

New approaches to rewarding pharmaceutical innovation

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Many observers take it as self-evident that patents are necessary for pharmaceutical drug innovation. Modern research, however, has raised questions about the effectiveness of patents in spurring innovative activity in general, and drug innovation in particular.¹⁻³ Mechanisms that may be more effective have been proposed, including “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 whether these proposed alternatives — either alone or in combination — would spur drug research and development or could be integrated into the current systems of drug safety and efficacy regulation, insurance, and patent treaties. In this article, we review the limitations of the drug patent system, describe some promising alternatives to patents and propose a program of research to evaluate these alternatives.

Limitations of the drug patent system

Current thinking about the role of patents in drug innovation can be summarized as follows. Research and development is very costly. No firm would invest the billion dollars or so required to bring a new drug to market if faced with the prospect of instantaneous competition from manufacturers of low-priced generic copies. Patent protection keeps generics at bay for a limited time, allowing the innovator to charge a price sufficiently high to recoup research and development costs.

However, the current drug patent system has its drawbacks. It is widely recognized that setting high drug prices to recoup costs restricts access to people with comprehensive insurance or sufficient ability to pay. In addition, aspects of the patent system increase the cost of discovering novel therapies, decrease sales revenues and thus reduce the financial incentive to innovate.

Increased drug discovery costs

The science that supports early drug discovery is funded mainly by governments and is conducted in academic or public-sector laboratories. 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 result in multiple companies pursuing every novel target, and keeping 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

Key points

- Aspects of the drug patent system impede the development of first-in-class drugs and reward the development of follow-on drugs (subsequent class entrants).
- Public subsidies of basic research and phase III clinical trials, as well as impact-based and royalty-based rewards for new drugs are promising alternatives to the drug patent system.
- Implementation of these alternatives would be challenging, with some options requiring that governments commit to stable drug-discovery funding streams.
- We propose a system of research to generate the evidence needed to resolve questions around these alternatives.

human genes and techniques to manipulate DNA and proteins, are patented. Innovating firms must therefore conduct research and development cognisant of the landscape of existing patents.⁵⁻⁷ Second, although 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 in clinical trials of drugs that target unprecedented mechanisms is a primary contributor to the declining productivity (i.e., increasing cost) of pharmaceutical research and development observed over the last several decades.^{8,9} The secrecy of the process and the unwillingness to share information about attrition in early 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.¹⁰

Decreased sales revenues

Aspects of the drug patent system make it challenging for companies to earn the sales revenues needed to recoup costs of research and development. 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. Profit

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raiders include counterfeiters as well as drug resellers (who engage in what is variously known as “parallel trade” or “drug reimportation”: buying drugs in low-price jurisdictions and selling them in high-price jurisdictions¹¹). 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. The threat posed by raiders dulls the financial incentive to innovate in the first place.

In addition, innovating firms engage in costly battles with rival firms, both generic and brand-name drug manufacturers. Generic drug manufacturers seeking to launch their product before the expiry of the last patent on a branded drug can challenge outstanding patents in court, claiming either patent invalidity or noninfringement. For their part, manufacturers of brand-name drugs can attempt to delay entry of generic copies through strategic patenting.¹²

The developer of a commercially successful first-in-class medicine can expect to lose profits to competitors developing therapeutically similar follow-on drugs (subsequent class entrants). Part of the profit loss comes from reduced sales revenues, estimated to be greater than the revenue loss from competition with generic drugs.¹³ 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 cost-control initiatives by drug plans that reduce sales revenues.

Follow-on drugs are not necessarily undesirable; many such drugs are therapeutically superior to the first-in-class drug and expand treatment options. But the issue here is not the existence of follow-on drugs. It is that the marketing exclusivity provided by patents enables the high prices that attract more follow-on drugs than might otherwise have been developed. 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 are among the most common targets for drug discovery. There are 518 protein kinases in the human genome; However, more than half of the current programs for drug discovery focus on the handful of kinases for which there is an existing drug.¹⁴

Other limitations

We have already described how the present patent system rewards the development of follow-on drugs, but there are additional distortions. First, patentees will often extend a drug franchise by formulating a slightly modified version of the molecule. Second, research and development tends to be focused on drugs on which patent monopolies can be profitably enforced. As a result, little research is devoted to new uses for generic drugs or nonpatentable molecules.¹⁵ A related issue is that little research and development is conducted into therapies for which research and development costs exceed

expected, risk-adjusted sales revenues. These include therapies for diseases affecting only small numbers of individuals globally as well as diseases affecting large numbers in poor countries. Finally, patents affect the amount of testing for safety and efficacy that companies voluntarily undertake. Because patents are time-limited, each year that is spent testing is one less year of market exclusivity. Patents may therefore lead to less testing compared with 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 costs for research and development of drugs, and extensive litigation. The current system also skews priorities for research and development toward 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 nonpatentable¹⁵ or produce clinically useful information on their drugs’ effectiveness.¹⁶ Ideally, drug discovery and commercialization would be rewarded without the distortions caused by patents.

