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Key Points: (max 4, max 20 words each)

1. Aspects of the international drug patent system penalize development of first-in-class drugs and reward follow-on drug development.
2. Public subsidies of ‘proof of concept’ and clinical trials, and impact-based and royalty-based rewards for new drugs are promising alternatives.
3. Implementation of these alternatives would be challenging. For instance, some require nations commit to stable drug discovery funding streams.
4. We propose further research including laboratory experiments and piloting of these mechanisms to assess their effectiveness.
1. Introduction

Many observers take it as self-evident that patents are necessary for pharmaceutical drug innovation. Modern research, however, has raised serious questions about the effectiveness of patents in spurring innovative activity in general, and drug innovation in particular.\textsuperscript{1,2,3} The literature has also proposed mechanisms that may be more effective, including both ‘push’ programs – public subsidies of biomedical research and clinical trials – and ‘pull’ programs – impact-based and royalty-based rewards for new drugs. It is unclear, however, if these proposed alternatives – either alone or in combination – would spur drug R&D or could be integrated into the current systems of drug safety and efficacy regulation, insurance, and patent treaties. In this commentary, we (1) review the limitations of the drug patent system, (2) describe some promising alternatives to patents, and (3) propose a program of research to evaluate these alternatives.

2. The system of drug patents

Current thinking about the role of patents in drug innovation can be summarized as follows. R&D is very costly, but once a new drug is developed, others can quickly produce low-priced generic copies. If faced with the prospect of instantaneous generic competition, no firm would invest the billion dollars required to bring a new drug to market. Patent protection keeps generics at bay for a limited time, allowing the innovator to charge a price sufficiently high to recoup R&D costs.

It is widely recognized that recouping R&D costs via high drug prices has a drawback. High drug prices restrict access to those with comprehensive
insurance or sufficient ability to pay; globally, many people lack both. But there is an additional problem. Aspects of the patent system increase the cost of discovering novel therapies, decrease sales revenues, and thus reduce the financial incentive to innovate.

2.1 Increased drug discovery costs

The science that supports early-stage drug discovery is funded mainly by governments and conducted in academic or public-sector labs. This research often identifies cellular proteins (known as ‘targets’) implicated in disease pathways. The commercial rewards that are linked to the discovery of ‘first-in-class’ medicines induce multiple companies to pursue every novel target, and also to keep their progress and results secret. Indeed, secrecy is paramount given the risk that competitors may patent a class of molecules with therapeutic promise, or worse, attempt to patent the target or pathway itself.4

In this environment, patents impede drug discovery in two ways. First, 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 cognisant of the landscape of existing patents.5,6,7 Second, while there have been some notable successes, hypotheses about disease mechanisms derived from animal models are often refuted in human clinical trials; this results in enormous costs to firms. Indeed, the high rate of attrition of drugs to novel targets in clinical trials is a primary contributor to the declining productivity (i.e., increasing cost) of pharmaceutical R&D observed over the last several decades.8,9 The secrecy of the process and the unwillingness to share
information about attrition in early-stage research and in clinical trials not only leads to the costly duplication of effort, but also fails to advance the understanding of human pathophysiology and pharmacology. Perhaps even more distressing is that this process leads to the exposure of patients to interventions that have no chance of success and a real chance of causing harm.\textsuperscript{10}

2.2 Decreased sales revenues

Aspects of the drug patent system make it challenging for companies to earn the sales revenues needed to recoup R&D costs. First, the time between discovery and drug approval consumes much of a molecule’s patent life. Second, the high profit margins provided by market exclusivity attract ‘raiders’ who attempt to appropriate these margins. The potential profits from patent 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.

Profit raiders include counterfeiters and drug resellers (who sell low-priced drugs in high-price jurisdictions). Innovating firms also engage in costly battles with rival firms, both generic and brand. Generic firms seeking to launch their product prior to the expiry of the last patent on a branded drug can challenge outstanding patents in court, claiming either patent invalidity or non-infringement. For their part, brand firms can attempt to delay generic entry through strategic patenting.\textsuperscript{11}

The developer of a commercially successful first-in-class medicine can also expect to lose profits to competitors developing therapeutically similar ‘follow-on’
drugs. Part of the profit loss comes from reduced sales revenues, estimated to be four times as large as the revenue loss from generic competition. Another part of this loss is due to the extensive promotional expenditures firms undertake to shift prescriptions from rivals. The proliferation of therapeutically similar drugs also appears to explain the growth of economic appraisal, prior authorization, beneficiary cost sharing and other drug plan cost control initiatives that reduce sales revenues.

