ONE

Introduction

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I. Context

The pharmaceutical industry serves a dual role in modern society. On one hand, it is a growing industry, and its output makes a direct contribution to gross domestic product (GDP). On the other, prescription drugs, this industry's major output, are an input in the production of good health. These products make an important contribution to the improvement of population health.

The purpose of this book is to investigate public policy issues in pharmaceutical innovation. In Section II we first describe the important characteristics of prescription drugs. We emphasize that these characteristics deviate from the standard conditions in a competitive market. In Section III we discuss the current performance of the pharmaceutical market. In Section IV we investigate market failures that persist in allocating research and development (R&D) resources and in the utilization of prescription drugs. In Section V we analyze the policy conflict between the economic and health sectors arising from pharmaceutical innovation. The final section discusses the structure of the book and the major content of the chapters.

II. Characteristics of Prescription Drugs

Prescription drugs have many complex characteristics, which, when taken together, have led to major controversies in public policy arenas, including pricing, patents, and incentives for research and development, as well as excess industry profits. Each characteristic is not unique to pharmaceuticals, but rather it is the characteristics, taken in combination, that make the industry unique.

Probabilistic Nature of Demand and Effectiveness

Prescription drugs are inputs in the production of good health. Individuals' demand for such drugs is not because they enjoy consuming them, but rather for their potential effects on their health. Thus, the demand for a drug is a derived demand stemming from the demand for good health. Since individuals face uncertainty in their health status, the demand for a drug is probabilistic, depending in large part on the person's health state. People take drugs as a treatment when they are acutely ill or have some chronic health problem, either to ameliorate the symptoms or to reduce the rate of progression of diseases. Not only is disease onset uncertain, but, as Arrow (1963) mentioned, the effectiveness of therapy is uncertain as well. For biological reasons, people differ in whether and the extent to which a drug produces the desired outcome as well as in adverse side effects of the drug. Also, although the efficacy (effectiveness in ideal use) is a condition for drug approval by government regulatory authorities, the environment in which randomized clinical trials are conducted to test for drug efficacy is often different from the environment in which the drug is actually used in the community. In practice, drugs are used for off-label indications and for populations other than those included in trials (e.g., racial or ethnic minorities, the elderly, and children).

Ideally people would be able to purchase insurance to protect against the possibility that a medical intervention is not successful. But as Arrow (1963) stressed, there is no market for insuring against such risk. Rather, health insurance covers the expense arising from the use of medical services. As a result, such organizational arrangements as nonprofit hospitals have arisen as imperfect substitutes for this missing market. The basic idea is that organizations not oriented toward the profit motive would be willing to devote the needed resources to care for patients, which profit-seeking organizations may not be prone to do. Arrow did not specifically mention prescription drugs, which, in any case, in 1963 were much less important than they are today. The pharmaceutical market is dominated by firms organized on a for-profit basis. This creates a potential conflict between pursuing profit and pursuing health and has led to some proposals for public production of pharmaceutical products, especially vaccines.

Financial Risk

The demand for prescription drugs is less predictable on an individual basis than is the demand for many other consumption goods, such as transportation and housing. Uncertainty in demand in turn creates a financial risk to individuals; spending on prescription drugs may be considerable, especially

for elderly persons and those with chronic diseases more generally. Unlike the missing market for insuring against the risk of an unsuccessful outcome of therapy, there is an insurance market to protect against financial loss arising from illness. Much spending on prescription drugs is covered by health insurance in high-income countries. Although insurance coverage for prescription drugs provides a social benefit in terms of risk protection, it also imposes a social cost from moral hazard that arises when drugs are covered. The socially optimal level of consumption is at the consumption level where the marginal social benefit equals the marginal social cost of such consumption. However, with complete insurance coverage, consumption may rise to levels far higher than this – to levels at which the marginal social benefit is far less than the marginal social cost.

