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The Pharmaceutical Industry: Challenges in the New Century

The golden age of medicine was traditionally looked at as the 1940s, 1950s, the development of antibiotics. Based on what we now know about the human genome, more careful targeting of discovery efforts, you haven't seen anything yet. The golden age of medicine clearly lies ahead of us.

—Henry McKinnell, Chairman and CEO, Pfizer¹

Early in the 21st century, the pharmaceutical industry, and especially its largest competitors, faced uncertain times. Many of the most pressing issues—patent expirations, price pressures, drug development challenges, regulatory issues, and political pressures—had existed for a decade or longer, but their growing intensity threatened to force industry players to discover new approaches to address them. Perhaps the most significant challenges were rapid scientific advances and the introduction of fundamentally new technologies that combined were changing the way drugs were discovered, developed, and tested. These advances had allowed smaller, specialized competitors to enter the industry and compete in new ways, and these competitors were making a significant and growing number of the new drug discoveries coming out of industry laboratories. The scientific and technical advances, along with the new competition, were forcing the large competitors that had dominated the industry for a century to rethink how they discovered, developed, manufactured, tested, marketed, and distributed their products, and also how they sought regulatory approvals and partnered with outside organizations. In 2004, it was clear that the industry must change. What was uncertain was change to what, and how quickly.

Industry Overview

Traditionally, the global pharmaceutical industry was characterized by rapid growth, high profits, and structural stability, even while showing dramatic innovation. Global sales reached \$466 billion in 2003, up from \$317 billion in 2000, while North American sales reached \$230 billion, up from \$153 billion over the same period.² The U.S market had been the fastest growing market and was expected to remain the fastest growing market “for the foreseeable future.”³ (See **Exhibit 1** for sales by region and **Exhibit 2** for sales by leading countries.) In the 1990s, the industry had been one of the most profitable in the world. For both 2000 and 2001, pretax margins at the top 10 global pharmaceutical companies ranged from 16% to 35% and averaged just over 26%.⁴

Professor Stephen P. Bradley and James Weber, Senior Researcher, Global Research Group, prepared this case. This case was developed from published sources. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management. Material for this case was drawn partly from Perry L. Fagan and Robert H. Hayes, “The Pharma Giants: Ready for the 21st Century?” HBS No. 698-070 (Boston: Harvard Business School Publishing, 1998).

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One recent disappointment, however, was stock price. Between the beginning of 1995 and the end of 2000, the S&P pharmaceutical index was up nearly fivefold while the broader S&P 500 index was up only threefold. From 2001 to 2003, both indexes fell; however, the pharmaceutical index lost slightly more than the broader market. (See **Exhibits 3a** and **3b** for the stock performance of the industry versus that of the broader market.)

The industry had exhibited structural stability in that most of the leading players had existed for nearly 100 years and some even longer. Despite the large size of the leading players, the industry remained highly fragmented, with hundreds of pharmaceutical companies competing in more than 20 different therapeutic categories. The industry's top 10 companies accounted for less than 50% of global sales. Nevertheless, a few giants, including Pfizer, GlaxoSmithKline, and Merck, had dominated their respective therapeutic categories for over half a century and typically had not competed on price for leadership of individual categories. (See **Exhibit 4** for sales and other data for the largest pharmaceutical companies.)

Outside Pressures

Several trends that had emerged in the 1990s to put downward pressures on drug prices continued to intensify. These trends combined to form one of the biggest challenges facing the industry in the decade to come—sales and profit growth, historically well over 10%, were expected to decline to the single-digit range.

In 2001, U.S. prescription drug sales increased 16.9% over 2000. This increase consisted of three components: 4.9% resulted from increased prices on existing products, 8.7% was from higher volume and the shift from less expensive to more expensive drugs, and 3.3% was from new drugs.⁵ (See **Exhibit 5** for the sales increase components for 1993–2000.) Further, drug purchases in the U.S. accounted for ten cents of every dollar spent on health care in 2001. (See **Exhibit 6** for a breakdown on U.S. health-care expenditures.)

Price Pressures from Managed Care

In the United States, the growth of managed care organizations (MCOs) pressured drug makers to reduce drug prices. Membership in MCOs in the United States increased from 5% of the insured population in 1980 to over 90% in 2001. (See **Exhibit 7** for a breakdown on health plan coverage by type over time.) Similarly, while very few drugs were purchased by U.S. insurers in the 1960s, by the mid-1990s, U.S. MCOs made 75% of all drug purchases.⁶ MCOs used their increased buying power to extract price concessions from drug manufacturers. MCOs also used formularies, or lists of approved medicines, to control costs. Many MCO plans paid only for drugs that appeared on their formulary. This gave them increased buying power and also allowed them to cut costs by using lower-priced drugs in place of higher-priced drugs. Increasingly, plans were instituting tiered formularies where generics and lower-cost branded drugs carried lower patient co-payments than branded drugs.

Competition from Generics

Pharmaceutical manufacturers were also under attack from generic substitutes for their flagship patented drugs. Generic drugs were priced typically at a 30% to 90% discount to the price at which brand-name drugs sold prior to patent expiration. Generics' share of the U.S. prescription drug market rose from 19% in 1984 to 47% in 2000 and it was estimated that this share would increase to

57% by 2005.⁷ This increase was driven largely by cost-containment efforts by MCOs, which routinely substituted generic products for patented drugs when possible.

The growth of generics had been fueled by the 1984 Waxman-Hatch Act, which reduced the barriers to generic entry by accelerating the approval process for the drugs. Instead of forcing generic drug makers to conduct their own lengthy and costly clinical trials, Waxman-Hatch mandated they show only that their drugs were chemically and biologically equivalent to the original patented versions. Whereas before Waxman-Hatch generic entry had taken years, after Waxman-Hatch generic substitutes began appearing in the market immediately after branded drugs lost patent protection, giving drug makers less time to recoup their research and development (R&D) costs. In 2002, the industry faced the expiration of patents on many blockbuster drugs. Between 2002 and 2006, approximately 40 drugs representing \$40 billion in 2001 sales would lose patent protection.⁸

There was some evidence that the shift from branded drugs to generics was happening even more quickly. Prior to 2002, analysts typically estimated a branded drug would lose 80% of its volume to generics within one year of patent expiration. In August 2001, Eli Lilly's antidepressant drug Prozac (\$2 billion in 2001 sales) went off patent and lost 70% of its volume in 45 days.⁹ Generic producers had an incentive to act quickly because the first producer to hit the market was granted a six-month period of exclusivity from other generic competition. Further, some generic companies were challenging the validity of the patents on certain drugs and seeking to introduce generic versions only a few years after the branded product was first marketed.

To help offset these losses and/or delay the introduction of generics, big-pharma companies began taking a number of steps. (The large, old pharmaceutical companies were often referred to as "big pharma," while the smaller, newer competitors were typically referred to as "biotechs.") These steps included obtaining patents on component chemicals, manufacturing methods, and product extensions/formula modifications; improving drug-delivery methods; converting drugs to over-the-counter status; and finally, turning to the courts to fight patent infringement in a process that could extend the period of branded exclusivity for 30 months.

Political Pressures

U.S. Drug Companies . . . spent almost two-and-one-half times as much on marketing, advertising, and administration as they spent on research and development in 2001, according to an analysis released today. The report debunks President Bush's recent assertion, and drug companies' claims, that high and fast-rising drug prices are needed to support R&D.

—Families USA¹⁰

The pharmaceutical industry faced political and social pressures related to drug costs and access. In 1992, U.S. President Bill Clinton and many in Congress were highly critical of pharmaceutical companies for their high profit margins and their alleged contribution to runaway U.S. health-care costs. Clinton initiated a review of the entire U.S. health-care system, which, although not implemented, recommended a new system of federal controls on health care, including price controls on prescription drugs. While the threat of a broad government takeover of the U.S. health-care system had largely disappeared by 2003, the possibility of more limited interventions, some focused on pharmaceutical products, remained.

Medicare During 2002 and 2003, the U.S. Congress debated providing some form of insurance coverage for prescription drugs for senior citizens through the Medicare program. Most members of the Republican Party, and the drug industry, favored a private insurance system whereby the government subsidized those who could not afford drugs. Supporters of this plan believed that it

would maintain existing pricing systems, which would enable pharmaceutical companies to develop new drugs. The Democratic Party proposed that the government purchase drugs and provide them to all senior citizens as part of the Medicare program. Pharmaceutical companies were concerned that if the government became the largest buyer of its products, it would have enough leverage to obtain price cuts approaching 40% and reduce the industry's ability to develop new drugs.¹¹ Prescription drug coverage had been a topic of debate at the federal level for years, however, and the lack of progress on the issue had led more than half of the 50 states to enact their own programs to cover Medicare beneficiaries.¹²

In December 2003, President George Bush signed into law the Medicare Prescription Drug Improvement and Modernization Act. Among its key provisions, the new law would create Medicare approved drug discount cards beginning in May 2004 that would enable participants to save between 10% and 25% on some prescription drugs. Participants with incomes below \$12,567 (single) or \$16,862 (married) could receive a \$600 per year credit. The discount cards were a temporary measure that expired in 2006. Beginning in 2006, Medicare participants could choose to participate in privately run drug coverage plans. Participants would pay a monthly premium of \$35 and the first \$250 in yearly drug costs. Beyond \$250, participants paid 25% of the drug costs up to \$2,250, 100% of drug costs between \$2,250 and \$3,600, and 5% of remaining drug costs.¹³

While the new Medicare law created significant new prescription drug benefits, it was also highly controversial. Critics contended that seniors could still spend large portions of their income on drugs, and that the law benefited drug companies more than Medicare recipients. One example of this was a provision in the Act that prevented the U.S. government from directly negotiating with drug companies on the cost of drugs provided through the program whereas the government regularly negotiated with suppliers of other products and services it purchased. Under the new law, such negotiations would be left to private insurers. Both supporters and opponents of the law complained they were misled regarding its full cost. In the months before he signed the law, the President proclaimed it would cost \$400 billion over ten years, however, members of his administration were privately estimating costs between \$500 billion and \$600 billion.¹⁴ Costs for the second ten years could reach \$2 trillion.¹⁵ One study estimated that \$139 billion of the \$400 billion would accrue to drug manufacturers in the form of higher profits from increased sales. Other studies also point to gains for drug makers, but at significantly smaller levels.¹⁶ The Act, and possible changes to it, were expected to be a significant issue in the 2004 presidential election.

International Differences

Cost containment was the "name of the game" among health-care payers worldwide. Unlike the U.S., most countries had government-controlled health-care systems, which typically meant governments were the major buyers of pharmaceutical products. This gave these countries leverage to gain price reductions not available in the U.S. The strength of the government-controlled systems made some countries less attractive markets for pharmaceutical companies. The pharmaceutical markets in Spain and Australia, for example, were expected to grow at over 10% annually through 2006; however, cost-containment efforts, which had led to price declines of 2% annually, were expected to continue to cause price deflation.¹⁷ European countries tended to purchase more generic drugs and older, lower-cost drugs, rather than relying on the latest discoveries. This led Europe, a market with approximately similar demographics to the U.S., to see its value share of global pharmaceutical purchases fall from 32% in 1990 to 22% in 2002.¹⁸ Japan and other major Asian markets also saw intensifying government effort to control prices.

