

Effects of Incentives on Pharmaceutical Innovation

Frank A. Sloan

Chee-Ruey Hsieh

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I. Introduction

By increasing total factor productivity, that is, in allowing more output to be produced for a given set of inputs, technological change is a major source of economic growth. According to one view, mere accumulation of capital, even when extended to include human capital, cannot sustain growth without end since at some point, continued accumulation of capital must inevitably encounter a substantial decline in the rate of return. For this reason, to ensure sustained economic growth, technological process is needed to avoid diminishing returns in the long-run (Barro and Sala-i-Martin 2004, p. 285). Further, although much new knowledge is a global public good, the amount of knowledge production within a country can boost a country's national income (Temple 1999).¹

In health care, there is a plausible link between technological change, in particular the rate of product innovation, and increased total factor productivity of health care inputs. Without technological know how, physicians and other healers, working in the 19th Century and earlier had a very low marginal product at best. The story of President Garfield's treatment and, in today's terms, unnecessary death in 1881, is just one of very

¹ Somewhat surprising to we outsiders who do not study the subject, empirical evidence on the role of growth in total factor productivity as a determinant of economic growth is conflicting. See e.g., Temple (1999), Bosworth, Collins, Durlauf et al. (2003), and Baker, DeLong, and Krugman (2005). One reason for the lack of conclusive findings is that technological change in the aggregate is measured as a residual, i.e., is not directly measurable. A further complication is that technological change is endogenous to various factors, reflecting ex ante returns on investment in research and development, which in turn reflects such factors as population and income ((see e.g., Kremer 1993). Government policies affecting such returns are plausibly related to such factors as income as well. Although both important and interesting, a full discussion of this topic is well beyond the scope of this paper.

many poignant illustrations.² The gains in health are indeed dramatic, and a large part of the gains plausibly reflect technological change.

In industrialized countries, life expectancy of females at birth over 160 years up to the end of the 20th Century increased by three months per year or 40 years in total (Oeppen and Vaupel 2001). There have also been substantial reductions in rates of disability in the last 100 years, although the improvements are not as well documented, especially before about 1980 (Crimmins, Saito, and Reynolds 1997; Friedman and Martin 1998; Costa 2000; and Manton and Gu 2001). Reductions in mortality have been attributed to such factors as improvements in nutrition, public health, vaccination, and new medical and surgical therapies with different factors receiving varying degrees of emphasis depending on the study (Cutler, Deaton, and Lleras-Muney 2006).

Certainly by every indication, the marginal product of personal health care services is substantially higher at the beginning of the 21st Century than it was in the 19th Century.³ The mechanisms through which technological change has affected gains in health are complex. Introduction of new health care products, such as vaccines, have had a direct effect on health.

But technological change has plausibly had indirect effects as well. For example, improvements in sanitation in part reflect a growing awareness of how infectious disease

² Garfield was shot twice. One of the bullets lodged in his back. Physicians could not find the bullet; they used unsterilized instruments and bare hands to search and dislodge the bullet. Alexander Graham Bell used a metal detector to search for the bullet, but this effort failed as well. Garfield died after 80 days. It is estimated that today he would have been released from the hospital after a two or three-day stay. Joseph Lister had developed sterile techniques in Great Britain in the 1860s, but these techniques had no diffused to the U.S. by the 1880s, although they were becoming common in Europe. Shaffer (2006).

³ For example, Lee (2005, p. 354) notes that in the mid-19th Century, there were few effective medical or health care services to be purchased. Markel (2006) depicts a lecture at the newly opened Johns Hopkins School of Medicine in which the course of fever was described at a time before the microbiological etiology of particular infectious entities were identified. Some medical care arguably had a negative marginal product, such as blood-letting, which continued throughout the 19th Century.

spreads.⁴ Nutritional gains reflect increased productivity in agriculture which is largely the result of technological change.⁵ One pharmaceutical innovation, aspirin, is unique in that it took decades after the innovation, for the full scope of applications in which it could be of benefit to be recognized.

Pharmaceutical innovations, including new vaccines, are among the more important new health care products. Vaccines for polio and smallpox have nearly eradicated these diseases. Before the advent of antibiotics, in both developed and developing countries, millions who would have otherwise died of diseases now became easily treatable. Antibiotics have nearly eliminated some diseases as major public-health problems in high-income countries, and have dramatically lowered incidence in low-income countries. Availability of new vaccines not only improved health, but these were non-factor neutral technological advances that could be administered by persons with relatively little training or expensive equipment. Nevertheless, in spite of the great gains that have been realized, no vaccines exist for such major diseases causing both loss of life and productivity in low-income countries, such as for malaria, schistosomiasis, and HIV, and a very imperfect one exists for tuberculosis. In spite of these advances made up to now, there is ample room for new pharmaceuticals, including vaccines, for the prevention and treatment of heart disease, cancer, and other major chronic diseases, making it particularly important to understand the effects of various incentives on pharmaceutical innovation.

Clearly many technological changes in health care provision in general and in pharmaceutical innovation are worth having. Given their importance, the main focus of

⁴ See e.g., Troseken and Beeson (2003) for an analysis of lead water mains in U.S. cities.

⁵ Nutritional improvements are described in Fogel (1997).

this paper is to analyze the determinants of R&D investment behavior in the pharmaceutical industry and review the empirical evidence on the impacts of various incentives on product innovation in this industry. Specifically, we analyze how various factors exogenous to individual firms, such as the market size, government health and industrial policies affect firms' incentives for pharmaceutical innovation under the patent system. In addition, we investigate how other incentive mechanisms can be designed to promote pharmaceutical innovation when the patent system fails.

Overall, the empirical studies provide consistent evidence that incentives affect firms' investments in pharmaceutical research and development. This may seem like an obvious finding to economists, but a widespread view is that such firms earn substantial rents and that product innovation can be realized by offering pharmaceutical companies appreciably lower returns than they enjoy currently.

Given market size and various government policies, the patent system provides strong incentives for pharmaceutical innovation in developed countries. However, there is market failure for some types of products, such as for R&D for some vaccines and for diseases mainly prevailing in lower income countries. Such market failure occurs because there are externalities in consumption of medical care⁶ and lower ability to pay for such care of persons in low-income countries. Given the low ability to pay, the market power derived from owning a patent is insufficient to generate a sufficiently-high anticipated product price to elicit the required return on R&D for products that primarily prevent and treat diseases that are mainly prevalent in low-income countries.

In Section II, we provide a synthesis of the literature on benefits of pharmaceutical innovation. Section III investigates factors that influence the firm's

⁶ People in rich countries have some concern about the welfare of others in poorer countries.

optimal investment decision on pharmaceutical research and development. Sections IV and V describe institutional features of pharmaceutical R&D and existing evidence on the effects of incentives on pharmaceutical innovation, respectively. Section VI analyzes incentive mechanism design under circumstances under which the patent system is insufficient to elicit appropriate amounts of pharmaceutical R&D. Section VII summarizes our results and discusses public policy implications based on these findings.

II. Benefits of Pharmaceutical Innovation

There is very little disagreement across the political spectrum with broad statements about the social value of new pharmaceutical products. Nevertheless, the subject of pharmaceutical innovation is very controversial one. New drugs tend to be much more costly than older ones, and whether or not the additional benefit exceeds the additional cost is widely debated, especially when much of the additional cost is covered by private or public health insurance. Insurance matters since much of the additional cost is shared by the pool of insureds or taxpayers, and insurance can lead to moral hazard, especially when other impediments to use, such as travel time, are reduced. The debate primarily occurs in high-income countries. In low-and middle-income countries, many new drugs are simply thought to be unaffordable.

Economists have quantified the benefits of innovation in health care (see e.g., Cutler, McClellan, Newhouse et al. 1998; Murphy and Topel 2003; Sloan, Ostermann, and Brown 2006). However, while this research deals with health improvements in general, it does not isolate the health benefits of pharmaceutical innovation in particular.⁷

Heidenreich and McClellan (2000) summarized findings from randomized controlled

⁷ Cutler et al. (1998) classified heart attack patients into several categories. One was “medical management.” This allowed them to assess outcomes from a combination of medical therapies including various drugs.

trials, which show the benefits of administering certain drugs introduced in the late 20th Century (such as beta blockers, ACE inhibitors, and thrombolytics) for treating patients admitted to hospitals with heart attacks. The advantage of using information from trials is that other confounding factors are not likely to have affected the health outcome so that the measured effect is truly that of the drugs.

But although they have important advantages, data from trials also have deficiencies. The outcomes measured tend to be short, such as mortality within 30 days after admission to the hospital, and results from a trial in which drugs are administered according to protocol may not generalize to the community where drugs tend to be used much differently.

The other approach is to use observational data to assess benefits. Observational data has several advantages. Sample sizes tend to be larger. Patterns observed are those for the technology as it is applied in practice, not, as in trials, in which technologies are applied under rather ideal circumstances. Further, it is possible to study longer-term effects and often for a larger number of outcome types than with data from trials.

Researchers have used observational data to quantify the benefits of pharmaceutical innovations in three different ways. First, many studies use cost-effectiveness analysis to investigate effects of a specific new drug on certain health outcomes. These studies provide useful information for insurance coverage and reimbursement decisions for individual drugs (Drummond 2006). However, these individual results cannot be generalized to evaluate the benefits of pharmaceutical innovation as a whole.

