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## Original Article

# Medicine for tomorrow: Some alternative proposals to promote socially beneficial research and development in pharmaceuticals

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**ABSTRACT** The current models of pharmaceutical drug discovery display significant inefficiencies. One inefficiency is the widespread prevalence of me-too drugs. Second, some patents can act as barriers to knowledge, by slowing down the pace of new discoveries. Third, there are higher costs for the public, who end up paying double costs – subsidizing or funding research and development (R&D) that leads to new discoveries on the one hand, and, on the other, paying the social costs of restricted access to knowledge when the discoveries are privatized. Fourth, when the market returns are the sole guide to R&D of new drugs, diseases that are prevalent in markets with weaker buying power are neglected. Thus, policymakers need to identify a new, more cost-effective and innovative productive system for R&D. Policymakers are faced with very complex choices in designing their regulations. They want to promote access to medicines, to lower costs and to encourage research. Politically, they have to balance pressure from the industry with increasingly forceful demands from health advocacy groups. The article looks at four different sorts of policies that may be used to address some of the inadequacies in the current system, especially with regard to the management of R&D: promoting prizes over patents; directing innovation toward socially beneficial outputs by adopting some form of value-based pricing; publicly funding clinical trials to reduce conflicts of interest while reducing costs; and actively managing frontier technologies to maximize positive social spillovers.

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## INTRODUCTION

The public sector plays a disproportionately large part in biomedical research and health interventions, in particular paying a large fraction of total pharmaceutical expenditures. As Boldrin and Levine<sup>1</sup> note with respect to the case of the United States: ‘... private industry pays for only about one-third of biomedical research and development (R&D). By way of contrast, outside of the biomedical area, private industry pays for more than two-thirds of R&D’.

These numbers may, however, understate the role of government. Even in the United States, where the proportion of government expenditure in pharmaceuticals and health care is lower than in most other developed countries,<sup>2</sup> public spending (through Medicare and Medicaid) accounts for a large fraction of all prescription drugs. (Indeed, in several industrialized countries, the public sector is the major or even effective sole procurer of pharmaceutical products.) As such, government is indirectly paying for a large fraction of the costs of private research and development (R&D). Just as importantly, public entities such as the National Institutes of Health conduct a large proportion of clinical trials.<sup>3</sup>

Given the significance of the role of the public sector in health-care research expenditures, the challenge for policymakers is to design a system in which production is organized to maximize the societal benefit from such public investment.

The production of knowledge is not like the production of ordinary goods and services, because knowledge is a public good. This means there is no easy answer to the question of what the best way of channeling resources efficiently is. At the current juncture, however, public policy in biomedical research is characterized by contradictory impulses.

On the one hand, efforts to increase the pace of innovation have meant an ever-increasing extension of intellectual property rights in the past 30 years, so as to

protect and encourage private investment in the sector. Fewer drug price controls, the extension of monopoly patent rights globally, limiting generic market competition and maintaining exclusive marketing arrangements all have the effect of increasing the price of pharmaceuticals, while potentially stimulating innovation.

At the same time, the efforts to cut spiraling medical costs and to extend health benefits to the population have necessitated significantly increased government intervention into the sector. Thus, lowering drug prices through publicly funded buyers and insurers, allowing compulsory licensing, and other such policies help limit price – at the potential cost of limiting innovation as well.

The tension between dynamic and static efficiency is well known: policymakers have to balance efficiency in the use of biomedical knowledge (reflected, for example, in increased access to medicines) with efficiency in the production of knowledge (reflected, for instance, in the selection of worthwhile research projects and the development of new and better therapies, as well as access to knowledge that is useful in the production of knowledge). The critique of the current system is not so much that current arrangements have not correctly balanced the dynamic and static benefits; rather, it is that the existing framework of R&D displays significant inefficiencies in both the use and production of knowledge, particularly with respect to the ways in which the patent system works. Moreover, changes in recent years (some noted above) may have exacerbated these problems.

One can point to several inefficiencies in the production of knowledge. The widespread prevalence of me-too drugs – drugs that are not significant improvements on existing drugs but which obtain patent protection – is a significant drag on innovation. Societal benefits per dollar of research are reduced. Not only are the benefits of the me-too drug of limited value,

but also the knowledge that there will be a future me-too drug for any big innovation may deter real innovation. Me-too drugs are designed to grab rents from genuine innovators, and with superior marketing can even absorb the bulk of the market – even if the drug is inferior in therapeutic value.

