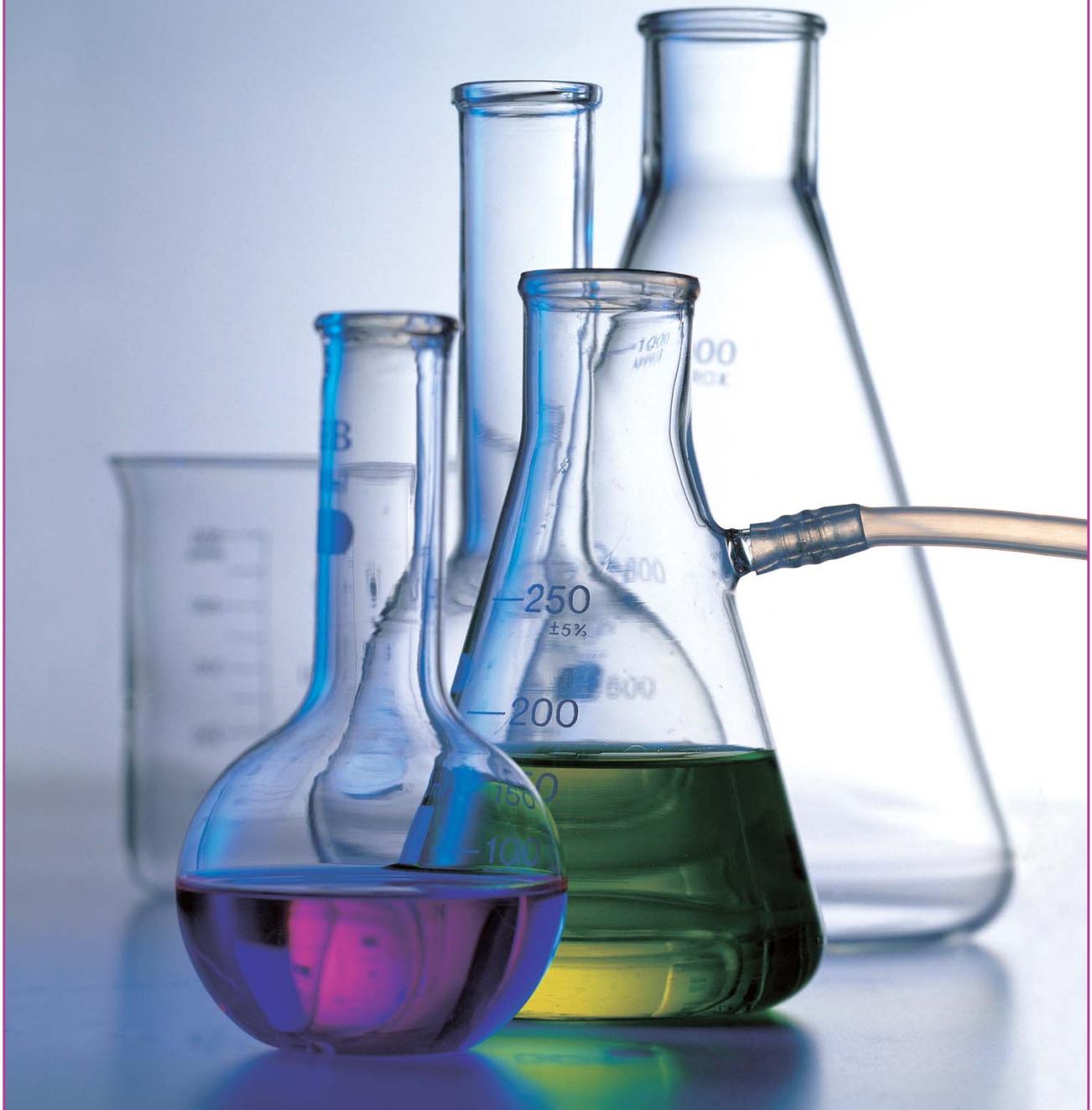
EXHIBIT
11

CONGRESS OF THE UNITED STATES
CONGRESSIONAL BUDGET OFFICE

A
CBO
STUDY

OCTOBER 2006

Research and Development in the Pharmaceutical Industry



Pub. No. 2589

A

CBO

STUDY

Research and Development in the Pharmaceutical Industry

October 2006

The Congress of the United States ■ Congressional Budget Office

Preface

Perceptions that the pace of new-drug development has slowed and that the pharmaceutical industry is highly profitable have sparked concerns that significant problems loom for future drug development. This Congressional Budget Office (CBO) study—prepared at the request of the Senate Majority Leader—reviews basic facts about the drug industry's recent spending on research and development (R&D) and its output of new drugs. The study also examines issues relating to the costs of R&D, the federal government's role in pharmaceutical research, the performance of the pharmaceutical industry in developing innovative drugs, and the role of expected profits in private firms' decisions about investing in drug R&D. In keeping with CBO's mandate to provide objective, impartial analysis, the study makes no recommendations.

David H. Austin prepared this report under the supervision of Joseph Kile and David Moore. Colin Baker provided valuable consultation. Jim Baumgardner, Anna Cook, Doug Hamilton, and Dennis Zimmerman of CBO provided comments, as did Iain Cockburn of Boston University, Mark Duggan of the University of Maryland, and Judith Wagner of the Institute of Medicine. (The assistance of external reviewers implies no responsibility for the final product, which rests solely with CBO.)

Christian Howlett edited the study, and Kate Kelly proofread it. Angela Z. McCollough prepared drafts of the manuscript. Maureen Costantino prepared the report for publication, with assistance from Allan Keaton, and designed the cover. Lenny Skutnik printed the initial copies, and Simone Thomas prepared the electronic version for CBO's Web site (www.cbo.gov).

Donald B. Marron
Acting Director

October 2006

Contents

Tables

Figures

Boxes

CHAPTER

1

Introduction and Summary

Recent concerns about escalating drug prices and rising health care spending have sparked considerable interest in how new drugs are discovered, tested, and sold—and in how well those processes serve the interests of U.S. consumers. Public dialogue on those issues, however, suggests that the complex economic forces that govern the drug-discovery process are not widely understood. Even some of the basic economic facts about the pharmaceutical industry have been subject to debate. This study describes the current state of pharmaceutical research and development (R&D), analyzes the forces that influence it, and considers how well markets are working to deliver new drugs.

Much of the public interest in pharmaceutical R&D concerns the relationship between drug prices, drug firms' costs, and the pace and direction of innovation. Average prices of new drug products have been rising much faster than the rate of inflation, and annual R&D spending has grown faster still. Nevertheless, introductions of innovative new drugs have slowed. At the same time, drug companies have been able to charge high retail prices for new drugs that are only incrementally different from older drugs whose prices have fallen. With consumers paying more for new drugs in the United States than almost anywhere else in the world, and with the perception that the drug industry has become less innovative, many observers have wondered whether some kind of policy intervention is warranted.

Pharmaceutical markets, however, are extremely complex in many respects. Large public-sector investments in basic biomedical R&D influence private companies' choices about what to work on and how intensively to invest in research and development. The returns on private-sector R&D are attractive, on average, but they vary considerably from one drug to the next. Consumer demand for prescription drugs is often indirect, mediated by doctors and health insurers. New drugs must undergo costly and time-consuming testing before they can be sold. Moreover, it may cost hundreds of millions of dollars to develop an innovative new drug that then will cost only a few cents per dose to manufacture—and the price of the drug will have no obvious connection to either cost. Comparative information about drug quality from unbiased, head-to-head clinical trials of competing drugs is seldom published, although it would help drug purchasers make the best choices—and in turn improve the market signals that guide private companies' decisions about research and development. An understanding of how such factors interact with the industry's R&D process is necessary to recognize the underlying causes of any failure of the market to encourage a socially optimal level of drug R&D.

