Articles

Are Prescription Drug Prices High?

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The U.S. pharmaceutical industry has been criticized because its products are perceived to be too expensive, yet prescription medicines remain the least expensive form of therapy. At this time, we are experiencing a dramatic increase in the risks and costs of pharmaceutical research and development (R&D). An example may be seen in the R&D history of lovastatin. The U.S. pharmaceutical industry continues to lead the world in the discovery and development of important new medicines because it assumes greater financial risk and invests more of its sales dollar in R&D than virtually any other industry. Where such a risk is posed, there must continue to be the potential for profits. Pharmaceutical companies must set responsible prices, must keep price increases down, and must help improve access to important medicines.

IN THE PHARMACEUTICAL INDUSTRY, THE ODDS AGAINST SUCCESS, whether statistical or financial, are daunting. Most research projects fail. On average, according to a new study by investigators at Tufts University (*1*), it takes 12 years, from synthesis to regulatory clearance, to bring a prescription drug to market in America. The average cost, which includes discovery and development, for one prescription medicine is $231 million (*2*).

Despite these obstacles and the financial risks they entail, the American pharmaceutical industry remains the world leader in the discovery and development of important new medicines (*3*). However, there are two basic threats to that leadership position, as witnessed by the decline in U.S. industry share of the worldwide pharmaceutical market from 38% in 1985 to 33% in 1989 (*4*). The first threat is to American preeminence in basic biomedical research, as evidenced by the deterioration of our system of science education, the looming shortage of American scientists, and the fact that Japanese inventors are now often first to arrive at the U.S. patent office with basic research discoveries (*5*). The second threat is the possible regulation of pharmaceutical prices, which would reduce the potential for the profits necessary to support the research investments of pharmaceutical firms. Historically, in the United States, when a firm has invested and worked against the odds to discover, develop, and market a new medicine, the firm has been free to charge a price that would produce rewards for investors.

In recent years, however, pharmaceutical companies have come under mounting criticism for their prices. Although the pharmaceutical portion of the American health care dollar continues to shrink (*6*), increases in the total cost of health care have become a matter of concern to the public and to public policy-makers. In that context, the high visibility of medicines has made them a special focus of concern, especially because their price increases, which were negligible through much of the 1970s, usually exceeded the general rate of inflation in the 1980s (*7*). This article deals with the cost effectiveness of pharmaceuticals, their pricing, and their profitability, and the fact that, as pressures to contain prices are increasing, so too are the risks and costs associated with pharmaceutical R&D. It concludes with a look at how these factors might affect patient access to new medicines and the attendant industry responsibilities.

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Cost-Effectiveness of Pharmaceuticals

Pharmaceuticals are only a small component of our nation's health care cost, accounting for only 7% of total U.S. health care costs, compared with 12% in 1965 (*6*). Although the primary goal of pharmaceutical research is to save lives and ease suffering, it can also save health care dollars. In 1990 alone, for example, the projected cost of cardiovascular disease and stroke to the U.S. economy was $95 billion, including the costs of hospital days, disability days, and $33 billion in medical care expenditures, not to mention the countless potential years of life lost before the age of 65 (*8*); for acquired immunodeficiency syndrome (AIDS) including the loss of productivity, the estimated 1990 cost was $26 billion (*9*). In 1989, cancer cost the nation $100 billion (*10*), and Alzheimer's disease cost $80 billion (*11*). Even if each of the medicines that may eventually be found to prevent or treat these diseases became a tremendous commercial success and generated $1 billion a year in sales [only three medicines did that in 1989 (*12*)], patient costs for the medicines would be far less than the costs of the diseases.

Viral diseases of childhood provide a striking example of the cost-effectiveness of modern pharmaceuticals. In 1983, the nation's health bill for measles, mumps, and rubella vaccination programs came to $100 million. According to the U.S. Public Health Service, the cost of these diseases, in contrast to the cost of preventing them, would have been $1.4 billion (*13*).

Studies suggest that Medicaid expenditures for patients taking anti-ulcer medicines, the H2 antagonists cimetidine and ranitidine, may be 70% less than for ulcer patients who do not take an H2 antagonist. The reason is that patients not taking an H2 antagonist have a much higher incidence of hospitalization and surgery than patients who do (*14*). Other studies show that antibiotics save money by shortening hospital stays (*15*).