Even when rents are not dissipated in this manner, patents act as a winner-takes-all competition, and hence the return in terms of the market is not a reflection of the marginal social contribution of the patent owner, which is related to having the drug on the market earlier than otherwise would have been the case. Indeed, much of the human genome research had little social value. There was a publicly financed global effort to decode the human genome. The race to beat that project to get a patent did have a social cost: by making the knowledge less accessible, social benefits from the human genome project were reduced.

A third inefficiency occurs when publicly funded or subsidized research is privatized by selling medical advances to private entities that then obtain patents on the advances. In these cases, the patent clearly has not advanced the state of knowledge. Society faces the social costs associated with restricting access to knowledge, without any putative dynamic benefits. (One can think of the sale as providing funds to the government; one has to assess as to whether this is the most efficient way of raising revenues. The costs, both in terms of access to drugs and future research, can be significant.)

Finally, as private incentives respond to the size of potential markets, several diseases that affect the poor, and thus have potentially limited markets, are not the focus of sufficient R&D investment. Here, the point is that ‘private profitability’ is not a good measure of social return – unless we believe that the social value of health increases commensurately with the ability to pay.

While the costs of the patent system in restricting access to knowledge are well

known, it is perhaps not so widely recognized that the system may impede innovation. Most research builds on prior research, and thus requires access to this prior knowledge. Patents are a form of a prize system in which returns are captured by the exercise of monopoly power. This means exclusion of benefits of usage, but can also impede the research process by limiting follow-on innovations that depend on knowledge previously generated, but privately owned.

A complicating factor in assessing the benefits of ‘static inefficiencies’ (justified as a means of providing the finance that is required to ensure dynamic efficiency) is that only a fraction of the revenues raised by, say, monopoly pricing gets translated into increased research. One can think of monopoly pricing as a tax, supposedly directed at funding R&D. But a relatively small fraction of the money raised goes to the intended purpose. It is as if we have an inefficient tax collection system.

Indeed, there are complex linkages between the R&D system and market distortions. The structure of marketing (detailers) is designed to reduce the elasticity of demand (a doctor who has participated in trials is more likely to prescribe the drug; a patient who gets a free sample is likely to stick with it so long as it has no adverse side effects and so long as it is reasonably efficacious). It is not a system designed to maximize information available to the practitioner, and therefore to maximize the quality of health care.

Both dynamic and static inefficiencies have been tolerated as long as the pharmaceutical industry has been in good health and drugs have been regularly developed and marketed. However, for the last few years, there has been an increasing concern in the research-based pharmaceutical sector as to the consequences of what has been termed ‘the patent cliff’. Between now and 2014, several blockbuster drugs that served to maintain the high levels of profitability of large pharmaceutical companies will go off patent,

leading to increased generic competition and the erosion of the most secure stream of cash flows. Products such as Lipitor (Atorvastatin) and Nexium (Esomeprazole) – among the world’s best-selling drugs – will be challenged by generic competition in the largest and most lucrative markets. At the same time, there is little concrete evidence that a new pipeline of drugs will be effectively developed and marketed, despite medical advances such as mapping the human genome.<sup>4</sup> Simultaneously, given the concerns over rising health costs and the prospect of health-care reform in the United States, there is increasing pressure on profits through buyers and insurers.<sup>5–7</sup>

These coeval factors together constitute a set of challenges for the pharmaceutical industry, which require a reorganization of their strategies for innovation and an overhaul of their long-term relationship with generics.<sup>8</sup> Already, the last few years have seen significant developments within the industry as a response.

First, there has been an important set of mergers, acquisitions and agreements (Eli Lilly–ImClone, Daiichi Sankyo–Ranbaxy, Novartis–Speedel, Teva–Barr, GlaxoSmithKline–Aspen and so on), which have been seen as ways to enter new markets with a generic arm and as a consolidation within the generic sector.

Second, there has been renewed interest in the creation of ‘authorized generics’ that maintain market share. Finally, there have been deals in which generics have been compensated to delay entry into lucrative markets (most egregiously in the case of Ranbaxy and Pfizer over Lipitor/Atorvastatin).<sup>9–11</sup>

From a social viewpoint, this period of flux also affords an opportunity for governments and policymakers to ask more fundamental questions about the process of innovation in pharmaceuticals. Specifically, is the current system the best way to go about discovering and testing novel therapies to ameliorate health throughout the world? If not, are there

alternative models for the R&D of new pharmaceutical products that are viable and that should be promoted, to maximize the social benefit of the efforts of pharmaceutical companies?

