For more than four decades, beginning with an investigation chaired by Senator Estes Kefauver in the 1950s, debate has raged over the economics of the pharmaceutical manufacturing industry. Critics point to monopolistic pricing and high profits; defenders emphasize the advances in medical therapy achieved by the industry. In this article, I will attempt to clarify components of the debate, although this discussion cannot resolve the uncertainties and value judgments required to achieve closure.

The bounds of the industry are indistinct. From statistics compiled by the industry’s principal trade association, “Big Pharma” companies reported U.S. prescription-drug sales in 2002 of $145 billion.\(^1\) Included in this figure are drug sales of companies that have successfully marketed new biopharmaceutical products. A higher estimate, $192 billion, comes from Intercontinental Marketing Services, a leading independent collector of industry data. The latter figure includes the sales of smaller companies, generic drug specialists, and some over-the-counter drugs.\(^2\) In 2000, prescription-drug outlays made up 9 to 10 percent of total U.S. health care expenditures.\(^3,4\)

**RESEARCH AND DEVELOPMENT, NEW PRODUCTS, AND PATENTING**

The pharmaceutical industry is the most research-intensive of U.S. industries that support their research and development with private funds (as distinguished from defense and space contractors). In 2002, Big Pharma companies devoted 18 percent of their sales revenue to research, development, and testing activities.\(^5\) The much lower percentages often reported in the press are misleading because they use companywide data, including the sales of less research-intensive activities such as pharmacy benefit-management services and the production of high-purity chemicals, cosmetics, prosthetics, over-the-counter drugs, vitamins, and so forth. Excluded from the 18 percent figure was roughly $10 billion of activity by start-up companies in biotechnology doing little else but research and development that had not yet yielded salable products.

From the industry’s research-and-development efforts has come a stream of new therapeutic products, most offering modest variations on existing therapies but some providing groundbreaking new approaches to the treatment of disease. From 1963 to 1999, the number of new chemical entities (or molecules) approved for marketing in the United States averaged 18.7 per year, with an upturn to 27 (plus 4 new biologic entities) per year during the 1990s and a downturn in number more recently.\(^6,7\)

Using advanced statistical techniques with available (but necessarily limited) data, Frank Lichtenberg found that the use of new drug therapies contributed appreciably to the extension of life spans and the reduction of hospital stays.\(^8\) Lichtenberg estimates that during the last two decades of the 20th century, drug innovations that were rated “priority” by the Food and Drug Administration (FDA) increased life expectancy in the United States by an average of 4.7 months.

Pharmaceutical companies customarily apply for patent protection on new chemical entities shortly before clinical tests in humans commence. The basic statutory patent life is 20 years, and by the time commercial marketing is allowed, approximately 12 to 13 years of basic product patent life remain, under regulatory conditions of the late 1990s.\(^9\) Drug patents provide particularly strong protection against competition from other companies because even a slightly different molecular variant must undergo the full panoply of clinical tests required by the FDA. Numerous cross-industry surveys have shown that managers of pharmaceutical research and development assign unusually great importance to patent protection as a means of recouping their investment in research, development, and testing.\(^10\) Striving to prolong the period of patent protection, pharmaceutical companies have obtained patents on minor variants in product
Differentiation can be physical, perceptual, or (most frequently) both. There is powerful evidence that the first successful product in some category — whether it is a drug, a breakfast cereal, or a detergent — implants an image of superiority in the minds of consumers and, for a drug, of the physicians who make decisions about prescriptions.\textsuperscript{13,14}

This images are built initially by innovations in technology or marketing and are reinforced by advertising and sales promotion.

The classic methods of sales promotion in pharmaceuticals were presentations made by “detail” people meeting face to face with physicians, plus advertising in professional journals. Since a permissive FDA ruling in 1997, direct-to-consumer advertising has grown rapidly. In 2001, U.S. pharmaceutical companies were reported to have spent $2.7 billion, or roughly 2 percent of domestic sales, on direct-to-consumer advertising, along with $5 billion on “detailing” efforts and $11 billion for the distribution (often by detailers) of free samples.\textsuperscript{5,2} The free-sample figure is based on the products’ retail value. The out-of-pocket production cost of samples could not have been much more than $2 billion to $3 billion.