This study presents basic facts about the pharmaceutical industry's spending on research and development and about the types and numbers of new drugs that result from it. The study also analyzes several major issues related to pharmaceutical R&D:

- What explains the cost of developing new drugs?
- Does federal investment in R&D stimulate or displace private investment?
- Has the drug industry's innovative performance declined?
- How profitable are drug firms, and how do profits affect the amount and type of R&D that companies conduct?

The Cost of Developing a New Drug

Research and development costs vary widely from one new drug to the next. Those costs depend on the type of drug being developed, the likelihood of failure, and whether the drug is based on a molecule not used before

in any pharmaceutical product (a new molecular entity, or NME) or instead is an incremental modification of an existing drug.

Innovative Drugs

A recent, widely circulated estimate put the average cost of developing an innovative new drug at more than $800 million, including expenditures on failed projects and the value of forgone alternative investments.[1] Although that average cost suggests that new-drug discovery and development can be very expensive, it reflects the research strategies and drug-development choices that companies make on the basis of their expectations about future revenue. If companies expected to earn less from future drug sales, they would alter their research strategies to lower their average R&D spending per drug. Moreover, that estimate represents only NMEs developed by a sample of large pharmaceutical firms. Other types of drugs often cost much less to develop (although NMEs have been the source of most of the major therapeutic advances in pharmaceuticals).

The study that produced that cost estimate also calculated how long it takes to develop a new drug and the relative contribution of capital costs to a drug's total R&D costs. On average, developing an innovative new drug takes about 12 years, the study concluded, and a firm's actual expenditures make up only about half of the total reported cost. The rest represents the financial cost of tying up investment capital in multiyear drug-development projects, earning no return until and unless a project succeeds. That "opportunity cost" of capital reflects forgone interest or earnings from alternative uses of the capital. (Opportunity costs are common to all innovative industries, but they are particularly large for pharmaceutical firms because of the relatively long time that is often required to develop a new drug.)

Research and development spending per NME has grown significantly in recent years, for various reasons. First, failure rates in clinical trials have increased, possibly because of greater research challenges or a willingness to test riskier drugs in such trials. Second, larger drug firms are said to have shifted the focus of their development efforts away from drugs for acute illnesses and toward drugs for chronic illnesses. Drugs that treat chronic illnesses can be more expensive to develop because they often require larger and longer clinical trials. Third, greater technological complexity in drug development and greater specificity in disease targets have helped to raise average R&D costs, as firms now identify drugs with particular molecular characteristics rather than using trial-and-error methods to find compounds that work in some desired way.

Not all new molecular entities provide unique therapeutic functions. Many NMEs are so-called "me-too" drugs. Despite that name, they are not necessarily imitations of other drugs. Rather, they may be innovative products that lost the race to be the first drug on the market in a given therapeutic class (such as antidepressants, antibiotics, or antihistamines). Such products can benefit consumers by competing with, and sometimes improving on, the pioneering drug in a class.

Incrementally Modified Drugs

Most new drug products have much lower R&D costs than NMEs because they are incremental improvements on existing drugs. Those costs can still be considerable if the new product requires clinical trials. Nevertheless, because non-NMEs constitute about two-thirds of the drugs approved by the Food and Drug Administration but account for only about one-third of the industry's R&D spending (by some estimates), their average direct cost may be only about one-fourth that of an NME. Their opportunity costs are also lower to the extent that they take less time to develop than drugs based on new molecules.

Incrementally modified drugs sometimes provide significant benefits to consumers. For example, more-convenient dosing forms (say, a pill that can be taken once a day rather than every four hours) can increase the likelihood that patients will take their medicine as directed and can result in better health. At the same time, given the indirect nature of demand in pharmaceutical markets, the higher prices that are charged for some drugs that are merely extensions of current product lines may not be commensurate with the additional value that those drugs provide.

The Role of Federal Research and Development

The federal government spent more than $25 billion on health-related R&D in 2005. Only some of that spend-

1. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

ing is explicitly related to the development of new pharmaceuticals. However, much of it is devoted to basic research on the mechanisms of disease, which underpins the pharmaceutical industry's search for new drugs.

The primary rationale for the government to play a role in basic research is that private companies perform too little such research themselves (relative to what is best for society). In general, the information generated by basic research can be readily replicated at low cost. Thus, many of the benefits of that research accrue not to the company that performs it but to the public and to other firms. With pharmaceuticals, those spillover benefits can be significant because the development of new drugs depends on scientific advances. Federal funding of basic research directly stimulates the drug industry's spending on applied research and development by making scientific discoveries that expand the industry's opportunities for R&D.

Government-funded basic research can also stimulate private-sector R&D indirectly. By supporting graduate students and postdoctoral researchers in academic labs where basic research is conducted, federal grants help to train many of the researchers who are hired by drug companies. That training enhances the productivity and profitability of the companies' R&D investments, while also allowing researchers to command higher salaries.

Given the extent of federal funding for life-sciences research, however, there is a risk that some of that funding could crowd out private-sector investment in R&D. In general, the government tends to focus on basic research, whereas private firms focus much more on applied research and development. That difference diminishes the risk of direct crowding out. But the distinction between basic and applied research is not well defined, and the division of labor between the two has become less pronounced as the potential commercial value of basic life-sciences research has become more widely recognized. Government and private R&D efforts have sometimes overlapped (as in the race to finish mapping the human genome); thus, the government may have funded some research that the private sector otherwise would have financed. Identifying specific cases where direct crowding out has occurred is difficult, but it is probably most likely to happen when the government funds research whose potential commercial applications are obvious and valuable.

Federal R&D spending can also crowd out private spending indirectly by causing labor costs to rise. Although students and postdoctoral researchers form part of the workforce for federally funded research, the government and the drug industry both draw on the same supply of trained professional researchers. That supply is relatively fixed in the short run, and higher R&D spending in either sector can cause salaries to rise by increasing the demand for researchers. That is more likely to occur when R&D spending is growing rapidly. In recent years, both real (inflation-adjusted) salaries for biomedical researchers and total employment in biomedical research have increased along with real R&D spending. When R&D spending is growing more slowly, however, there is probably little such effect on labor costs for professional researchers.

Assessing the Drug Industry's R&D Performance

Total spending on health-related research and development by the drug industry and the federal government has tripled since 1990 in real terms. However, the number of innovative new drugs approved by the Food and Drug Administration each year has not shown a comparable upward trend. NME approvals shot up for a few years in the mid-1990s and then fell again; on the whole, such approvals have consistently ranged between about 20 and 30 per year. Measured by the number of drugs approved per dollar of R&D, the innovative performance of the drug industry appears to have declined.

However, if new drugs were of higher quality than older drugs, on average, that improvement would partly or fully make up for a decline in the raw number of drugs per R&D dollar. Drug quality is multidimensional and difficult to measure, however. As a result, no careful and comprehensive estimate exists to show how changes in quality have affected the industry's actual R&D performance.

Other factors have contributed to the impression that the pharmaceutical industry's innovative performance has declined. Over the past decade, a growing share of the industry's R&D output has consisted of incremental improvements to existing drugs rather than new molecular entities. Performance measures that consider only entirely new drugs—such as the number of NME approvals per year—miss that shift and undervalue the industry's R&D output. Moreover, comparing output per

R&D dollar over long spans of time can be misleading because of shifts in the types of drugs being developed. Notwithstanding concerns about innovative performance and how to measure it, the range of illnesses for which drug therapies exist has never been broader, and technological advances have yielded new drug treatments of increasing sophistication, convenience, and effectiveness.

