

Promoting Pharmaceutical Research under National Health Care Reform

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Executive Summary

The pharmaceutical industry is suffering a productivity crisis, brought on by soaring R&D costs and competition with generic manufacturers. Upcoming health care reforms in the US will curtail the remaining incentives for pharmaceutical research, but also provide us an opportunity for rebuilding a more efficient set of research incentives. Continued research into medical technologies is essential for improving the quality of life of Americans and eradicating diseases, and has historically proven exceptionally cost effective. To maintain robust incentives for medical research and to cure defects of the patent system, we propose a National Pharmaceutical Innovation Fund. The Fund will compensate innovators based on market success and medical efficacy, measured by Quality-Adjusted Life Years (QALYs). By setting proper incentives, the Fund marshals private sector efficiencies, expertise, and resources to innovating improvements in medical treatments.

Introduction

Over the past half-century, pharmaceutical products have revolutionized health care in the United States and around the world. Pharmaceutical sales by U.S. firms grew to \$276 billion in 2006, and we have come to depend on the availability of advanced therapies in a wide range of medical fields. However, despite large increases in R&D spending, the number of new drug approvals has fallen sharply from 1990's highs, raising questions about the industry's long-term viability. At the same time, the United States now seems likely to restructure its health care system and restrict reimbursements for prescription drugs, potentially providing the killing blow to an industry on the brink. Though this is a significant danger to the industry, these reforms present an opportunity for the country to re-think its approach to pharmaceutical development.

The pharmaceutical industry has operated for decades under a set of incentives that made the industry very profitable for a time, but have not motivated it to focus its energies primarily on improving health and preventing disease. Cost-cutting measures associated with the impending reforms will curtail the remaining incentives to pursue innovative medical advances, further worsening the situation. In this proposal, we argue that the United States should use a portion of the savings from price reductions to fill the impending vacuum of research incentives. Creating a new set of incentives that align the interests of the pharmaceutical industry with the medical needs of the country will allow the full potential of the pharmaceutical industry to be unleashed.

This proposal is not a plan for general health care reform or a plan to modify the way that patents work in the present health care system, although we argue that the present patent system is significantly flawed. This proposal argues that the impending health care reforms will create a window of opportunity, in which we can apply the cost savings from price reductions to nurture a more productive pharmaceutical industry. First, we will discuss the way pharmaceutical research is performed, and the precarious state of the industry. Second, we will describe where we believe American health care is going, and how this will extinguish the remaining incentives for pharmaceutical research, but also provide us with the resources to craft a more intelligent set of incentives. After those arguments have been established, we will take for granted that American health care will change in the manner we describe, and argue why, in that context, we should introduce the National Pharmaceutical Innovation Fund. The Fund will provide financial compensation for innovative pharmaceutical products based on the true measure of their value - their contribution to the quality and length of human life.

The Pharmaceutical Research Process and the Productivity Crisis

Modern pharmaceutical research generally begins with a target - a molecule that we want to inhibit (inactivate) using a drug. In the case of an infection by a virus or microorganism, this could be an enzyme essential to that the replication of that infectious agent. Targets are normally identified through basic science research in the public sector, because this kind of research can take too long to pay off inside a pharmaceutical company. Once a target has been chosen for a drug discovery effort, a large library of compounds - hundreds of thousands of unique chemicals - are tested to see if they inhibit the target, in a process called High-Throughput Screening (HTS). These libraries are very expensive to maintain, and generally only large pharmaceutical firms have the infrastructure to perform HTS. If there are already known compounds that inhibit the target, such as a competitor's product already in the market, this can greatly speed the process of identifying a collection of new compounds. If compounds can be identified that are "hits" - show some inhibition against the target - work has only just begun. Variants of those compounds need to be created for improved potency. Patents on potentially useful compounds

are obtained as early as possible – long before a drug is given regulatory approval and can be marketed. This development process requires many different types of expertise, including medicinal chemists, pharmacologists, cheminformaticists, and biologists. In these fields, experience working on one project generates knowledge capital that improves outcomes on future drugs. The process becomes even more expensive as clinical trials begin, first with small numbers of patients and then growing larger if some success is demonstrated.

