

Pharmaceutical Price Controls and Patient Welfare

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Price controls could have a substantial negative effect on pharmaceutical research and development. Extensive research is required before the development costs of a new drug or its benefits are known; most new drug development projects fail, sometimes after substantial financial and time costs. These conditions pose intractable practical problems for the operation of price controls, which cannot rest on objective, predictable standards such as the benefits or costs of individual drugs. In the absence of objective standards, pressure from health care providers and others would create powerful incentives for price regulators to decrease drug prices toward marginal costs of production and distribution, well below levels sufficient to reward innovative research. This downwardly biased price-setting mechanism would apply with particular force to the few successful projects that yield innovative drugs, whose

prices would not be set by regulatory authorities until after research expenditures have been incurred and the new drugs are ready to enter the market. Manufacturers will expect price controls to reduce the potential payoffs from breakthrough drugs. This expectation would substantially reduce the incentives to pursue innovative research, as is evident in advanced economies in which price controls are now in force. Once established, price controls for pharmaceuticals, like those for medical services in the Medicare system, would also tend toward complexity and entrenchment of vested interests and could easily become permanent regardless of the harm they cause to patients.

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To provide readers with a counterpoint to the editorial on prescription drug prices in this issue (pp 1068-1071), we invited the Pharmaceutical Research and Manufacturers of America to explain the industry's approach to drug pricing. They responded by commissioning the following Perspective.

Considerable attention has been given to the idea of controlling pharmaceutical prices in order to curtail increases in health costs (1, 2). The prospect of price controls—either imposed directly or implied through mandatory purchasing arrangements—raises many questions. Arguably the most important issue is whether controls would substantially impede pharmaceutical research and development. Before addressing this question, however, we should note that price increases have played a relatively small role in the rapid increase in health care expenditures on prescription drugs in recent years. While expenditures for outpatient prescription drugs have been increasing at a rate of about 15% annually (3, 4), roughly three fourths of these increases have been caused by increased use of drugs and switching to newer and more effective drugs. Price increases (which tend to be overstated [5]) have accounted for only about one fourth of the increases (3, 4, 6).

In this article, I set forth five points. First, pharmaceutical research incentives arise primarily from subjective estimates of future prices and profits for new drugs if the research turns out to be successful. Second, price controls cannot rest on objective, predictable standards

and in particular cannot be based on either the benefits or costs of individual drugs. Third, in the absence of objective standards, price regulators would face powerful incentives to reduce drug prices below levels sufficient to reward innovative research. Fourth, research firms would anticipate the effects of price controls and would therefore curtail innovative research because potential payoffs were reduced. Finally, once established, price controls for pharmaceuticals, like those for medical services in the Medicare system, would tend toward complexity and the entrenchment of vested interests and could therefore easily become permanent regardless of the harm they cause to patients.

THE ROLE OF PRICES IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT

The primary incentive for pharmaceutical research is the prospect of being able to charge prices that reflect the willingness of patients and health care providers to pay for new therapies (7). The importance of this incentive is clear from the course of innovative research. An example is the search for a treatment for severe sepsis, a condition that affects at least 500,000 patients annually and carries mortality rates typically ranging from 35% to 50% (8). For decades, many pharmaceutical firms explored drug treatments without success (8–10). Recently, however, an independent monitoring board called an early halt to a clinical trial of a recombinant human activated protein C created by Eli Lilly because

it reduced mortality from sepsis by approximately 20% (10, 11). Although the new drug will be unusually expensive to manufacture (perhaps hundreds of dollars per treatment), it is likely to be quite profitable. A prominent stock analyst predicted pricing in the range of \$2000 to \$7500 or more per episode (saving a life approximately in 1 of every 12 cases), although the size of the treatable population, severity of side effects, and speed of acceptance by health care practitioners remain highly uncertain (9). The most important point, however, is that much more research is needed to address the remaining 80% of mortality from sepsis. It would clearly be to society's advantage if pharmaceutical firms hoping for large financial rewards continue this challenging line of research.

One could easily cite many other examples of costly and persistent attempts to solve what have proven to be very difficult problems. Relevant therapeutic areas include oral insulin for control of glucose in diabetes (12, 13), nerve damage from diabetes (14), gene therapy (15–17), and oral thrombolytics (18).

These examples illustrate a general point. The pharmaceutical research enterprise resembles the construction of office building complexes “on speculation,” that is, with no assurance of buyers or tenants. In the case of pharmaceuticals, however, “construction” times are typically longer and the risk for failure much greater. Small-probability, high-payoff pharmaceutical research is motivated primarily by the possibility of someday obtaining large profits from the rare success. This is reflected in the fact that even the largest pharmaceutical firms derive the bulk of their revenues from one to three individual drugs (19).