Even so, it is difficult to determine whether the returns to society from the money spent on drug R&D have declined or not. There are several possible reasons why the industry's R&D performance could have slipped. Companies may not yet have fully mastered the complex new research technologies with which they work; the pool of relatively inexpensive research discoveries may be temporarily depleted, pending further advances in basic science; and strong consumer demand for new drugs may have encouraged firms to invest in R&D beyond the point of diminishing returns. Furthermore, the frequency with which leading drug companies have merged with one another over the past decade—which may have resulted partly from a decline in the number of new drugs in development—has sparked concerns about the industry's R&D productivity. According to some observers, large firms tend to be less innovative than smaller firms. Those mergers have had little initial effect on the combined firms' total R&D spending, although the ultimate impact on the introduction of innovative new drugs remains uncertain.

If the industry's R&D performance has slipped, recent advances in basic sciences (such as molecular and cellular biology and biochemistry) could eventually reverse that trend by stimulating the development of more new drugs. In addition, new-drug approvals could increase simply because of the rising number of potential new products that have entered the development pipeline in recent years, according to drug companies. The greater commercialization of basic R&D and the increased specialization that has occurred in the drug industry may also enhance productivity. At the same time, though, the greater role of the private sector in basic R&D may have made the pace and direction of progress in drug development more dependent on financial factors in the industry.

The Drug Industry's Profits and R&D Investment

By standard accounting measures, the pharmaceutical industry consistently ranks as one of the most profitable industries in the United States. Those measures, however, treat most R&D outlays as expenditures rather than as investments that add to the value of a firm. Thus, they omit from a firm's asset base the value of its accumulated stock of knowledge. For R&D-intensive industries, such as pharmaceuticals, that omission can significantly overstate profitability. Adjusted for the value of its R&D assets, the drug industry's actual profitability still appears to be somewhat higher than the average for all U.S. industries, but not two to three times higher, as standard measures of profitability indicate.

The notion that pharmaceutical companies enjoy extraordinary profits is reinforced by the relationship between prices and costs in the drug industry. The industry's high R&D spending and relatively low manufacturing costs create a cost structure similar to that of, for example, the software industry. Both industries have high fixed costs (for research and development) and low variable costs (to put a software application onto a CD-ROM or to produce a bottle of prescription medication). Consequently, prices in those industries are usually much higher than the cost of providing an additional unit of the product, because revenue from sales of the product must ultimately cover those fixed costs.[2] Even though conventional accounting measures overstate the profitability of the drug industry, strong growth in the industry's R&D spending over many years suggests that the returns on pharmaceutical R&D have been attractive.

Ultimately, how adequately prices and profits indicate the kinds of drugs that consumers want to buy determines the extent to which the pace and direction of drug innovation are themselves adequate. High prices on new drugs encourage continued innovation. But because health insurance (private plans as well as Medicaid and Medicare) keeps consumers from bearing the full weight of those prices, the demand for new drugs is higher than it otherwise would be at any given price. That effect is magnified because employment-based health insurance benefits are not subject to income or payroll taxes, which reduces their cost to consumers. As a result, more people

2. Strictly speaking, a product's fixed development costs are not relevant to how it is priced because they are sunk (already incurred and not recoverable) before the product reaches the market. But a company incurs R&D costs in expectation of a product's likely price, and on average, it must cover those fixed costs if it is to continue to develop new products.

have health insurance, and many have higher levels of coverage, than would be the case otherwise.

The effect of health insurance on drug companies' revenues—combined with strong patent protection that helps firms maintain higher prices—may sometimes create incentives to invest too much in R&D (from the standpoint of the amount of investment that is optimal for society). The role of health insurance can be tempered in several ways, however. Insurers and other large buyers of drugs may be able to exercise more power to negotiate lower prices, and insurers can give patients and doctors stronger incentives to consider price differences between drugs. The more accurately a drug's price reflects its value to consumers, the more effective the market system will be at directing R&D investment toward socially valuable new drugs. However, prices can only serve that directing role to the extent that good information exists about the comparative qualities of different drugs and that consumers and health care providers use that information.

CHAPTER

2

Trends in R&D Spending and Output of New Drugs

The pharmaceutical industry spends more on research and development, relative to its sales revenue, than almost any other industry in the United States. According to various estimates, the industry's real (inflation-adjusted) spending on drug R&D has grown between threefold and sixfold over the past 25 years—and that rise has been closely matched by growth in drug sales. Despite those increases, there has been little change in the number of innovative new drugs approved for use each year, even though the federal government has streamlined its drug-approval process.

Only about one-third of the drugs approved annually in the United States are new compounds; the rest represent modified forms of—or new uses for—existing drugs. Firms develop new drug products in response to various factors. Those factors relate not only to likely demand in a given drug market—which is influenced by available health insurance coverage, doctors' prescribing practices, and demographic changes—but also to government policy toward drug safety and innovation and to the pace of scientific advances in the understanding and treatment of disease.

Spending for Research and Development

In 1980, U.S. companies spent a total of $5.5 billion (in 2005 dollars) on research and development of pharmaceuticals and medicines, according to the National Science Foundation (NSF). By 2003, that figure had grown to more than $17 billion—an average increase of 5 percent per year in real terms (see Figure 2-1). The pharmaceutical industry's trade association, Pharmaceutical Research and Manufacturers of America (PhRMA), reported even larger expenditures and faster growth. Spending by its member organizations rose more than sixfold between 1980 and 2004, from about $6 billion (in 2005 dollars) to $39 billion.[1] Those figures represent a real growth rate of about 8 percent a year, on average. By comparison, drug firms' gross margins—sales revenue minus costs and income taxes—have been increasing more slowly, by about 4 percent annually.[2]

The differences between NSF's and PhRMA's estimates of R&D spending stem largely from differences in which drug companies are included in the samples and which expenditures are counted. PhRMA's totals include all R&D spending in the United States by the association's members (foreign and domestic) as well as expenditures abroad by U.S. firms and U.S. divisions of foreign firms. Spending by foreign companies that occurs outside the United States is excluded. NSF's totals cover only domestic R&D spending by firms "engaged in for-profit activity in the United States." They exclude all research and development not conducted in the United States, including that performed by foreign subsidiaries of U.S. firms or by other foreign organizations.[3]

---

1. For comparison with NSF's numbers, total R&D spending by PhRMA members in 2003 was $37.6 billion in 2005 dollars (including $29.6 billion for domestic R&D by U.S. firms). PhRMA estimates that total R&D spending by the drug industry, including nonmember firms, was $49 billion in 2004, the first year the association estimated that total. Overall R&D spending by PhRMA members has grown even though the number of members has fallen by more than half since the early 1990s (to 34 organizations in 2004). Mergers account for some of that decline.

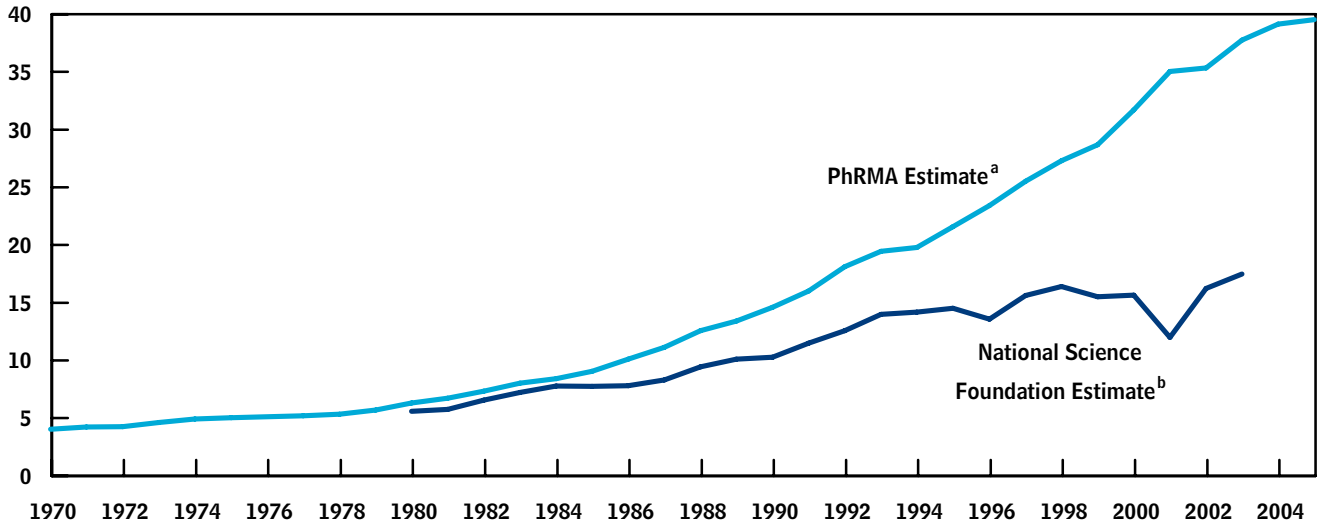
2. F.M. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 216-220.