Parallel trade - the reselling of drugs across borders - was a growing market factor. Largely illegal in the U.S., cross-border trading accounted for approximately \$12 billion (10%) of European

pharmaceutical sales. European governments encouraged the practice within Europe, but it was illegal to bring drugs into Europe from abroad without proper licensing. Manufacturers tried to segment pricing by market and took steps to make parallel trade difficult. Meanwhile, legal pharmaceutical arbitrage companies sought profit by purchasing drugs in low cost countries, re-labeling and repackaging them into the language of the destination country, and selling them in higher cost countries. The wholesale price of a daily dose of Prozac, for example, was \$0.64 in Spain, \$1.40 in Germany, and \$1.83 in Britain. Similarly, arbitrage companies could purchase Nasonex for \$3 less per bottle in France than in Britain.¹⁹

Free Rider Concerns Because drug prices in the U.S. generally were the most expensive in the world, there was a sense that U.S. consumers paid the high cost of drug development to the benefit of consumers worldwide. Europe, for example, paid 25% to 35% less for the same drugs, and 60% less per capita overall, than did U.S. consumers.²⁰ At the World Economic Forum in Davos in 2004, the commissioner of the U.S. Food and Drug Administration (FDA) referred to Europe free riding on U.S. funded research and noted that while the U.S. accounted for half the world's pharmaceutical revenues, it consumed far less of the world's output of pharmaceutical drugs.²¹

While consumers and politicians generally believed that the price imbalances acted to the benefit of non-U.S. consumers at the expense of U.S. consumers, a Bain & Co. study challenged this view. The study found that because drug makers earned higher profits in the U.S., they had shifted their R&D expenditures to the U.S. This led to more high-paying jobs in the U.S., a "brain drain" of top scientists from Europe to the U.S., and reduced tax collections in Europe. Because countries in Europe focused on cost containment in pharmaceutical purchases, European consumers had delayed access to new drugs and no access to other drugs because lower profit margins led manufacturers to focus on the U.S. market first. This led to poorer health outcomes. According to the study, while Germany saved \$19 billion through lower prices and reduced access, the country bore a cost of \$22 billion through a shift in R&D expenditures out of Germany, job losses, reduced tax revenues, poorer health outcomes and other factors.²²

Social Pressures

I do believe that the general public and the politicians do not keep in mind well enough what the citizen is spending his money for and that currently, we have the citizens spending more money for auto repairs . . . and that people spend nearly as much money making telephone calls as for prescription drugs. And I think we have to be able over time to re-calibrate the value of drug therapy for our health.

—Daniel Vasella, M.D., Chairman and CEO, Novartis²³

Drug Reimportation Because of the government sponsored Canadian health-care system, drug prices in Canada were often less than half the cost of the same medications in the United States. U.S. residents living near the border often went to Canada to buy their medications to reap the savings. Residents in other parts of the country were beginning to buy from Canadian mail-order and Internet pharmacies. (It was only legal to bring back drugs for personal use.) Elected officials were considering allowing U.S. distributors to reimport drugs from Canada that had been manufactured in the United States. Pharmaceutical companies were opposed to this idea because it would undercut the prices they could obtain in the U.S., which would hurt R&D efforts. They were also opposed for safety reasons—once the drugs left the highly controlled U.S. distribution system, they argued, there was no assurance that the drugs that were reimported had been handled properly or were even of U.S. origin. Such concerns were not unfounded. FDA investigations of drug counterfeiting were on the rise: 6 cases in 1999, 10 in 2000, 23 in 2001, and 16 in the first half of 2002.²⁴

In 2003 and early 2004, pressure mounted to allow reimportation. IMS Health Inc. estimated that reimportation from Canada increased from \$500 million in 2002 to \$1.1 billion in 2003.²⁵ State and local officials, faced with declining budgets due to the economic slowdown, also were exploring reimportation to save money on the drugs they purchased for their employees and retirees. The mayor of Springfield, Massachusetts, for example, was determined to set up a program to reimport drugs from Canada. He stated, "We are mad as hell and we can't afford it anymore." He estimated the city would save \$9 million per year out of the \$18 million it spent on drugs.²⁶

Major drug companies and the FDA were beginning to act to curtail reimportation. Companies including Pfizer, Eli Lilly, GlaxoSmithKline, AstraZeneca, and Wyeth, had taken steps to restrict or stop sales to Canadian sellers that attempted to purchase more drugs than needed for their market. (In response, the governor of Illinois was organizing a boycott of companies that sought to restrict such sales.) The FDA had sent letters to several drug reimporters warning them that their activities were illegal. In late 2003, a U.S. court issued rulings which closed down two such reimporters.

In 2004, the reimportation debate focused primarily on the Canadian to U.S. market, however, reimportation could potentially occur from any country.

HIV/AIDS In the 1990s, various combinations of drugs were discovered to be effective in slowing the progress of HIV/AIDS. The daily cost could exceed \$100 per day—expensive enough in the U.S., but simply out of reach for the tens of millions of people in Africa and other nations who had the disease. Drug companies were under great pressure to lower prices to poor nations. Social activists argued that the manufactured costs of the drugs were a few dollars per day per person, while drug companies argued that if they could not include R&D costs in drug prices there would be no incentive to develop drugs. The industry was also concerned that without adequate health-care systems in place in poor nations, it would be impossible to deliver the drugs, treat the patients, and monitor their progress even if the drugs were provided at no cost. The industry feared that low-priced or free drugs would find their way onto the black market and undercut prices in developed nations. By 2003, after intense negotiations and the commitment by various nations and organizations to improve health-care infrastructures, many pharmaceutical companies had signed agreements to provide reduced-cost HIV/AIDS medications for use in poor nations.

Privacy Health-care industry participants such as doctors and doctor networks, hospitals, insurance providers, and insurance payers (employers and the government) all had databases filled with patient data. Technology advances had increased the value of this data by making it possible to mine the data for information that could improve care, control costs, and increase sales. Organizations that had data could profit by sharing it. The databases, and the potential use and abuse of them, had led to a growing debate regarding the privacy of patient data. Individuals and consumer groups were asking for laws to protect privacy rights and to outlaw discrimination in employment, insurance, housing, and other areas based on medical data. At the same time, the pharmaceutical and health-care industries did not want any regulations that would tie its hands from managing care or add unmanageable layers of paperwork to get permission from individuals to use the data.

The 2002 U.S. Elections

One piece of good news for the industry came in the form of the November 2002 federal elections in the United States that left both the House of Representatives and the Senate (along with the President) in the hands of the Republican Party. In general, pharmaceutical companies felt the Republican Party was more aligned with its positions on issues such as Medicare reform to include drug coverage for seniors, drug reimportation, Waxman-Hatch Act (generics) reform, and drug liability reform to limit lawsuits. While the slim margin of majority held by Republicans and intense

pressure from various consumer groups prevented the Republicans from having a completely free hand, the industry was cautiously optimistic that legislation held up in previous years by a divided government would begin to move in its favor.

Rising Cost and Complexity

Drug Development

Downward pressures on prices coincided with a growing complexity in drug development and approval cycles, which drove up R&D and capital expenditures. Industry R&D expenditures at the top 50 companies globally (ranked by R&D spending) reached \$50 billion in 2001.²⁷ R&D as a percentage of sales for U.S. pharmaceutical companies rose to 18.5% in 2001, up from 15.9% in 1990 and 11.7% in 1980.²⁸ In contrast, the average R&D-to-sales ratio for all U.S. industries was below 4% in 2001.²⁹ (See **Exhibit 8** for R&D and capital expenditures of the large pharmaceutical companies.)

The high risk and research intensiveness of the pharmaceutical industry made drug development costly. According to one estimate, as much as 50% of all development dollars were expended on products that never reached the market.³⁰ Only one in 5,000 to 10,000 compounds tested in the laboratory became an approved drug. Of the products that did reach the market, only 30% achieved the commercial success necessary to recover the average research investment. Total drug development time (from initial testing of a compound to regulatory approval) grew from an average of 8.1 years in the 1960s to 14.2 years in the 1990s. (See **Exhibit 9** for the change in drug development time in the U.S., including a breakdown by development stage, from the 1960s to the 1990s.) As the development time grew longer, development costs increased from an average of \$54 million per drug in 1976 to \$802 million in 2000.³¹ A Bain & Co. study in 2003 found it cost \$1.7 billion to bring a new drug to market when commercialization and other costs were added to R&D costs.³²

Clinical trials—which in Phase I involved 50 to 100 healthy individuals, in Phase II 200 to 300 potential patients, and, in Phase III, often more than 3,000 individuals—accounted for two-thirds of product development costs. Firms applied to the authorities upon completion of testing and could begin marketing upon approval. The cost of worldwide testing for an initial application of a new product was estimated to be \$20 million to \$75 million. Approval by local governments added another \$1 million to \$2 million per country or region (\$5 million to \$6 million in Japan).

Food and Drug Administration

The drug development process was monitored carefully by the U.S. Food and Drug Administration and comparable institutions around the world. Rejection of an application at any stage of the development process or other regulatory delays could jeopardize the scheduling of a series of interdependent activities and greatly delay time to market. For a “blockbuster” drug, one day’s delay could mean several million dollars in lost revenues. The FDA required drug companies to monitor drugs after they reached the market and report on any safety issues. Problems that were not evident during the approval phase could arise after a drug was used by a larger number of people. The FDA occasionally pulled such drugs from the market or asked their manufacturers to voluntarily pull them. For example, in August 2001, Bayer Pharmaceutical pulled its cholesterol-lowering statin drug Baycol from the market following reports that linked it to at least 40 deaths. In addition to reviewing drugs, the FDA also monitored the drug-manufacturing process and could fine companies and/or close plants that did not meet manufacturing regulations.

The FDA had been criticized for the length of its review process and was working to speed up its review of new-drug applications. The FDA Modernization Act of 1997 sought to reduce the review time by requiring drug companies to pay fees totaling approximately \$700 million between 1997 and 2002 so that the FDA could hire more personnel and upgrade its systems. This investment and other changes at the FDA led to a decline in the review (approval) time from just over 30 months on average in the early 1990s to approximately 12 months at the end of the decade; however, it had increased again to 16.4 months in 2001.³³

Marketing Trends

Historically, pharmaceutical companies had relied on large sales forces. The largest companies, such as Pfizer and GlaxoSmithKline, had 10,000 to 15,000 sales reps in the U.S., while the U.S. market as a whole had over 80,000 reps. In a practice referred to as detailing, sales representatives would try to visit doctors to convince them to prescribe their company's drugs. While personal visits could be highly effective, reps faced a number of challenges. Doctors had busy schedules, so it was difficult for the reps to get to see them. Further, the visits tended to be short, averaging less than two minutes in which the rep was able to do little more than drop off promotional materials and free samples of drugs. To overcome these challenges, drug companies invited doctors to dinners, ball games, educational seminars, or other events at which they hoped reps would get more time. The reps also provided gifts, such as pens or mugs with company logos, and occasionally more valuable gifts such as vacation trips. Many reps and physicians did not feel comfortable with this system, and it was increasingly receiving negative attention in the press. A small but growing number of doctors were refusing to meet with drug company sales reps at all because of these practices.³⁴ In mid-2002, the pharmaceutical industry began to agree on a voluntary code to eliminate many of the excesses in the system, but the problem of selling remained.