The likelihood of success of any particular discovery effort is low, but also depends on the project pursued. If an existing drug has already shown efficacy against a certain target (the target has been "validated"), new discovery efforts directed at that target are at least 40% more likely to succeed (Ma and Zimmel 2002). The biology surrounding unvalidated targets can behave in unpredictable ways, and many of the best compounds in a test tube will not be effective in an organism, or will be toxic. Furthermore, follow-on drugs against validated targets are typically more profitable to the firm than the pioneer drug that paved the way for the medical advance (Ma and Zimmel 2002), discouraging pathbreaking research.

In fact, the pharmaceutical industry - once one of the most productive in the country - appears to be treading water, or even sinking. Jean-Pierre Garnier, formerly of GlaxoSmithKline, noted that "[f]rom December 2000 to February 2008 the top 15 companies in the industry lost roughly \$850 billion in shareholder value", citing "pricing pressures, regulatory requirements, legal entanglements, inroads by generics, and declining R&D productivity" (Garnier 2008). The number of new molecular entities (NMEs) introduced has plummeted from the highs of the 1990's, creating a "productivity crisis" (Woodcock and Woosley 2008). The state of the industry is weak, and upcoming health reforms threaten to weaken it even further.

The Future of Health Care and the End of the Old Ways

The current trajectory of the health care debate in the United States makes two big changes in the American health care system likely.

Expanded Federal Coverage. Of all countries in the OECD, the United States has the lowest coverage of its population by public health insurance (OECD 2004). One 2006 survey found that 68% of those surveyed favored providing coverage to everyone over keeping taxes low (Kaiser 2006). Presidential candidates have proposed expansions in the eligibility for Medicare, the Federal Employees Health Benefit Plan, and the State Children's Health Initiative.

Reduced Drug Prices. The United States is the only OECD country without some form of price controls for prescription drugs, though budgetary pressure from expanding federal coverage makes this increasingly likely. The Kaiser Family Foundation found in 2006 that "Drug/Insurance companies making too much money" ranked as the single largest item perceived by survey participants as causing high health care costs (Kaiser 2006). In January 2007, the U.S. House passed legislation authorizing Medicare to use to use its large market share to negotiate lower prices for prescription drugs, although the bill did not pass the Senate. Observers currently identify political pressure for price controls as a factor contributing to "great uncertainty" about the business prospects of the pharmaceutical industry (Grabowski 2004).

The anticipated cost-control measures will heavily reduce the level of investment into pharmaceutical research and development, which will have the effect of increasing the burden of disease. The U.S. Market made up 70% of pharmaceutical sales in 2006 (PhRMA 2008), with 40% of that coming from the public sector and 22% from Medicare alone (Poisal 2007). Medicare currently pays 54-82% more for patented drugs than other government-run health care systems, and pre-tax profit margins on pharmaceuticals in the U.S. are estimated to be four times

larger than those in regulated markets such as Canada and the EU (CBO 2004, Vernon 2005). These conditions cause changes in U.S. pricing to dramatically impact a worldwide industry.

The major motivation for researching a new drug is the opportunity to obtain a patent, which entitles the firm to a monopoly on the drug's sale for twenty years in the United States. By being a monopoly - the sole seller of a drug - the firm can charge prices heavily in excess of the marginal cost of production. However, if firms are facing a single large buyer (as predicted to occur following reform), the monopoly power becomes less valuable. The large buyer, possessing what is referred to in economics as a monopsony, can threaten to refuse to purchase the supplier's good, and force a large discount. This is why prices are so much lower in other wealthy countries. Because the U.S. market is substantially larger than others, it would be possible for a federal monopsony to demand greater discounts than those seen in other countries. These discounts would heavily reduce the profit margins pharmaceutical companies make in the United States. We call this state of affairs the "post-patent world", because patents will no longer give the pharmaceutical companies the same level of control over their prices.