The theory underlying the concept of a socially optimal level of consumption is static. That is, it does not account for the possibility that shifts in demand may increase rates of product innovation and hence future product demand as well. Widespread insurance coverage coupled with such secular changes as the aging of the population may induce firms to invest more in research and development than they otherwise would, and the resulting innovation may itself be a source of increased demand. In such a dynamic context, as a consequence of pharmaceutical innovation, many new drugs are introduced into the market each year, and individuals often opt for the newest drugs, especially when they have insurance coverage. The new drugs tend to be more expensive on average, leading to increased expenditures. The expenditure increases in turn have led to various forms of private and public cost containment, including price controls, drug formularies to restrict the drug choice set individuals face, and limits on total drug expenditures. Although cost-containment programs may reduce demand in the short run, in the longer run, they may also reduce the rate of product innovation.

Physicians as Agents for Patients

By definition, the notion that a prescription is required before a drug can be purchased means that physicians act as front-line professional agents, making consumption decisions on behalf of patients. The underlying rationale for requiring prescriptions is that patients possess insufficient information to know when specific drugs are appropriate for treatment. Conceptually and ideally, physicians would be perfect agents for their patients, prescribing in a way that patients would if they were fully informed about treatment appropriateness.

However, in the real world, except for professional ethics and guidelines, there is no effective institutional arrangement to deter physicians from acting

as imperfect agents. In many Asian countries, physicians both prescribe *and* dispense drugs. Thus, they are in a position to profit directly from the sale of prescription drugs, whether or not a well-informed patient would want to purchase such drugs. In Western countries by contrast, although the separation of prescribing and dispensing drugs has long been widely accepted by all parties, physician prescribing may be unduly influenced by pharmaceutical advertising and detailing as well as various inducements, such as free trips to attractive tourist spots where pharmaceutical companies provide opportunities for learning about their products as well as for various recreational activities. The existence of imperfect agents creates a potential conflict between pursuing health and pursuing profit: patients care about their health, but physicians may care about their financial well-being as well as their patients' physical and mental well-being.

Cost of Pharmaceutical Research and Development

Research and development for prescription drugs is a lengthy and costly process. Although there is no consensus about how to calculate the cost for research and development in the pharmaceutical market and on the actual size of the cost, there is a consensus that the mean R&D cost associated with introducing a new prescription drug is in the range of hundreds of millions of dollars (see DiMasi, Hansen, and Grabowski 2003; Light and Warburton 2005). The high cost is attributable in part to the strict criteria for drug approval set by government agencies (Grabowski, Vernon, and Thomas 1978; Cockburn and Henderson 2001). Governments in most countries require manufacturers to demonstrate both safety and efficacy before a drug can be approved for sale. Consequently, clinical trials for testing have become the most costly process in the development of a new drug.

If manufacturers sold drugs at the marginal cost of production and distribution, they would have no way to recoup the cost of R&D. To allow these firms to recoup such cost, in most countries, patents confer market power on new products, and monopoly profits provide the cash flow to cover and generate a return on investments in R&D. However, the patent system is a double-edged sword: it preserves the incentive for R&D on one hand, but on the other, it creates a barrier to entry in the pharmaceutical market. The barrier to entry results in higher prices and expenditures as well as lower levels of consumption of the new drugs than would prevail under competition. This has led some experts to suggest alternatives to the patent system, such as patent buyouts and advanced payment mechanisms that would preserve the incentive for product development, while at the same time eliminating or mitigating the negative effects of monopoly pricing under the patent system.

Deviations from the Competitive Norm

A basic tenet of economics is that competitive markets lead to efficient outcomes, that is, consumption at the level at which society's willingness to pay or, equivalently, the marginal benefit from consumption of the good, equals the marginal social cost of producing and distributing it. The market is indeed the best way to allocate resources if the market environment satisfies preconditions of competitive markets: (1) both buyers and sellers have full information, (2) the products in the market are homogeneous or heterogeneous but easily compared, and (3) entry into and exit from the market is free. Even dynamically, one expects under competition that investments in new products should be made up to the point at which expected rates of return equal the cost of capital. But the goal of equity is conceptually distinct from that of efficiency. A competitive market may not lead to an equitable outcome, and equity is an important consideration in health policy around the world.