Benign enlargement of the prostate gland affects at least 50% of men over the age of 50 (*16*). Today, for those in the advanced stages of the condition, surgery is the only option and more than 400,000 prostate operations per year are performed in the United States, with a mortality rate of approximately 1% and a cost of nearly $3 billion (*17*). At Merck, after 15 years of development, a promising

new enzyme inhibitor to control this condition is awaiting marketing approval from the U.S. Food and Drug Administration (FDA). The drug is designed to inhibit the synthesis of a hormone, dihydrotestosterone, that is associated with prostate growth, thereby hopefully shrinking the enlarged prostate. Because regression of the enlarged prostate is maintained and data suggest that Proscar can halt the progression of the disease, a long-term study is planned to demonstrate reduction in the need for prostate surgery.

Pricing and Profitability

In terms of pricing I can speak only for Merck because it is the only company whose pricing procedures I am familiar with and because antitrust laws prohibit any intercompany pricing discussions or practices. One of the most difficult challenges faced in marketing a new prescription medicine is the question of how much to charge for it. What is its value to society? To the individual patient? If cost-effectiveness were the final arbiter of pricing decisions, most pharmaceutical prices could justifiably be much higher than they are. At Merck, it is important to establish prices for our products that will produce an appropriate return on our research investment and maximize patient access. If the price is too high and the patient cannot afford the medicine, we have not fulfilled our reason for existence.

The basic principle governing the free enterprise system is that free and unrestrained competition should force fair prices. The more segmented the industry, the truer that is, and the pharmaceutical industry, led by Merck with a 9.3% U.S. market share and a 4.9% worldwide share, is highly competitive.

Research and development costs are a major consideration in setting the price of a new medicine. In general, the more expensive the research project, the higher should be the price of the resultant medicine. But the costs of R&D for a particular medicine are difficult to determine. At Merck, for example, our 4500 people in research are working at any one time to develop scores of investigational compounds and to invent hundreds more. In less than 6 weeks they work 1 million hours. It is impossible for us to pull out the costs of the successful projects that contribute, directly or indirectly, to the discovery and development of the rare compound that eventually becomes a prescription medicine. It is also impossible for us to isolate costs for all of the individual projects that fail. What we do know is that, on an industry-wide basis, counting all of the investments in the failed and successful projects, it costs $231 million (*1, 2*), on average, to bring one new prescription medicine to market in the United States.

Prices of existing therapies and competitive products already on the market are another consideration in establishing the price of a new medicine. When we introduced the anti-ulcer medicine famotidine to the U.S. market in 1986, the average price charged to the patient for one 40-mg tablet, the usual daily dose, was $1.89, which was comparable to the average prices of $1.83 for cimetidine and $2 for ranitidine (*18*) for equivalent dosage strengths.

For medicines that the company believes are clearly superior to earlier products, we do charge more. Such was the case when, in 1987, we introduced lovastatin, which the FDA had placed on the fast track for regulatory approval. The $1.57 a day cost to the average patient represented a premium over the $1.19 a day average patient cost in 1987 for gemfibrozil (*18*), the most widely prescribed cholesterol-lowering agent at that time.

When pricing a new medicine, we also have to consider the number of years of patent protection remaining. In the United States the patents on most new products from other, nonregulated industries are only months old when they reach the market (*19*). In contrast, the average patent life of a prescription medicine when it reaches the U.S. market is significantly less than the original 17-year patent term mandated by Congress. Although the Drug Price Competition and Patent Term Restoration Act of 1984 enables the restoration of up to 5 years of patent term on a number of newly approved innovative drug products, this is only a partial restoration for the years of patent life lost during the development and regulatory approval of a new drug. In the best case, with patent term restoration, we can obtain a maximum of 14 years of patent protection from the time of regulatory approval. Through May 1990, the U. S. Patent and Trademark Office has granted 77 restorations of patents for human or animal drug products, resulting in an average of 10 years and 7 months of effective patent protection for these drug products (*20*).

We always set out to price our products at similar levels from country to country. But variations in government price controls, exchange rates, dates of new drug approval, health care financing practices, and other factors tend to result in different prices for different countries. Above all, the company assumes a responsibility to make its products available to people who need them. So in countries where we believe prices for innovative medicines are set unfairly low, we try to market our medicines at those prices while lobbying for a change in the government's pricing policy.

