for most public drug plans), then exclusion from the formulary will markedly reduce sales. There is a double effect from exclusion: non-formulary drugs tend not to be used, not only because of the cost to consumers, but also because physicians are not accustomed to prescribing them.[29,30]

In summary, IP affords innovators some market power and this market power is complemented by widespread insurance coverage, which renders consumer demand less price sensitive. This has naturally resulted in high prices. However, more and more insurers 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 (when low willingness to pay thresholds are applied) and indirectly (by requiring firms to incur the time and expense of conducting economic appraisal studies).

2.4 Drug Access

Scholars distinguish two separate drug access issues. The first is that IP may result in less drug use, relative to a world in which the drug is available for sale at a competitive (generic) price. More precisely, some consumers, whom we can label "price sensitive", are unable or unwilling to pay the brand price but may be willing and able to pay the marginal production cost, which would be the generic price in a well-functioning generic market. These sales are valued at more than their resource cost, so society would gain if the drug company lowered its price for the price sensitive consumers. But to make these sales, the firm may need to reduce its price for everyone and, by so doing, may lose more revenues on its "price insensitive" customers – those who are willing to pay the brand 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; indeed this appears to be the reason that drug companies were reluctant to sell AIDS drugs at discounted prices in low-income countries.[31] There is also pressure from higher-income countries to get the same discounted prices offered in low-income countries. Recently some companies have used "tiered pricing" in which the price in the lowest-income countries is essentially just the manufacturing cost. However, even then, as observed by Flynn, Hollis and Palmedo[32], *within* many developing countries the most profitable price may be the one that targets chiefly price insensitive, high-income consumers.

While access problems are most acute in developing countries, they also affect insured residents of developed countries. With prices of over $50,000 for many

new biologic therapies, insurers (and especially government drug plans) are not listing some products in their formularies.

The second access issue is that IP directs R&D into therapeutic areas where expected revenues exceed anticipated drug development costs. Thus diseases with limited market demand have traditionally received little attention by drug companies. This includes especially pediatric uses of drugs that treat diseases common among adults and diseases affecting large numbers of individuals in poor countries (such as drug resistant TB, malaria, and other tropical diseases). This inequity in the distribution of R&D effort is morally problematic. It is true that this problem is not caused by IP. Diseases of poverty will tend to be neglected regardless of whether or not society extends IP protections to commercial drug developers. For such diseases to be the focus of R&D effort necessarily requires that affluent people underwrite R&D costs. However, if the decision has been made for the affluent to subsidize the costs of developing drugs with limited market demand, then it does not follow that IP is the best way to incentivize such R&D.

2.5 “Profit Raiding”

The final drawback of IP is that some portion of the innovator’s potential sale revenues will simply be lost. The reason is that the high profit margins provided by market exclusivity attract “raiders” who attempt to appropriate these margins. The potential profits from IP protection therefore decline, both by the profits actually appropriated by raiders and by the resources expended by the innovator to fend off raiders. Hence the threat posed by raiders dulls the financial incentive to innovate in the first place.

Counterfeiters, the clearest example of a profit raider, are attracted to patented drugs owing to their high margins and low transport costs. Historically, drug companies ignored the problem given that most contraband was sold in low-income 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,[33] resulted in large increases in counterfeit sales.[34] This counterfeit is increasingly difficult to distinguish from the genuine product and is infiltrating developed country markets. Drug companies 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.[34,35] Despite these efforts, losses from counterfeiting have been estimated to be as high as $45 billion (US) annually.[34] Lybecker[36] reports that counterfeiting remains a pervasive problem “impacting nations of every size and income level and drugs of every description.”

Drug resellers are another type of profit raider. 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

drug company can charge in different markets.[37] These variations present drug companies with a dilemma. On the one hand, profit maximization requires that they charge as much as each market will bear, so that less affluent 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 tradeoff, a drug company 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.[38] [39,40] Nevertheless, it is difficult to eliminate all arbitrage opportunities. For instance, Bart[41] 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. See also the chapter by Kanavos in this volume.[42]

Generic competition can also be a form of raiding, to the extent that it undermines the legitimate and expected exclusivity period. 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. Brand firms have responded by increasing the number of patents listed on each drug. Indeed, Frank[43] reports 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 earlier. Two studies have examined the impact of these developments on exclusivity periods. Grabowski and Kyle[44] examine drugs in the US for which there was generic entry in the period 1995-2005, and find that there was an increase in generic challenges in both small and large “blockbuster” pharmaceutical markets, which reduced market exclusivity periods. Hemphilll and Sampat,[45] examining data for 2001-2010, confirm increased numbers of challenges by generics, especially those that occur within the first five years a drug has been on the market. In contrast, however, they find that exclusivity periods have not changed significantly. Their explanation for this is that generic firms are chiefly challenging low quality patents, so that generic challenges are simply “maintaining” the traditional patent life by preventing low-quality patents from extending exclusivity.