In 1997, the FDA made a significant regulatory change that greatly increased the importance of advertising to consumers. (Direct marketing to consumers outside of the U.S. was more restricted and employed less frequently.) Although firms had been previously allowed to take their messages directly to consumers, there had been strict guidelines for ad content. For instance, warnings for drug side effects had to be prominent in print ads, while in TV ads there was usually no identifying information for a drug, only a description of symptoms followed by encouragement to see a doctor if those symptoms appeared.³⁵ Under the new regulation, marketers of pharmaceuticals were allowed to name a prescription drug and the illness it treated in direct-to-consumer television advertisements. Drug companies hoped that by using new advertising, they could increase sales by convincing consumers to ask their doctor about specific drugs. As a result of these regulatory changes, direct-to-consumer advertising expenditures reached \$2.8 billion in 2001, a 3.5-fold increase over 1996.³⁶ The growth was such that the drug with the largest direct-to-consumer budget in 2000, Merck's anti-arthritis drug Vioxx, outspent the marketing for PepsiCo's Pepsi product \$161 million to \$125 million.³⁷ GlaxoSmithKline led the industry by spending \$467 million in direct-to-consumer advertising, followed by Pfizer at \$336 million and Merck at \$320 million. The top 10 combined spent over \$2.3 billion.³⁸ Despite the recent growth in direct-to-consumer spending, in 2001 there was a decline in the rate of its growth. At the same time, direct-to-patient advertising, historically a small portion of drug advertising, was increasing. (See **Exhibit 10** for the 10 largest companies by selling expenditures and **Exhibit 11** for a breakdown on the promotional spending by the industry.)

Two more recent trends also had the potential to impact how pharmaceutical companies marketed their drugs: e-detailing and e-prescribing. With e-detailing, doctors and reps could communicate over the Internet using Web cams. The meetings could be scheduled at any time convenient for the doctor, perhaps in the evening, and the reps could sit in a centralized location anywhere in the world. E-

detailing enabled reps to more easily use visual materials while talking, and because travel was eliminated, the reps could speak with many more doctors in a day. There also was some early evidence that e-detailing meetings were much longer than the average face-to-face meeting—closer to 10 minutes than two.³⁹

E-prescribing involved doctors electronically submitting prescriptions, typically with a handheld device, while examining the patient. Fully integrated e-prescribing systems offered several important benefits. Doctors could obtain detailed information on a drug and immediately know if the drug being prescribed had any harmful interactions with other drugs being taken by the patient. MCOs could better ensure compliance with formularies and automatically suggest alternative drugs through the handheld device when a doctor prescribed a drug not on the formulary. Additionally, pharmacists spent less time verifying prescriptions and significant paper-handling costs could be eliminated. For the pharmaceutical industry, e-prescribing offered an opportunity to market directly to the doctor while he or she was making the prescribing decision and see whether various marketing techniques influenced that decision.⁴⁰

These new marketing trends had pharmaceutical companies rethinking their traditional reliance on detailing through sales forces. While the number of sales reps in the field increased to approximately 80,000 in 2001, the growth rate appeared to have slowed over previous years.⁴¹

Disease Management

Finally, in an effort to further reduce costs in the health-care system, MCOs, first in the United States and later in Europe, began seeking ways to manage disease comprehensively. Supported by pharmaceutical companies, MCOs began offering “disease management programs,” which offered comprehensive disease treatment guidelines for health-care providers and patients.

Pharmaceutical companies used disease management programs to demonstrate the cost effectiveness of prescription drugs relative to hospital-based care and to combat poor compliance rates for patients taking prescription drugs. Poor compliance was believed to have large economic costs, as measured by the increased frequency of hospital admissions and readmissions and costs associated with poor preventative health care. While there was evidence that disease management programs improved patient care and lowered costs, some industry observers viewed disease management as an attempt by pharmaceutical companies to escape commodity status.

Industry Consolidation

Intense competition and price pressures in global pharmaceutical markets had fueled ongoing merger and acquisition activities that were consolidating the industry. In the mid-1990s, no company held a 5% market share, while in 2003 the top three companies exceeded this mark. Through mergers and acquisitions, firms sought global scale and scope advantages in research, manufacturing, marketing, sales, and distribution.

In the early to mid-1990s, first Merck, and later Eli Lilly and SmithKline Beecham, integrated forward by purchasing pharmaceutical benefits managers (PBMs) to gain greater control over drug distribution channels.⁴² These companies later rethought these acquisitions, and by the late 1990s all but Merck had sold their PBMs. Merck later sold its PBM in 2003.

Between 1995 and 2000, several large mergers occurred. They included leading firms such as Glaxo and Wellcome, Pharmacia and Upjohn, Sandoz and Ciba-Geigy, Astra and Zeneca, and Pfizer

and Warner-Lambert. In April 2003, Pfizer acquired Pharmacia for some \$60 billion in stock, making it one of the largest deals ever in the industry. By combining their product portfolios the merged companies extended their coverage of therapeutic areas and gained greater clout with major drug purchasers. Acquirers instantly gained new products and customers. They also gained opportunities to reduce costs by rationalizing, for example, sales forces, manufacturing, and R&D facilities. (See **Exhibit 12** for mergers and acquisitions over \$1 billion, 1985–2004.) Despite the trend toward consolidation, some analysts noted that for these industry leaders to maintain historical growth rates, they would have to introduce between one and three blockbusters each year.⁴³

Other firms, Merck in particular, had decided not to merge and to instead rely on their own R&D programs to fuel growth. Merck had divested unrelated businesses, ramped up investment in R&D, and rededicated itself to producing blockbuster drugs through “breakthrough” research. While some analysts felt that this strategy left Merck in danger of falling behind in terms of its scale and ability to fund research, others felt that mergers were a distraction and that there was no evidence that larger R&D budgets improved R&D productivity.

The consolidation trend was not limited to big pharmaceuticals alone. Traditional pharmaceutical companies were buying small biotechnology companies to gain access to their drug discoveries and technologies. Increasingly, biotech companies were merging amongst themselves to obtain more diversified pipelines and diminish reliance on the few products that the typical biotech held internally. In 2003, such mergers were also driven by financial limitations within individual firms.⁴⁴

Alliances and Joint Ventures

In addition to mergers and acquisitions, pharmaceutical companies were seeking out strategic alliances and joint ventures. From 1986 to 1993 the number of strategic alliances in the pharmaceutical industry increased from 121 to over 400. By 2001, there were 425 pharmaceutical alliances in the first six months of the year, not counting an additional 383 alliances with biotechnology firms during the same six-month period.⁴⁵ Between big pharmaceutical companies, these alliances often served to enable partners to better leverage their own resources. For example, a European company with a valuable drug might seek to ally with a U.S.-based company with a strong sales force to market the drug in the U.S.

The Biotechnology Segment

In 1999, we were the biggest biotech company in the world. We were so happy—we were bigger than Genentech (formerly the biggest), but we have to compare ourselves to Pfizer and Merck and Eli Lilly and Johnson & Johnson.

—Dennis Fenton, Vice President, Amgen⁴⁶

The biotechnology segment of the pharmaceutical industry began in 1976 with the founding of Genentech. A company founder had discovered a genetic engineering technique for enabling cells in the laboratory to produce unusually large quantities of a certain protein. The technique had the potential to produce proteins with therapeutic properties. Genentech’s first commercial product, a growth hormone, was approved by the FDA in 1985. Within a few years, several hundred biotechnology firms had been formed to undertake commercial R&D. Companies such as Genentech, Amgen, Chiron, and Genzyme were among the first to demonstrate that competitive barriers in drug discovery could be breached. In addition, regulatory changes such as the 1994 European Community decision to grant Pan-European product approval for prescription drugs were making it easier for

these entrants to take their innovations to market. Shortly thereafter, biotechnology developer Biogen launched a drug on a Pan-European level without the benefit of individual country organizations.

Worldwide sales of the top seven biotechnology companies increased from \$6 billion in 1997 to nearly \$12 billion in 2001. By 2001, the FDA had approved approximately 130 biotechnology drugs and vaccines, and another 350 were in clinical trials. In 2001, there were 342 public biotechnology companies and nearly 1,500 biotech companies in total. These companies had 2001 revenues of \$27.6 billion and R&D expenditures of \$15.6 billion—up respectively from \$10 billion and \$5.7 billion in 1993.⁴⁷ (Biotechnology drug sales increased over 22% from 2002 to 2003 while the pharmaceutical industry as a whole grew by 11.5%.)⁴⁸ (See **Exhibit 13** for the top 20 biotech companies ranked by 2001 global sales, including income, R&D, and employee data.)

Most biotechnology companies had historically relied on traditional pharmaceutical companies. The pharmaceuticals often began by funding the biotech's research activities in exchange for the licensing rights to any drug discoveries. The relationship might evolve over time to include help with the developing, testing, marketing, and selling of drug discoveries and could involve joint-venture arrangements or lead to an acquisition. By 2003, most large pharmaceutical companies had developed "webs of alliances" with biotechnology companies.⁴⁹ Not all such alliances were successful, however. Bristol-Myers Squibb had invested \$2 billion in ImClone, forming one of the largest pharma-biotech alliances in the industry. ImClone's main product was Erbitux, a cancer drug being reviewed by the FDA. The alliance ran into trouble when the FDA unexpectedly rejected Erbitux in December 2001.⁵⁰

By 2003, an increasing number of biotech companies were becoming strong enough financially and savvy enough managerially to bargain for better terms from the pharmaceutical companies. Indeed, pharmaceutical companies were becoming more dependent on biotech companies for drug discoveries at a time when some biotech companies were becoming less dependent on them. Despite this trend, the majority of biotech companies, when they made a drug discovery, still needed the help of big pharmaceutical companies to bring that discovery to market.

The challenge facing the largest biotech companies was transforming themselves from one- or two-product companies into multiple-product companies. Amgen, for example, was launching four new products in 2002, and it expected to double sales by 2005.⁵¹ (Amgen reached this goal in 2003 when revenues hit \$8.3 billion, up from \$4.0 billion in 2001. In March 2004, Amgen announced it would acquire Tularik for \$1.3 billion to further enhancing its drug discovery capabilities.⁵²) Despite the success of the large biotechnology companies, the majority of the industry consisted of small companies with little or no sales that were still developing their first product.

New Science and Technology

Drug discovery today finds itself at the nexus of a vast constellation of such diverse bodies of knowledge as genomics, proteomics, genetic engineering, combinatorial chemistry, organic chemistry, analytic chemistry, robotics, computer science and mathematics, physiology and medicine. Integration of these diverse fields represents an extraordinary organizational challenge for companies involved in the drug discovery business.