The U.S. pharmaceutical industry has introduced a large majority of the world's new prescription medicines. In fact, there are only three other nations that have contributed to drug R&D in a meaningful way: the United Kingdom, Switzerland, and Germany. These four countries have contributed 80% of all significant products introduced in the last five decades, with the United States alone being responsible for one-half (*3*). Japan is developing quickly and may join this group in the near future (*5*). All five countries encourage innovation and reward success through pricing policies that are liberal, at least in the establishment of initial prices.

The perception of high prices leads to a perception of excessive returns, but an examination of the industry's profitability brings about a more realistic perspective. Return on assets (ROA) is the measure of cash flow as a percentage of gross assets and is an accepted measure of profitability for most industries. The 1989 average ROA for eight leading U.S.-based health care companies was approximately 16% (*21*). This percentage was based on an accounting methodology that considers research to be an expense rather than an asset, and the methodology does not factor in the lengthy time period required for drug development. Consequently, the accounting model makes the ROA number for the pharmaceutical industry appear high when compared to ROAs for other industries.

In order to provide a more realistic picture of returns for research-intensive industries, an economic ROA model, based on one developed by Kenneth Clarkson at the University of Miami, may be used. In this model, gross assets include R&D expenditures, which are capitalized and amortized on the theory that a firm's R&D expenditures to develop new products are part of the firm's economic asset base. Cash flow is also adjusted to reflect the capitalization of R&D. The economic ROA model would lower the ROA results for any industry, but the effect would be greatest for the research-intensive ones. The average 1989 R&D expenditure, as a percentage of sales, for the eight leading health care companies was 9%, as compared with the average of 8% spent by computer companies, 5% by chemical companies, 1% by oil companies, and 2% by food companies (*22*). For 1989, the economic model gives an average ROA for the group of eight leading health care companies of approximately 11%, much lower than the 16% computed by the accounting model.

Increasing Risks and Costs of Pharmaceutical R&D

The odds against getting a compound to market have been cited, for some years now, as 10,000 to 1 (*23*). This means that for every 10,000 substances examined, 20 enter animal studies, and 10 enter clinical (human) trials—but only one gains U.S. FDA approval. Regardless of the statistical measurement of the odds, which is somewhat artificial and may not reflect more recent approaches to drug discovery, the overall difficulty of the tasks facing biomedical researchers has actually increased over recent years because of the complexity of the diseases that still plague us.

The latest estimate of the cost of bringing a new medicine to market, $231 million, is almost double the amount, adjusted for inflation, determined 9 years ago (*24*). The reasons for the sharp increase suggested by the authors of the study are that the new research technologies are expensive, and the diseases for which treatments are being sought are complex. Approximately one-half of the $231 million is the total cost for work on failed compounds plus all the R&D costs, from researchers' salaries to new laboratory equipment, for the one successful compound. The other half is the capitalized expenditures, or the so-called opportunity cost of having funds tied up during the 12-year period of development (*1, 2*).

Compounding the risk and financial cost of bringing a drug to market is the shorter product life cycle of new prescription medicines. Generic drugs gained easier, faster entry to the market with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984. But an even greater impact on the average market life of a breakthrough compound has come from the rapid introduction of so-called follow-up medicines, which are chemically different from the breakthrough compound but are based on the same mechanism of action. They are introduced after the breakthrough drug has been shown to be safe and effective and can compete with it before its patent expires.

Seven of ten marketed prescription medicines do not recoup the average cost of R&D. An analysis of total sales performance of 100 new chemical entity medicines introduced from 1970 to 1979 showed that the medicines barely recouped the total of the R&D investments (*25*). If the economic performance of the anti-ulcer drug Tagamet (cimetidine) is removed, the result for the entire portfolio is lower than the cost of R&D. A highly successful breakthrough product is necessary if a company is to keep pace with R&D investment and the cost of capital.