Follow-on drugs are not necessarily undesirable; many followers are therapeutically superior to the pioneer and expand treatment options. But the issue here is not the existence of follow-on drugs. The issue is that the marketing exclusivity provided by patents enables the high prices that attract more follow-on drugs than would otherwise be the case. These competitors reduce profits accruing to the pioneer, and thereby dull the incentive to develop first-in-class drugs. Ideally, society would reward innovation in a way that makes it more profitable for firms to incur the financial risk of validating and then exploiting new therapeutic targets, than focusing on clinically validated targets and established markets.

A system with inadequate rewards for innovative research relative to imitation has predictable results. Consider, for instance, 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 an existing drug.
2.3 Distortion of R&D decisions

We have already described how the present system rewards the development of follow-on drugs. But there are other distortions as well. First, patentees will often extend a drug franchise by formulating a slightly modified version of the molecule. Second, R&D tends to be focused on drugs on which patent monopolies can be profitably enforced. As a result very little research is devoted to new uses for genericized drugs or non-patentable molecules. A related issue is that little R&D is conducted into therapies where R&D costs exceed expected, risk-adjusted sales revenues. These include not only diseases affecting only small numbers of individuals globally but also diseases affecting large numbers in poor countries. Finally, patents affect the amount of safety- and efficacy-testing that firms voluntarily undertake. Because patents are time-limited, each year spent testing is one less year of market exclusivity. Patents might therefore lead to less testing compared to other incentive schemes.

In summary, the patent system yields high prices for drugs, with attendant problems of access, counterfeiting, cross-border trade in pharmaceuticals of dubious quality, high levels of marketing and promotion, insurance cost control schemes, increased drug R&D costs, and extensive litigation. The current system also skews R&D priorities towards incremental improvements to existing blockbusters, and away from drugs for neglected diseases and the diseases of poverty.

We are not the first to identify these issues and recommend solutions. Other commentators, however, tend to address one or two defects of the patent system.
in isolation. Specific proposals include extending patent protection to firms that either develop drugs that are otherwise non-patentable, or produce clinically useful information on their drugs’ effectiveness. Ideally, one would reward drug discovery and commercialization without the distortions caused by patents.

3. Alternatives and complements to patents

Whereas we currently reward innovation via the possibility of charging high prices, alternative mechanisms may work better. Push-type mechanisms subsidize the cost of drug discovery; of these, two programs have received the most attention: 1) public subsidies for basic research, and 2) public subsidy of Phase III clinical trials.

3.1 Public support for basic research

Public subsidies for basic research are not new – indeed, much of the budget of the US National Institutes of Health and the Canadian Institutes for Health Research sponsors basic research germane to pharmaceutical R&D. What is new are proposals that target the high failure rate of drugs in clinical trials. One option is public subsidy of large-scale, not-for-profit consortia that conduct the basic research necessary to identify and validate drug targets in humans. The idea is to declare proof-of-concept trials as the boundary between pre-competitive and competitive drug discovery, and to fund this collectively. Specific aspects of this proposal include: (i) to spread risk, the costs of this research are shared by all stakeholders (industry, non-profit research institutions and governments); (ii) the research findings are 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 patent rights over future scientific discoveries and to negotiate legal agreements to share existing knowledge or reagents; and (iii) the research is conducted in partnership between academic and industrial scientists, so as to capitalize on their respective skills and promote collective learning and technology transfer.

3.2 Publicly funded clinical trials

Public funding of Phase III clinical trials would relieve drug companies of the single largest cost of drug R&D (about 21%)\textsuperscript{21}. At the same time, public spending on clinical trials would be relatively modest, for three reasons: (i) Governments already spend a lot on clinical trials. In Canada, for instance, tax subsidies contribute about 50% of trial costs.\textsuperscript{22} (ii) Governments likely face a cost of capital less than the 11% cost faced by the pharmaceutical industry. Since clinical trials must be conducted before marketing approval, development costs are very sensitive to the cost of capital. (iii) Public funding may temper the tendency of regulators to impose additional restrictions on the conduct of clinical trials\textsuperscript{23,24} or to mandate that inefficient statistical decision rules be used to assess safety and efficacy;\textsuperscript{25,26} governments would face the full cost of meeting these requirements. 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.