In what follows, we argue that current systems of regulation, incentives and constraints lead to socially undesirable and wasteful efforts. We propose some alternatives for consideration, which could, we believe, be effectively implemented by policymakers in different countries. Some of these proposals have been considered by us in earlier work and we revisit them here. In what follows, we consider some of the more glaring inadequacies of the current system for considerations of innovation and the potential remedies for them. Such an exercise will certainly not exhaust the irrationalities present. It can only highlight those that we consider to be of greatest importance.

## **SOME PROBLEMS WITH THE CURRENT SYSTEM**

### **Neglected diseases and the prize system**

The ‘90–10 rule’ of pharmaceutical research (the idea that 90 per cent of pharmaceutical research goes toward tackling diseases that affect 10 per cent of the global population) persists. This is not at all surprising from an economic viewpoint. The size of the private market in terms of potential revenue (not individuals benefited) is simply too small for a disease like Schistosomiasis or Trypanosomiasis for major research-based pharmaceutical companies to invest in R&D. This is because these are diseases of the poor and those who are faced with this disease lack the ability to pay for even a part of the fixed costs of production. Although governments of these countries can (and do) spend resources to develop medicines or to provide preventative treatments, these efforts are necessarily limited. Furthermore, the expertise in developing effective and new chemical entities is something that is very often

confined to private sector firms in the developed world.

Scholars and commentators have noted that there are mechanisms whereby this seemingly insurmountable set of obstacles can be overcome. Most importantly, the prize fund mechanism is a way in which to provide a certain guaranteed return to an innovator to cover the (considerable) costs of production.<sup>12</sup> Under such a system, a guaranteed prize (let us say US\$1 billion) will be provided to the first producer of a viable therapy for a neglected disease. Once produced and paid for by the prize, the drug can be provided at cost. Drugs that provide little additional therapeutic value will be provided compensation from the fund, but at a substantially reduced amount.

Such a program can be funded either by industrialized countries or philanthropic organizations. Indeed, there is no reason why there cannot be a collective fund organized by the countries that are most severely affected by the diseases, so as to scale up their own abilities. Further, within some developing countries (such as India and Brazil), there are vibrant pharmaceutical firms that could be ready partners for the testing and marketing of new drugs.

Prizes form an alternative to the patenting system but are similar in that they provide a reward for innovation that guarantees the fixed costs of innovation and a markup once the drug has been produced. There are by now several versions of a prize fund that have met with reasonable amounts of interest from the academic community and the medical/public policy communities at large. The details vary, but the fundamental design (to motivate research by guaranteeing the size and viability of the market for a drug targeting neglected diseases) remains. Among the most well known are the Advanced Market Commitment for vaccines, which has already been launched, the Health Impact Fund,<sup>13</sup> and the CPTech proposals.<sup>14,15</sup>

Although all have their advantages and disadvantages, it would appear paramount that

the particular design of a prize fund should not mimic the negative impacts of the patent system. Thus, proposals for the prize fund should ideally not limit generic competition once the drug has been identified. If a prize fund limits competition post-reward (through exclusive marketing arrangements, for example), the full social benefits of competition (lowering prices as much as possible through process innovations and so on) will not be realized, even if prices are lower than they may be otherwise. Moreover, market competition provides the only effective mechanism to enforce market discipline and ensure that drugs are provided as close to cost as possible, following the discovery of the new chemical entity.

Other programs such as those of the International AIDS Vaccine Initiative, the Medicines for Malaria Venture, the Global Alliance for TB Drug Development or the Drugs for Neglected Diseases Initiative rely on similar strategies whereby the initial cost of the drug is not paid for by higher final drug prices or by long patent monopolies. Such public-private partnerships have met with some success. Unlike the prize fund though, they require the funding agency to provide the outlay for R&D before bringing the new chemical to fruition, which may not always be possible. Providing prior funding requires, in addition, the funder of the prize to make a selection among candidates. One of the advantages of the patent and prize systems is that there is *self-selection*. Those who believe that they are most likely to succeed compete.