These reduced profits will severely reduce the level of research and development. Decreased profits have two effects: they decrease the incentives for companies to invest in research by decreasing the return, and they also increase the cost of capital for that research because firms no longer have their profits to finance future investments. A model by Filson and Masia (2007) predicted that a 20% profit reduction would cause firms to eliminate 50% of their discovery programs, as well as forcing the majority of small firms out of the market entirely. The authors concluded that "in the long run, the impact would be devastating." A different model by Abbott and Vernon (2007) made similar predictions. In an empirical analysis, Golec et al. (2008) found that discussion of the proposed 1993 Health Security Act reduced pharmaceutical research and development that year by \$1 billion, even though it never became law.

Rather than lamenting political pressure to cut costs, upcoming health care reforms are an opportunity to rebuild the pharmaceutical innovation system from the ground up. The current crisis in the industry has not been exclusively caused by the patent system, but the patent system has strongly contributed, as we will describe later. Moving to a price controlled system in the U.S. should save enormous amounts of money that can be redirected to new research incentives. In Medicare alone, if patented drugs were bulk purchased near generic prices, combined savings to the Federal Government, state governments, and individual premium payers would add up to \$600 billion in the 8 year period between 2006-2013, even after accounting for an increase in utilization (Baker 2006). By using a portion of these funds to support a new incentives system, we could channel the innovative capacity of the pharmaceutical industry directly toward important medical advances. A new funding system should achieve three different things:

- It should focus our research effort on our medical needs.
- It should maintain the efficiencies of private industry.
- It should be low cost and cost effective.

After examining why pharmaceutical research is worth supporting, we will introduce our plan to do so - the National Pharmaceutical Innovation Fund - and demonstrate how it achieves these three goals.

The Pressing Need for Continued Pharmaceutical Research

Even in a wealthy country like the United States, disease exacts a heavy burden. Michaud et al. (2006) estimated that Americans lost 33 million Disability Adjusted Life Years

(DALYs) in 1996, with over half coming from premature death. Noncommunicable diseases such as cardiovascular disease, cancers, and neurodegenerative disorders made up almost 80% of the total. Properly focused research can reduce this burden, and the efficacy of pharmaceutical intervention has been well studied. By analyzing only drugs with novel mechanisms, Lichtenberg (2003) calculated that each new drug introduced between 1970 and 1991 reduced the mortality caused by its associated disease by an average of 18,800 life years in the United States, when compared with the average reduction in mortality. The disease burden in the developing world is even greater, as has been well documented. However, we focus this proposal on the disease burden within the United States, because it has been historically difficult to convince the governments of the most economically developed nations to guarantee substantial resources toward diseases that do not affect their populations. Still, it has been observed that chronic conditions experienced in high-income and low-income countries are converging, so stimulating research in the United States and making products available at marginal cost should improve health for low-income countries as well (Otterson 2006).

The National Pharmaceutical Innovation Fund

To maintain robust incentives for pharmaceutical companies to continue to research and develop new medical technologies in the post-patent world, we propose that the federal government establish a National Pharmaceutical Innovation Fund (concept originally proposed by Hollis 2005). The Fund will provide an alternative way for companies to receive compensation for medical innovations. After patenting their innovation, pharmaceutical companies will have a choice: they can choose to exploit market exclusivity and enjoy patent rents, as they do in the current system, or they can agree to freely license their patent to any U.S. firm that wishes to manufacture their product, and receive compensation from the Fund in return.

The Fund will be financed by a fixed amount each year by the Federal Government. Compensation to firms for a product that is licensed according to the terms of the Fund will be determined by the size of that product's "claim." Each product's claim on the fund is equal to the number Quality-Adjusted Life Years (QALYs) that the product added to the U.S. population that year, compared to the existing technology at the time that product was introduced. Claims last for the duration of the patent. The number of QALYs that a product produces is a result of how effective it is and how many people have access to it, including generic versions produced by patent licensees. Under these terms, pharmaceutical companies will have an incentive to develop the best cures for the worst diseases that affect the most people, as well as an incentive to insure that their product is as affordable and accessible as possible. Each year, the money in the fund is divided up proportionally based on the size of all the claims active that year.