Alternatives and complements to patents

Publicly funding of basic research and clinical trials

Alternatives to the patent system may spur innovation more effectively. These alternatives include “push” programs, which subsidize the cost of drug discovery. Two push programs have received the most attention: public subsidy of basic research^{10,17,18} and public subsidy of phase III clinical trials.^{1,19-21}

Public subsidies for basic research are not new. Indeed, much of the budgets of the US National Institutes of Health and the Canadian Institutes of Health Research sponsor basic research germane to pharmaceutical research and development. What *are* 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 these trials collectively.^{10,17,18}

Specific aspects of this proposal include (a) sharing the costs of this research among all stakeholders (industry, nonprofit research institutions and governments) to spread the risk; (b) placing the research findings 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 (c) conducting the research in partnership between academic and industrial scientists to capitalize on their respective skills and promote collective learning and technology transfer.

Public funding of phase III clinical trials would relieve drug companies of the single largest cost of research and develop-

ment (about 21%).²² At the same time, public spending on clinical trials would be relatively modest, for three reasons. First, governments already spend a lot on clinical trials. In Canada, for instance, tax subsidies contribute about 50% of trial costs.²³ Second, governments likely face a cost of capital that is less than the 11% cost faced by the pharmaceutical industry. Because clinical trials must be conducted before marketing approval, development costs are sensitive to the cost of capital. Third, public funding may temper the tendency of regulators to impose additional restrictions on the conduct of clinical trials^{24,25} or to mandate that inefficient statistical decision rules be used to assess safety and efficacy;^{26,27} 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.

Royalty-based schemes

“Pull” programs come in two flavours: royalties paid by generic drug firms to innovator firms, and publicly 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 that was in effect between 1923 and 1993, and proposals forwarded by the Commission of Inquiry on the Pharmaceutical Industry in 1985.²⁸ Another possibility is that firms bid for the rights to “drug candidates” (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 would win the auction but would cover remaining costs for drug development and clinical trials, as well as marketing costs. Bids would therefore reflect the firms’ expectations of these remaining costs, the likelihood of regulatory approval and, conditional on approval, the drug’s commercial prospects and marketing costs. Governments could supplement royalty rates if they deemed that certain drug candidates needed additional incentives.

Reward-based schemes

Kremer and Glennerster proposed that governments guarantee subsidies for a prespecified number of units of vaccines developed for use in low-income countries.²⁹ These subsidies would at once create a commercial incentive for vaccine research and development and reduce prices to consumers. This pull program has been adopted and funded by a group of industrialized countries, including Canada (e.g., Advance Market Commitments for Vaccines, www.vaccineamc.org). A generalized version of this mechanism is found in the Health Impact Fund, proposed by Hollis and Pogge.³⁰

The Health Impact Fund 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 Health Impact Fund therefore would reward the development of drugs that realize their *raison*

d’être, that is, improving health. At the same time, by keeping drug prices closer to variable costs, resale, counterfeiting and proliferation of follow-on drugs would be rendered less lucrative.

The Health Impact Fund would create another significant advantage as a supplement to the patent system. Because the patent system is market driven, firms have little incentive to conduct research and development into medicines to treat important diseases afflicting mainly poor people. The Health Impact Fund, 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 fund could similarly be used as an incentive to develop new uses of older drugs for which there would otherwise be no significant reward.

Implementation issues

Implementation of these alternatives raises many questions. The first of these is whether participation by drug companies 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 toward the cost of drug discovery. Funding streams must be predictable if firms are to commit funds to research and development projects. This requires an agreement that binds governments to commit resources. Our existing system is defective because, although the Agreement on Trade-Related Aspects of Intellectual Property Rights requires uniformity of patent length and nondiscrimination, it fails to prevent countries from negotiating aggressively on the prices of new drugs. Ideally, countries would contribute toward 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 clinical trials were publicly funded, there would likely be no shortage of firms seeking funding for drug candidates. Should public funding be linked to the ultimate success of the trial, or simply to the promise shown before the trial? How should conflicting priorities among different disease advocacy groups and among different jurisdictions be resolved?

Finally, there are 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 entry of generic drugs in the growing class of biologic drugs? If we use the Health Impact Fund, how exactly should health gains be measured? If we use royalties, how developed should molecules be before they are put up for tender?

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 collaborative research consortia that would assess clinical proof-of-concept trials. This analysis should include, among other things, the legal and economic implications of the patentability of inventions that arise subsequent to the consortium's work, antitrust issues, the prospect of races to develop products following public validation of targets, and the determination of 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 engage in a theoretical analysis of royalty mechanisms and their implementation.

Third, we propose a trial of the Health Impact Fund's approach to measuring health impact. Since the Health Impact Fund would rely on assessments of health impact, it is important to know how such assessments would be performed and how firms would respond to being paid based on health impact. Such a trial could be done for a single drug in a country or region. The Health Impact Fund 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.³¹

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. Although the patent system operates poorly in pharmaceutical markets, it is at least familiar. The alternatives are not. However, there is increasing recognition by industry and governments that the current situation — declining productivity of research and development coupled with stagnant sales revenues — is untenable and that major changes are required.^{32,33} 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.

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