—Gary Pisano, Professor, Harvard Business School⁵³

Throughout the 20th century, advances in the understanding of living organisms and related technologies had forced pharmaceutical companies to continually adapt their R&D approaches so as to be able to apply the new technologies and remain competitive over the long term. The leading firms knew how to do this, were used to doing it, and had done so successfully through several generations of scientists.

In the latter part of the century, however, this story began to change. The pace of change had quickened to the point where recent advances were not fully absorbed before still more discoveries came along. Further, many advances were so fundamentally different from what came before that companies often needed new people, facilities, capabilities, and relationships to implement them. By 2003, it had reached the point where it was no longer possible for a single company to hold internally all the capabilities necessary to remain at the top of the industry. The technological and scientific advances were changing the very nature of the pharmaceutical industry from how drugs were discovered and developed to how they were tested and used in practice.

Historically, nearly all drugs were discovered through a process of randomly screening organic and synthesized chemical compounds to see if they were useful disease therapies. Companies developed large libraries of compounds and tested them one at a time against disease targets in living cells. Scientists had long believed that many diseases were caused by the failure of proper interactions between cell receptors (locks) and signaling genes and proteins (keys); however, because very little was known about these interactions, researchers were forced to rely on the random approach. During the 1990s and into 2003, pharmaceutical companies, biotechnology companies, and academic institutions developed scientific knowledge and laboratory techniques that increased the size of the compound libraries, increased the understanding of the locks and keys, and increased the speed and efficiency of testing compounds against disease targets.

Advances in several fields could be combined into new methods for searching for potential drugs. For example, rational drug design was an approach that attempted to use advances in biochemistry, chemical synthesis, and computer science, to name a few, to design molecular keys by working backwards from knowledge of the disease target. This approach was eliminating some, but not nearly all, of the randomness in traditional drug design.

Another new approach was to try to cure diseases with gene therapies rather than treating disease symptoms with drugs. In diseases caused by a missing or faulty gene, gene therapy attempted to introduce the correct gene and permanently cure the disease. While gene therapy had significant potential, it was extremely complex, and progress had been slow. Once perfected, the technique could potentially have a large impact on the pharmaceutical industry. Where traditional drugs were developed for large populations, gene therapy might have to be customized for each patient.

Finally, the process of medical diagnosis itself was being revolutionized by “DNA chips” capable of identifying a piece of DNA from among a small number of known variants, thus allowing patients to be screened quickly and cheaply for genetic “defects” or predisposition to disease. Unfortunately, the ability to test for genetic predispositions to disease had advanced far beyond the ability to treat many of the diseases that might be discovered.

Outsourcing

Size is not something that works in R&D. Big pharma companies will more and more become marketing and distribution engines, leaving the research and science to biotech companies.

—Jacques Theurillat, Finance Director, Serono⁵⁴

As a result of the multitude of new technologies and approaches, big pharmaceuticals were outsourcing an increasing portion of their R&D efforts. In 2002, some companies were allocating close to 30% of their R&D budgets to outsourcing—compared with an industry average of 16% in 1996 and 8% in 1990.⁵⁵

In addition to outsourcing drug discovery to biotechnology companies, major pharmaceutical companies were outsourcing clinical trials to a new type of company referred to as a contract research organization (CRO). Clinical trials were the most costly part of the drug development process, and drug makers hired CROs to develop faster and cheaper ways of conducting the trials, some of which occurred in multiple countries simultaneously and involved hundreds or even thousands of patients. Companies offering “virtual” clinical trials, in which trials were run by computer simulation using virtual patients, were also on the horizon. This approach promised to further speed development and perhaps partly address the growing problem of finding enough patients to participate in clinical studies. Although pharmaceutical companies were increasingly turning to CROs (such outsourcing grew by nearly 70% between 1997 and 2002), they tended to hire them on a project-by-project basis to keep costs low. Such short-term assignments limited knowledge transfer and other benefits that could potentially make the partnerships more effective.⁵⁶

Some industry observers believed that the rise of new research companies could be a two-edged sword for large drug makers. On one side of the argument were those who believed that big-pharma companies could acquire the rights to new products for far less than it would take to develop their own and with less risk. Further, with few exceptions, these biotech firms would be unlikely to ever, on their own, achieve the R&D or marketing scale necessary to compete with the industry leaders. On the other side of the argument were those that saw the new technologies as lowering the entry barriers and bringing in new forms of competition that the traditional pharmaceutical companies could not ignore. As the biotech companies gained strength, the alliances they offered to the big companies would likely become more costly. However that argument turned out, others were concerned that traditional drug R&D methods might no longer be as effective as they were, while new R&D technologies might not be advanced enough yet to yield many drugs.⁵⁷ This could lead to a slowdown in market growth and in the availability of new drugs.

Declining R&D Productivity

Until the pharmaceutical industry writ large adopts as a central tenet of their activity the best and highest use of these new technologies—i.e. the discovery of new protein and antibody drugs—you will not see productivity pick up. We view as an industry with great alarm what appears to be the floundering of our best (big pharma) partners. It is time for them to realize that beating the same dead horse of small molecule (traditional) discovery should change.

—William Haseltine, Chief Executive, Human Genome Sciences⁵⁸

One emerging trend was that the industry seemed to be becoming less productive in terms of discovering and launching new drugs to replace those going off patent. In 2001, 28 new drugs were introduced, the lowest level since 1994, despite record levels of R&D spending. Further, a Bain & Co. study found that by 2003 only one in 13 drugs that reach animal testing ultimately reach the market. This was down from one in eight between 1995 and 2000.⁵⁹ Some argued that productivity had fallen because the low-hanging fruit had been found and new breakthrough drugs were becoming more difficult to find. Others argued productivity was down for two reasons. First, significant R&D resources had been invested since the mid-1990s in developing new drug research technologies that had yet to bear fruit. Second, the FDA had changed approval policies aimed at making new drugs safer. However, since drugs take years to be developed, the drugs being rejected under the new standards had been developed under the previous standards. This situation was expected to improve in the coming years as drugs developed under the new policies began to seek approval.

Other Science and Technology Issues

The new genetic technologies added pressure to the manufacturing side of pharmaceutical companies. Under traditional R&D methods, the product was discovered early in the R&D process so companies had years to develop manufacturing techniques and could estimate early on what manufacturing developments were needed and what they might cost. With genetic engineering and rational drug design, the product was largely unknown until much later in the development process. It was more difficult to estimate what it might cost to manufacture the drug, and it was conceivable that an effective drug could be discovered only to find that it was cost prohibitive to produce.

Because much of the knowledge underlying the new science was publicly available, once a drug discovery was made there was an increased likelihood of a fast follow-on drug being discovered that addressed the same disease target without infringing on the patent of the first drug. This led to a significant decrease in the number of years a new drug held a monopoly position. (See **Exhibit 14** for declining exclusivity periods for patented drugs.)

Much of the genetic research and other technologies were being developed in the United States, and this had led to a shift in pharmaceutical R&D expenditures from Europe to the U.S. In 1995, 36% of R&D dollars were spent in the U.S. This proportion increased to 47% in 1999 and was estimated to exceed 50% in 2001.⁶⁰ By 2002, over 75% of gene-based drug R&D was conducted in the U.S.⁶¹

Overall, a variety of new technologies were impacting and improving all phases of drug discovery and development. These technologies required new approaches to operating and managing drug company laboratories. For example, the importance of information technology activities and their integration into the laboratories was increasing. Where, historically, scientists had worked largely independently, R&D in the new environment required more collaboration.

The Blockbuster Model

The Tsunami of information generated by the Human Genome Project is forcing drug companies to retool themselves as information brokers. . . . Their survival will depend on finding new ways to spin gene data into blockbuster drugs.

—Enal Razvi, Vice President, DiscoverRx⁶²

In 2003, the pharmaceutical industry faced a number of issues that could potentially alter the nature of the industry and change how the leading companies competed. One issue was whether the blockbuster model that the leading competitors had followed to great success for more than a decade would remain a viable option in the decade ahead.

The reliance of leading drug companies on blockbuster drugs, those with sales over \$1 billion per year, had increased dramatically over the past decade. Between 1991 and 2001, the number of blockbuster drugs grew from four to 55, and their share of the market went from 6% to 45% of pharmaceutical sales. At Pfizer, blockbusters accounted for 80% of its pharmaceutical sales. Despite this growth, only five companies had more than two blockbuster drugs in 2001.⁶³

In the blockbuster model, pharmaceutical companies focused much of their research efforts on discovering the next drug that could achieve blockbuster status. Such drugs tended to dominate a therapeutic category and allowed a company to have a large sales force focused on the doctors and buyers in that category. While discovering a drug that benefited a large group of people who could afford to purchase it was the first step in creating a blockbuster, it was also necessary to have a large, well-trained, well-funded sales force to drive sales. Once the sales force was in place selling the first

blockbuster, R&D dollars were focused on other potential blockbusters in the same category. Companies had historically discovered their own potential blockbusters but in recent years were increasingly acquiring the discovery through an alliance with or acquisition of another company.

A growing concern was that managed care systems forced doctors to see many more patients and often at less pay. This left doctors with little time to listen to detailers. Managed care systems also employed formularies that limited the doctor's ability to choose which drugs to prescribe. These forces could make it harder for companies to drive a drug to blockbuster status.

The blockbuster model was not foolproof. There was no guarantee that a new blockbuster would be discovered, and if it was, no guarantee that a rival would not discover a better drug to treat the same condition. Further, when a blockbuster lost patent protection, sales of that drug fell quickly. Because most firms only had a small handful of blockbusters, each one was critical to the company's success. Nor was there an unlimited number of disease markets, such as cholesterol or arthritis, where breakthrough discoveries were likely and that were large enough to support blockbuster drugs. Finally, the rising cost of drug discovery and commercialization, combined with declining R&D productivity, was reducing investment returns. Bain & Co. estimated that the return on investment under the blockbuster model had declined to 5%, a figure "significantly lower than the industry's risk-adjusted cost of capital."⁶⁴

Despite the growth over the past decade, some industry watchers believed that the future was less certain. One observer explained that with declining periods of exclusivity and quicker launches of generics, large drug companies needed to change: "Companies dominant in the blockbuster arena have to become fleet of foot in order to protect their franchise. . . . I believe the industry needs to spend more time, not just focusing on blockbusters, but focusing also on more specialized products. In the future I believe there will be a role for both. However, big pharma will continue to have a need for blockbusters to fuel the beast of their engine."⁶⁵ David Lipson, group director of marketing science at IMS Health Consulting, wrote:

The age of the blockbuster isn't over yet, but for a product to achieve that status, conditions must be just right. Celebrex and Vioxx entered a huge, well-developed market of perennially unsatisfied but motivated patients with a non-life-threatening disease. And the therapies offered significant perceived advantages over older products. There may be other markets with those characteristics, but not many. . . . Clearly there will be fewer blockbusters in the future.⁶⁶

Looking further ahead, Lipson identified a second and fundamental issue facing the industry: "But even the exceptional blockbuster may soon cease to exist. Genomics will surely change the nature of the market from selling one product to millions of patients to selling 'designer' drugs in small volumes to limited patient populations."⁶⁷

Big Pharma in 2003

AstraZeneca

AstraZeneca formed in 1999 when the British firm Zeneca acquired the Swedish company Astra. (Until the 1990s, Zeneca had been primarily a chemical company.) Shortly thereafter, the combined company divested most of its non-pharmaceutical businesses. In 2001, AstraZeneca divested its Cellmark division, which had pioneered the use of DNA testing in forensics. This left the company to focus almost exclusively on prescription drug products, which accounted for over 97% of total sales.