Quality Adjusted Life Years are a standardized form of measuring medical efficacy that have been in use for over three decades (Stassi 2006). Though difficult to apply and not an exact measurement by any means, standardizing the methodology used for assessment makes it possible to compare the social benefit of different innovations. QALYs have been used in cost-effectiveness evaluations of medicines in the United Kingdom, Australia, and New Zealand (Hollis 2005), and their wider use is being urged in the United Kingdom (Office of Fair Trading 2007) and in the United States by bodies including the Office of Management and Budget (Hollis 2005). No country that moved to a QALY-based performance evaluation system has ever opted to abandon it (Drummond 2007). A firm that invented a widely employed vaccine would reap high rewards from the Fund, while a lifestyle-oriented drug, though widely sold, would not be compensated as highly because it has a smaller effect on QALYs. Because a firm can choose

whether to license any individual product according to the terms of the Fund, the incentive to produce high-demand lifestyle drugs would still exist because they can make a profit in the private market.

Why Rely On Private Pharmaceutical Companies?

Unique infrastructure, expertise, and integration. At present, large compound screening libraries and automated screening facilities are concentrated inside the pharmaceutical industry, as well as the bulk of medicinal chemistry, pharmacology, molecular modeling, and pre-clinical testing expertise (Nathan 2007). Though there have been efforts to make these resources available to the public sector through public-private partnerships, these have run into difficulties because of the scale, specialization, and integration required (Nathan 2007). The development of a drug is never a straight line from screening to the clinic. Along the way, pre-clinical data will be used to reanalyze computational modeling data, and pharmacological data will be used to redirect medicinal chemistry efforts in library design. The vertical integration of each aspect of the discovery process greatly facilitates the iterative, trial-and-error process of drug discovery. Furthermore, Cockburn and Henderson (1999) found that "spillovers" of accumulated knowledge capital from one successful project inside a firm to another were a key advantage of the large-scale pharmaceutical company. Their analysis indicated that "the benefits of spillovers can be realized only by incurring the costs of maintaining "absorptive capacity" - the ability to capture new spillovers." The vertical integration and absorptive capacity of pharmaceutical companies are unique, valuable, and difficult to replicate in the public sector.

High-risk decisions over resource allocation. A key problem in pharmaceutical R&D management is deciding how to allocate scarce resources toward the projects that are most likely to succeed. Discovery programs can and do fail at every step in the process, and of 250 compounds patented and investigated at a pre-clinical stage, five might reach Phase III clinical trials and one might be FDA approved (Vogel 2007). The risks involved make the direct accountability of researchers to investors essential (Hollis 2007). When the government chooses specific programs to research, the taxpayer is the riskholder and pays for failed investments, but does not earn profit from successful ones, except through improved medicine. The separation of risk, reward, and management found in government-directed programs makes them much less efficient at pursuing research in a high-risk field such as pharmaceutical development. Government direction is necessary for fields with long timeframes and no immediate economic benefit, such as basic biology. A taxpayer supported, private approach – like the one we propose – will be more successful in improving human health in the short-term.

The failure of "Push". An alternative approach to generate medical advances in a post-patent world would be for the government to select specific research projects to fund, or "push", essentially replacing the role of private pharmaceutical companies. This is a historically unsuccessful approach, most famously in the expensive failure of the USAID malaria vaccine program (Kremer and Glennerster 2004). Kremer and Glennerster note that "[e]ven after it was clear that USAID's malaria vaccine initiative was not going well, researchers kept requesting added funding and administrators kept approving it" (p. 49). Governments are notoriously bad at picking which specific technologies deserve further research and funding. Japan, although known for its technological prowess, had many hiccups along its path to development because its government-controlled technology strategy. Japan's Ministry of International Trade and Technology (MITI) (now METI), among other things, didn't see the value in transistors and discouraged Sony from acquiring them from American companies (Pirog and Cooney 2004).

These failures are not coincidences. In government-supported research, pursuing one project instead of another generally means awarding research grants to an entirely different group of investigators. This gives investigators an incentive to overstate progress and the likelihood of success, as has historically been the case. Within one company, changing projects does not generally require large changes in personnel, giving everyone within the company an incentive for candor about which projects are the most likely to succeed. Furthermore, companies that mismanage projects internally will be replaced by those that generate success.

The contemporary failures of pharmaceutical companies are failures of incentives.