The market for pharmaceutical products clearly deviates from these preconditions in important respects. Product heterogeneity is the least critical of these preconditions since competitive markets would require only that consumers be able to assess differences in value (or quality) between goods with different products. Inadequacy of information, however, is a major problem, not only for consumers of prescription drugs, but for physicians in their roles as prescribers as well. Furthermore, whatever its merits may be, the patent system precludes free entry.

In spite of these deviations, many countries rely on markets to allocate resources for prescription drugs. The market may not be an ideal solution, but this approach must be compared with the alternatives.

III. The Performance of Pharmaceutical Markets: The Four "Highs"

Critics of the pharmaceutical industry as it operates in major industrialized countries base their evaluations in large part on four "highs": (1) high R&D cost, (2) high marketing expenditures, (3) high prices, and (4) high profits.

That research and development for new drug is a lengthy and costly process is universally accepted. Pharmaceutical firms typically allocate a relatively larger share of their resources on R&D than do their counterparts in most other industries or relative to spending by the public sector. For example, R&D expenditures as a percentage of GDP ranged from 2% to 3% in major developed countries, such as the United States, Japan, Germany, and France, during 1988–2002 (National Science Council 2004). By contrast, pharmaceutical manufacturers of patented drugs consistently spent

over 10% of their sales revenue on R&D during the past two decades. Furthermore, the share of R&D expenditures as a percentage of sales revenue in this industry has increased over time. Taking the top 10 pharmaceutical firms in the United States as an example, the share of sales revenue spent on R&D increased from 11% in 1990 to 14% in 2000 (Kaiser Family Foundation 2001).

However, taking the high cost of R&D as a given, critics have noted that pharmaceutical firms spend an even larger share of their sales revenue on marketing. The largest U.S. pharmaceutical firms spent over one third of their annual sales on average on "marketing and administration" during 1990–2000 (Kaiser Family Foundation 2001).

Unlike other industries, until recently when direct-to-consumer advertising has emerged in the United States and in New Zealand, market efforts of pharmaceutical firms have not been aimed at consumers directly, but at physicians. The rationale is that the physician acts as a professional agent for the patient in the market for prescription drugs. Pharmaceutical manufacturers justify their expenditures on marketing to physicians on grounds that they are educating physicians about appropriate uses for the drug. The critics, while acknowledging such marketing efforts have some educational value, argue that marketing exerts an undue influence on physicians for the financial or other reasons already discussed. Many of the differences between products highlighted in marketing and advertising efforts are not to inform physicians but to increase demand for their products beyond levels of demand that would exist if physicians were perfect agents for their patients and to make demand for their products more price inelastic than they would be, absent marketing efforts. Greater price inelasticity confers market power on sellers, permitting them to charge a higher price. Similarly, there is controversy about whether direct-to-consumer advertising improves consumer welfare by leading to more appropriate use of pharmaceutical products, or whether it simply leads to excess use of the advertised products.

The third high is the high price of pharmaceuticals, which is particularly observed in countries in which there are no government-imposed restraints on pricing. In the United States in particular, there is no direct government intervention in pricing; but at the same time, the market for generic drugs is highly developed. Generics provide some limits on what some sellers of branded products can charge. The rationale for high prices is that they permit an adequate return on the high investments on R&D. However, whether or not the return is adequate or more than adequate is a highly controversial issue.

There are appreciable price gaps between branded and generic drugs in the U.S. pharmaceutical market, ranging from 40% to 83% (Caves, Whinston, and Hurwitz 1991). Since the incremental manufacturing costs for branded and generic drugs are almost identical, the price difference between these two types of drugs is largely attributable to the difference in price markup over marginal cost. Entry into the market for generic drugs is not completely free since generic manufacturers must demonstrate chemical equivalence and drug safety to public regulators; entry is relatively free. Thus, the market structure of generic firms resembles the competitive norm more closely.