In the most thorough study of the pricing of new drugs, which focused on drugs introduced from 1978 to 1987, Lu and Comanor found that molecules contributing important therapeutic gains, as evaluated by FDA staff, were priced at about 3.2 times the level of substitute products that were deemed to be inferior; those offering modest gains were priced, on average, at 2.17 times the level of substitute products; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15} Introductory prices tended to be 8 to 10 percent lower, on average, at 2.17 times the level of substitutes; and products providing little or no gain were at rough parity with existing substitutes.\textsuperscript{15}

In 1980, roughly 30 percent of prescription-drug purchases were paid for directly or indirectly by insurance plans; the remainder came from consumers’ pockets. By 2000, the insured fraction had
It is sometimes asserted that drug prices are high because research-and-development costs are high and must be defrayed. Assuming that companies maximize their profits or the contribution of profits to the repayment of past research-and-development costs, this is a fallacy. Sunk research-and-development costs are bygones and are therefore irrelevant in current pricing decisions. For rational profit maximizers, what matters is the position of the demand curve (including adjustments for expected competitive reactions) and the variable costs of production and distribution. To be sure, errors may be made under conditions of uncertainty, and prices may be held below the profit-maximizing level if adverse public reaction is feared. It would be equally wrong, however, to infer that drug prices are unrelated to the cost of research and development. The short-term monopoly profits that can be realized from patented and successfully differentiated drug sales are the lure, which prompts investments in research, development, and testing. Indeed, the linkage is surprisingly close: as drug prices rise or the difference between drug sales revenues and production costs increases, research-and-development outlays also tend to rise relative to their trend; as drug prices fall, so in tandem do research-and-development outlays. But the chain of causation runs from the expectation of high profits to increased research-and-development outlays. Similar logic holds for promotional outlays, which tend to be concentrated in the early phases of a drug product’s marketing cycle.

Year after year, the pharmaceutical industry has ranked at or near the top of *Fortune* magazine’s annual list of the most profitable American industries, which are rated in terms of accounting returns as a percentage of either stockholders’ equity or total assets. But here, too, there is an element of fallacy. Under standard accounting practice, outlays for research and development are written off in the year they occur. But, in fact, such expenditures are an investment, yielding fruit many years after they are incurred. They ought, in principle, to be included in the company’s assets and then depreciated over an appropriate time period. When they are not, the capital base to which profits are related in standard measures tends to be undervalued, and percentage returns on that capital base are overstated. A government study found that, when appropriate corrections were made, the true returns on investment by the pharmaceutical industry during the 1980s were only 2 to 3 percent higher, on average, than “normal” competitive rates of return, which were estimated to average roughly 10 percent (excluding the effects of inflation). This differential of 2 to 3 percent might have been attributable, at least in part, to technological risks not readily avoided through the portfolio strategies available to financial market investors. Whether the differential has remained within that range in recent years has not been tested by broadly accepted analyses.

### Methods of Restraining Pricing Power

Health care payers are understandably concerned about the potential for monopoly pricing and the high prices of pharmaceuticals. In virtually all industrialized nations, government agencies implement explicit price controls. These take several forms, including capping the prices of new drugs at the level of prior substitute therapies and sometimes of the lowest-price substitute; allowing prices that are no higher than those levied for the same product in other named “reference” nations; item-by-item price setting that takes into account, among other things, the degree of innovation of the drug and whether it is locally produced; imposing on individual physicians annual budgets for drug expenditures, which if exceeded lead to fee reductions; and (only in the United Kingdom) rate-of-return profit regulation akin to the system used for regulated public utilities in the United States.

The United States and Switzerland are considered to be the least aggressive among industrialized nations in imposing governmental price controls. Excluded from “controls” in this context are the competitive bidding procedures used by large governmental purchasers such as the Department of Defense and the Veterans Administration. The principal exception to a no-government-controls policy thus far in the United States has been for drugs reimbursed under Medicaid, which in 1999 covered $16.6 billion in prescription-drug purchases. Perhaps most important is the rule of “maximum allowable cost,” under which providers are reimbursed no more than the price of the lowest-price approved version of a drug, which, after pat-
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International Price Differentials

It is common knowledge that for many of the largest-selling, still-patented drugs, prices charged by Canadian pharmacies are often much lower than those charged by their counterparts in the United States. The reason is that in Canada, pervasive price controls limit a manufacturer’s prices to the