The crisis in pharmaceutical productivity described earlier is not an indictment of the private approach to pharmaceutical research. Rather, it reflects a market failure in medicine to adequately reward major advances. Several recent phenomena have amplified this problem. First, when a drug's patent expires, other companies can market the same product as a generic version. Because these other companies did not invest in the expensive discovery and clinical trial process, they can profit by selling the drug just above the marginal cost of production. Competition from generics has soared in the years following the 1984 Hatch-Waxman act, from under 20% of the market in 1984 to 51% in 2002 and 67% in 2007 (Grabowski 2004, PhRMA 2008). Second, as regulators have demanded more comprehensive clinical trials, the time period between FDA approval and patent expiry has shortened. Furthermore, even while a drug is still under patent, other companies can release so-called "me-too" drugs - slightly different compounds that affect the same target and achieve the same therapeutic result, competing for market share with the original innovator. Though many follow-ons do improve on the original drug, do not differentiate themselves at all and exist to grab market share (Booth and Zimmel 2003). Between 1960 and 1998, the average time period between a pioneer drug with a new target and the first me-too drug decreased from 10.2 to 1.2 years (Cohen 2006). As the potential returns from true innovation shrink and shrink, firms redirect their R&D efforts away from riskier but potentially pathbreaking projects, as many have advocated on economic (rather than medical) grounds (Booth and Zimmel 2003, Cohen 2006). The post-patent world is approaching even without health reform.

The National Pharmaceutical Innovation Fund creates a much more favorable set of incentives for pathbreaking medical research. Innovative firms no longer need to compete with generic manufacturers - in fact, all sales by licensed manufacturers increase the size of a product's QALY claim and increase the rewards to the original innovator. Firms will still have an incentive to make their products 'best-in-class' in order to avoid competition from follow-ons, and because research on validated targets is lower risk. Furthermore, the Fund also addresses another cause of insufficient innovation that is not caused by competition. Pharmaceutical firms are often faulted for failing to sufficiently research absolute cures and vaccines, because it is in their economic interest to instead treat and manage symptoms (Sloan and Easley 2007). However, cures and vaccines are the types of treatments that are likely to create the biggest QALY improvements and therefore earn the largest rewards from the Fund. The National Pharmaceutical Innovation Fund will give greater incentives to research novel drugs with large gains in health outcomes, because the rewards are proportional to increases in medical efficacy.

Cost and Cost Effectiveness

Estimates can be made about how much the Fund will cost, but these are necessarily inexact for two reasons. First, while we believe health care reform including monopsony pricing is imminent, the exact structure could take many different forms. Second, there is no "correct"

level of support for pharmaceutical research. However, substantial incentives are clearly feasible. Taking the \$600 billion over 8 years of savings described earlier as a starting point, a Fund budget of \$30-\$60 billion annually (increasing over time) is reasonable to imagine while still reducing costs from their present highs. A drug is generally considered a phenomenally successful "blockbuster drug" today if it can obtain sales of \$1 billion annually worldwide in the years before they go off-patent. The fund would not serve as the sole source of revenue for firms - firms that elected to license their drug according to the terms of the fund would still obtain profits from their own sales of the drug domestically and internationally, albeit at lower, generic prices. The purpose of the fund is not to reproduce the high-price, high-profit golden era of the pharmaceutical industry - the purpose is to provide the right set of incentives for true innovations that make substantial increases in health outcomes. Finally, it is important to note that the fund has the virtue of being self-regulating. When only a small number of drugs are licensed through the Fund, the payouts to each of them are very large, and as the fund is divided between a larger number of drugs, firms may find it more beneficial to maintain their patent monopoly for specific drugs (such as follow-ons) rather than license those drugs.

Most importantly, the Fund would increase the efficiency of research toward medical breakthroughs, enabling us to get more for less. The nature of the science surrounding drug development makes the present system inadequate for rewarding innovators. Pioneering research is discouraged when less risky follow-on products are just as profitable and reduce the market share of the actual innovator. By introducing the National Pharmaceutical Innovation Fund, research effort that was previously directed toward grabbing market share with a nearly identical product will be redirected toward making the largest improvements in health, because this is where the largest rewards will lie.