In addition to strategic patenting, brand drug companies have used two other strategies to mitigate profit loss from generic competition. First, a brand firm may launch a generic version of its branded drug product – a so-called “authorized generic” – to compete with independent generics for price-sensitive consumers. Second, if generic entry is likely, there may be an arrangement between the firms to delay generic entry. Such arrangements can be profitable because the brand firm, should it retain market exclusivity, can typically earn a higher margin on the generic firm’s unit sales than the generic could itself earn. So the brand firm can pay the generic firm the margins that it would have made and still have money left over. These arrangements have attracted considerable attention under antitrust laws; naked pay-for-delay settlements are now prohibited in the United States.[46] More recently the US Federal Trade Commission has challenged settlements in which the compensation to the generic for delayed entry is a promise of less aggressive competition.[47]

Finally, we note that the market entry of follow-on drugs can be considered a form of profit raiding, although unlike the case of counterfeiters, follow-on drugs provide benefits to consumers, in the form of expanded treatment choices some of which are therapeutically superior to the pioneer drug.

3. Alternative Push and Pull Schemes

Analysts have proposed a variety of different push and pull schemes that are claimed to yield more therapeutically valuable drugs per dollar of public support. We outline these proposals below.

3.1 Alternative Push Programs

Push programs aim to reduce the cost to drug companies of conducting R&D. Governments are already heavily involved in basic medical research, and this research substantially reduces the costs of bringing new drugs to market. However, there has been much interest recently in push programs that extend beyond basic clinical research, and into development problems that have traditionally been the domain of pharmaceutical companies. Of these, two proposals have received the most attention: 1) public subsidies for translational research,[48-50] and 2) public subsidy of Phase III clinical trials.[14,51-53]

3.1.1 Public subsidies for translational research

A key determinant of the cost of bringing new drugs to market is the rate of failure of drugs in late stage clinical trials (where drugs are tested on large number of subjects with the disease). Drug candidates that are abandoned at this stage can be enormously costly. A high profile example was the failure of Pfizer's drug torcetrapib in Phase III trials in 2006; the development costs on this ultimately unsuccessful product totaled $1 billion.[54]

The failure of drug candidates is due to an incomplete understanding of human pathophysiology and pharmacology. Two aspects of the reward systems that drive commercial drug discovery inhibit learning. First, as was noted earlier, drug companies keep the results of their drug development programs secret, at least before patents are filed; this secrecy is in part due to the IP system. Second, due to the high risk of failure in pursuing risky hypotheses, companies tend to focus only on those targets that are well-studied in academic labs. But academia focuses on only a small fraction of potential targets. There are about 3,000 targets in the human genome that are potentially susceptible to a drug.[55] Of these, by 2006 only a few hundred targets had been shown to be therapeutically useful and modifiable by metabolically accessible, non-toxic drugs.[56] Drug companies are understandably reluctant to invest significantly in their own target validation programs given the high risk of failure and concerns that competitors will use this information to develop competing drugs.

Rai et al[57][48,57] and Edwards et al[48] concur that this work requires the expertise and resources of both the academic and industrial pharmaceutical sectors, and therein lies the problem. Academic researchers collectively may have greater insight of the disease relevance of targets than do individual drug companies,

given that the public sector collectively spends far more than does industry on understanding basic disease mechanisms. Drug companies have the expertise and resources needed to carry out the systematic steps of drug discovery. They also hold three other key inputs for target validation: (i) proprietary collections of small molecules that are needed to assess the functional attributes of proteins, (ii) the expertise of medicinal chemists needed to produce new ones and (iii) the expertise and resources to develop and test biologics. To date, most collaborations between industry and academia are conducted within closed IP frameworks, in part because drug companies are reluctant to share their knowledge and resources widely, lest they benefit competitors.