3. National Science Foundation table, "Company and Other (Except Federal) Funds for Industrial R&D Performance, by Industry and by Size of Company: 1953–98," notes section, and "Technical Notes for 1998," available at www.nsf.gov/statistics/iris/excel-files/NSF%2001-305/tn.doc.

Figure 2-1.

Estimates of the U.S. Drug Industry's Annual Spending on Research and Development

(Billions of 2005 dollars)



Source: Congressional Budget Office based on the sources described below.

Note: Spending was adjusted for inflation using the biomedical research and development price index from the Bureau of Economic Analysis.

a. Expenditures reported by members of the Pharmaceutical Research and Manufacturers of America (PhRMA). Unlike the National Science Foundation data, PhRMA's estimates include research and development performed outside the United States by U.S. companies (or U.S. divisions of foreign companies) as well as further research and development that occurs after a drug has gone on the market. The data come from Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006).

b. The data series starts in 1980 and ends in 2003. It includes only research and development conducted in the United States on drugs that have not yet reached the market. Data for 1980 to 1998 come from the National Science Foundation table "Company and Other (Except Federal) Funds for Industrial R&D Performance, by Industry and by Size of Company: 1953-98," available at www.nsf.gov/statistics/iris/search_hist.cfm?indx=10 (see the row for "Drugs and Medicines"); data for 1999 to 2003 come from National Science Foundation, Division of Science Resources Statistics, annual "Research and Development in Industry" tables, available at www.nsf.gov/statistics/industry (see the rows for "Pharmaceuticals and Medicines").

The National Science Foundation's estimates also exclude spending on phase IV clinical trials (which are conducted after a drug has reached the market) and on the development of manufacturing processes—both of which PhRMA counts as R&D. In addition, NSF's figures do not include R&D by pharmaceutical firms that sell their own products, if sales activities account for the largest share of their payroll. (The Census Bureau classifies such firms as part of the "wholesale trade" sector.)[4] NSF estimates that postmarketing expenditures have recently constituted nearly 20 percent of PhRMA's total.[5] With those expenditures and drug R&D by "wholesale trade" firms included, NSF's total for 2003 would be within $1.7 billion, or about 5 percent, of the PhRMA estimate.[6] Much of the remaining difference can be explained by PhRMA's inclusion of some overseas R&D spending.

Those differences aside, the rise in research and development spending in both sets of estimates partly reflects an

4. NSF uses Census Bureau classifications and says that "true drug manufacturers are often assigned to the wholesale trade industry" because of a trend toward drug firms selling their own products. See Raymond M. Wolfe, *Increase in U.S. Industrial R&D Expenditures Reported for 2003 Makes Up for Earlier Decline,* National Science Foundation InfoBrief (December 2005), p. 4, available at www.nsf.gov/statistics/infbrief/nsf06305/nsf06305.pdf.

5. Personal communication to the Congressional Budget Office by Raymond Wolfe of the National Science Foundation.

6. See National Science Foundation, National Science Board, *Science and Engineering Indicators 2006,* vol. 1 (January 2006), pp. 4-17 and 4-18 and note 18, available at www.nsf.gov/statistics/seind06/pdf/volume1.pdf.

increase in the average R&D cost per drug that is attributable to a variety of factors. The scope of drug research has greatly expanded, fueled not only by growth in sales revenue for drugs but also by advances in basic science. The number of drug targets (typically, a protein molecule on which a drug is intended to act) has gone from 500 to more than 3,000 in recent years, and according to one analyst, "the expansion of research activity to investigate them is a natural . . . consequence."[7] The same scientific advances have also induced a shift from "chemistry-based" drug development to drug research based on molecular biology, which has led pharmaceutical firms to spend more for capital equipment and training. Further, in the wake of a 1980 decision by the U.S. Supreme Court governing the patenting of living organisms, biological molecules can now be patented.[8] That development has created a marketplace for basic research in the biological sciences. Consequently, pharmaceutical companies now often pay for access to basic research performed by specialized firms—research that traditionally would have been conducted in the public domain. Those additional research expenses have contributed to drug firms' higher R&D spending, even though the net cost to society of that research has not necessarily changed.[9]

R&D Intensity

The pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm.

Because increases in spending on drug R&D have been nearly matched by increases in revenue from drug sales, the industry's R&D intensity—the ratio of research and development spending to total sales revenue—has not risen to the extent that R&D expenditures have. Over the past 25 years, R&D intensity has grown by about 50 percent. Most of that growth occurred in the 1980s; since then, the industry's R&D intensity has hovered around 19 percent, according to PhRMA (see Figure 2-2).[10]

A relatively close relationship exists between drug firms' current R&D spending and current sales revenue for two reasons. First, successful new drugs generate large cash flows that can be invested in R&D (their manufacturing costs are usually very low relative to their price). Second, alternative sources of investment capital—from the bond and stock markets—are not perfect substitutes for cash flow financing. Those alternative sources of capital are more expensive because lenders and prospective new shareholders require compensation (in the form of higher returns) for the additional risk they bear compared with the firm, which has more information about the drug under development, its current status, and its ultimate chance of success.[11]

The National Science Foundation also estimates that the R&D intensity of the pharmaceutical industry has been fairly stable in recent years, ranging between about 8 percent and 10 percent since 1985. That estimate is less than half of PhRMA's, in part because NSF includes less-R&D-intensive products not related to prescription pharmaceuticals (such as vitamins, over-the-counter drugs, reference chemicals sold to researchers for experiments, and consumer and animal care products). Even at that lower estimate, pharmaceuticals ranked as the most R&D-intensive industry in the U.S. manufacturing sector for most of the 1990s, according to NSF (until it was overtaken by communications equipment, whose R&D-intensity was 12.7 percent in 2003).

The relative stability of the relationship between pharmaceutical R&D and sales revenue suggests that firms find it most profitable to invest any additional dollar of sales rev-

7. See Iain M. Cockburn, "Is the Pharmaceutical Industry in a Productivity Crisis?" (paper prepared for the National Bureau of Economic Research's Innovation Policy and the Economy Conference, Washington, D.C., April 19, 2006), available at www.nber.org/books/innovation7/cockburn4-29-06.pdf; and Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs,* vol. 23, no. 1 (January/February 2004), p. 12.

8. *Diamond v. Chakrabarty,* 447 U.S. 303.

9. Substituting private payment for public funding of basic scientific research may have a cost to society if it affects the pace or direction of that research; otherwise, it simply transfers the responsibility for paying for the research from the public sector to the private sector.