Second, several other studies have empirically estimated the relationship between pharmaceutical spending level and health outcomes using variation across countries and over time within individual countries. This group of studies has generally found that higher pharmaceutical spending is associated with better health outcomes, as measured by such health indicators as increased life expectancy or lower infant mortality rates (Cremieux, Jarvinen, and Long et al. 2006). These findings suggest that spending more on pharmaceutical products, such as introducing new drugs into the formulary, is good for population health.

A third type of study focuses on the role of pharmaceutical innovation as a whole on population health. This approach uses the cumulative number of new molecular entities available in the market or average vintage of drug to measure pharmaceutical innovation and empirically estimates their impact on population health. These studies have found a significantly positive relationship between pharmaceutical innovation and life expectancy (Hsieh, Lo, Hong et al. 2006). The results imply that pharmaceutical innovation as a whole is worth the increased spending, but not imply that the marginal benefit of each new pharmaceutical technology exceeds its marginal cost.

In a number of papers, Frank Lichtenberg (e.g., Lichtenberg 2003) has assessed benefits of new drugs. His research assesses effects of a broad range of drugs, including older and new drugs, finding that the introduction of new drugs does have benefits in terms of decreased mortality. An econometric issue with observational data, but not with data from randomized clinical trials, is that other factors, such as health behaviors, may not be held constant. Lichtenberg (2003) argues that such other factors should not be correlated with the fraction of total drugs that are new, his measure of innovation. Also,

his results are not sensitive to inclusion of two other variables. Based on his findings, he concludes that new drugs have important effects on longevity across a broad range of therapeutic categories with the implication being that pharmaceutical innovation is of social value and is worthy of public support.

There is another school of thought that new drugs are often not productive, certainly not relative to their added cost. This body of research starts with the finding that there are appreciable differences in spending on personal health care services among countries and within regions of countries, in particular, the U.S., but differences in health status are not associated with the spending differences.⁸ In economic terminology, the marginal product of such spending is low, very low, or even zero. In health jargon, this is called “flat of the curve medicine.”

Proponents of the view that much new technology is not that productive make the argument for medical care in general, not only for new drugs, this category of spending is treated with the same brush as other medical services. The implication for public policy makers is to hold on to your (you as citizen or bearer of the private insured individual) or the public’s wallets, that is, implement various cost containment strategies, including price controls and restricted drug lists (“formularies”).

Skinner, Staiger, and Fisher (2005) attempt to reconcile the two views with a graph shown as Fig. 1, which depicts the relationship between a health outcome, such as survival, and expenditures on medical care. Each curve is a health production function (PF) showing the effects of expenditures on survival. The PFs shift for one of two reasons: technological change or a policy change resulting in more efficiency in the care

⁸ Much of this research has been conducted by Jack Wennberg and his colleagues at Dartmouth. See e.g., Fisher et al. (2003a,b) and Skinner, Fisher, and Wennberg (2005).

provision. Between one period (1986) and another (2006), some suppliers of health care services move from Point A on the 1986 production function to Point C on the inefficient 2006 production function. Other providers who have become more efficient move from Point A to Point B on the efficient 2006 production function. Technological change is productive; the slopes of the arrows in Fig. 1 are fairly steep, suggesting that technological change boosts efficiency for both inefficient and efficient providers—more so for the latter. However, for a given technology, added spending can have a low marginal product. Cross sectional comparisons are between points such as B and C or between B' and B and C' and C.

The implication is that innovation in general and pharmaceutical innovation in particular is productive and should be promoted. However, there is plausibly considerable heterogeneity in effects. Thus, mean effects are not likely to be equal in effect among drugs in a therapeutic category. Moreover, health care inputs, including drugs, can be applied at a margin at which they are not very productive, and incentives should be implemented to prevent such overuse. In sum, pharmaceutical innovation is productive on the whole, but this does not imply that every new drug technology is always productive at the margin at which it is used. This rather straightforward point is often confused by lobbies for the pharmaceutical and other groups charged with advocating for manufacturers of pharmaceuticals and other medical products.

Middle- and low-income countries are likely to be much further to the left on the expenditure axis than are high-income countries. In middle-and low-income countries, spending is likely too far to the left on the expenditure axis, particularly for the latter. These countries can benefit from technological advances as well as movements to the

right along a production function. Given lack of availability of health inputs, particularly lack of highly skilled personnel and equipment which is complementary with many innovations emanating from high-income countries, new methods of preventing disease may be given a highly relative priority than new methods of diagnosing and treating disease. Developments of new vaccines, which require less skilled personnel than other health interventions to administer, are relatively attractive for these countries for this reason. A special issue for these countries is that the populations lack the ability to pay for new health products. As a result, some form of outside intervention is needed to provide adequate incentives for the types of innovation that will benefit these societies.⁹ We analyze this issue in greater detail in Section V.

III. The Determinants of Pharmaceutical R&D Investment Behavior

For private firms, the goal of investing in R&D is to maximize profit. Thus, the R&D investment decision making process of pharmaceutical firms is similar to that of by firms in other industries. Optimal investment decisions are made by investing up to the point at which marginal returns from investment equal the marginal cost of capital.

Marginal returns can be represented by a marginal efficiency of investment schedule (MEI). The MEI shows investment projects ranked by their anticipated rates of return. As the firm invests more in a given period, the MEI declines (Fig. 2). The shape and position of the MEI reflects demand curves for the final product as well as the marginal product of making the product once the investment has been completed.

The marginal cost of capital (COC) schedule shows the marginal cost of capital as investment activity expands in any period. The COC can have a zero or a positive slope.

⁹ There is a general literature on the complementarities between skill levels and choice of technology. See, e.g., Caselli and Coleman (2006).

A positive slope indicates that the firm must pay a higher price for capital if it invests more. For simplicity, the COC is shown with a zero slope in Fig. 2. The position of the COC depends in part on creditors' assessment of the risk that the creditors will receive payment for principal and interest, that is, the firm's bankruptcy risk as well as conditions in the capital markets more generally.

Optimal investment in general and R&D investment by a pharmaceutical company is shown where the MEI and COC curves intersect, point E, and the amount of investment chosen by the firm is I^* . Here, anticipated marginal returns from investment in R&D and the marginal cost of funds for such investment are equal; at this level of investment, the firm achieves the maximum expected profit from its R&D investment.

More formally, such firms face a two-step decision process. In the first step, they decide whether to devote resources to a specific R&D project. Firms expend the resources if the marginal return is greater than equal to the marginal cost of funds and reject the project otherwise. In the second step, the firm decides on the optimal price at which to sell the newly invented good. This price determines the profit flow at each date and hence the rate of return on the investment.

The problem is solved by backward induction. First, the optimal price is derived under the assumption that the R&D investment has already taken place. Optimal pricing reflects government patent policy since patents confer market power on firms contemplating an R&D investment. Second, results from the first stage are used in calculating whether or not the investment should be undertaken which is based on a comparison of *anticipated* marginal returns and marginal cost of capital.

Governments are interested in the amount of private investment undertaken for several reasons, including the effect of such investment on aggregate economic activity, the employment effects, as well as the effects of the output of such investments on the welfare of their citizens. R&D investment is only different in the relative weights given by the public sector to the various benefits of such investment.

To assess effects of specific government policies affecting incentives for firms to undertake R&D investment, specifically investments in pharmaceutical R&D, economists have classified incentives to stimulate R&D into two categories: (1) pull and (2) push incentives (see e.g., Kremer and Glennister 2004).

Pull incentives affect the demand for the final product resulting from the R&D and hence shift the MEI curve outward. Such shifts occur for example in response to an increase in market size, reflecting in part countries' decisions to cover the new product under their public insurance systems as well as coverage decisions by private insurers, and an increase in the willingness of such insurers to pay a higher price for the new product. The MEI shifts for non-policy reasons as well, such as from increases in population size, increases in the number of types of persons especially likely to use the new product, as well as growth in income which affects individuals' willingness (and ability) to pay for the new product.

Referring to Fig. 2, the MEI curve shifts outward to MEI' if there is an exogenous change that leads to an increase in the expected revenue of R&D output. Other things being equal, the new MEI curve (MEI') intersects the COC curve at point E_1 ; the firm's optimal R&D investment now becomes I^d . The increase in R&D investment, as measured

by the difference between I^d and I^* , represents the new R&D investment induced by an exogenous change, such as a pull incentive.

Push incentives affect the marginal cost of funds to the firm for investments in R&D. For example, a government grant, a more generous depreciation policy, or investment tax credit, by affecting the cash flow associated with the investment, affects the supply of funds. Likewise, granting the firm access to funds from the sale of securities, the income from which is not subject to personal income taxation increases the supply of funds, that is shifts the COC downward (and if positively sloped to the right). Macroeconomic policies affecting market rates of interest will also affect the COC.

The COC curve shifts downward to COC' if there is an exogenous change that leads to a decrease in the user cost of capital for R&D investment. Other thing being equal, the new COC curve (COC') intersects the MEI curve at point E_2 with I^c being the firm's new optimal R&D investment. The increase in R&D investment, as measured by the difference between I^c and I^* , represents the new R&D investment induced by push incentives.