To accelerate the process of target validation, Rai et al[57] propose that a trusted agency provide a sort of matchmaking service between academics and drug companies. The agency would assess targets discovered by academics using the small molecule libraries owned by drug companies and notify both parties if a target was hypothesized to have therapeutic potential. If both parties wanted to deal, the agency would help broker an IP agreement. Edwards et al[48] suggest that target validation, which only occurs after extensive clinical trials, is best conducted as part of an open-access, not-for-profit collaboration between the academic and commercial sectors. Placing research findings in the public domain in real time and unencumbered by IP restrictions would disseminate findings rapidly and widely, avoid duplication of effort, and conserve the considerable time and energy that is required to allocate IP rights over basic scientific discoveries. The open access model would also prevent the exposure of research subjects to experimental drugs that are often ineffective, and known to be so by at least a few commercial players and regulators.

But why would academics and industry collaborate? Edwards and colleagues argue that drug companies that contribute their equipment, molecular libraries and the expertise of their scientists would gain more from the collaboration (i.e., access to novel drug targets and influence over research directions) than they would lose from sharing their resources with potential competitors. To prevent free-riding, they propose that membership should be restricted to organizations that make a meaningful, and agreed-upon, contribution. For academics to commit fully, the collaboration must offer an attractive opportunity to conduct intellectually satisfying research and to receive peer recognition.

There is some evidence that such collaborations between academic and industrial scientists can be successful. The Structural Genomics Consortium (SGC), founded in 2003 accounts for about 15% of all the human protein structures in the public databases and is using this information to collaborate with industry medicinal chemists to generate open access chemical inhibitors of new drug targets.[58] The SGC is funded by the Canadian and Ontario governments, the Wellcome Trust and eight drug companies, and all research output is released without restriction under an open access policy. Edwards and his colleagues are initiating a parallel effort in which a consortium of academic institutions and major drug companies collaborate openly to test the disease relevance of novel drug targets in humans. [59]

3.1.2 Public subsidies for clinical research

Several commentators, including Lewis, Reichman and So[51], Baker[52], Boldrin and Levine[14] and Jayadev and Stiglitz[53], have advocated the public funding of Phase III clinical trials. Public funding of clinical trials would relieve drug companies of the single largest cost of drug R&D. At the same time, public spending on clinical trials would be relatively modest, for two reasons. First, governments already subsidize clinical trials through the use of tax subsidies. Second, governments likely face a cost of capital less than the 11% cost faced by the pharmaceutical industry.[6] Since clinical trials must be conducted before marketing approval, development costs are very sensitive to the cost of capital. In addition to being relatively economical, publicly funded safety and efficacy trials can produce information that is more credible and clinically useful than industry-funded trials, which are naturally designed to maximize the expected profits rather than the expected clinical benefits[51]

The public agency responsible for the trials would presumably need a way of deciding which drug candidates are eligible for public funding. One concern is that the agency's choice of drugs whose trial costs are eligible for public subsidy may be subject to undue political interference. Moreover the agency may not be well informed of the most promising drug candidates. These issues could be dealt with to some extent by providing public subsidies only to those drugs that cleared the clinical trials.

3.1.3 Product-development partnerships

As noted earlier, there are very weak incentives for commercial drug companies to invest in the development of drugs targeting malaria, tuberculosis and other diseases prevalent in developing countries. Governments and private foundations, however, have made substantial investments in research that addresses the gap. But pharmaceutical companies themselves have the crucial advantages of substantial expertise, technological capabilities, and large libraries of potentially interesting compounds. So it was natural for "product development partnerships" (PDPs) to arise between governments or foundations and for-profit pharmaceutical companies. The difficulty was that for-profit companies wanted to be able to earn a return on their investment, while governments and foundations were especially interested in ensuring that the prices of products were low enough to enable widespread use in poor countries.

A key innovation in developing these PDPs was identifying how pharmaceutical companies could be rewarded for their participation, in a way that also allowed the "public" partner to achieve its goals. Modern PDPs have typically satisfied the divergent goals of their partners by splitting the market for the product into a commercial one, left to the industry partner, and a humanitarian one, in which some arrangement was made to achieve wider access, usually through at-cost pricing or through licensing to competitive producers.