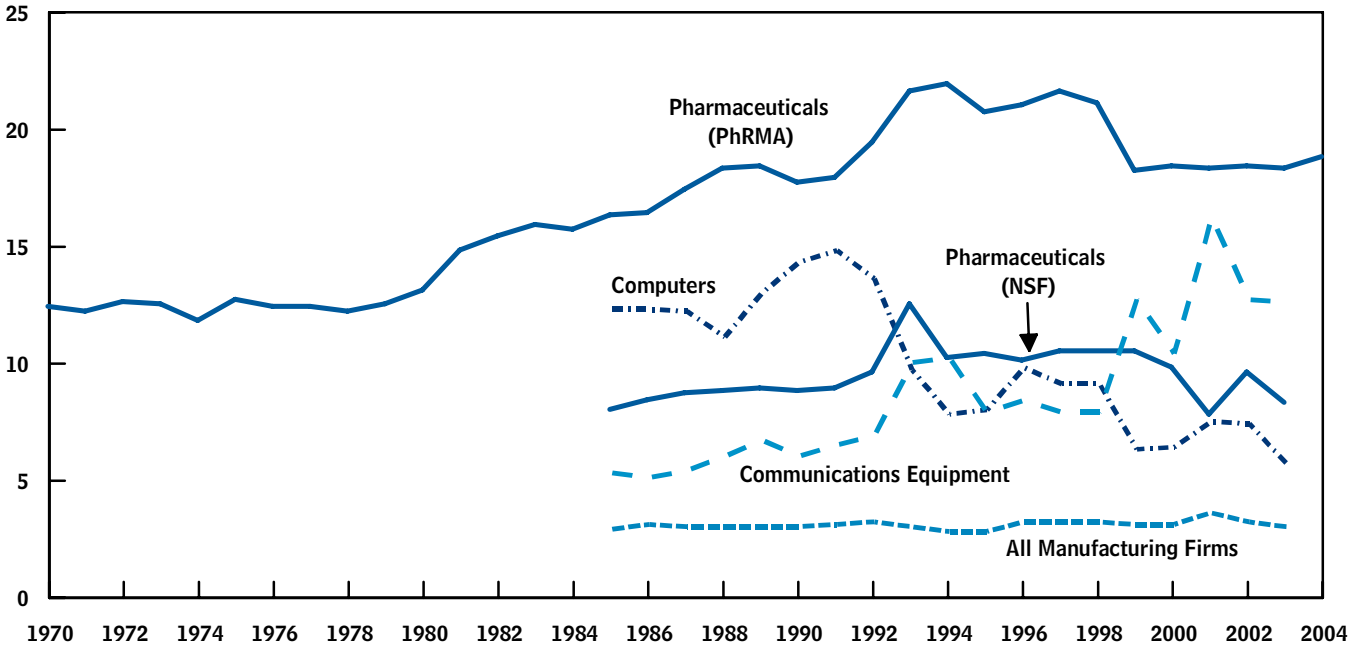
10. Although Figure 2-2 depicts domestic R&D as a share of domestic sales (according to PhRMA), total R&D intensity—including non-U.S. R&D and international sales by U.S.-owned firms and all R&D by U.S. divisions of foreign-owned firms—has been comparable. Total R&D intensity ranged from 9 percent to 15 percent through the late 1980s and has been about 16 percent to 17 percent since then.

11. See Uwe E. Reinhardt, "Perspectives on the Pharmaceutical Industry," *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 136-149.

Figure 2-2.

Research and Development Spending as a Percentage of Sales Revenue for Various U.S. Industries

(Percent)



Source: Congressional Budget Office based on Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2005* (Washington, D.C.: PhRMA, March 2005); and National Science Board, *Science & Engineering Indicators 2000,* Appendix Table 2-57, available at www.nsf.gov/statistics/seind00/pdf/append/c2/at02.pdf, and *Science & Engineering Indicators 2006,* Appendix Table 4-22, available at www.nsf.gov/statistics/seind06/pdf/volume2.pdf.

Notes: Industry data for which no source is shown come from the National Science Foundation. The NSF data are in two series: 1985-1997 and 1999-2003. The first series is based on the Standard Industrial Classification system. In the second series, some industry classifications changed because firms were recategorized according to the North American Industry Classification System. The data for those two periods are not fully comparable. Because no data were available for 1998, CBO used 1997 values for 1998 for graphing purposes.

No estimate was reported in 1991 for communications equipment; for graphing purposes, CBO used the average of the 1990 and 1992 values for that industry.

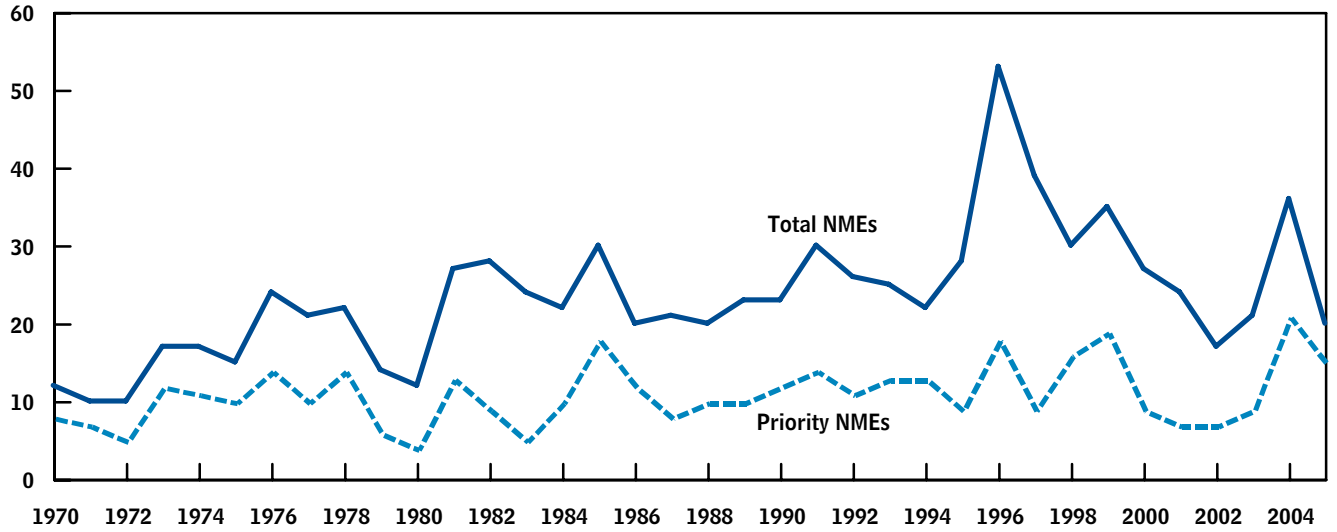
enue in their own drug research. However, changes in real drug prices can affect companies' R&D intensity or their propensity to invest in R&D from their revenue.[12] The reason is partly that, as noted above, higher drug prices tend to increase firms' cash flow, and internally generated cash is a relatively inexpensive source of investment capital. But changes in price levels also affect firms' expectations about profits. Thus, higher real drug prices may increase the value of completing existing projects more quickly and encourage companies to undertake more new research than they would otherwise. Both effects involve increased R&D spending and thus greater R&D intensity. Analysts generally view that connection as having clear implications for efforts to reduce industry prices and profits, in that such interventions would dampen R&D investment.[13]

12. One study concluded that a 10 percent increase (or decrease) in real U.S. drug prices would, if everything else remained the same, boost (or reduce) R&D intensity by almost 6 percent. See Carmelo Giaccotto, Rexford Santerre, and John Vernon, *Explaining Pharmaceutical R&D Growth Rates at the Industry Level: New Perspectives and Insights,* Publication 03-31(Washington, D.C.: AEI-Brookings Joint Center for Regulatory Studies, December 2003).

13. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," p. 220.

Figure 2-3.