### **Rewarding genuine innovation through value-based pricing**

The current patent system treats all new chemical entities as innovative, and equally so. This is a source of substantial inefficiency. From a social viewpoint, the degree of innovation of a new chemical entity should not be decided by whether it is 'non-obvious' (a necessary standard for patent protection) but by considering whether it affords



significant additional clinical benefits. The fact that the current system provides rewards to non-obviousness and not additional therapeutic value is reflected in many therapeutic categories, but most evidently in the market for statins. It is well recognized that there is broad substitutability between competing brands (except at high doses) between statins. However, the fact that there is a large market for these drugs and that patenting drugs in this category is relatively easy has meant that pharmaceutical companies have spent an enormous amount of resources in undertaking clinical trials and marketing for drugs that are very similar to existing products. Although these so called 'me-too' drugs may have some increased therapeutic value and increased consumer welfare through product competition (see in this regard Lichtenberg and Philipson<sup>16</sup>), it would be difficult to claim that the marginal social benefit from each additional drug is close to matching the marginal social and private cost. Moreover, given the perverse incentive structure, a considerable amount of research is directed toward such ventures. One estimate suggests that expenditure on such costs constitute 80 per cent of R&D expenditure.<sup>17</sup> Finally, as drugs are so similar and have been very costly to produce – a common, if disputed, estimate is \$800 million per new chemical entity<sup>18</sup> – profit-making firms must spend enormous resources on brand differentiation and advertising to maximize their market share – once again, an expenditure with little or no clear social value.<sup>19</sup>

As we have pointed out in our earlier paper,<sup>20</sup> there may be ways in which to limit this inefficiency by providing better incentives to pharmaceutical companies, which simultaneously lower costs. Among the more interesting ideas in this regard is the idea of value-based pricing. In systems where the purchase price of drugs is negotiated by centralized government entities or large intermediaries, linking the price that regulators are willing to pay for a metric

of additional value to health will limit the current system's perverse incentives to overproduce me-too drugs. Certainly, for the implementation of such a program, the devil is in the details. The metric by which to measure the added value of the drug is not something that is obvious, and choosing the appropriate measure is a matter of social, medical and ethical debate. However, in systems where there is such a negotiation over drug prices, there is substantial interest in such a proposal. For example, the British Office of Fair Trading recently proposed that the United Kingdom replace profit and price controls with a value-based approach to pricing, which would work to relate the expenditure of drugs to their incremental clinical and therapeutic value to patients and the broader National Health Service. As Claxton *et al*<sup>21</sup> point out, there is a direct way to implement this by measuring the effect of new drugs' quality-adjusted life years. Apart from doing away with the arbitrary system of profit controls currently in place, such a program will reduce the incentive to produce and market me-too drugs, while simultaneously making more fundamental breakthroughs more profitable and certain. At the moment, the production of truly socially beneficial drugs can be discouraged by the potential threat of an inferior rival me-too drug that is better marketed.<sup>22</sup>

### **Reducing R&D costs and conflicts of interest in drug discovery: Promoting public funding of clinical trials**

In Jayadev and Stiglitz,<sup>20</sup> we pointed to another severe problem in the production of new drugs, and a potential remedy. As many scholars have noted, cost increases in clinical trials, especially during stage (III) trials, have made the overall production cost of a new chemical entity prohibitively expensive. Indeed, some estimates suggest that clinical trials account for around half of the final cost of drug production. Given this fact, enhancing efficiency and reducing costs in

clinical trials may be key to renewing the vibrancy of research in pharmaceuticals.

One proposal to achieve these ends that appears very appealing is the idea to publicly fund clinical trials in pharmaceuticals. Detailed proposals have been made by Lewis *et al*<sup>23</sup> and Baker.<sup>17</sup> The proposals differ in their details, but both involve federal oversight of the clinical trial process and putting an arms-length distance between production on the one hand and the process of testing of claims on the other. The fundamental purpose is to do away with the intrinsic conflict of interest whereby drug companies that produce the drugs also pay for their evaluation (which is essentially the purpose of the clinical trial). This has led to many (predictable) negative outcomes, such as attempts to conceal information about side effects and overstating clinical benefits. The Vioxx issue is a case in point.

But, while establishing oversight and distance is the proposals' major advantage, there are several incidental benefits, the most important of which is that it would make the market for drugs more efficient and competitive.