Thus, during the early 2000s, several important PDPs have been established, and some have been successful in delivering products to market. These PDPs have become a central component of the war on neglected diseases. The most substantial PDPs, according to funding received, are the International AIDS Vaccine Initiative and the Medicines for Malaria Venture (MMV), which are both funded at close to $100m annually.[60] MMV has a large portfolio of products at different stages of development. Unlike a traditional drug company, which has a portfolio of drugs in different therapeutic areas, MMV is focused only on malaria. This approach would create undesirable risk for a for-profit company; but it is efficient for MMV because its advisory committee has the opportunity to compare many different prospective products and to choose a portfolio optimized to achieve success in addressing medical needs. Most other PDPs focus on one or two therapeutic areas, a feature that distinguishes them from private companies and offers a strategic advantage for development work.[60]

3.2 Alternative Pull Programs

The push programs reviewed above aim to reduce the cost to drug companies of conducting R&D. Pull programs, conversely, provide rewards for the end products of the R&D process – new drugs. The alternative pull programs differ from the IP model in one key respect: instead of granting the innovator the right to exclude others from selling the drug, innovators are rewarded with payments that are proportional to the drug's value. This means that under the alternative models, competitive entry occurs sooner, so that sales volumes are greater and prices lower. With prices closer to competitive levels, drug access would be improved and resale, counterfeiting and other forms of profit competition would be rendered less lucrative.

These proposals can be categorized along several dimensions.

3.1.1 Measurement of drug value

Under the current IP system, drugs that the market deems to be more valuable earn greater profits. But 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. Pharmaceutical markets are extraordinary because the consumer neither chooses the medicine (the physician does) nor pays for it (the insurer does). Market demand for drugs thus reflects physicians' prescribing decisions, insurers' coverage decisions (and related cost containment policies), and consumer willingness to pay for insurance and amounts not covered by insurers. While physicians act as expert agents on behalf of patients, many physicians are doubly protected from pricing concerns, since they do not pay even co-payments.

Different schemes use different measures of drug value. Sanders' Medical Innovation Prize Fund Act[61] would grant a public agency the power 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. DiMasi and Grabowski[62] 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.

Other proposals would rely on forecasts of the profitability of new drugs. Kremer [63] proposed that a public agency assess drug value by auctioning off IP rights to a new drugs. In most cases – say, nine of ten auctions – the winning bid would be used only to set the reward payment to the innovator and the patents would then placed in the public domain. In a randomly selected tenth auction, the winning bidder would receive the IP rights at the bid price. A defect of this scheme is that 10% of all new drugs remain under patent. However, this is necessary if auction participants are to take the bidding seriously.

David Levine[64] has proposed a mechanism that could be useful in cases where a public sector agency or perhaps an open source drug discovery consortium has identified a compound with some therapeutic promise, but whose properties have not been subject to any clinical testing. Levine proposes that drug companies bid for the rights to these compounds. 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,[65] 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.

How would drug companies fare under these proposed schemes relative to the existing IP system? In theory, Kremer's proposal would give innovators the present discounted value of their anticipated monopoly profits, so over the long term, firms would fare just as well as in the existing system, if expectations are unbiased. Indeed, since rewards are less variable under the Kremer approach, it might even be preferred to the IP system. Should Levine's proposal be adopted, competition among firms would decrease the rewards to the firms' opportunity cost – the most that they could earn in some other venture. Kremer therefore rewards the market value of the innovation, which itself is determined by willingness to pay on the part of drug plans and consumers while Levine covers firms' cost of innovation.

The proposed Health Impact Fund (HIF) offers a mechanism that rewards firms in a way related to both value and cost. A drug enrolled in the HIF would be sold at cost but would earn payments proportional to its measured impact on

population health in each of the 10 years following market launch. The proposal also allows for supplementary rewards for 5 years should its sponsor receive approval to use the drug for new indications.[66] Each annual payment represents a share of a reward fund; the reward fund share for an enrolled drug in a given year is equal to the drug's share of the global health produced by all participating drugs in that year. Health impacts would be measured using many of the same health technology assessment procedures currently used by drug plans when deciding whether or not to reimburse a new drug.[67,68] For example, if all participating drugs were estimated to have produced twenty million QALYs in a given year, and if an enrolled drug had produced two million of these QALYs, then it would receive ten percent of the fund. Contributions to the HIF reward fund by donor countries would be proportional to donor's Gross National Income.

Participation in the HIF by drug companies would be voluntary; a drug developer could elect to exercise its IP privilege or relinquish high prices in exchange for the reward payments. By making the scheme optional, developers could earn at least as much as they would under the existing system. At the same time, because firms would compete over a fixed pool of rewards, the expected reward must be equal to the cost of development for the firm with a marginal project. Thus, this system makes rewards depend explicitly on the marginal cost of innovation.