Number of New Molecular Entities Approved by the Food and Drug Administration Each Year



Source: Congressional Budget Office based on Food and Drug Administration, Center for Drugs and Biologics, *New Drug Evaluation Statistical Report* (1985), Table III-1, Graph III-2, and Appendix B, and *New Drug Evaluation Statistical Report* (March 1986 and April 1987), Table II-1 and Graph II-2; Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management, *Offices of Drug Evaluation Statistical Report* (1987-1989), Table II-1, Graph II-1, and Graph II-2; Food and Drug Administration, "CDER NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type" (March 22, 2005), available at www.fda.gov/cder/rdmt/pstable.htm; and Food and Drug Administration, "FDA Facts: The Center for Drug Evaluation and Research," available at www.fda.gov/bbs/topics/news/2006/NEW01342/Fact_Sheet_CDER.pdf.

Notes: New molecular entities (NMEs) are drugs that contain an active substance not previously approved for marketing in the United States. "Priority" NMEs are ones that receive accelerated reviews by the Food and Drug Administration because of their potentially significant therapeutic value. (Before 1992, priority NMEs were known as category A or B drugs.)

Data for 2004 and 2005 include therapeutic biologic products.

Output of Innovative New Drugs

Continued growth in R&D spending has appeared to have little effect on the pace at which new drugs are developed. Annual approvals of innovative new drugs—so-called new molecular entities—by the Food and Drug Administration (FDA) increased over the 1980s and peaked sharply in the mid-1990s but then experienced a pronounced six-year decline.[14] In that decline, the total number of NMEs approved each year fell from a high of 53 in 1996 to 17 in 2002 (see Figure 2-3). Annual approvals rebounded to 36 by 2004 but fell again in 2005, to 20.[15] (The number of applications for approval of new molecular entities has exhibited a similar pattern. Applications rose sharply in 1995—the year before the peak in approvals—generally declined from 1998 to 2002, and rose again in 2003 and 2004.) The drop in approvals since 1996 could simply mark a return to their long-term average, but even so, the pace of new-drug approvals has not matched the rise in real R&D spending. As a result, the average R&D cost per new drug has grown significantly.

14. The FDA defines an NME as "a medication containing an active substance that has never before been approved for marketing in any form in the United States"; see Food and Drug Administration, Center for Drug Evaluation and Research, "FDA's Drug Review and Approval Times" (July 30, 2001), available at www.fda.gov/cder/reports/reviewtimes/default.htm.

15. See Food and Drug Administration, "FDA Facts: The Center for Drug Evaluation and Research," available at www.fda.gov/bbs/topics/news/2006/NEW01342/Fact_Sheet_CDER.pdf. Of the 20 NMEs approved in 2005, 15 were given priority review.

Most of the upsurge in NME approvals that occurred in the mid-1990s resulted not from "priority" NMEs—those judged by the FDA to provide "a significant therapeutic or public health advance" over existing drugs—but from an increase in approvals of "standard" NMEs.[16] Approvals of priority NMEs have shown no sustained increases or decreases over the past 20 years.

Some analysts have concluded that the spike in total NME approvals may have been partly caused by a federal law designed to hasten the review process, the Prescription Drug User Fee Act of 1992.[17] The law imposed a large increase in the filing fee for new-drug applications submitted for FDA approval; that increase funded additional FDA staff to review applications.[18] As a result, the median FDA review time fell by nearly one-half, from 22 months in 1992 to 12 months in 1999.[19] That change suggests that if a backlog of applications existed when the law was enacted, faster processing could have contributed to the record number of NME approvals in 1996. A backlog may have accumulated in the early 1990s, because the annual number of applications was rising at that time, while FDA approvals were falling. The decline in NME approvals in the late 1990s would be consistent with a decrease in the backlog, although NME applications were also in decline at that time. It is not clear why the number of applications rose and then fell, but that pattern could indicate that the prospect of faster (and thus less costly) reviews induced firms to complete, and to prepare approval applications for, their late-stage development projects more quickly.

The number of NME approvals has varied more widely over the past 10 years than it did before—meaning that the number of drugs under patent, and thus firms' revenue streams, have become more variable. Most manufacturers of brand-name drugs earn the majority of their revenue from drugs under patent. Wider fluctuations in revenue heighten companies' uncertainty about their main source of R&D funding. If that variability persists, firms may have to rely to a greater extent on external, more costly forms of financing. Such a change could make firms less likely to invest in drug projects with smaller, more uncertain, or more distant payoffs.

Leading Therapeutic Classes

Brand-name drug products span a wide array of therapeutic classes (groups of drugs that are similar in their chemical structure, pharmacological effect, or clinical use). In 2003, 17 therapeutic classes included at least three brand-name drugs that ranked in the top 200 for prescriptions dispensed among all brand-name drugs (see Table 2-1). Those products are mostly newer drugs, since sales of brand-name drugs typically drop sharply once generic versions become available. As such, the 17 therapeutic classes indicate where the industry's recent R&D spending has been directed.

In several classes—such as antihypertensives, antibiotics, and antidepressants—a striking number of brand-name drugs are available. That is particularly true of therapeutic classes with higher sales. In addition to the first (or pioneer) compound, some leading classes have as many as five to 10 subsequent brand-name drugs (known colloquially as me-too drugs). Those other drugs are not necessarily imitative: often, advances in basic science can spark multiple competitive innovations, with total R&D costs that may be as high as or even higher than the costs of developing the pioneer compound.[20] In fact, most of the me-too drugs developed in recent years were in clini-

16. Food and Drug Administration, "FDA's Drug Review and Approval Times." Priority NMEs receive accelerated FDA reviews (intended to take no more than six months). The FDA adopted the priority classification system in 1990; it previously used an A-B-C scale in which 'A' corresponded to drugs offering significant therapeutic gains.

17. Public Law 102-571. For its effect on NME approvals, see Ernst R. Berndt and others, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews: Drug Discovery,* vol. 4, no. 7 (July 2005), pp. 545-554.

18. In 2007, the fee will be $896,200 for an application with clinical data. See Food and Drug Administration, "Prescription Drug User Fee Rates for Fiscal Year 2007," *Federal Register,* vol. 71, no. 148 (August 2, 2006), p. 43780, available at www.fda.gov/CBER/pdufa/userfees07.pdf.

19. Food and Drug Administration, "FDA's Drug Review and Approval Times." The median approval time increased somewhat in 2000, in part because the FDA processed fewer of its speedier priority applications that year.

20. U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards,* OTA-H-522 (February 1993), p. 7.

Table 2-1.

Therapeutic Classes with Three or More Leading Brand-Name Drugs in 2003

Therapeutic Class (Major subclasses)	Number of Drugs in the Top 200[a]	Total Sales (Billions of dollars)[b]	Prescriptions (Millions of units sold)[b, c]
Antidepressants (SSRIs, SNRIs)	8	11.6	114.5
Antihyperlipidemics (Statins)	6	11.1	108.4
Antiulcerants (Proton-pump inhibitors)	5	10.4	70.0
Antihypertensives (ARBs, ACE inhibitors)	11	5.8	88.1
Antibiotics (Broad- and medium-spectrum)	9	5.5	89.2
Diabetes Therapies (Oral, injectible)	6	4.9	63.5
Antiarthritics (COX-2 inhibitors)	4	4.8	48.4
Antipsychotics	3	4.2	20.2
Antihistamines (Oral)	3	4.1	63.2
Neurological Drugs (For seizures or pain)	5	4.0	36.2
Other Vascular Drugs (Calcium- or beta-blockers)	7	3.7	68.7
Antiasthmatics	5	3.6	28.1
Analgesics (Nonnarcotic)	3	2.8	20.1
Bone Density Regulators	4	2.3	32.0
Oral Contraceptives	3	2.1	44.4
Antiallergy Drugs (Nasal steroids)	4	2.0	29.9
Analeptics (ADHD treatments)	3	1.3	16.9

Source: Congressional Budget Office based on "The Top 20 Brand Drugs in 2003 (by retail dollars)," *Drug Topics* (March 8, 2004); "The Top 20 Brand Drugs in 2003 (by units)," *Drug Topics* (March 22, 2004); and information about therapeutic classes from IMS Health.