The effectiveness of push incentives depends on the elasticity of MEI, that is, the percent rate of change (decline) in the MEI for a given percent change in investment. The elasticity of the MEI reflects anticipated product demand conditions in part, for example, how responsive demand for the new product is to price. A given push policy will be more effective, other factors equal, if the MEI is more elastic.

Conversely, one can think of push disincentives. For example, as mentioned above, the position of the COC is affected by the anticipated credit risk of the firm. If the firm's assets are subject to expropriation by the government, or if its assets were subject

to risk of a terrorist attack, this would raise the firm's COC, thereby discouraging private investment.

There are negative pull incentives as well, for example, if countries' drug coverage and payment policies become more uncertain. As a consequence, firms may add a risk premium in calculating their optimal investment decisions, which can be represented in formal analysis of investment decisions in alternative ways. Or the national agency responsible for approving new drug products for sale in a country can lengthen or add complexity to its approval process. This in turn delays the time in which positive cash flow from the new product can be anticipated and lowers the expected rate of return. In general, the probability that a new drug will ever appear on the market is reflected in the MEI. If government regulatory agencies become more stringent in approving drugs, this too affects private investment in R&D.

Theoretically, the relative effectiveness of pull versus push incentives cannot be deduced, but rather must be established by examining the empirical evidence. That is, in theory, the effect of push incentives (I^c-I^*) is not necessarily less than the effect of pull incentives (I^d-I^*). It has been argued on the basis of institutional factors (see e.g., Kremer and Glennister 2004) that pull incentives tend to be more promising. With pull incentives, the reward is for results; with push incentives, by contrast, rewards can be made on the basis of promises. For example, an applicant for a government grant, a push incentive, can make various claims about the uniqueness of an approach, but once awarded the grant, there is no direct incentive to deliver on the promise except the threat that non-performance will result in fewer grants in the future. Unfortunately, conclusive empirical evidence from comparisons of pull versus push incentives is lacking.

A combination of pull and push incentives can produce more substantial induced investment than when only one type is applied alone (Fig. 2). For this reason, rather than choose between the two, a government may include a mix of pull and push policies in its R&D stimulus package.¹⁰ This policy will shift the MEI upward and the COC curve shift downward at the same time, leading to a new equilibrium point for optimal investment decision is at E_3 and I^{c+d} . In this example, the new R&D investment induced by adopting both pull and push incentives simultaneously ($I^{c+d}-I^*$) is greater than any new investment induced by pull incentive (I^d-I^*) or push incentive (I^c-I^*) alone.

Of course, governments may not develop strategies to maximize the value of investments in R&D. Public policy decisions are guided by purely political decisions as well. Also, there may be important implementation barriers specific to particular investment stimulus policies.

This reservation withstanding, the above analysis provides a general conceptual framework for understanding the effect of various incentives on the firm's R&D investment decision. Below, we will review the empirical evidence on these incentive effects, focusing specifically on pharmaceutical industry. As background to this discussion, we first describe important characteristics of pharmaceutical research and development.

IV. Institutional Features of Pharmaceutical R&D

In characterizing pharmaceutical R&D, it is important to consider three factors that are rather unique to this sector. First, pharmaceutical companies typically allocate a relatively larger share of their resources to investments in R&D than do their counterparts

¹⁰ As we will discuss below, the 1982 U. S. Orphan Drug Act incorporates both pull and push incentives to promote pharmaceutical innovation for rare diseases.

in most other industries. For example, in the United States, R&D expenditures as a percentage of sales ranged from three percent in motor vehicles to eight percent in communication equipment in 1995. By contrast, pharmaceutical manufacturers spent over 10 percent of sales revenue on R&D in the same year (Murphy and Topel 2003, p. 66). Furthermore, there is a secular trend in the share of R&D expenditures as a percentage of sales revenue in this industry has increased over time. For example, among the top 10 pharmaceutical firms in the U.S., the share of sales revenue spent on R&D increased from 10.9 percent in 1990 to 13.7 percent in 2000 (Reinhardt 2006). The U.S. pharmaceutical is not unique among high-income countries in this regard.

Second, the mean of R&D cost per new chemical entity (NCE) is very substantial. Danzon, Nicholson, and Pereira (2005) attributed the high R&D cost in this sector to three factors. (1) The dollar allocation by firms to both drug discovery and drug development is high. DiMasi, Hansen and Grabowski (2003) estimated that the mean out-of-pocket R&D cost for new brand drug (NCE) approval in the 1990s exceeded 400 million (in 2000 dollars). About three-quarters of these R&D expenditures are spent on pre-clinical and human testing required by the regulatory agency in the U.S., the Food and Drug Administration, to establish proof of safety and efficacy (Maurer 2006). (2) Pharmaceutical R&D is a time-consuming process. It has been estimated that it takes 12 to 15 years to successfully develop a new drug. By applying a real discount rate of 11 percent to capitalize the out-of-pocket cash flows over these lengthy periods, the estimated average R&D cost per NCE increased to US\$802 million (in 2000 dollars) (DiMasi, Hansen and Grabowski 2003). (3) There are higher failure rates in the drug discovery and development process than for products in many other sectors.

The third rather unique characteristic of pharmaceutical R&D is that pharmaceutical R&D is highly dependent on patent protection to recoup the R&D investment. Pharmaceutical companies are more dependent on patent protection than are many other research-intensive industries (Mansfield 1986; Levin, Klevorick, and Nelson et al. 1987; Cohen, Nelson and Walsh 2002). This is because the difference between the marginal cost of bringing the first unit of a product to market (first copy cost) and marginal costs of units beyond the first is extremely large. Compared to the high R&D cost per new NCE, the estimated cost of applying for an abbreviated new drug approval required for bring the imitative products (generic drugs) into the market was approximately US\$603,000 in the early 1990s (Reiffen and Ward 2005), which only accounts for 0.15% of out-of-pocket R&D cost per new NCE. Therefore, the research-base of the pharmaceutical industry could not long survive without patent protection (Reinhardt 2006).

The conceptual basis for this statement is easily understood. Once the new product has been developed, the marginal cost of manufacturing and distributing a new drug is quite low. If new drugs were priced at their marginal cost, there would be no way for the firm to recoup the high fixed cost of R&D. The fixed cost of R&D must be covered somehow, and the method used to date has been to allow pharmaceutical companies to have a monopoly on their new products for a stated period of time so as to recoup their investments from the monopoly profit. This is not unambiguously a good approach in that there is a welfare loss from monopoly pricing.

V. Incentives under the Patent System

Overview

Given the importance of patent system in the pharmaceutical industry, we first review the empirical evidence on the effect of various incentives under a system that patent protection could provide effective incentives for innovation.

The patent system gives the protection of intellectual property right to innovators for the new products they developed and brought to the market. This protection provides a legal barrier for other imitative firms to enter the market. In the context of pharmaceuticals, this means a firm that would sell a drug based on the same chemical formula as the new drug developed by the innovator firm. Therefore, the innovators possess market power to price their products above the marginal cost of production.¹¹ On the one hand, this market power provides a mechanism for the pharmaceutical research firm to recoup the R&D cost and hence create incentives for innovation. But on the other, such market power allows firms to set higher prices, which in turn restricts the use of the drug below the socially optimal rate of use. That is, at the monopoly price, there are consumers with a willingness to pay in excess of the marginal cost of producing the good.

Furthermore, rather than engage in simple monopoly pricing, that is, charge a single monopoly price, pharmaceutical firms often engage in price discrimination to sell identical products to different sets of consumers at different prices. Price discrimination allows firms to extract even more money from consumers (more consumer surplus) than under simple monopoly pricing, but it has the positive feature of leading to output levels that are closer to the socially optimal rates of output than occurs under monopoly pricing.

¹¹ Under perfect competition, many firms compete in the market. The individual firm is a price taker in the sense that the firm does not have any power to influence the market price but rather to accept the price determined by the market. In the long run, the equilibrium price (P) prevails in the market is equal to the marginal cost of production (MC). By contrast, in a market structure with imperfect competition, firms are price makers in the sense that they can decide their own prices. In this case, the equilibrium price exceeds the marginal cost of production. The difference between price and marginal cost is a markup ($P-MC$); the markup ratio $((P-MC)/P)$ can be used to measure the market power possessed by an individual firm.

In the policy arena, one often hears complaints about the high price of new products, which imposes substantial cost burdens on public and private payers as well as individuals who pay new prescriptions out-of-pocket. Economic efficiency often plays a secondary role to the distribution effects in public policy decision making.

The fact that marginal cost of new drugs is so low once these products are developed, receive government approval, and are marketed and the required rate of return for firms to engage in R&D investment activity is so high (given where the MEI intersects the COC curve) before new drugs are developed, approved, and marketed creates a time inconsistency problem in the policy arena.

At a given point in time, the amount of pharmaceutical innovation is fixed. Therefore, the optimal allocation of resources in the short-run is guided by setting the social marginal benefit equal to marginal social cost of producing and distributing the good. In the absence of externalities, this static efficiency criterion could be achieved by market competition pushing prices of new drugs down to their marginal costs. However, given the high R&D cost in the pharmaceutical industry, the competitive price does not allow firms to recoup the expenditure on their R&D investment. Consequently, dynamic efficiency considers optimal resource allocation over time, which requires pricing a new drug at a high level to preserve incentives for R&D investment behavior, assuming reliance on the patent system. It is very tempting for public decision makers in small countries to emphasize the static efficiency criterion since they perceive that their policies will not affect the development of new products in any event. Policymakers with short time horizons in larger countries may be similarly tempted.