In 1975, the year I joined Merck, the chief executive officer was concerned that for some time the company had introduced few important new medicines in the United States, despite having spent approximately $500 million dollars on R&D in the previous 10 years. But he did not cut back. Instead, he increased the R&D budget. The company had been experiencing what industry analysts call a "dry spell," but the term can be misleading because it implies that research has been unproductive. In Merck's case, in 1975, the discovery work and much of the development work had been done for several important new medicines, and the chief executive was confident of their eventual marketing. The result of the company's persistence—the paradox of the high-risk pharmaceutical business is that the route to success is to invest more—was the introduction of a number of important new products for arthritis, hospital infections, glaucoma, and muscle spasms. Another so-called "dry spell" occurred for the company from 1979 to 1985 with few product introductions. This was followed by an unprecedented flow of new products, culminating in the introduction of lovastatin in 1987.

The total Merck R&D expenditure for the period 1969 to 1989 was about $5.7 billion. For the 20 years from 1969 to 1989, R&D expenditures grew at a compound annual rate of over 13%, and that growth rate has increased over recent years (Fig. 1). Our 1990 R&D expenditures were $854 million, up from $750 million in 1989. Some analysts, reflecting American businesses' myopic view of financial performance, reported that we were spending too much on R&D in 1990, and that this outlay might possibly hurt our short-term earnings. In 1991, we intend to spend $1 billion.

Discovery and Development of Lovastatin

By the time I joined Merck in 1975, company scientists had been studying cholesterol biosynthesis for more than 20 years. I decided we would devote large resources to the cholesterol project and use this as a test of my belief that recent breakthroughs in the sciences, especially biochemistry and enzymology, had made a rational research approach feasible. We would focus on enzyme inhibition as a major tool for the laboratories because so many of history's great drugs, from aspirin to penicillin, were eventually shown to be enzyme inhibitors. To head the cholesterol project I selected Alfred W. Alberts, who had worked with me in lipid biochemistry at the National Institutes of Health and Washington University. An abbreviated chronology of the road to lovastatin is presented below.

Early 1950s. Jesse Huff and associates at Merck began researching the biosynthesis of cholesterol, building on contributions made over many years by leading researchers such as Konrad Bloch and Feodor Lynen (*26*).

1956. Karl Folkers, Carl Hoffman, and others at Merck isolated mevalonic acid (*27*). Huff and associates then demonstrated that mevalonic acid could be converted into cholesterol (*28*).

1957. Not then aware of the significance of the discovery of mevalonic acid, Merck scientists continued through 1956 and into 1957 to look for resins that would bind to bile salts (derived from cholesterol in the liver) in the intestine. After having tested over 100 resins, they found that one (cholestyramine) reduced cholesterol from 10 to 15%. But the sand-like texture of the product made it unpalatable, and constipation was an unpleasant side effect.

1958 to 1959. 3-Hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, the enzyme that converts HMG-CoA into mevalonic acid, was shown by Feodor Lynen, Peter Overath, and Nancy Bucher at the Max Planck Institute to be a major rate-limiting step in cholesterol synthesis (*29*). Other investigators showed the reductase could be manipulated by diet or other environmental factors (*30*).

1960s. The fibrate compounds worked so well in rodents that many companies continued research programs on them throughout the decade. (It turned out that rodents were poor animal models for other cholesterol-lowering agents.)

1973. Michael S. Brown and Joseph S. Goldstein of the University of Texas Health Science Center discovered the importance of receptors for low-density lipoproteins (LDLs), particles circulating in the blood that carry most of the blood cholesterol (*31*).

Andrew Kandutsch and Harry Chen of the Jackson Laboratory in Bar Harbor (*32*) and Brown and Goldstein (*33*) reported that oxygenated sterols decreased the activity of HMG-CoA reductase in cultured cells. Merck and other companies pursued the lead, but this class of compounds proved unsuccessful. Sterols were effective in vitro but not in animal experiments.

1974. Merck scientists set up a cell culture assay in an attempt to identify substances that were potent specific inhibitors of the enzymes of cholesterol synthesis.

1976. In work that began at Washington University in 1974 and ended at Merck in 1975, Alberts, T. Y. Chang, others, and I showed that animal cells with a single enzyme defect lost the ability to make cholesterol and, as a result, lost their viability. When such cells were supplemented with cholesterol, they grew normally (*34*). In Japan,

Akira Endo and co-workers succeeded in isolating a compound, called compactin, and showed that it was a specific inhibitor of HMG-CoA reductase and that it functioned in vivo to block cholesterol synthesis and lower cholesterol levels in the blood (*35*).

