

HEALTH POLICY REPORT

The Pharmaceutical Industry — Prices and Progress

F.M. Scherer, Ph.D.

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

formulation and production processes, and some have entered into agreements delaying entry of generic manufacturers challenging their patents. Several of these competition-impeding agreements were abandoned in recent years after antitrust complaints.¹¹

Only about 21 to 23 percent of the new chemical entities that are subjected to human testing emerge at the end of the process with marketing approval; the rest fail at various stages. A recent survey estimated that the cost of research, development, and evaluation of new chemical entities approved by the FDA, mostly during the 1990s, was \$802 million on average, with the costs of preclinical research and failed tests allocated to the “winners.”¹² However, this estimate must be regarded with caution. Only about half the estimated price tag entailed actual out-of-pocket costs; the remainder was an estimated 11 percent annual cost of financial capital invested in research and testing. Also, the voluntary sample from which the estimates were drawn numbered only 10 companies, including mainly Big Pharma members that placed a disproportionate emphasis on drugs for chronic diseases, which require extensive testing to identify long-term effects. Higher costs for testing may also have been incurred to differentiate a drug’s efficacy from that of rival products. There is reason to believe that drugs used to treat acute symptoms and those directed toward small “orphan” markets are developed at a much lower average cost. On the other hand, some costs are ignored — notably, those incurred for academic research that often identifies molecules likely to have therapeutic effects.

MONOPOLY PRICING POWER

Once a patented drug enters the market, its producer has some degree of monopoly power — that is, the ability to hold the product’s price appreciably above the current production cost without incurring dramatic losses in sales. This is a broader definition of monopoly power than the classic notion of a market in which there is only one seller. Few drugs lack any substitutes at all. What matters most is that the drugs are differentiated substantially from their substitutes; the seller can then make a trade-off between price and volume. Differentiation occurs because various chemical molecules targeted toward a particular disease have diverse therapeutic effects and contraindications. 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.^{13,14} These 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.^{1,2} 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 substitutes; and products providing little or no gain were at rough parity with existing substitutes.¹⁵ Introductory prices tended to be 8 to 10 percent lower, on average, for each additional competing substitute drug available at the time of the introduction of the product. Pricing strategies have changed perceptibly since the period studied by Lu and Comanor, but I am not aware of any similar follow-up study.

Insurance coverage for drugs reduces the sensitivity of consumers’ demand to price differences and enhances the ability of pharmaceutical companies to set their prices well above the cost of production and distribution, all else being equal. Insurance coverage of drug purchases in the United States increased dramatically during recent decades. 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

increased to 68 percent.¹⁶ Further increases are likely as the changes in the 2003 Medicare law take effect.

LINKING PRICE, PROFIT, AND RESEARCH

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.^{17,18} 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).^{19,20} 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.²¹ 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.²² 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.²³ 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-

ents have expired, is usually a low-price generic product. Also, pharmaceutical companies are required to extend on brand-name drugs reimbursed by Medicaid a rebate that is at least as great as the largest discount offered to purchasers in the private sector for the same drug, and in no case less than 15.1 percent of the announced wholesale price. At the state level, Medicaid reimbursement is sometimes denied case by case for the most expensive drugs that still have patent exclusivity.

Under Medicare, the regulatory scheme is more complex and rapidly changing. The 2003 Medicare act extended the federal insurance program so that in 2006 Medicare will begin covering most outpatient purchases of drugs by seniors, but the act precluded governmental “negotiation” with producers to secure lower prices. Medicare Part B already covers several hundred drugs, notably those administered in physicians’ offices and in clinics for hemodialysis and cancer chemotherapy. From 1992 to 1997, such drug purchases were mainly reimbursed at “average wholesale price” (AWP), which is, in effect, the wholesale list price announced by manufacturers and published in the so-called Red Book. Beginning in 1997, reimbursement rates were pegged at 95 percent of the AWP for single-source drugs (usually, those that still have patent protection) and, for multisource drugs, 95 percent of the lower of either the median AWP of all generic forms or the lowest AWP of brand-name products.²⁴ Since the prices at which private organizations actually purchased drugs tended to be well below the AWP (for reasons to be discussed shortly), the government frequently paid more than the best available price. In such cases, care providers were reimbursed more than they paid their drug suppliers, which in effect cross-subsidized other services and distorted choices toward the drugs with the largest gap between the AWP and the actual purchase cost. This tangle of regulatory problems was the subject of complex remedial changes in the 2003 Medicare act, which, among other things, reduced the rates of effective reimbursement and increased direct payments to providers for administering the drugs.

Powerful checks against the pricing power of pharmaceutical companies for drugs with feasible substitutes have emerged during the past three decades with changes in hospital purchasing practices and the growth of institutions such as health maintenance organizations (HMOs) and pharmacy-benefit managers (PBMs). The most important development has been the increasing substitution of

generic drugs for so-called “branded” drugs. Hospitals and HMOs establish substitution rules specifying the drugs of which generic versions are favored or required, and for outpatient purchases, the choice of low-cost alternatives is encouraged by graduated patient copayments — lowest for generic drugs, higher for favored branded drugs, and still higher for the most costly branded drugs. Pharmacies have incentives to substitute generic drugs when permitted because the dollar margins on generics (often negotiated with PBMs) tend to be higher, on average, than those for the original branded products. Such substitutions were encouraged by changes in previously restrictive state pharmacy laws.²⁵ After passage of the Hatch–Waxman Act of 1984, which substantially eased requirements for pre-entry clinical testing for producers of generic drugs, the use of generic drugs in the United States rose from an estimated 18 percent of prescriptions (by number) in 1980 to 47 percent in 2000.²⁶

HMOs, hospitals, and PBMs also use formularies to encourage pharmaceutical companies to offer substantial price discounts on drugs still under patent protection, asserting in negotiations, in essence, “If the discount you grant us is insufficient, you’re excluded from our formulary altogether. Or if we don’t exclude you, we will assign you an adverse position relative to alternative branded drugs in our prescriber guidelines.” A government study revealed that in 1991, the “best price” offered by a manufacturer to a private-sector customer implied a discount of 50 percent or more off the wholesale list price for 32 percent of all patented drugs.²⁷ Paradoxically, such discounting has been inhibited by the “most favored customer” rule under Medicaid. If a drug company offers an unusually large price concession to a hard-bargaining HMO or PBM, it must also extend that discount on its possibly large volume of Medicaid sales. As a result, the substantial discounts achieved before the rule’s enforcement began in 1991 subsequently dwindled to values in the neighborhood of the 15.1 percent discount mandated by Medicaid.^{27,28}

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.²⁹ The reason is that in Canada, pervasive price controls limit a manufacturer’s prices to the

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.^{30,31} 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.³² 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.^{33,34} 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.

CONCLUSIONS

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.³⁵

Within the United States, political pressure to contain rising drug costs seems inevitable. Strengthening the efforts of HMOs and PBMs to countervail 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.