Therefore, the key policy challenge is how to achieve an appropriate balance between static efficiency that considers short-term benefits from greater price competition and dynamic efficiency that considers long-term benefits from appropriate incentives for innovation (Grabowski 2006).

A policy tool that can be used to achieve this balance is the effective patent life (EPL). EPL is defined as follows:

$$\text{EPL} = \text{Nominal Patent Life} - \text{Time Lost Prior to Regulatory Approval}$$

The current patent system gives the protection of intellectual property right for 20 years by the World Trade Organization, and this nominal patent life often begins before human clinical trials. As mentioned above, the new drug development process takes about 12 to 15 years on average. Thus, much of the nominal patent life was lost before the product is approved by the regulatory agency. Grabowski and Vernon (2000) estimated that EPL for a representative new drug compound was less than 10 years in the U.S. during the early 1980s. This result suggests that a policy of increasing the effective patent life can provide a significant incentive for R&D investment.

Since the nominal patent life is now fixed at 20 years, a policy instrument the government can use to increase EPL is through the reduction or restoration of patent time lost during the clinical and regulatory periods. In the United States, the Food and Drug Administration classifies the review process for new drug application (NDA) into two categories: (1) priority review; and (2) standard review. Drugs offering “significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease” are assigned to priority review. Drugs that “appear to have therapeutic qualities

similar to those of one or more already marketed drugs” use the standard review process (U.S. Food and Drug Administration 2006).

Ridley, Grabowski and Moe (2006) estimated that on average the standard review takes 18.4 months in the U.S. while priority review only take 6.4 months. This suggests that a priority review process could increase EPL by one year. Based on the sales data from U.S. top 10 pharmaceuticals, the market value of increasing EPL by one year is approximately US\$ 300 million (in 2004 dollars)(Ridley, Grabowski, Moe 2006). This policy would provide a major incentive to encourage firm to invest new drugs with important therapeutic gain over the existing drugs.

In 1984, the United States enacted the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act. This law increased the EPL through a partial restoration of the patent time lost during the clinical and regulatory periods (Grabowski 2006). The passage of Hatch-Waxman law increased the EPL by 2.3 years (Grabowski and Vernon 2000).

Market Size

A second pull incentive for increasing pharmaceutical innovation is through the expansion of market size. The market size of prescription drugs depends on several factors, such as the demographic structure of population, health policies, and income level (the consumer’s ability to pay). Several studies have documented the empirical relationship between market size and pharmaceutical innovation from various settings.

Acemoglu and Linn (2004) measured changes in market size from demographic trends in the U.S. During a recent 30-year period, demographic trends have led to a decline in the market for drugs mostly consumed by the young (age 0-30). By contrast,

markets for drugs mostly consumed by the middle-aged have increased. More specifically, Acemoglu and Linn's measure of potential market size for each drug category involved a combination of the number of consumers and their incomes. They found that the change in potential market size has a significantly positive impact on pharmaceutical innovation, as measured by the number of new drugs entering the U.S. market. A one percent increase in potential market size leads to about a four percent increase in the entry of new drugs, either in the form of new non-generic drugs or new molecular entities.

Finkelstein (2004) investigated whether profit incentives affected by changes in health policies affect the R&D investment behavior in the vaccine industry. These health policy changes were considered in her study. In 1986, the U.S. government introduced a no-fault compensation system for injuries attributable to use of certain childhood vaccines. This system reduced expected liability costs for vaccine manufacturers since compensation for injuries under no-fault was much lower than under the tort system previously applicable to such injuries. In 1991, the U.S. Centers for Disease Control recommended that all infants be vaccinated against hepatitis B. In 1993, Medicare provided insurance coverage for influenza vaccinations administered to its beneficiaries. These latter two policies increased the potential market size for vaccines, which in turn, in combination with the adoption of no-fault system in 1986, substantially increased the expected return from developing new vaccines for infectious diseases. By comparing changes in the number of new vaccines clinical trials between treatment diseases (affected by the policies) and control diseases (not affected by the policies), she found evidence linking the policy changes and to rates of innovation in vaccine markets. Her

estimates indicate that a \$1 increase in annual expected market revenue from a vaccine leads to a six cent increase in vaccine R&D investment.

Acemoglu, Cutler and Finkelstein et al. (2006) further investigated whether the introduction of Medicare in 1965 increased pharmaceutical innovation. The authors hypothesized that the necessary (but not sufficient) condition for this to happen is that Medicare has increased the demand for prescription drugs among the elderly. Before 2006, Medicare did not provide coverage for prescription drugs, but did provide coverage for other types of medical care. To the extent that physicians' services and drugs are complements, decreasing the price of physicians' services to the U.S. elderly would be expected to increase the demand for pharmaceutical products as well. By comparing the drug expenditure between "treatment" (persons aged 65 to 74) and "control" groups (persons aged 55 to 64), the authors found no evidence of increased pharmaceutical innovation attributable to the introduction of Medicare, which presumably would have operated through the mechanism of increased market size of drugs used by the elderly. It is much too early to tell whether or not the Medicare prescription drug benefit introduced in 2006 will increase drug innovation.

Lichtenberg (2005) investigated the effect of market size, as measured by the burden of disease, on pharmaceutical innovation. He measured the burden of disease by the number of disability-adjusted life-years attributable to the disease in 2001, as calculated by World Health Organization (WHO). Disease burden potentially represents a more accurate measure of potential use than broad demographic characteristics such as age. Lichtenberg found that the amount of pharmaceutical innovation, as measured by the number of new chemical entities launched since 1982, is positively related to the burden

of disease in developed countries, but there is no statistically significant relationship between disease burden and innovation in developing countries. For diseases more commonly found in developing countries, the burden of disease is not identical to market size of pharmaceuticals because per capita incomes are lower, there is weak patent protection, and government regulation places binding constraints on drug pricing.

The existing body of evidence on a positive effect of market size on pharmaceutical innovation suggests that pharmaceutical firms may not have sufficient financial incentives to discover and develop new drugs with small market sizes. Although developing countries account for 78 percent of the world's population and 85 percent of the global burden of disease (Lichtenberg 2005), new molecular entities for treating tropical diseases in humans in an important subset of developing accounted for less than 1% of all new molecular entities licensed worldwide during 1975-1997. Given the evidence that the larger burden of disease does not provide adequate profit incentives to induce pharmaceutical innovation in the low-income countries, it is important to investigate how alternative incentive mechanisms could work to promote pharmaceutical innovation for the prevention and treatment of diseases that are mainly prevalent in low-income countries. We return to this issue in Section VI.

Price Regulation

Many developed countries provide insurance coverage for prescription drugs. Consequently, most pharmaceutical expenditures in these countries are paid by third party payers.¹² As a by product of pharmaceutical innovation, new prescription drugs are introduced into the markets in these countries annually. Added expenditures from these

¹² For example, as noted by Ess et al. (2003), about 75 percent of pharmaceutical expenditure is public financing in Europe. In the United States, near 70 percent of prescription drug spending was paid by private insurer and Medicaid in 1998 (Berndt 2002).

new drugs, however beneficial they may be in terms of their health-enhancing effects, increase pressure on public budgets. Therefore, these countries have implemented a number of regulatory mechanisms to control the growth of spending on pharmaceuticals (Ess, Schneeweiss, and Szucs 2003).

The most commonly used form of regulation aimed at controlling increases in public expenditures on pharmaceuticals involves direct control of product prices. In contrast to the expansion of effective patent life and the market size, price regulation on pharmaceutical products *decreases* incentives for R&D investment. This is a negative pull policy.

Several studies have documented the empirical relationship between price regulation and disincentive for innovation in the pharmaceutical industry. In conceptual terms, price regulation directly affects the firm's R&D investment behavior through the following two channels (Vernon 2005). First, price regulation reduces the price of regulated products and hence it decreases the expected returns of R&D output. Second, the decrease in the expected returns of R&D output in turn decreases the profit margin, thereby negatively affecting availability of internal funds for investment, an effect reflected in the COC curve. The cost of capital from internal funds may be lower than that of external funds, such as debt and equity, if the capital market is not perfect so that the opportunity cost of financing investments varies according to the source of funding (see e.g. Shyam-Subder and Myers 1999). Showing this in a supply and demand for capital framework for investments funds framework of Fig. 2 would require that we draw the COC with a positive slope. Price regulation would then shift the COC curve upward

to the left, leading firms to invest less in R&D than before price constraints were imposed. Clearly, price regulation provides a disincentive for pharmaceutical innovation.

By using a panel data containing 14 large pharmaceutical firms in the world from 1994 to 1997, Vernon (2005) estimated effects of expected-profitability and cash-flow on R&D investment intensity, as measured by the ratio of R&D expenditures to total sales. He used the firm's current period pre-tax pharmaceutical profit margin as a proxy to measure the expected future profitability. Also, he used the percentage of pharmaceutical sales from non-U.S. markets to measure the firm's exposure to price regulation and simulate effects of price regulation.