AstraZeneca was in the midst of a high-profile patent dispute to head off generic competition for Prilosec—its ulcer/heartburn medication, which in 2000 was the largest-selling drug in the U.S. with nearly \$5 billion in sales. Prilosec was scheduled to go off patent in April 2001, but it received a six-month extension from the FDA until October 2001 for evaluating its pediatric use. AstraZeneca then filed lawsuits against would-be generic competitors arguing that generic products would violate patents on the drug's coating that expire in 2007. The generic competitors delayed entering the market until the court case was decided because if they lost they would likely have to pay damages to AstraZeneca. This effectively protected Prilosec from generic competition until the court case was decided. In October 2002, the court ruled, somewhat surprisingly, in AstraZeneca's favor. Various aspects of the ruling were under appeal by both sides in the case in December 2002, and generic competition had yet to enter the market. The delays were worth approximately \$10 million in daily sales for AstraZeneca and were enabling the company to shift Prilosec users to another of its ulcer/heartburn products.

AstraZeneca had a strong pipeline, with several potential blockbuster drugs in late-stage development. Two of these drugs, however, had received approval setbacks in mid-2002 that would delay their introduction and reduce sales. The company had increased R&D and marketing expenditures in anticipation of the launch of these products. To further strengthen its pipeline, AstraZeneca had entered into over 200 collaborations with biotechnology companies and universities in 2002. The company had also introduced procedures designed to remove potential drugs early in the development process if tests indicated those drugs had a higher risk of failure in later stages.

In November 2002, AstraZeneca became the first major pharmaceutical company to open a research center in China. AstraZeneca intended to use the center to form alliances with Chinese research organizations and to speed the introduction of new drugs in China. The research center joined other AstraZeneca marketing, sales, and manufacturing operations already in the country, which was expected to become the fifth-largest pharmaceutical market by 2010.⁶⁸ The move was spurred by patent and trade regulation changes being made in China in relation to the country's entrance into the World Trade Organization.

GlaxoSmithKline

GlaxoSmithKline was formed out of a long line of mergers including the most recent, Glaxo Wellcome's \$75 billion acquisition of SmithKline Beecham in late 2000, which at the time made the new company the largest in the industry. The two London firms were each themselves the product of major mergers during the previous decade. The companies pursued the merger to gain scale advantages, particularly in R&D and marketing.

GlaxoSmithKline was a leader in many therapeutic drug categories including being the largest seller of HIV/AIDS drugs and one of the top vaccine producers. While GlaxoSmithKline earned just over 80% of its sales from pharmaceutical products, it continued to invest in its consumer health-care segment, which consisted of branded over-the-counter medicines such as Nicorette smoking-control products and Tums antacids. GlaxoSmithKline was the world's second-largest oral care products company, with brands that included Aquafresh toothpastes and Poligrip denture products.

GlaxoSmithKline had one of the strongest early-stage pipelines in the industry. To develop new products faster, the company had reorganized a portion of its scientists into "centers of excellence for drug discoveries." GlaxoSmithKline hoped these smaller, entrepreneurial groups could more quickly and efficiently determine which discoveries merited being brought into clinical development.

To support sales until internally discovered products reached the market, GlaxoSmithKline spent considerable effort to in-license potential drugs discovered elsewhere. In 2001, it in-licensed 10 such drugs, several of which were in late-development stages. GlaxoSmithKline believed that with its large drug development and marketing and sales organization, it could compete as the partner of choice in the industry for both biotechs and other pharmaceutical companies. As they had with other large pharmaceutical companies, however, industry analysts had expressed doubts that GlaxoSmithKline would be able to bring enough new products to market to offset patent expirations and to maintain historical growth rates.

Despite its leadership position, in 2003 GlaxoSmithKline faced patent disputes that threatened to undermine the sales of several of its best-selling products. For example, the company's top-selling drug, Paxil, earned sales of approximately \$3 billion (10% of total company revenues). Its patent was set to expire in 2006; however, a generic manufacturer was seeking to introduce a different form of the medicine as early as late 2003 depending on the outcome of a court battle.

GlaxoSmithKline stirred the drug reimportation debate in January 2003 when it announced it would stop selling its products to wholesalers that supplied any one of 29 Canadian pharmacies that in turn sold to U.S. customers. At least one leading wholesaler announced it would stop such sales. GlaxoSmithKline indicated that it was protecting the safety of U.S. consumers and that because the practice was against the law, the company could not knowingly participate. In response, at least one Canadian pharmacy called on its customers to boycott GlaxoSmithKline products, although the pharmacy admitted that a large boycott was unlikely. An association of Internet pharmacies was seeking a court order to block GlaxoSmithKline's prohibition.

During 2002 and into 2003, analysts repeatedly mentioned that Bristol-Myers Squibb was ripe to be taken over. GlaxoSmithKline was named as a likely buyer so it could keep pace with Pfizer following its acquisition of Pharmacia.

Johnson & Johnson

Johnson & Johnson (J&J) pursued a more diversified strategy than other pharmaceutical companies. The company operated dozens of businesses in three major segments: pharmaceuticals, consumer, and medical devices and diagnostics. The businesses operated in a decentralized structure and with a decentralized management philosophy so as to encourage entrepreneurial initiative and enable a fast, flexible strategic approach. In recent decades, the company pursued growth through small to medium-sized acquisitions while avoiding major acquisitions. It sought to hold the number one or number two market share position in each of its businesses.

J&J was one of the fastest-growing and consistently growing major health-care companies. Unaudited financials results for 2002 showed the company with 70 straight years of sales growth and 18 straight years of double-digit earnings growth. A strong balance sheet and credit rating positioned the company well to continue its acquisition strategy in the first decade of the 21st century.

J&J's largest business segment, pharmaceuticals, was also its fastest growing. It accounted for 45% of total sales in 2001, up from 33% of sales in 1996. The pharmaceutical segment had grown nearly 16% yearly over this period. Drug products were developed and sold through several of J&J's businesses. These products included Procrit, a biotechnology drug used to treat anemia with sales over \$4 billion, and drugs in over 10 other therapeutic categories. In 2001, J&J made its largest acquisition when it acquired Alza for \$11 billion. In addition to a number of drugs with increasing sales, Alza had developed several drug-delivery technologies. Drug delivery, which involved how medicines enter the body (oral, transdermal, implantable, and liposomal), was becoming an area of

increasing importance for pharmaceutical companies. J&J's exposure to generic competition was somewhat less than that of other large pharmaceutical companies. While its businesses tended to operate independently, in 2001 the company merged two of its major pharmaceutical R&D labs in an effort to improve productivity and increase knowledge transfer across the company.

The medical devices and diagnostics segment contributed 34% of total sales and included businesses such as cardiovascular diagnostic equipment, surgical equipment, joint-replacement products, contact lenses, and numerous other products. The segment had grown 7% yearly for the most recent five years. J&J expected to launch a new product, called Cypher, a drug-coated stent, in March or April 2003. This would be the first drug-coated stent approved by the FDA. Being first in the market, J&J was expected to obtain a leadership position in what looked to be a \$5 billion yearly sales business. Finally, J&J's consumer segment earned the remaining 21% of sales and had grown at less than 2% over the five-year period. Consumer products consisted of well-known brands such as Tylenol, Motrin IB, Band-Aids, Johnson's Baby products, and Neutrogena skin-care products.

Merck

In contrast with much of the industry, Merck pursued a strategy of not becoming involved in a major merger or acquisition. Instead, it focused on developing breakthrough drugs—those that offered advances over current drug therapies—rather than producing “me too” products. Executives believed that in an age of price pressures from major drug purchasers, offering novel medicines was a way to ensure that the company's products remained on drug formularies while at the same time delivering high margins. (In 2001, Merck's margins were the highest in the industry.) They also believed that Merck had sufficient scale to go it alone and that a major merger or acquisition would distract them from their primary mission.

To discover and develop these breakthrough drugs, Merck searched where there was “new knowledge” in disease states and new technologies to address them. This led it to hire a leading geneticist to run its research labs, open a major research center in Boston, and acquire a biotechnology company in San Diego. Part of this strategy included having its key scientists create “virtual labs” with the most advanced science in their fields whether sourced internally or externally. Merck had greatly increased its efforts to identify collaborative opportunities and also developed the organizational processes necessary to act quickly when they arose. Approximately one-third of Merck's pharmaceutical revenues came from products licensed from outside sources.

Merck, however, was under pressure to perform without a merger and was in the midst of a difficult patent expiration period. Five drugs that accounted for nearly 50% of its pharmaceutical sales in 1999 went off patent between mid-2000 and mid-2002. Merck had 11 new drugs in its pipeline that it expected to either launch or file for FDA approval between 2003 and 2006. Several of these products had blockbuster potential. Additionally, Merck remained one of only two U.S. pharmaceutical companies and one of four worldwide that was involved in vaccine development and manufacturing. To tide itself over, Merck initiated efficiency and productivity improvements efforts throughout the company, particularly in manufacturing, marketing, and sales. For example, in 2001–2002 it grew its sales force by 1,500 while holding selling, general, and administrative costs steady.⁶⁹

Novartis

Novartis, based in Switzerland, was formed through the merger of Sandoz and Ciba-Geigy in 1996. In the late 1990s, it pursued a “life sciences” vision by trying to find synergies across its pharmaceutical, agriculture, and nutrition businesses. It also tried to merge with two U.S. companies,

American Home Products (Wyeth) and Monsanto, but neither deal was completed. (In 2001, Novartis had acquired 20% of Roche Pharmaceuticals.) In 2000, Novartis exited the agriculture business to focus on health-care activities, primarily branded pharmaceuticals but also over-the-counter medicines, generic drugs, vision-care products, infant formulas and foods, nutritional/health foods, and animal health. The company also heavily invested in marketing and sales, particularly in the U.S. Marketing's increased prominence gave it a greater voice in R&D activities, and that helped ensure scientists worked on products that could be successful in the marketplace. In 2001, Novartis was the fastest-growing company in U.S. pharmaceutical sales. In 2000 and 2001, the company introduced more new drugs than any competitor in the industry.

In 2002, Novartis increased its focus on core pharmaceutical activities by divesting much of its nutrition/health foods business. It also strengthened its generics business by acquiring Lek, one of the leading pharmaceutical companies, and generic drug producers in Central and Eastern Europe. The acquisition made Novartis the world's largest generic drug producer at a time when most other top pharmaceutical companies had exited the business. Following the acquisition, generics would make up approximately 10% of company sales.