Is pharmaceutical research worth supporting directly? Cremieux and coauthors concluded that "the evidence relating pharmaceutical spending and health outcomes seems overwhelming. International studies, national studies, and disease-specific analyses indicate that pharmaceutical products have been a worthwhile investment over the last half century. With rates of return exceeding 10 to 1 based on measures of increased life expectancy alone, pharmaceutical products have successfully improved health outcomes in developed countries at a cost dwarfed by the value of increased longevity." (Cremieux et al. 2007)

Response to Criticisms

QALYs are difficult to calculate. Though the QALY measurement is artificial, the application of a consistent methodology makes it possible to evaluate medical efficacy. The widespread use demonstrates the success countries have had with an empirical approach. Because all products compete for the same pot of money, firms will have an incentive to act as watchdogs on other firms. Firms will also have an incentive to conduct direct comparisons in clinical trials, which are underused and will improve doctors' abilities to prescribe appropriately.

Places an extreme premium on being first to market. It is possible that multiple firms will be pursuing similar discovery programs simultaneously, competing to get their products approved first in order to represent the QALY improvement over existing technology. To avoid a potentially dangerous rush to market while still rewarding innovators and not copycats, the Fund could use a benchmark on what qualifies as "existing technology" as the best treatment one to two years prior to the approval of the new drug.

Agency capture. Any government agency responsible for billions of dollars in disbursements is at risk of being influenced by those it regulates (see, e.g., Moynihan 2002). In this case, the Federal Government will already be the major purchaser of pharmaceutical

products, so even without the Fund it will be essential that the government make unbiased determinations of product utility. The same protocols that keep purchasing independent from political clout - protected civil servants in authority positions, prohibitions on a revolving door between government and industry, restrictions on lobbying, and transparency of all decision-making - should apply to management of the Fund.

Politically untenable. While pharmaceutical companies have certainly preferred strong protections for intellectual property in the past, it is easy to see how they would support the creation of the Fund. In the system of strict price controls we anticipate, the creation of the Fund will amount to a major new source of funding which it is impossible to imagine them opposing. Because licensing any particular drug to the fund is optional, firms will have the flexibility to pursue the strategies they believe are most profitable. Taxpayer opposition to the corporate subsidies would be small if the Fund is successful in creating medical advances, and support to companies from the Fund is closely tied to the social values of their technologies. Patients' rights groups would strongly support the increased research the fund provides.

Alternatives

A National Pharmaceutical Innovation Fund is not the only way to maintain incentives for innovation after impending health care reform. Other proposals, however, do not fulfill the criteria of appropriately focusing funds, maintaining efficiencies, and keeping costs low.

Patent-term extensions. In the past, the United States has responded to threats to R&D incentives by extending patent-terms. While extending patent terms would increase incentives for pharmaceutical firms to invest in R&D, as noted above, patents do not directly create incentives for improved health. In the "post-patent world", even extended patents would see diminished usefulness due to monopsony pricing. Extending patent-terms would be a missed opportunity to create incentives for firms to invest in better, more health-focused R&D.

Disease specific funds. Some authors suggest having separate funds for different diseases (see, e.g., Wei 2005). Historically, however, these programs inaccurately assess what types of research are likely to succeed. Private companies are better at determining health needs than governments because their survival depends on it. We believe that leaving the determination of which diseases to pursue to the market – but holding them to the standard of quality and duration of life - will result in better allocation of resources.

Prize Awards. Though commonly suggested, it is very difficult to specify in advance appropriate conditions for the prize. If it is possible to specify conditions, firms have an incentive to meet only the technical specifications rather than producing the best possible product. If the prize is awarded prematurely, no funding remains for continued improvement. Lump-sum prizes do not tie the size of the award to market success, and success with prescribing doctors and consumers is the best test of a drug's true demand and utility.

Conclusion

Price reductions in the post-patent world will significantly damage research into pharmaceutical products that have the potential to improve health and extend life. By adopting a National Pharmaceutical Investment Fund, the Federal Government can maintain many of the efficiencies of the private market while improving on the inefficiencies. The infrastructure, expertise, and risk-management abilities of private industry would be preserved, while the effort spent on me-too products and products that do not significantly improve health would be reduced. Pharmaceutical products have tremendous returns in increased lifespan and quality of life, making continued support an important national priority.

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