Fall 1978. After spending 3 years developing systems to search effectively for HMG-CoA reductase inhibitors in an assay that measured the formation of mevalonic acid from HMG-CoA, Alberts and staff began screening microbial extracts. At the beginning of the second week of testing, Chen noted that no mevalonic acid had formed in one particular assay. Retesting of the sample confirmed its inhibitory activity (*36*). It is unusual to meet with such quick success; frequently, thousands of samples have to be tested.

December 1978. Alberts showed that the extract prepared from the organism blocked cholesterol synthesis in cultured cells (*36*).

February 1979. Hoffman, who helped discover mevalonic acid 22 years earlier, and associates isolated the pure inhibitor, lovastatin, from the fungal microorganism that was identified as *Aspergillus terreus* (*36*). Endo isolated monacolin K, a compound identical to lovastatin, from a different organism, and he filed for a Japanese patent, based on inhibitory activity alone, without providing structural data (*37*).

June 1979. Merck filed for a U.S. patent on lovastatin, complete with structural details.

August 1979. Merck scientists, after crystallizing lovastatin and implementing special isolation and fermentation techniques, undertook animal toxicology studies (*38*).

April 1980. Clinical trials began (*39*).

September 1980. I made the decision to discontinue clinical trials of lovastatin because of rumors (to this day never substantiated) that the closely related compound, compactin, caused certain cancers in dogs. Nothing we had seen with lovastatin had given us any cause for concern, but we could not ignore the rumors about a chemically related HMG-CoA reductase inhibitor. It appeared that the lovastatin project was dead.

November 1980. A patent was granted for lovastatin in the United States (*40*) and subsequently in a number of countries abroad. In other countries, patents went to Sankyo for monacolin K.

July 1982. Merck made lovastatin available, under an arrangement approved by the U.S. FDA, to several prominent clinicians, including Roger Illingworth of Oregon Health Sciences University and Scott Grundy and David Bilheimer of the University of Texas, who had asked for it to treat patients with severe hypercholesterolemia unresponsive to available agents. The drug showed dramatic activity in lowering LDL cholesterol and total cholesterol in the blood, with very few side effects (*41*).

August 1982. We reinstituted animal studies.

May 1984. We began long-term toxicology studies in dogs and large-scale clinical tests in patients at high risk of coronary disease. Clinical results were apparent within months. No agent had ever effected such dramatic drops in cholesterol levels. The drug was well tolerated, unlike some previous cholesterol-lowering agents (*38*).

October 1986. The results of our long-term toxicology studies in dogs were analyzed. The studies included extremely high doses. No tumors were noted (*38*).

14 November 1986. We sent our New Drug Application (NDA) to the U.S. FDA: 160 volumes of human, animal, and in vitro data.

31 August 1987. Lovastatin was given FDA approval for patients with high cholesterol levels that could not be reduced by diet. The drug was later approved for marketing in 42 additional countries.

The reports of dramatic medical results from lovastatin therapy had been coming to us since 1982. Total cholesterol levels of 300 mg/dl and above dropped to around 200, to the initial astonishment of the physicians conducting the trials. Patients with blood cholesterol levels of 450 mg/dl and above, who had undergone coronary bypass surgery, and in some cases cardiac transplants, had decreases, within weeks, of 30% or more in blood cholesterol (*42*). We believed we had produced a breakthrough medicine. Our NDA, which the FDA had approved in just 9 months, included data on more than 1200 patients, and the agency judged the drug to be safe and effective. But, to be sure that there were no side effects too rare to be picked up in clinical trials, we carefully monitored its use after marketing approval because that is the ultimate test of any new medicine—its use by many patients in uncontrolled settings. Extensive scientific studies further defined safety and efficacy.

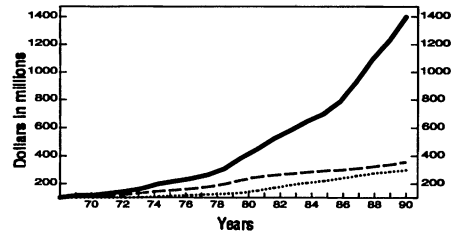

Fig. 1. The price index of Merck medicines (dotted line), the CPI (dashed line), and Merck's spending on R&D (solid line)—each one starting at an index level of 100 in 1969.