There are several arguments in favor of promoting public funding of clinical trials. First, maintaining an objective distance between producer and a clinical trial agency would limit the incentive to push me-too drugs through the trial phase in the first place. Such an agency could quickly point to the degree of improvement (if any) provided by the drug and could weed out drugs that had little therapeutic value. Second, such a program could actually enhance the research process by making the information conducted in clinical trials publicly available. The public-good nature of information thus provided would benefit other researchers, and possibly improve the information available for those using the drug. Third, there is a distortion in the current system in which the testers of the drugs – doctors participating in trials – are incentivized to promote the drug. Often, doctors are paid to recruit patients into the

clinical trial, and can be recompensed thousands of dollars per patient. These relationships can be quite extensive: one report suggested that as many as 37 per cent of internists surveyed in the state of Maryland 'engag[ed] in pharmaceutical-sponsored clinical trials and/or lectures to supplement their incomes' (cited in Hafemeister and Bryan<sup>24</sup>). Clearly, doctors who participate in trials are more likely to prescribe the drug and thereby reduce competition. Even when there is not an explicit monetary reward, high switching costs effectively lock in a part of the market and reduced competition. Unlike with private industry-conducted clinical trials, in a publicly funded clinical trial system, there is little or no incentive for those undertaking the trials to overcompensate or otherwise bribe doctors to prescribe the drug. Nor is there any incentive to lock in a particular drug. Fourth, the current system is stacked against smaller (and typically more innovative) biotech and pharmaceutical firms that do not possess the large cash reserves that larger pharmaceutical companies do, and thus are often forced into partnerships to bring a drug through the trial process and to market. As such, this will enhance research competitiveness and efficiency. Finally, a more transparent and open system will greatly enhance confidence and trust in the drug discovery process.

How might such a public system be funded? One could consider both national and international efforts to promote such a system. While at the moment the expertise in running clinical trials is limited, especially at phase (III), there is a great deal of interest in expanding capacity, especially in developing countries. Thus, clinical trial outsourcing agencies are increasing in number and more operations are moving to places such as India, where costs are significantly lower. Independent contractors for clinical trials are sure to take advantage of such cost differentials. Even if the system were to be entirely nationally based, one can envision paying for clinical trials by imposing a charge

on the sale of final drugs, or a general tax or by dedicating a stream of expenditures as part of health reform. The costs of the drug testing will be paid one way or the other. A well-designed tax would be both more equitable and more efficient.<sup>25</sup>

### **Limiting costly duplications and promoting research commons for frontier technologies**

All competition in innovation will involve some duplication of R&D efforts. As several papers have shown theoretically, the overall impact of patent competition in particular has ambiguous effects on the overall intensity of R&D efforts.<sup>26,27</sup> While this is cause for concern in general, it is more urgently so with respect to pharmaceuticals where the initial R&D cost is high enough to force companies that lose the patent race to find ways to differentiate the product just enough to obtain its own patent and its own part of the market. There is little relation then between private and social returns, as we have emphasized in the case of me-too drugs. In a perhaps even more troubling vein, the race to patent the human genome has followed a similar pattern. Although it is true that the race made the knowledge available earlier, some of that knowledge was immediately enclosed by patents that limited both further innovation and use. A case in point is that of Myriad Genetics, the holder of the *BRCA* patents used for detection of breast cancer. The exorbitant cost for genetic tests has meant that many women who might otherwise have been tested must forego that option and be unable to take remedial action and therapy until it is too late.<sup>28</sup>

Although such an enclosure has had effects on limiting usage, it has also had perhaps more serious negative impacts on discouraging further innovation by insisting on expensive licenses or not allowing any usage of the scientific information at all. In a novel paper, Williams<sup>29</sup> compares the subsequent scientific research and product development outcomes on genes sequenced by the private firm

Celera and the public Human Genome Project. Her analysis suggests that Celera's intellectual property, which enclosed knowledge, led to a 30 per cent reduction in subsequent scientific and product development outcomes.