Note: SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; ADHD = attention-deficit hyperactivity disorder.

a. Includes only unique new molecular entities (not variants such as different dosing mechanisms) that are among the top 200 drugs on the basis of units sold.

b. Total for the top-200 drugs shown here, not the entire therapeutic class.

c. Number of units sold is measured in terms of packages (such as bottles), not individual doses.

cal trials before the respective pioneering drugs received approval from the FDA.[21]

In cases where actual imitation occurs, it can still create consumer benefits (as it does in the markets for cars, colas, computers, or any other product). Me-too drugs benefit consumers by competing with incumbent products and providing alternatives for people who do not respond equally well to all drugs. Some of those benefits come at the expense of producers of pioneering drugs, who see their monopoly profits eroded by competition.[22] But total benefits to society increase when consumers have more choices.

The availability of so many brand-name drugs in popular therapeutic classes may result partly from the willingness of insurers and patients to sometimes pay high prices for drugs that are only slightly better than less expensive competitors. Drugs may be able to command a price premium in such cases for several reasons:

- Consumers and health professionals do not always have enough information about differences in quality between drugs or about the clinical significance of those differences,

21. See Joseph A. DiMasi and Cherie Paquette, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development," *PharmacoEconomics,* vol. 22, supplement 2 (2004), pp. 1-14.

22. For evidence of price competition among brand-name drugs, see Z. John Lu and William S. Comanor, "Strategic Pricing of New Pharmaceuticals," *Review of Economics and Statistics,* vol. 80, no. 1 (February 1998), pp. 108-118. See also Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998), p. 27.

- Some patients place a high value on small improvements in quality,
- Doctors may be generally unaware of drug prices or may not take them into account, or
- Consumers' incentives to consider the prices of various prescription drug choices may be weak.

To the extent that incomplete information and weak incentives distort drug prices, they also distort firms' decisions about drug R&D, and they may partially explain the existence of multiple competing drug products in some markets. (The availability of comparative drug information and the strength of price incentives are discussed in Chapter 6.)

Companies are also drawn to invest in particular therapeutic classes by expected growth in those markets. Various institutional and demographic factors affect that growth. For example, the number of new drugs in therapeutic categories that are associated with young people has declined—and the number of new drugs for older adults has increased—as the baby-boom generation has aged. That demographic shift has allowed economists to identify the effect of changes in market demand on spending for drug R&D: one study estimated that 1 percent growth in the potential market for a category of drugs leads to an increase of roughly 4 percent in the entry of new nongeneric drugs in that category.[23] In addition, research spending by private industry on malaria drugs increased after the General Agreement on Tariffs and Trade was amended to address concerns about intellectual-property rights.[24] And federal policies relating to immunizations, liability limitations for vaccine manufacturers, and Medicare coverage decisions have had "substantial" and "sustained" effects on the private-sector's development of certain new vaccines, according to another study.[25] The study concluded that for every additional dollar in expected revenue because of those policies, firms invested an average of six additional cents (in present-value terms) in R&D on related vaccines.

The drug industry's practical opportunities for technological innovation are strongly affected by advances in basic science, but those advances too are responsive to demographic and institutional factors, as reflected in public priorities for spending on basic R&D.[26] Health insurers' decisions about coverage can also affect the types of products that drug companies try to develop.[27] Ultimately, the relationship between higher sales and more drug choices in a therapeutic class not only reflects the attraction of R&D dollars to potentially larger markets and to research opportunities created by advances in science but also reflects the market expansion that can occur when multiple drugs offer consumers additional therapeutic choices and lower prices through competition.

Modifications and Approved New Uses of Drugs

On average, only about one-third of new-drug applications submitted to the FDA are for new molecular entities. Most of the rest are either for reformulations or

23. See Daron Acemoglu and Joshua Linn, "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," *Quarterly Journal of Economics* (August 2004), p. 1051.

24. See Jean Lanjouw and Iain Cockburn, "New Pills for Poor People? Empirical Evidence After GATT," *World Development,* vol. 29, no. 2 (February 2001), pp. 265-289. At that time, some developing countries also strengthened their intellectual property protection for drug innovations.

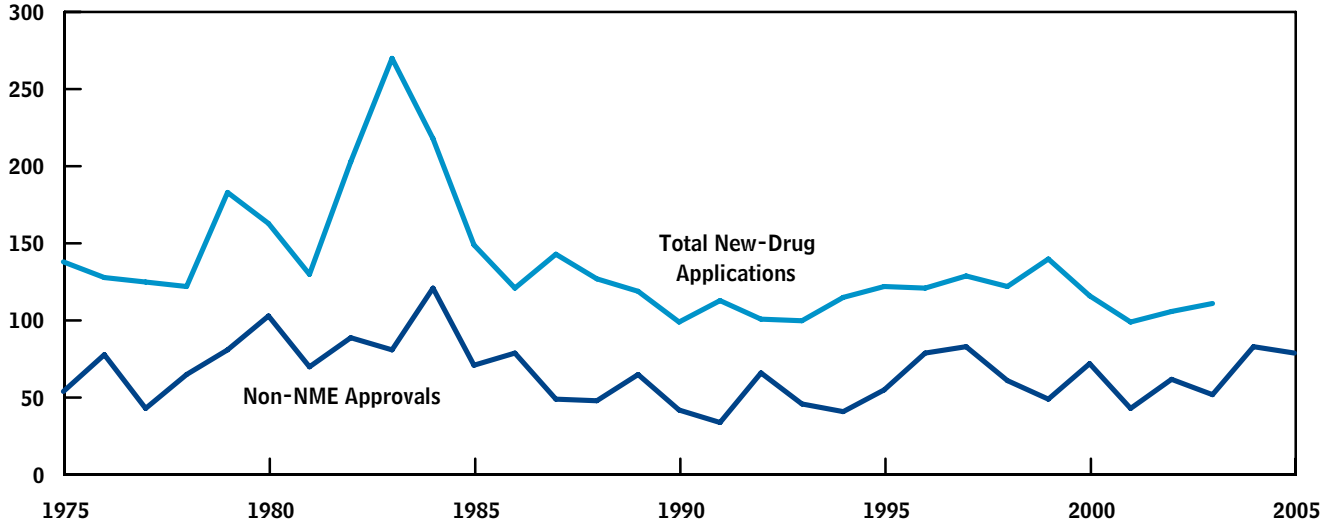
25. See Amy Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* (May 2004), p. 528. The policies studied were a 1991 recommendation by the Centers for Disease Control that all infants be vaccinated against Hepatitis B; a 1993 decision by Medicare to cover influenza vaccinations without copayments; and the 1986 adoption of the Vaccine Injury Compensation Fund, which indemnified drug firms against liability stemming from childhood vaccinations against polio, diphtheria-tetanus, and measles-mumps-rubella. Some of the increased R&D spending might have been socially wasteful in the sense that firms raced to develop new vaccines and may have duplicated some of their rivals' research. Finkelstein concluded, however, that the combined social benefits of those vaccine policies (the flu vaccination policy in particular) far outweighed the costs.

26. See Michael R. Ward and David Dranove, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry,* vol. 33, no. 1 (January 1995), pp. 70-87. The authors found that research at the National Institutes of Health tended to be directed toward illnesses with growing mortality rates (consistent with a process incorporating public comment and advocacy), whereas private-sector research was more responsive to the prevalence of an illness, as that relates to potential market size.

27. For a detailed discussion of that issue, see Burton Weisbrod, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature,* vol. 29, no. 2 (June 1991), pp. 523-552.

Figure 2-4.