In January 2002, Novartis introduced a discount-card program under which low-income seniors in the U.S. without prescription drug coverage could purchase Novartis drugs at up to 40% of retail prices. In April 2002, Novartis joined a consortium of eight drug makers to offer a discount card good on over 150 products from the participating companies. The program, similar to others in the industry, was aimed at alleviating some of the pressure it faced over the high cost of drugs.

On the R&D front, in mid-2002 Novartis reorganized all its worldwide labs into the Novartis Institute for Biomedical Research. The group would be headquartered in Cambridge, Massachusetts, one of the top three biotechnology locations in the world (along with San Francisco and San Diego) and near major universities, biotechnology companies, and teaching hospitals. (The move was part of a trend in the industry for big pharmaceutical companies to open labs in one or more of the three sites and also a shift of R&D from Europe to the U.S.) The company's new head of research, Mark Fishman, was noted for his criticism of traditional research methodologies, such as sequential R&D activities and over reliance on mice as the research animal in preclinical trials. Instead, Fishman proposed more parallel R&D activities, using the most appropriate test animals for the conditions being studied and increasing the involvement of university scientists and practicing clinicians in R&D.⁷⁰ In addition to relying on its own R&D activities, Novartis allocated approximately 25% of its R&D budget to alliances with outside biotechnology firms and academic laboratories.

In January 2003, Novartis increased its ownership position in Roche to 33% and announced it ultimately planned to acquire the company, but Roche founding-family shareholders held 50.1% of shares and indicated they did not plan to sell. Should a merger take place, the combined companies would become the second-largest company in the industry.⁷¹

Pfizer

The Pfizer story was one of growth by acquisition, alliances, and co-promotion. The U.S.-based company had moved from the 14th-largest drug producer in 1990 to the largest in 2002. In 2000, Pfizer acquired Warner-Lambert in the largest deal in the history of the industry. The deal gave Pfizer control of the blockbuster drug Lipitor, as well as the opportunity to reduce costs by nearly \$2 billion. Analysts believed the integration of the two firms was a success. Along with its acquisitions came several non-core businesses, such as Adams confectionary and Schick and Wilkinson shaving products, that Pfizer was looking to divest. In December 2002, Pfizer sold Adams for \$4.2 billion.

In April 2003, Pfizer acquired Pharmacia for \$60 billion to add breadth and depth to its product lines; acquire the blockbuster Celebrex, which it had been co-promoting with Pharmacia; and cement its position as the largest drug maker. The deal made Pfizer the largest pharmaceutical company in the U.S., Europe, Japan, and Latin America and gave it an approximately 13% share of the global pharmaceutical market. The combined company spent over \$7 billion on R&D and employed over 30,000 in its worldwide sales force.

Alliances and co-promotion of drugs developed elsewhere had also played key roles in Pfizer's growth. The company had made hundreds of research alliances and sought to be the "partner of choice" in the industry. Part of the strategy behind this was to ensure a strong pipeline of new products during times when its own laboratories were having only limited success. The last major drug developed by Pfizer was Viagra in 1998, and in 2001 approximately \$10 billion of its \$24 billion in major pharmaceutical product sales came from drugs discovered by outside firms.⁷²

A second part of this strategy, analysts believed, was that by keeping its large marketing and sales organizations busy, the company could maintain access to doctors, which was becoming increasingly difficult to do in the face of increased patient loads and time pressures. Doctors were more likely to grant access to sales representatives from companies with new products to discuss.⁷³

In January 2002, Pfizer joined the ranks of companies offering drug discount cards in the U.S. The program offered selected Pfizer drugs at a flat rate of \$15 per monthly prescription—some \$50 less than the average retail cost of a Pfizer drug. Internationally, Pfizer had played an active role in providing HIV/AIDS drugs to developing nations in Africa and in other areas of the world.

Looking Ahead

Technological advances were beginning to change how drugs were discovered and developed. Biotech companies that barely existed until the 1990s were becoming stronger. Amgen, the largest biotech, had become the 21st-largest pharmaceutical company in 2001. How long would it be before a biotech was in the top 10? Big-pharma companies had historically adapted to new technologies, but the development and selling of designer drugs might lead to an industry structure unrecognizable to the leaders of 2003.

The pharmaceutical industry had also become a political lightning rod. It seemed to be "in the news" on a regular basis, and the press was not always favorable. There were numerous stories about the high profits drug makers earned while many people, such as senior citizens in the U.S., had to choose between buying medicine and buying food. Similarly, there was pressure on the industry to lower its prices on HIV/AIDS drugs for poor nations as the pandemic seemed to explode in the late 1990s. Finally, the patient data-privacy issue was increasingly in the press and was felt strongly among many consumers. While it was unclear what effect these issues might have, growing public pressure could lead politicians to enact laws to the detriment of the industry.

The pharmaceutical industry had weathered challenging times for decades and in 2003 remained one of the world's most successful industries in terms of growth, profits, and value to society. The industry as a whole could continue its run of success in the decades to come, but what it would look like, and who would still be around, remained to be seen.

Exhibit 1 Global Pharmaceutical Sales by Region, 2000 - 2002^a

Region	2000	%	2001	%	2002	%	2003	%
	Sales \$ Billions	Global Sales	Sales \$ Billions	Global Sales	Sales \$ Billions	Global Sales	Sales \$ Billions	Global Sales
North America	\$152.8	48%	\$181.8	50%	\$203.6	51%	\$229.5	49%
Europe (EU)	75.3	24	88.0	24	90.6	22	115.4	25
Rest of Europe					11.3	3	14.3	3
Japan	51.5	16	47.6	13	46.9	12	52.4	11
Asia(excluding Japan)								
Africa, and Australia	18.7	6	27.9	8	31.6	8	37.3	8
Latin America	18.9	6	18.9	5	16.5	4	17.4	4
Total	317.2	100	364.2	100	400.6	100	466.3	100

Source: Adapted from IMS Health, World Review, 2001; IMS World Review 2002; IMS World Review 2003; and IMS Consulting, from IMS Health Company Web site (Press Room, Top-Line Industry Data), <<http://www.imshealth.com>>, accessed February 11, 2003 and March 15, 2004.

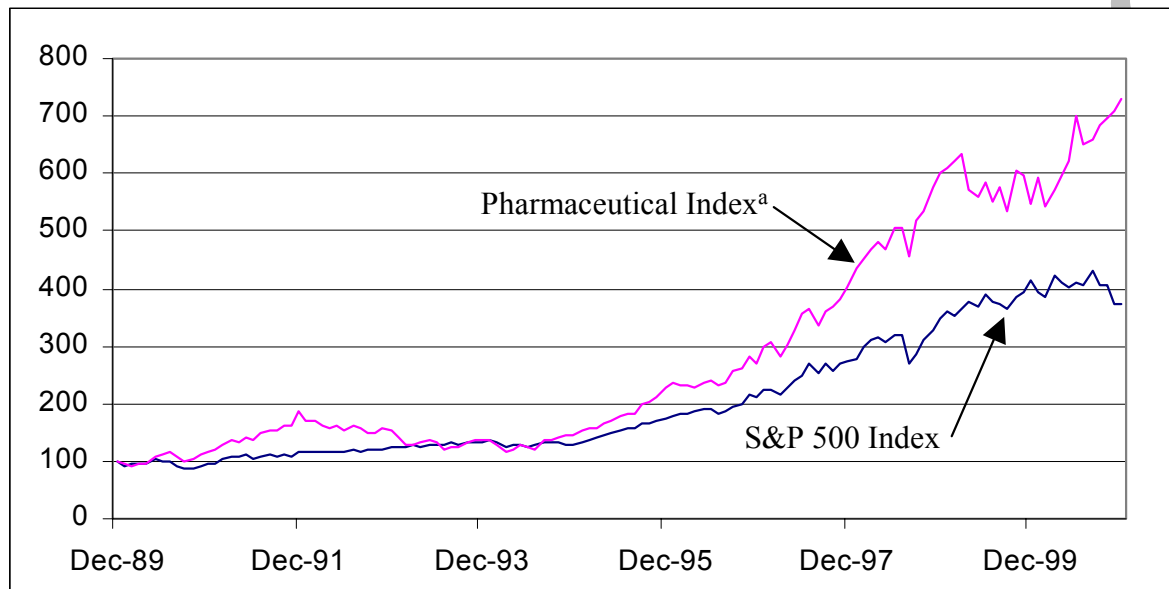
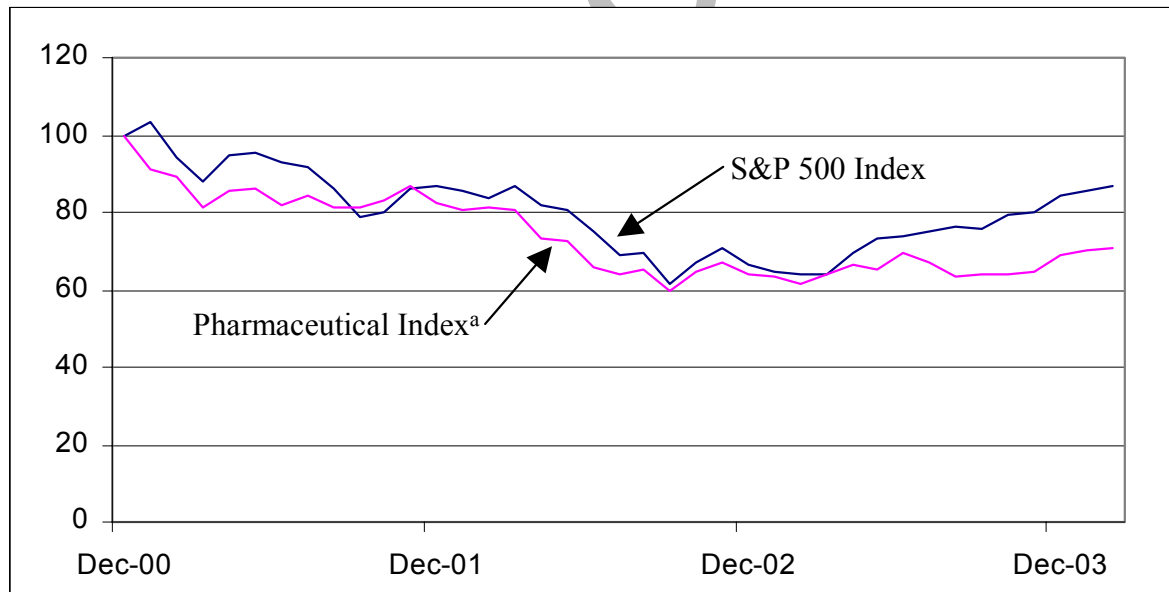
^aSales cover direct and indirect pharmaceutical channel purchases from pharmaceutical wholesalers and manufacturers in over 65 key international markets. Figures include prescription and certain over-the-counter data and represent manufacturer prices.