His empirical analysis yielded three important findings. First, both pharmaceutical profit expectations and lagged cash flows have significantly positive impacts on the firm's R&D investment intensity. Second, the average pre-tax pharmaceutical profit margins in the non-regulated (the U.S.) market are approximately four to five times as large as those in the regulated (non-U.S.) markets. Third, simulations revealed that R&D investment intensity would decline by from 23 to 33 percent if the U.S. also adopted a price regulation. The cash flow effect would account for about half of this decline in R&D, and the rest of the decline would come from the expected profit effect.

Giaccotto, Santerre and Vernon (2005) used U.S. industry-level data for the years 1952-2001 to estimate the relationship between real drug prices and R&D investment intensity. They measured the real price of drugs by dividing the pharmaceutical consumer price index (CPI) by the all-items CPI. They found that real drug prices have a significantly positive impact on R&D investment. The elasticity estimate of about 0.6 suggests that a 10 percent increase in growth of real drug prices leads to a 6% increase in

the growth of R&D investment. Based on this result, they simulated the effect of price regulation by assuming that the federal government limited the rate of growth in drug price increases to the rate of growth in the general CPI from 1980 to 2001. They found that the capitalized pharmaceutical R&D expenditure during this period would have declined about 30 percent as a consequence of implementing such price regulation.

In addition to the direct effect on the firm's R&D investment behavior, price regulation also affects incentives for pharmaceutical innovation indirectly through its impact on market competition. Several studies have shown consistent evidence that regulation leads to a downward sloping price curve over the drug's life cycle and undermines market competition (Danzon and Chao 2000; Ekelund and Persson 2003). Both effects create disincentive for pharmaceutical innovation.

Lu and Comanor (1998) and Ekelund and Persson (2003) provide interesting comparisons of pricing of new pharmaceuticals in an unregulated (U.S) market versus a regulated market (Sweden). Lu and Comanor found that in a market not subject to price regulation, pharmaceutical companies adopt a penetration strategy in pricing their new products that little or no therapeutic advantages over existing products by setting launch prices at or below those of their substitutes. However, the mean real price increased substantially over time and thus, there is an upward-sloping price curve with time over the drug's life cycle.¹³ By contrast, Ekelund and Persson (2003) found that real prices for new brand drugs (NCEs) fall substantially over time for all class of therapeutic innovations, new products that represent real breakthroughs and those which represent at most minor advances over existing products in the regulated Swedish market. This result

¹³ By contrast, Lu and Comanor (1998) found that new drug with important therapeutic gain adopts skimming strategy to launce new product at a relatively higher price over the existing product but gradually reduce the price as more competitors enter into the market.

is consistent with empirical results obtained by Danzon and Chao (2000) for Japan, Italy, and France.

Regulatory pressure on prices over the product life cycle may provide a disincentive for the pharmaceutical firm to develop new product with important therapeutic gain (Danzon and Chao 2000). Pharmaceutical firms in regulated countries tend to introduce line extension by a stream of minor new products (such as new dosage forms) in order to obtain a higher price. Grabowski and Wang (2006) used global NCEs and first-in-class NCEs to measure the importance of pharmaceutical innovation across countries. They defined global NCEs as those introduced in at least four of the G7 countries (Canada, France, Germany, Italy, Japan, UK, and US) which are the world's largest pharmaceutical markets. They defined first-in-class NCEs as the first NCE in a therapeutic class. They found that global NCEs account for over half of all NCEs launches in the U.S. during the period of 1982 to 2003, and first-in-class NCEs account for about a fifth of all NCEs launches in the U.S. during the same period. By contrast, the shares of global NCEs and first-in-class NCEs were only about 10 and three percent, respectively, in Italy and Japan, which provides strong empirical support for the view that price regulation reduces pharmaceutical innovation.

Ekelund and Persson (2003) moreover, found no correlation between the number of branded substitutes and the launch prices in the Swedish market, which stands in contrast to Lu and Comanor's (1998) finding that the number of branded substitutes has a substantial negative effect on launch prices in the U.S. market. These contrasting findings imply that price regulation discourages price competition between branded drugs. Danzon and Chao (2000) obtained evidence that price regulation undermines generic

competition in countries such as France, Italy, and Japan. Generic competition often leads to a large decline in sales of branded drugs within a very short period (Grabowski 2006). The threat of generic competition consequently forces firms manufacturing branded products (those still under patent) to implement various strategic responses. One such response available to producer of the branded product is to invest in new products and maintain a healthy pipeline of products under development.

Market pressure arising from generic competition is clearly one of the key incentives for pharmaceutical innovation. The decline in generic competition resulting from price regulation therefore weakens incentives for innovation signaled by market pressure emanating from generic competition.

Furthermore, price regulation reduces incentives for innovation through its impact on the launch delay of new drugs. Danzon, Wang and Wang (2005) pointed out that the price regulation imposes two negative external effects on the firm's expected revenue. First, it induces a parallel trade that the arbitrageur purchases prescription drugs in low price countries and resell them in high price countries. Second, price regulation creates an external reference based on which countries set the regulated price. In such cases, accepting a lower price in one country may undermine the price the firm can obtain in another country. As a result, the pharmaceutical firm may postpone the launch of new drugs or chooses to have no launch at all if the regulator sets the price too low.

Based on a sample containing 85 new chemical entities (NCEs) launches between 1994 and 1998 in 25 major markets, Danzon, Wang, and Wang (2005) found that the expected price of a new product, which is measured by lagged average price of other drugs in the same or related therapeutic class, significantly affects the timing and

occurrence of launch. Countries with lower expected prices tend to have fewer launches and longer launch delays. Clearly, delays in launch of new drugs or no launch at all reduce the expected revenues that the firm can recoup for R&D investment and hence it reduces incentive for pharmaceutical innovation.

In sum, the existing literature indicates that price regulation affects innovation incentives in the pharmaceutical industry through the following four channels. First, price regulation directly influences the firm's R&D incentives by reducing the expected profit from innovation and increasing the cost of capital for R&D investment by decreasing internal funds for investment. Second, price regulation reduces the drug's effective product price over its life, which in turn, creates incentives for pharmaceutical firms to focus on quick but minor innovations in order to secure higher prices on new products. Overall, pharmaceutical innovation in countries subject to a strictly regulated system lags behind that in countries with less regulated or unregulated systems. Third, price regulation drives out competition in pharmaceutical markets and this in turn further reduces competitive pressures to develop new products. Fourth, price regulation negatively affects the timing and occurrence of new product launches which in turn reduces the expected revenues from countries throughout the world.

Industrial Policy

Industrial policies refer to government policies designed to promote growth of a specific industry in a country. Such growth may be viewed as desirable for several reasons, including its effects of employment, synergies with other industries, and in the case of pharmaceuticals, the potential impact on population health. Industrial policies may be of either the pull or the push varieties. In the context of pharmaceuticals,

industrial policies have mainly been of the push type, targeting the availability of funds for investments in R&D. One specific example of push policy is a tax credit for R&D expenditures. This policy reduces the cost of capital for R&D investment and hence increases the firm's incentive to undertake such investment.

The 1983 Orphan Drug Act in the U.S. is a well known example of a government using tax credits to promote pharmaceutical innovation. The rationale for the Act was to stimulate R&D investment in drugs with relatively small potential market sizes. The Act provides a tax credit for up to 50 percent of certain clinical testing expenses by pharmaceutical firms to generate required data for marketing approval.¹⁴ Following implementation of the Orphan Drug Act, the mean annual number of new drugs brought to market for treating rare diseases increased tremendously, from one per year during 1973-1982 to 12 during 1983-1989 (Lichtenberg 2001).

Public Investment on Basic Research

The pharmaceutical R&D process can be decomposed into two distinct stages: (1) discovery and (2) development (Cockburn and Henderson 2001). The discovery stage includes the basic science research and the application of “upstream” basic research to search for new compound for developing new drugs. The development stage refers to “downstream” market-oriented R&D, including preclinical testing and three phases of clinical tests to demonstrate the safety and efficacy of the specific compound.

A characteristic of the upstream basic research is its public good nature. For this reason, private firms do not have incentives to invest in basic research. Rather, as with financing of other public goods, such as national defense, financing of basic scientific

¹⁴ In addition, this Act provides seven years of marketing exclusivity, which is a pull incentive that increases the expected market revenue from developing the drug for treating rare diseases.

research is highly depending on public funding.¹⁵ In spite its public good nature, upstream basic research is not free from the firm's stand point (Gambardella 1995).

Dissemination of scientific knowledge from public to private sectors can be costly and time consuming. Firms must invest in knowledge capital so that they can access and absorb upstream basic research findings (Cockburn and Henderson 1998). The form of investment in knowledge capital includes some in-house basic research and maintaining an extensive connection between pharmaceutical company scientists and publicly-funded researchers by collaborative efforts in publishing scientific papers. Cockburn and Henderson found that the number of coauthorships of scientific papers is positively related to the firm's private research productivity, as measured by the number of important patents.