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median of prices charged in seven reference nations. What is little known is that the Canadian price-control scheme was accepted by multinational pharmaceutical companies in 1987 as preferable to Canada’s previous policy of licensing out at a 4 percent royalty rate the right to produce generic substitutes for drugs still covered by patents. Low, regulated prices in Canada encourage drug-purchasing trips to Canada by many U.S. citizens, as well as the emergence of electronic middlemen brokering mail shipments to U.S. patients from Canada and, most recently, decisions by purchasing organizations in some states to buy their drugs from Canada. The latter two developments have been opposed by the FDA, which has argued that “unapproved” drugs might be imported, and by U.S. drug manufacturers, which have attempted to ration the supply of drugs to re-exporting wholesalers and retailers at volumes just sufficient to satisfy Canadian demand. If the latter effort succeeds and re-exporting continues to grow, Canadian consumers will face shortages, with further repercussions and controversy.

The difference in pricing policies between Canada and the United States is only the tip of a very large iceberg. For the 60 percent of the world’s population living in nations with annual per capita incomes of less than $1,000, prices at U.S. or even Canadian levels would preclude most treatments for such containable diseases as AIDS and tuberculosis and for much else. World health authorities have encouraged multinational drug companies to sell their products in those nations at sharply discounted prices — often at less than a fifth of First World prices. This form of price discrimination can be shown by economic analysis to be a desirable solution to the problem of providing drugs to the poor while permitting some recoupment of research-and-development costs. However, this pricing approach poses two problems. First, as with Canada, the lower prices create incentives for the re-export of drugs to higher-price jurisdictions, possibly undermining the discriminatory system. Second, citizens in high-price nations may believe that they are being treated unfairly, or even that the prices they pay are elevated in order to subsidize low-price sales in the Third World. The subsidy inference is wrong as long as Third World sales are made at prices that cover incremental production and distribution costs. But the perception exists and is a source of discontent and possible political action. The solution must come from an educational effort to dispel the subsidy myths and from appeals to compassion on the part of citizens of rich nations.

To sum up, the complex economics of pharmaceutical research and development and pricing pose many policy dilemmas. There is a natural tendency for voters and their legislators to demand policies that repress prescription-drug prices. However, the more pervasive and tougher price controls are, the less stimulus there will be to develop new, more effective medicines. One might propose that rich nations enter a mutual accord to forgo price controls so that research and development will be stimulated and their financing more widely and fairly shared. But that is unlikely on political grounds.

Within the United States, political pressure to contain rising drug costs seems inevitable. Strengthening the efforts of HMOs and PBMs to counter-vail the pricing power of pharmaceutical makers, as encouraged in the 2003 Medicare bill, could help stem the tide. One prerequisite for success under the HMO or PBM approach is to eliminate rules requiring that the most favorable price negotiated by a private entity also be applicable to purchases directly reimbursed by federal and state agencies, notably under Medicaid. The ability of HMOs and PBMs to use their formulary choices as a bargaining tool could be enhanced with better information on the relative therapeutic efficacy of still-patented drugs. To this end, the FDA might insist that whenever possible, the best-accepted approved drug be used instead of inert placebos in double-blind phase 3 clinical trials. This would require a change in approval standards, letting new drugs pass muster even if they are not demonstrably better than existing therapies, as long as they are not significantly inferior.

If private cost-containment initiatives should fail, pressure for formal governmental price controls will increase. In that case, too, better and worse policy alternatives exist. Targeting the most profitable “blockbuster” drugs, as proposed in 1993 as part of the ill-fated Clinton health care reforms, could have an especially debilitating effect on research-and-development incentives. Less impairment of such incentives would be expected with a...
system such as that used in Great Britain, under which drug companies are allowed a generous profit rate of return on their assets, including capitalized research-and-development investments. Even that system, however, biases the results against smaller but innovative drug companies, which in the United States have made important contributions. Achieving the best trade-off between technological progress and the affordability of drugs remains a challenging goal.

Dr. Scherer reports having served as an expert witness on behalf of Apotex, Canada, in an action brought by Eli Lilly and on behalf of plaintiffs in a class-action suit against Abbott Laboratories. I am indebted to Judith Wagner for constructive comments above and beyond the call of duty.

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