Exhibit 2 Leading 10 Global Pharmaceutical Markets—Projected Pharmaceutical Sales and Growth Rates Through 2005^a

Region	Annual Sales 2000 (US\$ B)	Projected Annual Sales 2005 (US\$ B)	Projected Compound Annual Growth Rate 2000-2005 (%)	Projected 10-Country Market Share 2005 (%)
Australia	\$3	\$5	9.3	1.1
Belgium	2	3	5.6	0.7
Canada	6	10	10.7	2.4
France	16	22	6.0	5.0
Germany	17	24	7.5	5.6
Italy	11	16	8.2	3.6
Japan	58	66	2.3	15.1
Spain	6	10	9.9	2.3
U.K.	11	16	8.3	3.7
U.S.	150	263	11.8	60.5
Total	281	434	+9.1	100.0

Sources: IMS Health Pharma-Prognosis International, 2001-2005, as depicted in "IMS Health Forecasts 9 Percent Annual Growth In 10 Leading Global Pharmaceutical Markets Through 2005," IMS Health News Release, June 14, 2001, from IMS Health Company Web site (Press Room, News Releases), <<http://www.imshealth.com>>, accessed February 11, 2003.

^aSales cover direct and indirect pharmaceutical channel purchases from pharmaceutical wholesalers and manufacturers in 10 key international markets. Figures include prescription and certain over-the-counter data and represent manufacturer prices.

Exhibit 3a Industry Stock Index (month end, December 1989—December 2000)**Exhibit 3b** Industry Stock Index (month end, December 2000—February 2004)

Source: Datastream International.

^aDatastream Pharmaceutical Industry Index.

Exhibit 4 Largest Pharmaceutical Companies, 2001 (\$ millions)

Company	Total Sales	Pharmaceutical Sales	Percent Pharmaceutical	Sales in the United States	Stock Price Change (1-yr) ^b
Merck ^a	\$47,716	\$20,456	43	\$12,519	-6.1
Johnson & Johnson	33,004	14,851	45	10,922	-6.3
Pfizer	32,084	25,518	80	17,631	-27.5
GlaxoSmithKline	29,847	24,775	83	15,474	-22.1
Aventis	21,228	15,168	71	na	-27.0
Bristol-Myers Squibb	19,423	15,287	79	10,505	-46.4
Novartis	19,302	12,014	62	6,787	+5.8
Roche Holdings	18,277	10,156	56	na	Na
AstraZeneca	16,848	16,480	98	10,067	-29.9
Abbott Laboratories	16,285	9,000	55	na	-34.3
Wyeth	14,129	11,717	83	6,983	-39.3
Pharmacia	13,837	11,970	87	6,512	+3.8
Eli Lilly	11,543	10,856	94	7,627	-16.6
Schering-Plough	9,802	8,369	85	na	-42.9
S&P 500 Index	--	--	--	--	-27.7

Sources: Adapted from company annual reports and "On Treacherous Ground, 50 of the world's biggest pharmaceutical companies are challenged to perform in the most difficult environment ever," *Med Ad News*, September 1, 2002; and Kathy Blankenhorn and David Lipson, "Business watch: 2001 in review; despite economic challenges, pharmaceutical industry still maintains steady growth," *Medical Marketing & Media*, May 2002, p. 46.

^aMerck total sales not including Medco were \$21,347,000, of which 96% were pharmaceutical.

^bOne-year change in stock price from February 4, 2002 to February 4, 2003.

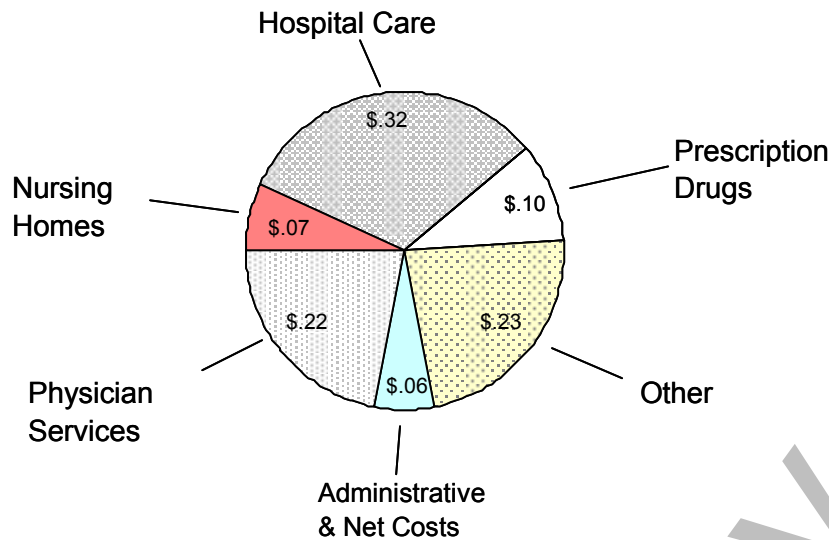
Exhibit 5 Sales Increase Components

Pharma's revenue growth in the past decade has resulted from a combination of price increases, new products, and a shift to more expensive products.

Year	Total Pharma Revenue Growth (%)	Price Increase (%)	New Products (%)	Higher Volume and Shift to More Expensive Products (%)
1995	9.7	1.9	2.8	5.0
1997	14.2	2.5	5.0	6.7
1999	19.0	4.0	4.0	11.0
2001	16.9	4.9	3.3	8.7

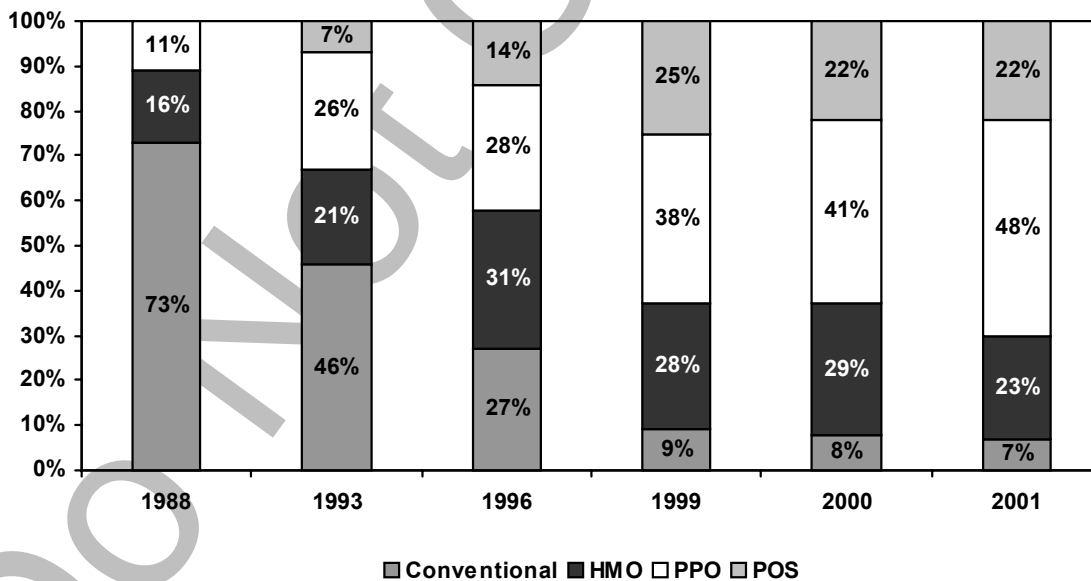
Source: Adapted from David Lipson, "A Five Year Forecast: Clear Seas Ahead?" *Pharmaceutical Executive*, July 22, 2002, <www.pharmaportal.com>; and Blankenhorn and Lipson, "Business Watch, 2001 in Review."

Exhibit 6 Health-Care Dollar, 2001



Source: Pharmaceutical Research and Manufacturers of America (PhRMA), Pharmaceutical Industry Profile 2003, (Washington, D.C.) p. 33.

Exhibit 7 Health Plan Enrollments for Covered Workers by Plan Type, 1988–2001



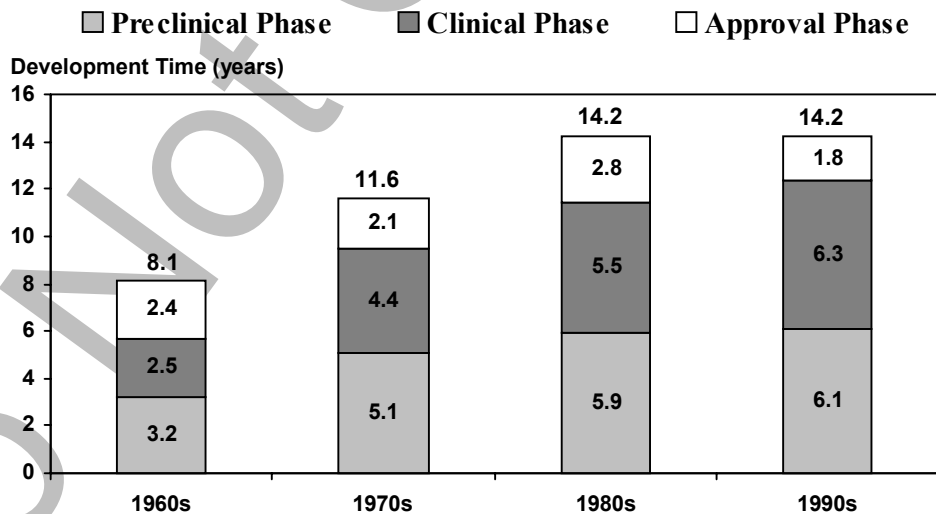
Source: Pharmaceutical Research and Manufacturers of America, 2002 Industry Profile, Washington, D.C., 2002, p. 54.

Exhibit 8 Top 20 Companies Ranked by R&D Expenses with Capital Expenditures (\$ millions)

Rank	Company	R&D 2001	Capital Expenditures 2001
1	Pfizer, Inc.	\$4,847	\$2,203
2	GlaxoSmithKline Plc.	3,816	1,622
3	Johnson & Johnson	3,591	1,731
4	AstraZeneca Plc.	2,773	1,385
5	Aventis SA	2,665	1,108
6	Novartis	2,480	814
7	Merck & Co.	2,456	2,725
8	Roche	2,305	1,163
9	Pharmacia Corp.	2,263	1,020
10	Bristol-Myers Squibb Co.	2,259	1,023
11	Eli Lilly & Co.	2,235	884
12	Wyeth	1,870	1,924
13	Abbott Laboratories	1,578	1,164
14	Bayer Group	1,337	2,096
15	Schering-Plough Corp.	1,312	759
16	Sanofi-Synthelabo SA	923	506
17	Boehringer Ingelheim GmbH	912	--
18	Amgen Inc.	865	442
19	Takeda Chemical Industries Ltd.	824	--
20	Schering AG	773	345

Source: Adapted from *Med Ad News*, Vol. 21, No. 9, September 1, 2002; Standard & Poor's Research Insight; and company annual reports.

Exhibit 9 Total Drug Development Time from Synthesis to Approval



Source: Pharmaceutical Research and Manufacturers of America, 2002 Industry Profile, PhRMA, Washington, D.C., 2002, p. 19.