Since the private research mainly focuses on downstream market-oriented R&D for developing new drugs, Cockburn and Henderson (1998)'s work suggests that upstream basic research and downstream market-oriented R&D are complements rather than substitutes in the pharmaceutical R&D process. Based on detailed case histories for the development of 21 important drugs introduced between 1965 and 1992, Cockburn and Henderson found that 14 drugs were developed with at least some input from the public sector. This evidence suggests that the investment in basic research by the public sector plays a very important role on the rate of drug discovery and development.

Specifically, the public investment in upstream basic research provides the input for downstream market-oriented R&D in three ways: (1) it provides the fundamental biological and chemical knowledge for the discovery of new drugs; (2) it provides

¹⁵ For example, the U.S. Federal Government spent \$8.8 billion for health-related research in 1995, which accounted for 36 percent of the non-defense Federal Research budget (Cockburn and Henderson 1998).

clinical knowledge for the design of human clinical trials required by regulatory agencies as proof of drug safety and efficacy; (3) it provides insights for potential new indications for drugs once they have been approved (Cockburn and Henderson 1998). Increases in public investment in upstream basic research decrease the cost of acquiring knowledge capital for pharmaceutical innovation, which in turn provides an incentive for increasing spending on downstream R&D investment by private firm.

VI. Other Incentive Mechanisms When Patents Fail

Overview

Under the patent system, pharmaceutical firms receive the rewards for their R&D investment through market valuations, that is, the monopoly profit they can earn due to the entry barrier that the patents erect. Firms' decision rule for R&D investment is to maximize profit, not to maximize health gains (see Sec. III above). This implies that the allocation of R&D resources by private firms is guided by market demand (or ability to pay) rather than on the basis of health needs. In high-income countries, people are able and willingness to pay for good health. Thus, there is no significant deviation between ability to pay and health need. The patent system appears to function fairly well in providing incentives for pharmaceutical innovation.

By contrast, there is a substantial disparity between ability to pay and health need in low-income countries. Judging from global burden of disease, there is a great health need in low income countries (Jamison 2006, p. 31). In these countries, income is low and effective demand for disease prevention and therapy is correspondingly low. Consequently, R&D investment spending on the search for prevention and cure of some diseases which are highly prevalent in low-income countries is low or even negligible,

indicating there is indeed a mismatch or market failure in allocating R&D resources according to health needs.

There is another type of market failure in vaccine R&D investment which arises from external benefits in consumption. The social benefits of vaccines not only include internal benefits from disease prevention for specific individuals who are vaccinated but also include external benefits from preventing the spread of disease to others. Individuals' willingness to pay for vaccines is not likely to reflect external benefits from being vaccinated. Vaccines for major communicable diseases may have much larger social benefits than many drugs. Compared to drugs, firms tend to earn lower profits from vaccines than from drugs (Kremer and Snyder 2003). Thus, private firms have less incentive to discover and develop new vaccines because of the low profit, although their potential value to population health is very high

In such two cases, the patent system may not generate a sufficient incentive for pharmaceutical innovation. Therefore, researchers have investigated other mechanisms to stimulate pharmaceutical innovation when the patent system fails. One alternative is a system of rewards paid by the government or private foundations (hereinafter referred as sponsors) to pharmaceutical firms. Under the reward system, the property rights of the innovation are purchased by the sponsors in the form of rewards; sponsors in turn place the innovation into the public domain, making it available freely to competing manufactures. Thus, an advantage of the reward system is the sponsor can provide incentives for pharmaceutical R&D investment without granting the firms monopoly power over price and removing the legal barrier for other firms to enter into the market. As a result, the new drugs can be sold at the price equal to marginal cost, which in turn

reduces the welfare loss from patent, increases the accessibility of new drugs, and reduces the cost burden on payers.

One of the practical issues faced by the reward system is how to decide the size of rewards. Theoretically, the problem is rather straightforward. One could compute the consumer surplus, assuming pricing a marginal cost and at the output at which the demand curve intersects the marginal cost curve. As shown in Figure 3, the consumer surplus is represented by the triangle area AP_cE . The size of this area (in dollars) divided by the quantity Q_c is equal to the size of rectangle P_rP_cEC . This suggests that sponsors can set the rewards equal to $P_r - P_c$ per unit of output up to the quantity of Q_c . Under this reward system, the innovative firm receives the subsidy in the amount of consumer surplus from the sponsors as a reward to recoup its spending on R&D investment. The new pharmaceutical product in turn can be produced and sold in a competitive market by the innovative firm or other firms at price P_c .

The analytical framework of Fig. 3 shows that the reward system provides two advantages over the patent system. First, the reward system avoids the social welfare loss created by the patent system. Under the patent system, the monopoly price of new pharmaceutical product is P_m , which is higher than the competitive price (P_c) and hence reduces the quantity of consumption to Q_m . This in turn leads to a social welfare loss in the amount of the decrease in consumer surplus minus monopoly rent. Second, sponsors can choose the magnitude of research incentives by adjusting the level of rewards. For example, to the extent that there are consumption externalities, one would need to adjust for this since the consumer surplus as revealed by the market would be an underestimate. The maximum price would be the area of the adjusted (for externalities) consumer

surplus divided by socially optimal output (again accounting for externalities). Based on these two advantages, Shavell and Ypersele (2001) concluded that an optional reward system, which the firm can freely choose between rewards and patents, is superior to the patent system.

In practice, computing the maximum price or reward is of course more complex than this. For one, Garber, Jones, and Romer (2006) caution that with insurance and moral hazard, the monopoly profit may exceed the relevant consumer surplus. The relevant surplus is calculated before insurance. Thus, it is conceivable that rewards to firms under the patent system are too high.

Also, the calculations involve new not existing products. Thus, many assumptions are required to obtain estimates of maximum prices or rewards. If rewards are set to low, incentives for innovation will be insufficient. However, there is also a risk if rewards are set too high. In particular, there will be too much investment in R&D (Comanor 2006). The following subsections analyze three proposals that use the reward system to provide incentives to develop new drugs and vaccines for developing countries.

Advanced Purchase Commitments

Kremer and Glennerster (2004) propose to use the advance-purchase commitment as an incentive mechanism to induce innovation for malaria vaccine. This approach offers the innovator a subsidy of a fixed value per unit for a given number of units if the innovators develop a new vaccine that satisfies certain technical characteristics.

The rationale of this approach is to use the subsidy offered by the sponsors to close the gap between high R&D costs for new vaccines and low ability to pay in low income countries. As Fig. 4 illustrates, ability to pay for certain amount of vaccines is

represented by the market demand curve D . The market price would equal to P if a country needs to consume OQ amount of vaccine in order to effectively prevent a certain disease. However, the average cost of a vaccine at this quantity is C . The pharmaceutical firm does not have incentive to invest for vaccine R&D because the sustainable market price (P) is insufficiently high to allow it to recoup the R&D cost (C). If the sponsor offers a subsidy in the amount of $C-P$ per unit up to quantity OQ , then the total revenue received by the innovator equals to market revenue (as represented by $OPEQ$) plus the sponsor's subsidy (as represented by $PCBE$), which is large enough to cover the R&D cost. In sum, advance-purchase commitment increases expected revenues from investments in R&D without constraining to the extent of the patent system.

A principal difficulty with advance-purchase commitments, however, concerns the sponsor's need to identify the desired, feasible technical characteristics of a vaccine which has not yet been developed. This difficulty in turn creates two distortions in incentives for R&D investment (Hollis 2006). First, firms lack incentives to develop a new product that exceeds the technical standard set by sponsors. Therefore, it provides no incentive for firm to conduct incremental innovation that could improve the quality of new product over time. Second, the sponsors run a risk of exhausting the funds available for subsidy if the technical standard is set too low. By contrast, the firm would have no incentive to develop the new product if the technical standard is set too high. If the sponsor allows some flexibility in identifying the technical standard, the system would leave a great deal of discretion to the hands of the members of the technical committee. This discretion in turn makes the subsidy program become committee-driven rather than

market-driven. The funds for the subsidy not be used in a socially optimal way as a consequence.

Optional Rewards Based on Therapeutic Effect

Hollis (2006) proposes an optional reward system under which the pharmaceutical firm can choose between the reward system and patent systems, and the firm is paid for pharmaceutical innovation directly by sponsors based on the therapeutic effectiveness of drugs if he opts for the reward system. This system explicitly links profitability of drug innovations to their therapeutic impacts rather than on consumer ability to pay. Thus, this payment scheme closes the gap between pursuing profit and pursuing health and hence it provides an incentive to guide R&D resources into drugs which have large health impacts rather than on products demanded by relatively affluent persons.

Compared to the Advanced Purchase Commitment, the advantage of the optional reward system is that sponsors do not need to set technical specifications in advance. Rather, sponsors only need to evaluate therapeutic effectiveness after the new drugs have received regulatory approval. Therefore, success of the optional reward system lies in the details of implementation, such as whether or not there are valid and reliable measures of treatment effects, and whether or not the commitment of payment for innovative drugs is regarded as credible by the firms that do the investing (Sloan and Eesley 2006).

Several countries have adopted various methodologies of comparing costs of new drugs with their effects on health outcomes, termed “economic evaluation” (Drummond 2006). Although the methodologies have shortcomings and many practical issues remain, the international experience suggests that the policy on measuring therapeutic effect has proved workable and, to date, no country formally adopting economic evaluation has

abandoned the policy. Although developing countries may have a greater difficulty in collecting data for measuring therapeutic effect than do developed countries, there will inevitably be learning by doing. Some mistakes must be made for progress against some major diseases to be realized. Thus, the proposal for making rewards a function of both therapeutic impact and the number of persons affected is both a feasible and efficient approach to induce pharmaceutical innovation for diseases concentrated in low income countries.