Because the IP system, as well as the systems proposed by Kremer and Levine, are market-driven, firms have little incentive to conduct R&D into important diseases afflicting chiefly the poor. The HIF, in contrast, could be used to reward the development of drugs with large health impacts, even if the beneficiaries are themselves not funding the reward payments. The HIF could similarly incentivize the development of new uses of older drugs for which there would otherwise be no significant reward.

The HIF is but one approach that could be used to fund the development of drugs that are intended for use in low income regions. The Advance Market Commitment is another. Several governments and the Bill & Melinda Gates Foundation have funded a $1.3B program to subsidize the provision of the pneumoccal vaccine in the poorest countries. The subsidy is at a fixed rate per vaccine delivered, and firms were intended to compete for a share of the $1.3bn by accelerating the development of vaccines that would treat the most common strains of pneumonia in developing countries and rapidly scaling up production.[69]

A criticism of the HIF is that it requires a relatively complex centralized system of health impact assessment. However, many drug plans presently require forecasts of the health impacts of new drugs being considered for formulary inclusion, so the criticism is somewhat misplaced. It is true that the HIF requires measurements of actual -- rather than anticipated -- heath impacts, and also requires a standardized measure of health impact. These measures would likely vary somewhat by country, depending on the institutional features of health care, as well as health risks specific to each setting. So health impact assessment is front and center of the HIF approach whereas under existing assessment

procedures, drug plans appear to be satisfied with a lower standard of evidence (i.e. anticipated, not actual health impacts), especially if the price charged is attractive. A pilot of the HIF could involve a performance-based reward applied in a single country to one or more drugs, to test the ability to measure impact in a credible way, and also to see whether firms would respond to the incentives inherent in the system.

It is also useful at this point to note some drawbacks of the auction mechanisms contemplated by Kremer and Levine. The auction format is widely used to elicit private information. But Grinols and Henderson[70] question the utility of the auction mechanism for reward determination 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. Auctions are also subject to gaming by bidders, so they need to be carefully designed.

Kremer's proposal has one additional defect. The innovating firm receives a lump sum payment prior to the drug actually being sold and receives nothing thereafter. Hence there is little incentive for the firm to promote its drug (which is often an important component of achieving widespread sales) or to investigate new uses for the drug.[71] The HIF, and the approach advocated by Levine, on the other hand, reward innovators in proportion to their market sales and therefore retain incentives for promotion and on-going product development.

3.1.2 Financing reward payments

The mechanisms proposed by Kremer[63], Sanders[61], and Hollis and Pogge[66] would finance rewards using public funds, whereas Levine's scheme is self-financing.

Public funding has both pros and cons. On the one hand, because the technology embodied in a new drug is a classic public good, prices should ideally be close to competitive levels. With publicly financed rewards, drug prices would be lower than in royalty-based schemes, assuming that the funding scheme set limits on pricing, for example by requiring generic licensing. Public funding could also simultaneously address equity goals through the distribution of the financial burden of R&D across taxpayers. In a privately financed scheme, this burden is distributed among 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).

Public funding also has drawbacks. Public funding of investment into innovation requires taxation, which distorts labour-leisure choices and consumption decisions. This drawback should not be overstated however: most prescription drug spending in developed countries is already publicly funded, either directly (through a public drug plan) or indirectly (through tax subsidies for private drug coverage). 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.

Both the existing IP system and the proposed publicly financed rewards systems rely on contributions by different jurisdictions to finance drug 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 R&D in the existing patents system, by contrast, are opaque. The reason is that while the TRIPS agreement requires uniformity of patent length and non-discrimination, it fails to prevent countries from negotiating aggressively on the prices of new drugs, or reducing the period of market exclusivity by delaying formulary approval. Ideally, countries would contribute towards innovation in proportion to their ability to pay. Such an allocation of contribution is not only ethically attractive, but it is also likely to be roughly efficient in a Ramsey sense.[72]

A dedicated, publicly financed international reward fund has an additional advantage over the IP system. National governments are responsible for setting IP 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 much political kudos for supporting innovation, and, indeed, are rewarded by plan sponsors for reducing prices. Plan sponsors presumably care about innovation but if there is any impact of their price controls on drug innovation, this is likely small and indirect and occurs only after a considerable lag. As a result these plans tend to focus myopically on cost control. A national government, conversely, could benefit politically from financing a drug innovation fund: it would create lower drug prices, no doubt popular with constituents, and it would support drug innovation in a very direct, visible way. In addition, it is the national government that has relationships with other national governments, and these relationships can be used to help deter free-riding.