Exhibit 10 Top 10 Corporations by U.S. Detailing and Journal Advertising Spend, 2001

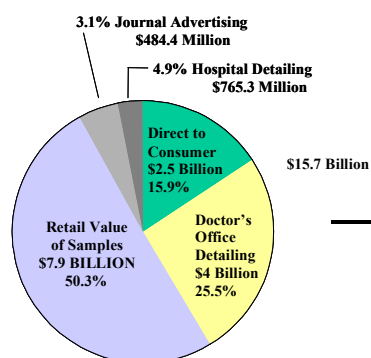
Rank	Corporation	2001 Total Dollars ^a
1	Pfizer	651
2	GlaxoSmithKline	567
3	Merck	435
4	Johnson & Johnson	363
5	AstraZeneca	300
6	Novartis	263
7	Pharmacia	254
8	Aventis	247
9	Bristol-Myers Squibb	246
10	Schering-Plough	246

Source: Adapted from Blankenhorn and Lipson, "Business Watch, 2001 in Review."

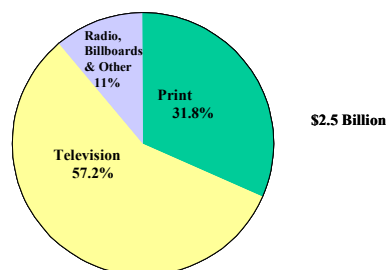
^aRepresents the cost, in millions, of detailing office and hospital-based physicians and the cost of advertising in medical journals. Cost of contacts and cost of professional physician advertising are added together. Data are based on a custom corporate definition to reflect 2001 merger and acquisition activity.

Exhibit 11 Promotional Spending on Prescription Drugs, 2000

Breakdown of Spending, 2000



Direct to Consumer



Source: Adapted from "Prescription Drugs and Mass Media Advertising, 2000," National Institute for Health Care Management, Washington, D.C., July 22, 2002, <www.nihcm.org>.

Exhibit 12 Mergers and Acquisitions in the Pharmaceutical Industry over \$1 Billion, 1985–2004

Date Effective	Target Name	Acquirer Name	Value of Transaction (\$ millions)
02/13/04	IGEN International Inc.	Roche Holding AG	1,227
02/11/04	Esperion Therapeutics Inc.	Pfizer Inc.	1,281
01/22/04	SICOR Inc.	Teva Pharmaceutical Inds Ltd.	3,401
04/29/03	Scios Inc.	Johnson & Johnson	2,323
04/15/03	Pharmacia Corp.	Pfizer Inc.	59,515
12/02/02	Nycomed Pharma AS	Investor Group	1,126
10/01/02	Nippon Roche KK	Chugai Pharmaceutical Co. Ltd.	2,384
02/12/02	COR Therapeutics Inc.	Millennium Pharmaceuticals Inc.	2,417
10/02/01	Dupont Pharmaceuticals Co.	Bristol-Myers Squibb Co.	7,800
09/28/01	FH Faulding & Co. Ltd.	Mayne Nickless Ltd.	1,218
06/22/01	ALZA Corp.	Johnson & Johnson	11,070
05/11/01	BioChem Pharma Inc.	Shire Pharmaceuticals Group	3,748
03/02/01	Knoll AG (BASF AG)	Abbott Laboratories	6,900
12/26/00	SmithKline Beecham	Glaxo Wellcome	75,000
11/10/00	Dura Pharmaceuticals Inc.	Elan Corp. PLC	1,708
08/31/00	Jones Pharmaceutical Inc.	King Pharmaceuticals Inc.	3,523
07/10/00	Rexall Sundown Inc.	Koninklijke Numico NV	1,768
06/19/00	Warner-Lambert Co.	Pfizer Inc.	89,168
05/24/99	Synthelabo SA (L'Oreal SA)	Sanofi SA (Societe Nationale)	11,118
05/17/99	Agouron Pharmaceuticals Inc.	Warner-Lambert Co.	2,196
04/19/99	Astra AB	ZENECA Group PLC	34,637
11/30/98	Chiron Diagnostics Corp.	Bayer AG	1,100
08/07/98	RP Scherer Corp.	Cardinal Health Inc.	2,542
03/05/98	Corange Ltd.	Roche Holding AG	10,200
02/11/97	Roussel-Uclaf SA (Hoechst AG)	Hoechst AG	3,393
12/17/96	Ciba-Geigy AG	Sandoz AG	30,090
12/29/95	Fisons PLC	Rhone-Poulenc Rorer Inc.	2,888
11/02/95	Pharmacia AB	Upjohn Co.	6,989
07/18/95	Marion Merrell Dow Inc.	Hoechst AG	7,264
05/01/95	Wellcome PLC	Glaxo Holdings PLC	14,284
03/31/95	Boots Co. PLC-Pharmaceutical Op	BASF AG	1,583
12/21/94	American Cyanamid Co.	American Home Products Corp.	9,560
11/03/94	Syntex Corp.	Roche Holding AG	5,307
11/02/94	Sterling Winthrop Inc.	SmithKline Beecham PLC	2,925
06/30/91	Sanofi-N Amer Ops, Latin America	Sterling Drug-N Amer Operation	2,400
01/03/91	El du Pont de Nemours-Pharm	Merck & Co.-European Prescript	1,250
07/31/90	Rorer Group Inc.	Rhone-Poulenc SA (France)	3,476
12/15/89	AH Robins Co., Inc.	American Home Products Corp.	3,194
12/02/89	Marion Laboratories Inc.	Dow Chemical Co.	6,209
10/04/89	Squibb Corp.	Bristol-Myers Co.	12,094
07/26/89	SmithKline Beckman Corp.	Beecham Group PLC	7,922
02/29/88	Sterling Drug	Eastman Kodak Co., Inc.	5,100
11/22/85	Richardson-Vicks Inc.	Procter & Gamble Co.	1,674
10/01/85	GD Searle & Co.	Monsanto Co.	2,700

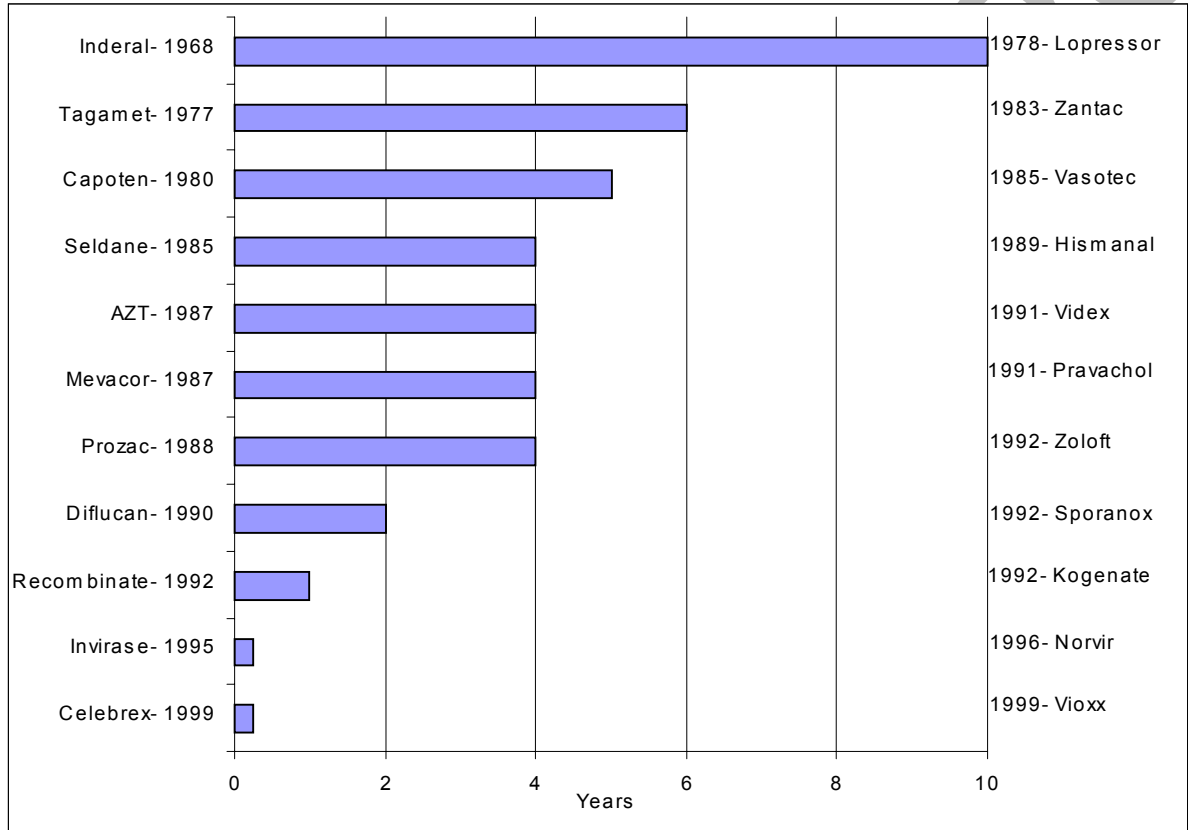
Source: Adapted from Securities Data Company, Inc. and Thomson Financial.

Exhibit 13 Top 20 Biotechnology Companies in 2001

Rank 2001	Corporation	Location	Revenue (000)	Net Income (000)	R&D (000)	Total Employees
1	Amgen Inc.	California	\$4,015,700	\$1,119,700	\$865,000	7,700
2	Genentech Inc.	California	2,212,277	150,236	526,230	4,950
3	Serono SA	Switzerland	1,376,470	316,721	308,561	4,501
4	Genzyme Corp.	Massachusetts	1,223,630	(112,156)	526,200	5,200
5	Chiron Corp.	California	1,140,667	180,036	344,415	3,736
6	Biogen Inc.	Massachusetts	1,043,360	272,683	314,556	1,992
7	MedImmune Inc.	Maryland	618,679	148,960	82,985	877
8	CSL Ltd.	Australia	441,846	40,422	41,972	--
9	Celltech Group Plc.	United Kingdom	436,343	(79,898)	--	2,029
10	Genencor Intl. Inc.	California	326,018	17,774	60,103	1,144
11	Idec Pharmaceuticals	California	272,677	101,659	86,299	692
12	Cephalon	Pennsylvania	266,643	3,349	84,249	1,127
13	Millennium Pharm.	Massachusetts	246,216	(192,005)	400,575	1,900
14	Nabi Biopharm.	Florida	234,829	104,682	15,330	615
15	Gilead Sciences Inc.	California	233,769	52,271	185,553	1,000
16	Vertex Pharm.	Massachusetts	167,490	(66,233)	148,673	1,000
17	Berna Biotech Ltd.	Switzerland	166,807	24,504	16,662	641
18	Celgene Corp.	New Jersey	114,243	(1,912)	67,653	383
19	Bio-Technology Gen.	New Jersey	101,965	(30,287)	25,576	378
20	SangStat Inc.	California	94,509	(9,379)	17,863	263

Source: Adapted from Andrew Humphreys, "Merging to be free: Looking beyond partnerships with big pharma, biotechnology companies consolidate to build product portfolios and pipelines on their own," *Med Ad News*, Vol. 21, Issue 7, July 1, 2002, and company annual reports.

Exhibit 14 Trend in Exclusivity Periods for Patented Pharmaceuticals



Source: Pharmaceutical Research and Manufacturers of America, 2002 Industry Profile, PhRMA, Washington, D.C., 2002, p. 33.

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