Improving Patient Access to Medicines

The history of the discovery and development of lovastatin illustrates well the interdependence of basic and applied pharmaceutical research, as well as how long, tortuous, and risky the pharmaceutical discovery and development process can be. Only the potential for significant reward would assure continued investor support for such high-risk investment. Innovative pharmaceutical companies are in business to make money, as well as to market new medicines, and, unless they do both, they would be out of business, and the flow of new medicines would be reduced.

At the same time, a pharmaceutical company should recognize the importance of exercising price restraint. Figure 1 compares the price index of Merck medicines, the Consumer Price Index (CPI), and Merck's spending on R&D. Between 1969 and 1973, while inflation pushed consumer prices up substantially, Merck had virtually no price increases. During the rest of the 1970s, Merck did raise prices periodically, but still at rates much lower than inflation.

During the 1980s, in order to narrow the gap between the CPI and the Merck price index and thus recover some portion of what we had lost to inflation, we increased prices faster than the rate of inflation during the decade. Over the full 20 years, however, the CPI rose from 100 to 336 (*43*) while Merck's price index increased significantly less, reaching 287 in 1989. Meanwhile, the company's spending for research and development over the 20-year span rose much more rapidly, up from an index of 100 in 1969 to more than 1200 in 1989. In both 1989 and 1990, our price increases amounted to 4.7%, lower than the rate of inflation for each year and also well below the pharmaceutical industry average. Merck's price increases on individual product lines ranged from 0 to 5%.

Last year, Merck announced a goal of keeping future price increases within the rate of inflation in the United States and of generally limiting price actions to one per year, given stable market conditions and government policies that are supportive of innovation. Responsible pricing and distribution practices can help ensure that patients can obtain the medicines they need. The special nature of its products demands that the pharmaceutical industry, more than perhaps any other, be responsive to social needs.

Merck also announced last year the Equal Access to Medicines Program aimed at overcoming the current lack of availability of some important medicines to poor people under Medicaid. In return for a discount that reflects a pharmaceutical manufacturer's lowest

U.S. prices, states would include more open access to medicines, particularly new medicines, under their Medicaid plans. A majority of states quickly accepted the Merck program. In October 1990, Congress enacted legislation that substantially incorporated the policies embodied in the Equal Access to Medicines Program. The legislation will facilitate price discounts for the state and federal Medicaid programs and mandate that all 50 states provide more open access to medicines.

Special efforts must be made to get important medicines to the poor in developing countries. In 1987, Merck announced that we would donate our breakthrough medicine ivermectin, for the control of river blindness (onchocerciasis), wherever it is needed for as long as it is needed. In most cases, a single yearly treatment with ivermectin would prevent the ravages of onchocerciasis, a centuries-old parasitic disease that now affects an estimated 18 million people—primarily in West and Central Africa but also in Central and South America—and threatens 85 million more. This effective and well-tolerated drug has been called one of the most important breakthroughs in tropical medicine in this century (*44*).

Merck did not set out originally to give the product away; however, most of the people who need it are poor and live in remote places. After months of discussions with international aid organizations that were prospective buyers, we realized that the process of obtaining funding for purchases of ivermectin would take too long. Meanwhile, people were suffering and sometimes going blind.

More than a million people are covered by ivermectin treatment programs to date. But the medicine must somehow reach millions more. If we can reach a sufficient number of people, the disease can be controlled as a major public health problem. In theory, river blindness could even be eradicated, provided it were possible to have every person harboring the parasite take ivermectin annually for at least 10 years. Merck is committed to trying.

When Merck management was debating whether to donate ivermectin for the control of river blindness, we considered many factors, including the loss of potential revenues, the major marketing challenge involved in getting the medicine to people in remote areas of the world, and the question of what impact the donation would have on research for tropical diseases. Would the donation be a disincentive to other firms? Since making the donation decision, we have heard no criticism.

The innovation-based pharmaceutical industry is committed to improving the quality of health care through pharmaceutical research. That commitment must extend to keeping prescription drug prices at reasonable levels, for good new therapies are useless if patients cannot access them. If a pharmaceutical company can meet these demands of the market—innovation and reasonable pricing—profits will follow.

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