Priority Review Voucher

Ridley, Grabowski, and Moe (2006) propose a reward system under which firms receive a “priority review voucher” if they successfully develop new drugs for treating diseases concentrated in low-income countries. The voucher is transferable and gives a privilege to the bearer of the voucher to use the priority review process in the new drug application for another drug. As mentioned above, compared to the standard review process, the priority review process for new drug application in the United States leads to an increase in effective patent life (EPL) by one year. It has been estimated that the market value of one-year EPL for blockbuster drug is approximately US\$ 300 million (Ridley, Grabowski, and Moe 2006).¹⁶ Thus, the voucher would generate significant rewards to innovators if there is a market for the priority review voucher that the innovators can sell this voucher to other pharmaceutical firms who have a potential to develop blockbuster drugs.

The rationale of this incentive scheme is to use the market mechanism in developed countries to solve market failure in developing countries. By linking incentives

¹⁶ Blockbuster drugs indicate those with annual sales exceeding \$1 billion in their fifth year on the market (Ridley, Grabowski and Moe 2006).

in two different markets, this system provides benefits not only for developing countries but also for developed countries. The drug that consumers and payers in developed countries value more would reach the market sooner if the voucher market functions well. Furthermore, the advantage of the priority review voucher is that effective incentives for induced innovation are not limited by the size of funds available to sponsors. Rather, the sponsor relies on market mechanism in developed countries to create incentive for pharmaceutical innovation in developing countries. The size of rewards is determined by the market, instead of relying on the judgment of committee members or on cost-effective analysis conducted by an outside advisory group. As a result, both the administration cost and rewards cost to sponsor (and taxpayer) are low, thus this incentive scheme could be applied to a wider class of diseases than those of the above two incentive systems.

VII. Conclusion

This paper's focus is on positive and normative aspects of setting incentives for pharmaceutical innovation. Overall, our literature review reveals that profit incentives do affect pharmaceutical innovation. In this context, incentives do matter. The empirical evidence we have reviewed shows a consistent pattern that R&D investment decisions by pharmaceutical firms are significantly and substantially affected by changes in profit incentives exogenous to individual firms. Specifically, increases in effective patent life, market size, and the public investment in upstream basic research provide important incentives for pharmaceutical innovation. By contrast, price regulation on pharmaceutical products discourages such innovation.

This analysis offers several implications for public policy. First, economic growth is the engine of stimulating pharmaceutical innovation. Economic growth not only leads

to an increase in ability to pay but also is associated with demographic change and population aging. Both factors increase the market size for drugs treating chronic diseases. As a result, global economic growth would boost global demand for pharmaceuticals, which in turn creates strong incentives for pharmaceutical firms to invest in drug discovery and development.

Second, health policy has important consequences for pharmaceutical innovation. On one hand, expansion of insurance coverage for prescription drugs and/or vaccines increases the market size of these products and hence creates incentives for innovation. In this case, innovation in pharmaceuticals is consistent with public goals in both economic and health sectors. On the other hand, no matter how attractive it is as a short-run fix to rising public expenditures on pharmaceuticals, price regulation on prescription drugs or vaccines reduces incentives for R&D investment. This creates a conflict in policy goals between the economic sector which aims to promote innovation and technical change and health sector which seeks contain health care cost.

Third, our conclusion that incentives matter implies that there is a market failure in allocating R&D resources for essential drugs in developing countries due to the lack of profit incentive there. The patent system fails to provide effective incentives to develop therapies for diseases concentrated in low-income countries. Several papers have focused on the design of alternative other incentive mechanisms to induce innovation for essential drugs and vaccines in developing countries. This paper has reviewed three proposals for alternatives to patents. Conceptually, these proposals substitute rewards for patents and provide a pull incentives to promote innovation. Specifically, the advance-purchase commitment uses the subsidy to close the gap between lower ability to pay and higher

R&D cost. The optional reward system close the gap between pursuing profit and pursuing health by paying the rewards to innovators on the basis of therapeutic effectiveness. The system of priority review voucher corrects the market failure by linking incentives for developing essential drugs in developing world with incentives for pursuing profit resulting from blockbuster drugs in the developed countries. However, these are theoretical concepts rather than implemented payment schemes that have been subject to empirical evaluation. Patents will continue to do the heavy lifting in promoting investment in R&D in the pharmaceutical sector for some time to come.

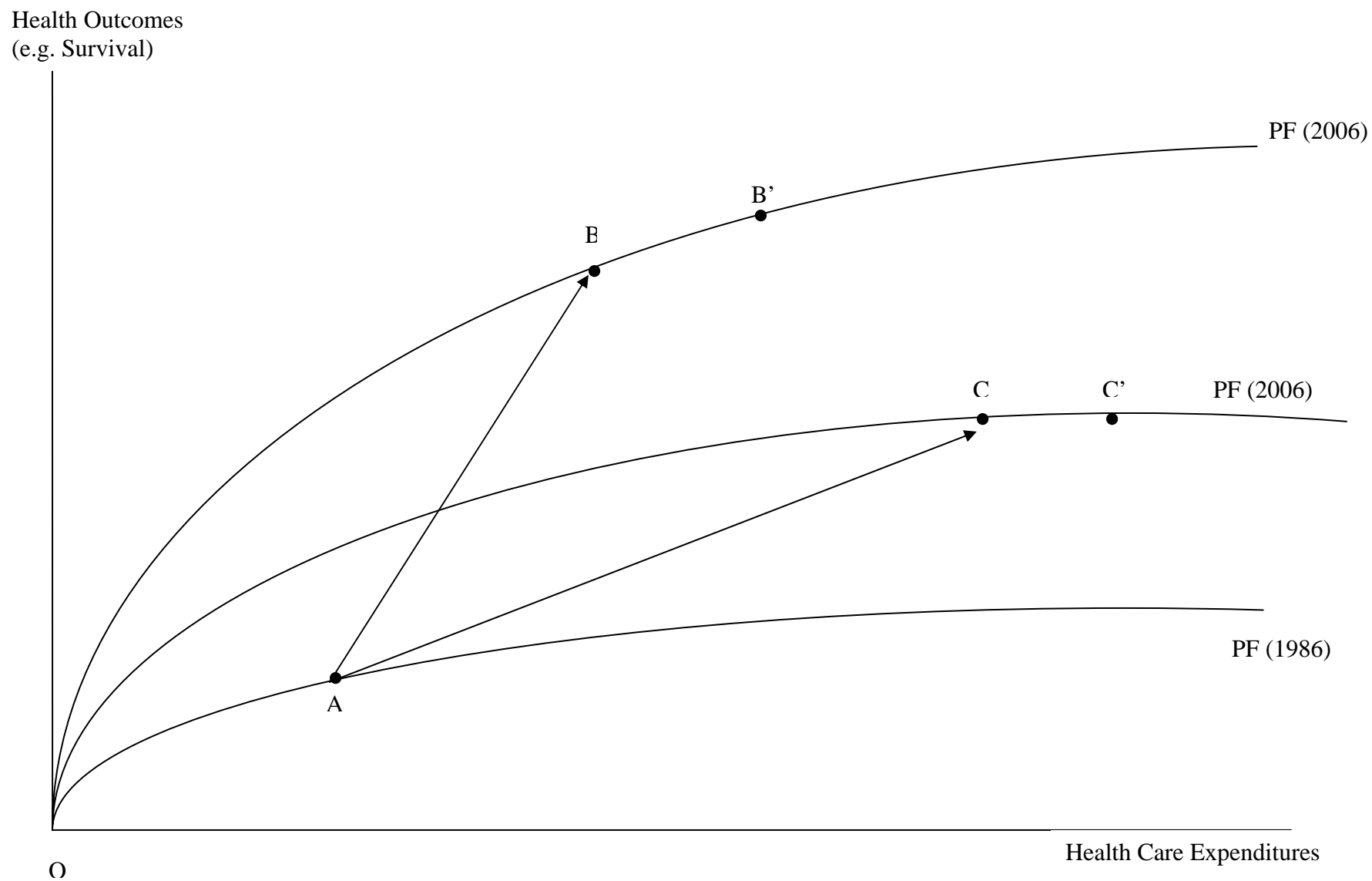


Figure 1. Health Production Function (PF) and Technological Change in Health Care