The mapping of the human genome is sometimes termed a frontier technology, as the potential for enormous gains in health outcomes and further knowledge arises from it. Other examples include the technology for polymerase chain reactions or gene transfer technology. Ensuring access to such knowledge is critical to ensuring that the maximum social benefit, both in the short and the long run, flows from it. Perhaps the best way to ensure this is to change the regulatory system so that frontier technologies are as much in the public domain as possible at the outset. Unlike most goods, scientific knowledge does not suffer from a commons problem, simply because knowledge is non-rivalrous.<sup>30</sup> But it can suffer from a severe anti-commons problem (as is evident from Williams' analysis). It is inefficient to restrict access to knowledge. Given this, policies should aim to maximize the utilization of such breakthroughs.

Several proposals have been made in this regard, which deserve further consideration. Kremer's<sup>31</sup> proposal for a patent buyout and the subsequent placing of the knowledge in the public domain is one such proposal. A system in which several countries put aside the funds for such buyouts as part of an R&D treaty can be envisioned. Such a patent buyout pool could complement or be part of a prize fund encouraging patent commons, wherein companies voluntarily place their intellectual property in the public domain. Such an initiative should be distinguished from a patent pool wherein only those contributing their patents to the commons are allowed to use the others' intellectual property. The latter – while potentially beneficial to avoid patent thickets and anti-commons problems – can also limit competition and innovation by excluding



those who have little intellectual property to contribute in the first place. However, considering the fact that genuine patent commons are likely to be undersupplied, other policies might need to be adopted. For example, public research could be given blanket exemption from having to pay licensing fees for frontier technologies. Similarly, if there is an urgent and compelling health need, a compulsory licensing framework can be adapted within industrialized countries to allow for the use of such technologies. Another option is to encourage a compensatory liability scheme, whereby users of the technology are not prevented from the use of the information, but must pay a fixed fee for its use. In addition to these, Reichman and Giordano Coltart<sup>32</sup> provide a much more detailed and nuanced set of policies that are legally permissible to manage frontier technologies and to allow for knowledge spillovers.

## CONCLUSION

In this article, we have examined some of the major problems with the current models of pharmaceutical drug discovery. All across the world, pharmaceutical costs continue to rise; R&D-based pharmaceutical companies in the large industrialized markets are increasingly concerned about the implications of greater government regulation and other measures, partially intended to lower prices. There is genuine concern about the slowing down of the pace of production of new and innovative drugs. Generic companies – especially those in the developing world – are faced with the prospect of extinction and/or severe restructuring (partly as a result of increased patent stringency related to Trade Related Aspects of Intellectual Property Rights (TRIPS)). Policymakers are faced with very complex choices in designing their medical and industrial regulations.<sup>33</sup> They want to promote access to medicines, to lower costs and to encourage research. Politically, they have to balance pressure

from the industry with increasingly forceful demands from health advocacy groups.

Therefore, it is an opportune and critical time to consider what can be done about the glaring irrationalities in the current system, especially with regard to the management of R&D. We have considered four different sorts of policies that may be used to address some of these inadequacies: promoting prizes over patents, directing innovation towards socially beneficial outputs by adopting some form of value-based pricing, publicly funding clinical trials to reduce conflicts of interest while reducing costs, and actively managing frontier technologies to maximize positive social spillovers. Some of these ideas are already under active consideration in various forms by governments and stakeholders across the world. As the industry struggles toward a new model, we hope that these proposals come to be seen as attractive ways to direct innovation in which the social benefits are highest. Further, we hope they can promote innovation in ways that make the benefits of the knowledge produced widely available – both to promote future innovation and to ensure improved health outcomes now and in the future.

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  27. Loury, G. (1979) Market structure and innovation. *The Quarterly Journal of Economics* 93(3): 395–410.
  28. The recent court decision invalidating the Myriad patents may curtail some of this kind of socially inefficient expenditure.
  29. Williams, H. (2009) Intellectual property rights and innovation: Evidence from the human genome. Harvard University, mimeo.
  30. The standard commons problem is that free access to the commons results in overusage, such as overgrazing or overfishing.
  31. Kremer, M. (1998) Patent buyouts: A mechanism for encouraging innovation. *Quarterly Journal of Economics* 113(4): 1137–1167, MIT Press.
  32. Reichman, J.H. and Giordano Coltart, J. (2008) A holistic approach to patents affecting frontier science: Lessons of the seminal genomic technology studies. Duke Law School, 17 April, mimeo.
  33. Needless to say, there are other issues that we have not addressed here, which are also important in promoting global health outcomes, notably remedying some of the excesses of the TRIPS agreement and bilateral trade agreements.