Variation between countries in pricing and access to generics provide natural experiments to aiding our understanding about how countries' public stances toward the pharmaceutical sector affect market performance and consumer (patient) welfare. International comparisons of drug prices indicate that, on average, drug prices in the United States are higher than those in other developed countries with various forms of government regulation of pharmaceutical product prices (Danzon and Furukawa 2003). Whether or not this implies that prices in the United States are excessively high is a complex question; on the one hand, higher prices may lead to excess profits and returns that exceed the levels needed to elicit socially optimal levels of investments in research and development. Furthermore, high prices raise equity concerns, especially for less affluent persons, as do cross-subsidies by U.S. households of research and development that benefit users in other countries as well. On the other hand, profits and returns on R&D may not be excessive but rather represent the amounts required to generate socially optimal levels of R&D as well as employment opportunities in areas where the R&D takes place.

One measure used by economists to gauge profitability of a firm is the price-cost margin [(price-marginal cost)/price]. Scherer and Ross (1990) found that the price-cost margin in the pharmaceutical industry was 61.4%, compared to 30.5% on average for industries overall. In terms of price-cost margins, the pharmaceutical industry ranked sixth out of 459 manufacturing industries. Such evidence suggests that profits are high, but not necessarily that they are excessively high.

IV. The Performance of Pharmaceutical Markets: Market Failure in Pharmaceutical Markets?

Judging from the relatively larger share of R&D expenditures of total pharmaceutical firms' sales revenues, it would appear that the market mechanism functions fairly well in providing financial incentives for R&D. However, the

distribution of R&D expenditures across disease groups is uneven, which could indicate a market failure in the allocation of R&D resources from a global viewpoint. The search for prevention and cure of some diseases, such as for infectious diseases that are highly prevalent in low-income countries, seems to be conducted at a far lower level, at least relative to the need, than is the search for new methods for preventing and curing diseases more common in higher-income countries, for example, development of a vaccine against malaria versus new drugs for fighting depression (Kremer and Glennerster 2004; Berndt et al. 2005). Kremer and Glennerster (2004) indicated that new molecular entities for treating tropical diseases in humans accounted for less than 1% of all new molecular entities licensed worldwide during 1975–1997. However, given the widespread incidence of tropical diseases in low-income countries, the drugs developed for treating these diseases could potentially yield important impacts on health outcomes. Empirical research has shown that market size, which reflects both populations with particular diseases and willingness to pay for drugs among those affected, influences the rate of pharmaceutical innovation (Acemoglu and Linn 2004; Finkelstein 2004). Low income is a determinant of market size.

With the market mechanism, the driving force that allocates resources for R&D is pursuit of profit instead of pursuit of health. The decision rule for R&D investment is to maximize profit, not to maximize health gains. In defense of pharmaceutical firms, they have an obligation to their shareholders to maximize profit. Further, for many diseases concentrated in poor countries, income is so low that effective demand for disease prevention and therapy is correspondingly low. Without financial assistance from outside the poor countries, treatments for these diseases are at a financial disadvantage. There is indeed a market failure in allocating R&D resources according to health needs. This type of market failure can be remedied only by intervention from private foundations and/or governmental organizations.

A case in point about underinvestment in R&D applies to vaccines, which may have both preventive and therapeutic uses. One reason for underinvestment in vaccine research is that vaccines not only prevent disease for specific individuals who are vaccinated but also prevent the spread of disease to others. Individuals' willingness to pay for vaccines may not reflect the external benefit from being vaccinated. Vaccines for major communicable diseases may have much larger social benefits than many drugs. Compared to drugs, firms earn fewer profits in the vaccine market (Kremer and Snyder 2003). Thus, private firms have less incentive to discover and develop new vaccines because of the low profits, although their potential value to population health is very high. Again, intervention from private foundations

and governments is needed to deal with this type of market failure. Markets cannot accomplish desired social objectives on their own.