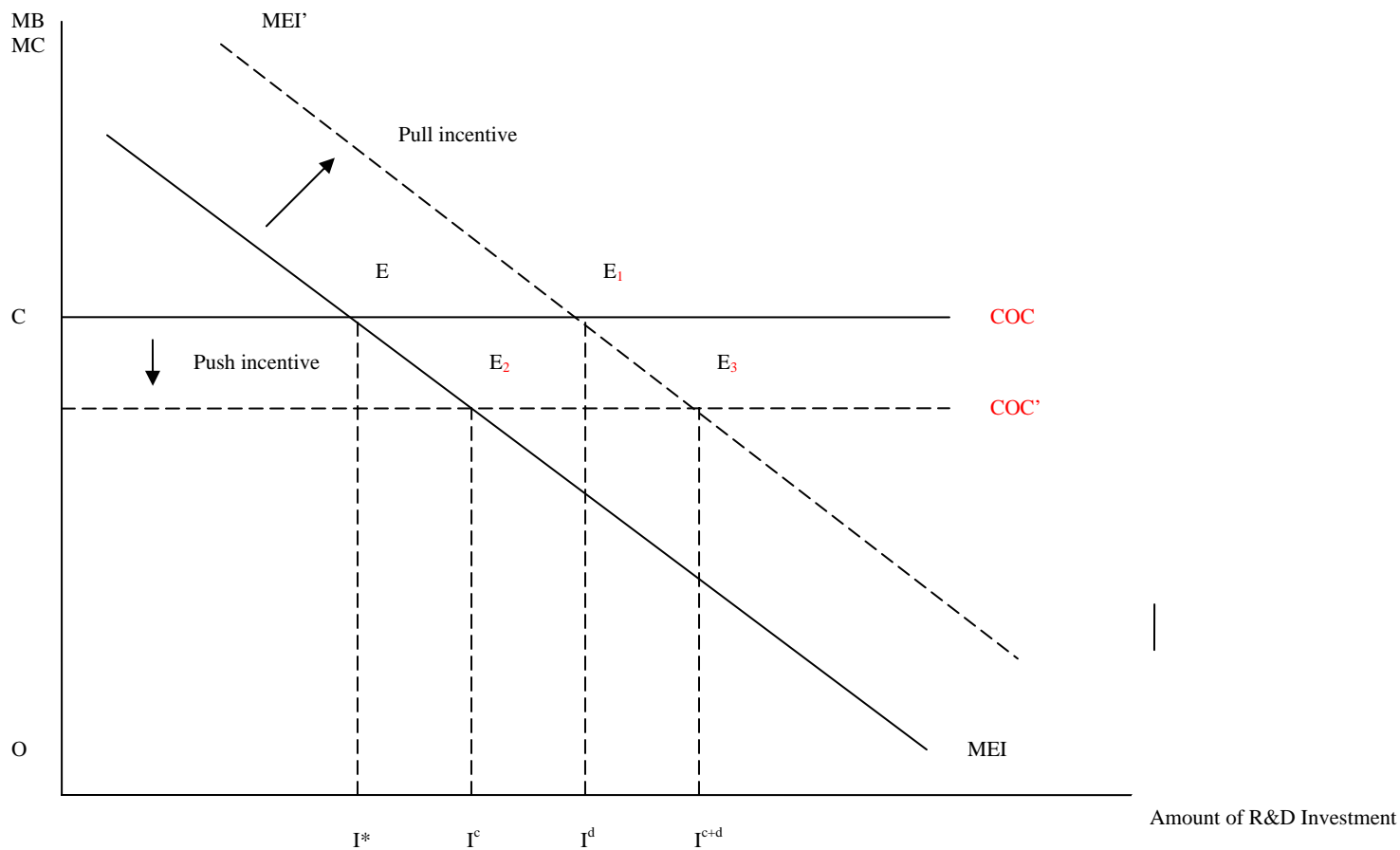


Figure 2. Optimal R&D Investment and Induced Innovation by Pull and Push Incentives

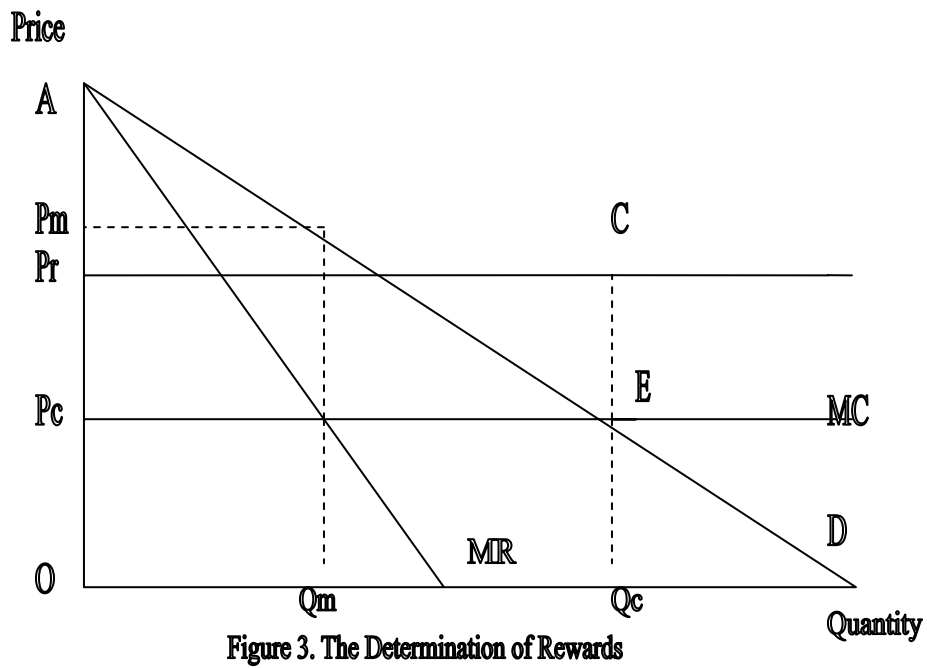


Figure 3. The Determination of Rewards

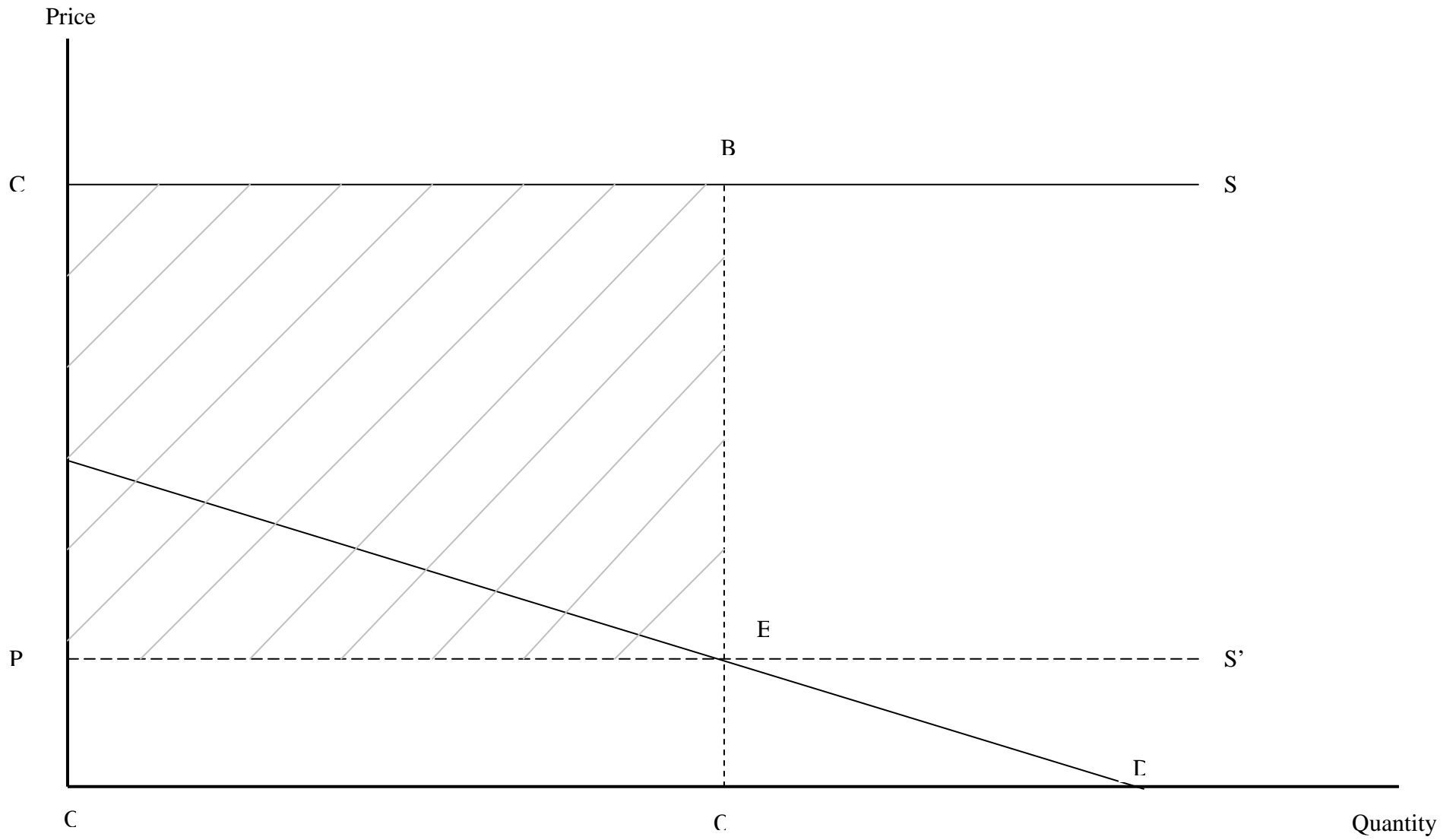


Figure 4. Innovation Incentive Created by Advanced Purchase Commitments

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