3.3 Royalty-based schemes

Pull programs come in two flavors: 1) royalties paid by generic firms to innovator
firms, and 2) publically funded payments proportional to the value of the new
drug. Royalty schemes have a long history in Canada, dating back to the
compulsory licensing regime in effect between 1923 and 1993, and proposals
forwarded by the Commission of Inquiry on the Pharmaceutical Industry in
1985.27 More recently, David Levine proposed that firms bid for the rights to drug
candidates; these are promising compounds that have yet to be 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 product receive regulatory
approval. The firm bidding the lowest royalty rate wins the auction but would pay
for remaining drug development and clinical trial costs, as well as marketing
costs. Bids would therefore reflect firms’ expectations re: (i) these remaining
R&D costs, (ii) the likelihood of regulatory approval, and (iii) conditional on
approval, the drug’s commercial prospects and marketing costs. Governments
could supplement royalty rates if it deemed that certain drug candidates needed
additional incentives.

3.4 Reward-based schemes

Kremer and Glennerster28 proposed that governments guarantee subsidies for a
pre-specified number of units of vaccines developed for use in low-income
countries. These subsidies would at once create a commercial incentive for
vaccine R&D and reduce prices to consumers. This ‘pull’ program has been
adopted and funded by a group of industrialized countries, including Canada.29 A
generalized version of this mechanism is found in the Health Impact Fund (HIF),
proposed by Hollis and Pogge.30
The HIF is an optional ‘pay-for-performance’ scheme that would operate alongside the patent system. Participating firms would be required to sell their drug worldwide at a regulated price near the average cost of production and distribution. In exchange for selling at low prices, following market approval, firms would receive 10 annual payments based on measured health impact. The HIF therefore rewards drugs to the extent that they realize their *raison d’être*, that is, improving health. At the same time, by keeping drug prices closer to variable costs, resale, counterfeiting, and follow-on drug proliferation would be rendered less lucrative.

The HIF creates another significant advantage as a supplement to the patent system. Because the patent system is 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.

4. Implementation issues

Implementation of these alternatives raises many questions. The first of these is whether drug company participation in these programs should be mandatory or optional. If the former, should we rely on royalty-based mechanisms – which require minimal government involvement – or should the public sector assume a larger role? If participation is optional, what is the lowest (public) cost incentive
package that would induce firms to willingly relinquish their patent privilege? And what would this entail? Would it be sufficient, for instance, to provide public subsidy of target validation and clinical trials?

The second key question pertains to international contributions towards the cost of drug discovery. Of critical importance, funding streams must be predictable if firms are to commit funds to R&D projects. This requires an agreement that binds governments to commit resources. Our existing system is defective because 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. Ideally, countries would contribute towards innovation in proportion to their ability to pay.

Third, implementation of the alternative systems requires a means of allocating public funds across different initiatives. For instance, if Phase III trials were publicly funded, 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 there are various questions specific to each type of incentive mechanism that might be used. If we rely on generic drug companies to create the competitive pressure that reduces drug prices, how do we encourage generic entry in the growing class of biologic drugs? If we use the HIF, how exactly
should health gains be measured? If we use royalties, how developed should molecules be before they are put up for tender?

5. Moving forward

We propose a program of research to generate the evidence needed to resolve some of these issues. First, there should be an objective analysis of the proposed open access proof-of-concept trials. This should include, among other things, the legal and economic implications of (1) the patentability of inventions that arise subsequent to the consortium’s work, (2) antitrust issues, (3) the prospect of product development races arising from public validation of targets, and (4) how to determine which pathways and targets should be selected and prioritized. Once these issues have been addressed, governments and industry should collaborate to support a consortium to carry out proof-of-concept trials.

Second, we propose that companies and governments should engage in a theoretical analysis of royalty mechanisms and their implementation.

Third, we propose a trial of 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. Such a 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.

In addition to theoretical and field evaluations of the push and pull mechanisms described, we propose laboratory experimentation to explore the features,
possible problems, and unexpected interactions of these proposals. Studying the outcomes of social experiments in laboratory conditions may seem contrived, but the literature in the area suggests that it can be effective. Finally, we propose that when suitably developed, these alternative mechanisms be evaluated using randomized social experiments.

We recognize that there will likely be resistance to these initiatives. While the patent system operates poorly in pharmaceutical markets, it is at least familiar. The alternatives are not. The good news is that there is increasing recognition by industry and governments that the current situation – declining R&D productivity coupled with stagnant revenues – is untenable and that major changes are required. Countries must begin to move ahead in attempting reforms in an experimental spirit, with a readiness to learn and revise on the basis of experience.
References

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