It has been alleged that much pharmaceutical innovation involves introduction of "me-too" drugs, which have therapeutic qualities similar to existing branded drugs. Although the patent system creates a legal barrier to entry in the pharmaceutical market, this barrier is not absolute. A patent is based on the molecular entity, not on a drug's therapeutic class. Thus, pharmaceutical firms can focus on developing new molecular entities that satisfy the regulatory authorities as being a new product. Randomized controlled trials are still needed for regulatory approval of a drug, and as already noted, trials are expensive. Current regulations do not require the new entrant to show that its drug is more effective than existing products (Angell 2004). According to the U.S. Food and Drug Administration (2005), 431 new molecular entities were approved by the U.S. government during 1990–2004. Of these, only 183 new molecular entities provided a substantial therapeutic advance as compared to existing products. Pharmaceutical firms devoted about 60% of their R&D resources to discovering and developing new molecular entities offering little therapeutic advantage over the existing products. The argument is that rather than focus research and development efforts on fundamental innovations, which could lead to major improvements in the public's health, firms are attracted to large existing markets, and R&D resources are misallocated as a result.

Although, in one sense, development of "me-too" drugs represents a misallocation of resources and hence a market failure, in another sense, a strong case can be made for them. For one, me-too products are common in virtually all markets. There is not just one midsize vehicle in the U.S. automobile market. In many ways, the midsize vehicles or the various laptop computers are all me-too's. Some people may prefer one of the me-two vehicles because they like the car's contours or its cup holders. Or they might prefer the durability of one brand of laptop computers if they are prone to dropping them. Similarly, drugs in the same therapeutic class may differ in certain ways, such as their side-effects profiles. Moreover, with multiple drugs in a therapeutic class, a private or public purchaser can bargain with sellers over price. A credible threat of excluding a drug from the purchaser's formulary gives it market power. Without me-too's, pharmaceuticals would have more market power under the patent system than they do currently.

Having good information is critical to making good choices in any market. Although the physician acts as an agent for the patient, the information possessed by the physician is often incomplete; clinical trials needed for

regulatory approval do not require head-to-head (pharmaceutical product-to-product) comparisons. Without being required to do so, private firms lack incentives to provide public information on the relative effectiveness of their drugs since public information is just like other public goods that everyone can access it once it becomes available. Private firms have incentives only to produce private information that increases sales of their products. Incomplete information provision in turn creates possible misallocations, including underuse or overuse of specific drugs (Angell 2004; Newhouse 2004).

V. The Dual Roles of the Pharmaceutical Industry

Societies are interested in prescription drugs and pharmaceutical innovation in large part because of the potential health benefits obtained from drugs. But particularly in light of increased global competition in many sectors, many countries are looking for sectors in which they have a comparative advantage. Pharmaceuticals and biotech are viewed favorably in many higher-income countries because they rely on highly educated workforces, and production may be less likely to be outsourced to countries in which prevailing wages are lower. This dual role greatly increases the complexity of public-sector policy making.

The Pharmaceutical Industry's Role in the Economic Sector: Industrial Policy

Innovation is an engine of economic growth (Romer 1990). Innovation allows more output to be produced with fewer resources (labor, capital, etc.): that is, it increases productivity. To pursue economic growth, some countries, the United States for example, rely on market mechanisms to encourage innovation, whereas other countries, Japan for example, use industrial policy to pick the winner. Although strategies for encouraging product innovation are different between countries, existing empirical evidence consistently indicates that technological innovation is the leading cause of economic growth in developed countries (Kim and Lau 1994).

Scientific advances, the major source of technological change, occur at different periods in different fields. Major advances in information science in the 1980s and early 1990s led to substantial innovation in information technology. In the early twenty-first century, major advances are occurring in genomics, and, consequently, technological change in biotech and pharmaceuticals appears to be increasing. Compared to the innovation