This reasoning offers a perspective from which to assess historical data on the costs of drug development (working out to an average of about half a billion dollars per new drug that is approved by the U.S. Food and Drug Administration) (19, 20). These costs should not be seen as a series of investments followed by effective marketing. Rather, they were financial risks borne in the hope that society would be willing to pay for effective new treatments after research was completed. From these risk-taking activities emerged statins, cyclooxygenase-2 inhibitors, biotechnology thrombolytics, and many other innovations, along with numerous costly, now-forgotten failures. Financial calculations suggest that after accounting for risk and the role of research and development as an investment, pharmaceutical industry profits have not persistently exceeded competitive levels (21).

In addition, advances in research technology have accelerated the pace of competition in terms of both prices and multiple entry into new therapeutic categories (22, 23).

POSSIBLE FOUNDATIONS FOR PHARMACEUTICAL PRICE REGULATIONS

To assess the potential effects of price controls, we must consider how regulatory agencies would establish price ceilings for individual drugs. In principle, ceilings could be based on the benefits conferred by drugs, the costs of developing and distributing individual drugs, or some combination of the two. In practice, however, these approaches are infeasible.

Price ceilings cannot be based on the medical and economic benefits of individual drugs for the simple reason that those benefits are the primary determinant of the very prices that controls are designed to reduce. Of course, a regulatory agency could control prices anyway, on the assumption that health care payers overestimate the value of some drugs. In doing so, however, the agency would rely on the questionable assumption that price controllers are better judges of the value of drugs than are patients and their health care providers. Provision of better information rather than application of price controls would be a more appropriate remedy.

Cost-based controls raise equally fundamental difficulties. The essential problem is that development costs must be incurred before it is possible to know what benefits a drug will provide. It is well known that medical and economic benefits cannot be reliably determined until well after marketing commences, when it is possible to assess such factors as risk–benefit profiles, size of treatable populations, scope of application, ease of compliance, acceptance by the medical community and health care payers, frequency of and tolerance for interactions and impact on health care and employer costs, perceived value of convenience and of relief from pain and suffering, changes in medical practice, and competing new therapies (24).

The costs of developing a new drug are also impossible to predict. Unpleasant surprises can occur at any point, even late in phase III clinical trials, when a firm may learn that an entire line of research has failed to yield a single marketable drug (25). The drug development process involves a series of go-or-no-go decisions in which future costs are balanced against expected ben-

efits. Often, the result is the marketing of drugs that recover no more than the costs incurred in the final stages of development.

Hence, the costs of developing a specific drug and the ultimate benefits of that drug are not necessarily related. This raises severe practical problems in using costs as a basis for price ceilings. One is determining the relevant costs, given that research and administrative expenses are shared among numerous drugs and, sometimes, firms. An ironic difficulty is that most market prices would appear to be too low relative to costs rather than too high, because roughly two thirds of new drugs never yield sufficient profits to recover full development costs (19, 20). In addition, regulators would have to assess the degree of financial risk that was overcome in the drug development process. There appears to be no objective way to measure these subjective risks, as shown by the fact that some firms are willing to allocate large sums to projects that competitors deem totally unpromising. It would be particularly difficult to take into account research failures and bankruptcies that may have preceded the creation of a financially successful new drug.

No reliable way to surmount these difficulties has been devised. Some analysts, on the other hand, have proposed that price controls be supplemented or replaced by measures to restrict or penalize advertising and promotion, on the assumption that such expenses form an inherently wasteful component in drug prices (2). This idea has little economic foundation, however. It is well established that advertising makes markets more competitive (26, 27). Moreover, advertising is often socially beneficial. Compelling evidence indicates systematic underdiagnosis and undertreatment of depression, elevated serum cholesterol levels, obesity, hypertension, and other serious conditions (27–31). Advertising, including direct-to-consumer advertising, helps to overcome such information deficits, as recent pronouncements by the U.S. Food and Drug Administration and results of surveys have shown (27, 32–34).

HOW PRICE CONTROLS WOULD WORK

In the absence of an objective way to determine prices that would provide reasonable research incentives, regulators would have to apply vague notions of fairness and crude measures of value. Decisions would be dominated by political forces, including managed care

organizations, domestic versus foreign manufacturers, patient groups, insurance firms, employee benefit managers, labor unions, and other advocacy groups, many of whom would hope that pharmaceutical prices could be arranged so that other groups (or even citizens of other nations) could bear a disproportionate share of the research costs. These advocates, and the price regulators themselves, would know that drugs would continue to be available as long as price ceilings exceeded the costs of manufacturing and distribution, regardless of how much money had been spent on research and development or had been lost by firms that tried and failed to develop similar drugs. On the other hand, the beneficiaries of drugs still in development would be unaware of the stakes and thus unable to provide a countervailing force.