Publicly financed rewards schemes, then, are in some ways more transparent than existing arrangements. As a result, countries would be less able to shirk their responsibility to finance drug R&D. But this very transparency could make it difficult to strike a deal in the first place. Indeed, some commentators[62,73] suggest that it would be very difficult for national governments to agree on a division of R&D costs and a means of enforcing the agreement. Moreover, these commentators suggest that it would be difficult to devise a sharing rule that is responsive to changes in countries' willingness and ability to pay.

Nevertheless, the calls for a global R&D treaty continue. The World Health Organization's "Consultative Expert Working Group" on R&D Financing has expressed preliminary support for a recommendation that countries begin negotiations towards such a treaty, but since the possible components are disparate and vague (and indeed the proposal includes no specific items that should be included in the treaty) it is difficult to know what is being proposed.

Although prospects for an R&D Treaty are unclear, other international agreements appear to be feasible. For example, Lawrence Gostin and colleagues have proposed a research program for a "global health governance framework" which would set out minimal responsibilities for countries in terms of

meeting health requirements of their citizens, as well as international obligations to help build the capacity of low- and middle-income states.[74]

In summary, the alternative pull programs described here reward new drugs in differing ways. Sanders would vest a public agency in the United States with the power to decide on rewards based on domestic sales only. Kremer would use anticipated market demand and Levine would use anticipated market demand and the risk adjusted cost of running the clinical trials required by the regulatory authorities. The HIF would set rewards in proportion to the health gains generated by the use of the new drug globally. The HIF proposal is unique in that it is intended to supplement, rather than replace the IP system. Levine's proposal is unique in that it is self-financing; any firm could sell a newly approved drug, but each seller would be required to pay a royalty to the innovator on each unit sold. This royalty rate essentially reflects the anticipated risk adjusted cost of generating the evidence needed to gain regulatory approval. The remaining approaches require a dedicated, publicly financed reward fund to remunerate innovators. The funds required vary between proposals. Since the HIF is a supplement to the IP system, the financing required would be less than in the proposals advanced by Sanders and Kremer. A wholesale replacement of the IP system would undoubtedly require contributions by different countries. This requires an international agreement be struck, an outcome that some analysts view as politically intractable.

4. Discussion

The proposed mechanisms described here hold the promise to enhance the effectiveness of public support for the drug discovery enterprise. Implementation of these initiatives, however, requires that a variety of issues be addressed.

These include the following.

Which reforms are feasible? Of critical importance, revenue streams must be predictable if firms are to commit funds to R&D projects. Should the IP system be replaced with a rewards scheme, then there needs to be an agreement that binds governments to commit resources. An agreement that reallocates the hundreds of billions of dollars spent annually on pharmaceutical R&D at this time is likely not politically feasible. However, more modest reforms might be possible. In particular, push type programs that seek to reduce the private cost of drug discovery and commercialization, and pull type programs that supplement, rather than replace, the IP system would be less disruptive to the status quo, would have more predictable consequences on firm's profitability, and would involve smaller public sector financial commitments. At the same time, push type policies, should they be successful, would reduce private drug development costs and hence the reliance on IP to recover development costs. This may, in turn, facilitate further reforms to the IP system.

The public private consortiums engaged in translational research are particularly promising. However, some critical problems need to be considered. How can

the consortium satisfy the many competing interests? In particular, how should the consortium decide on which therapeutic areas to investigate? Should this be decided by a vote or by consensus? Should there be sanctions applied to members that are found to not cooperate fully? For example, it may become apparent that a drug company withheld from the consortium research output that would have been useful. Should this result in expulsion from the consortium? Which drug companies would conduct clinical trials on drug candidates that emerge from a consortium? What restrictions will there be on the pricing of such drugs, given the contributions by academics and public funders? More generally, how should a consortium interact with the existing IP regime? Resolution of these issues would appear to be vital to the success of a consortium.

Another promising avenue is public funding of Phase III trials. If there were public funds, however, there would likely be no shortage of drug candidates seeking funding. Should public funding be linked to the ultimate success of the trial, or simply to the promise demonstrated prior to the trial? How should conflicting priorities among different disease advocacy groups and among different jurisdictions be resolved?

Finally, more work is needed to operationalize the HIF's health impact measurement technology. Since the HIF relies on assessment of health impact, it is important to know how such assessment would be performed and how firms would respond to being paid based on impact. A pilot trial could be done for a single drug in a country or region. The HIF also requires further analysis of antitrust issues and evaluation of its likely effectiveness.

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