These circumstances would generate a powerful downward bias in regulated prices. This bias would apply with particular force to newer and more innovative drugs, which tend to make the greatest contribution to increases in expenditures (6). By consistently failing to reflect the value of innovative drugs, controlled prices would signal to manufacturers of future innovative therapies that they would not be able to charge prices that represent the contributions of their drugs. A common example of how price regulation falls into this pattern is the use of “reference prices,” wherein new or improved drugs are given the same price as older drugs in the same therapeutic class (35, 36).

THE POTENTIAL IMPACT OF PRICE CONTROLS ON RESEARCH AND DEVELOPMENT

Price controls would form an integral part of the incentive structure for future research. Consider the situation of the hundreds of pharmaceutical firms and start-ups now researching the myriad unsolved problems so elegantly outlined in the 25 February 2001 special issue of *JAMA*. These firms would allocate their research budgets with due regard for the fact that prices for the drugs they develop would be determined by a control agency facing intense pressure for low prices, and that the agency would set prices only after the drugs had been developed and tested and any costly failures had been abandoned. No one can predict what price the Health Care Financing Administration would permit for a breast cancer cure after the cure is ready for widespread use, but we can be certain that the agency would

wish to minimize the costs to the governments and managed care organizations that would have to pay for the drug. Firms undertaking the small-probability, high-payoff research that is essential to pharmaceutical advances would therefore have compelling reasons to doubt that they could obtain the financial returns necessary to recoup their costs for research and associated risk-bearing. Venture capitalists and other outside sources of research funding would have similar doubts.

Thus, price controls would have strong and adverse effects on pharmaceutical research. History provides concrete evidence of this. The health care plan advanced by the Clinton administration in 1993 included a provision to cap the prices of breakthrough drugs. During 1994 and 1995, while this plan was debated, annual increases in domestic pharmaceutical research budgets decreased to 4% before returning to normal levels of around 11% (27, 37). Also significant is the recent and rapid shift in the locus of pharmaceutical research and development toward the United States and away from the European Union, which was implementing ever stricter price controls. The U.S. share of the 50 best-selling drugs worldwide increased from 19 in 1988 to 33 in 1998, when the U.S. produced 8 of the 10 top-selling drugs (38, 39).

Also relevant is the gulf between research in therapeutic areas that offer substantial potential payoffs and those in which rewards are limited by price controls. A clear example is the contrast between more rapid progress on a large number of orphan drugs for relatively rare diseases in the United States and the slow progress on drugs for such massive problems as malaria (40, 41). A leading reason for this disparity is the strong likelihood that the nations with the largest markets for a malaria treatment or vaccine would erect implicit price controls by disregarding patent rights to a breakthrough drug (41–43).

OTHER PROBLEMS WITH PRICE CONTROLS

Disincentives for innovative research are not the only problem caused by price controls. Another is an irresistible tendency toward ever greater complexity and uncertainty. This is apparent in pharmaceutical price controls in other nations (35, 44) and in the workings of Medicare reimbursement system for medical services in the United States (45–47). The ultimate scope and complexity of controls simply cannot be predicted. How, for example, would regulators handle the question of con-

tinuing research on an existing drug? Pfizer is reported to have undertaken some \$400 million of clinical testing of atorvastatin (Lipitor) in the hopes of documenting efficacy for expanded uses (48). Would Pfizer have to petition for a price increase to pay for this additional risky research?

Price controls also create vested interests, which make it extremely difficult to dismantle controls even when their harms are apparent. Advanced nations with pervasive pharmaceutical price controls, such as Japan, have for decades denied innovative drugs to their citizens even as domestic pharmaceutical firms prosper by pursuing low-risk research on products of marginal value (49).

CONCLUSIONS

Pharmaceutical price controls offer short-term gains for a small proportion of patients at the cost of curtailing research that promises to bring far better therapies in the future. The notion that controls could provide reasonable incentives for future research has no foundation. There is no objective basis for price ceilings, largely because most research costs are borne long before the economic and medical benefits of a research stream can be known, a fact that poses intractable difficulties in such matters as taking reasonable account of the risks of research and development. Once a drug is on the market, regulators would face overwhelming incentives to cater to political forces by setting prices that are well below market levels but high enough to cover marginal production and distribution costs. Such a system would severely undermine incentives for future research; in addition, these prices would tend to become permanent.

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