Number of Non-NMEs Approved by the Food and Drug Administration Each Year, Compared with Total New-Drug Applications



Source: Congressional Budget Office based on Food and Drug Administration, Center for Drugs and Biologics, *New Drug Evaluation Statistical Report* (1985-1987), Table II-1, Table III-1, and Graph II-1; Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management, *Offices of Drug Evaluation Statistical Report* (1987-1989), Table II-1; and Food and Drug Administration, "CDER NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type" (March 22, 2005), available at www.fda.gov/cder/rdmt/pstable.htm.

Note: NME = new molecular entity. Non-NMEs include modifications of, or new approved uses for, existing drugs.

incremental modifications of existing drugs or for new "on-label" uses (additional health conditions for which an existing drug can be prescribed). None of those types of new drugs involve a new active ingredient, although firms must conduct clinical trials to gain FDA approval for new uses.

Whereas almost half of NME applications are classified by the FDA as "priority," most of the other new-drug applications are rated as "standard."[28] Even so, modifications to pharmaceutical products can create substantial value for consumers. For example, more-convenient dosing forms can increase the likelihood that patients will take all of their medication as directed and thus improve their health outcomes. In addition, approved new on-label uses can become the primary source of demand for a drug, suggesting that the new use is more valuable to patients than the original use.[29]

The annual number of non-NME drug approvals has varied greatly over the past 15 years, with no pronounced trend (see Figure 2-4). However, comparing patterns in those approvals with patterns in the annual number of new-drug applications of all types suggests that applications tend to precede approvals by a year or two.

28. From 1990 to 2004, the FDA approved 1,284 new drugs, including 431 new molecular entities. Of those NMEs, 42 percent were rated "priority," versus 12 percent of non-NMEs. See Food and Drug Administration, "CDER NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type" (March 22, 2005), available at www.fda.gov/cder/rdmt/pstable.htm, and "FDA Facts: The Center for Drug Evaluation and Research," available at www.fda.gov/bbs/topics/news/2006/NEW01342/Fact_Sheet_CDER.pdf.

29. For example, about three-quarters of the demand for drugs in the therapeutic classes of selective serotonin/norepinephrine reuptake inhibitors (SSRIs and SNRIs) and H_2-blockers/proton-pump inhibitors (H_2/PPIs) comes from patients with conditions other than the ones for which the drugs were originally approved (acute-phase major depression and duodenal ulcers, respectively). See Ernst R. Berndt, Iain M. Cockburn, and Karen A. Grépin, "The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilization in Original and Supplemental Indications," *PharmacoEconomics* (forthcoming, 2006).

The practice of incrementally changing and improving existing products is common to all industries. For the drug industry, however, several government policies have given firms extra incentives to alter their products. The main such policies have been provisions of the 1984 Hatch-Waxman Act and the drug rebate system in the Medicaid program.[30]

The Hatch-Waxman Act protects new versions of existing drugs for a limited time from competition from generic drugs. By awarding three years of market exclusivity to incrementally modified versions of original, patented drugs, the law gives companies an additional incentive to alter their existing drugs.[31] That incentive has grown over time as generic competition has become more effective and materialized more quickly.

The Hatch-Waxman Act also eliminated clinical trials for generic versions of existing brand-name drugs. Increasingly, once generic versions do enter a market, they quickly gain market share at the expense of brand-name drugs. In the first few years after the law took effect, the average market share of generic drugs one year after the patent on a brand-name drug expired was 35 percent. A decade later, that figure had almost doubled to 64 percent. By the late 1990s, nearly all brand-name drugs could be expected to face generic competition once their patents expired.[32] The loss of sales to generic versions can occur particularly quickly for best-selling drugs. For example, Prozac lost more than 80 percent of its U.S. sales to lower-priced generic versions in the first month after its patent expired.[33]

To have their products covered by the Medicaid program—which provides prescription drugs to most of the roughly 60 million lower-income people enrolled in the program—drug manufacturers must enter into a rebate agreement with the Centers for Medicare & Medicaid Services.[34] For a brand-name drug purchased in the fee-for-service sector on behalf of a Medicaid beneficiary, the manufacturer agrees to rebate to Medicaid a percentage of the price it receives on certain private-sector sales of that drug.[35] Like the changes in the Hatch-Waxman Act, that rebate affects firms' incentives to incrementally modify certain drugs. If a company raises the price of a brand-name drug faster than the rate of inflation, it must pay a larger rebate. However, that provision does not apply to the way a modified version of an existing drug is priced in relation to the original drug. Thus, if a manufacturer wants to raise the price of a drug more quickly while avoiding the additional rebate, it can develop a new version of the drug—for example, with a different dosage or form of delivery—and introduce it at a higher price.

For firms, that option is more valuable when Medicaid is a drug's primary source of revenue. Indeed, a recent study finds that newer drugs with high Medicaid sales and no generic competitors "are significantly more likely to [be introduced in] new versions" than other drugs are.[36] Modified products command significantly higher prices for the same dosage—in the range of 7 percent to 20 percent higher—than earlier versions of the drugs do. (In general, generic competition makes it more difficult to charge higher prices for brand-name drugs because such

30. The Hatch-Waxman Act (Public Law 98-417) is officially the Drug Price Competition and Patent Term Restoration Act of 1984.

31. In addition, the FDA provides expedited regulatory approval of incrementally modified drugs, via the so-called 505(b)(2) pathway.

32. See Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry.*

33. Henry Grabowski, "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," in John V. Duca, ed., *Science and Cents: Exploring the Economics of Biotechnology* (Dallas: Federal Reserve Bank of Dallas, September 2003), p. 92. Patricia M. Danzon, Andrew Epstein, and Sean Nicholson state that generic drugs now gain over 80 percent of prescription volume within one year. See Danzon, Epstein, and Nicholson, *Mergers and Acquisitions in the Pharmaceutical and Biotechnology Industries,* Working Paper No. 10536 (Cambridge, Mass.: National Bureau of Economic Research, June 2004), footnote 2.

34. For Medicaid enrollment numbers, see Congressional Budget Office, "Fact Sheet for CBO's March 2006 Baseline: Medicaid and the State Children's Health Insurance Program," available at www.cbo.gov/budget/factsheets/2006b/medicaid.pdf

35. For more information about Medicaid's rebates from drug manufacturers, see Congressional Budget Office, *The Rebate Medicaid Receives on Brand-Name Prescription Drugs* (June 21, 2005), and *Prices for Brand-Name Drugs Under Selected Federal Programs* (June 2005).

36. See Mark Duggan and Fiona Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," *Quarterly Journal of Economics,* vol. 71, no. 1 (February 2006), pp. 20 and 23. Note that because Medicaid's share of sales of antipsychotic drugs has fallen since that study was conducted, the program's effect on the introduction of new versions of those drugs may have declined.

competition increases the likelihood that a drug will lose sales to generic versions if its price is set too high.)

Medicaid's pricing rules have affected some drug companies' decisions about R&D by encouraging the development of incrementally modified versions of drugs with high Medicaid sales. Those rules avoid other difficulties and R&D distortions that the government could create if it tried to set drug prices itself. But studies of the impact of the Medicaid rebate program, along with studies of the effects of the Hatch-Waxman Act, illustrate that firms' R&D investments are responsive not only to market forces but also to public policy—sometimes in unanticipated ways.

CHAPTER

3

What Does It Cost to Develop a New Drug?

An innovative new drug that contains a previously untried active ingredient can take years to develop and test. After sifting through a large set of chemical compounds to find one with the desired action, a firm must test the drug using a formal and rigorous protocol so that its safety and efficacy can be determined with statistical validity. That testing can take much longer than the laboratory research that produced the drug. With expenditures steadily accumulating at each stage, the research and development costs of developing a new drug can be high. Moreover, for every successful new drug, a firm will have had many failed drug projects that did not survive clinical trials or that never won approval from the Food and Drug Administration. Estimates of average R&D costs per drug include the costs of those failures.

The total cost of developing a new drug may be twice as high as those direct costs, however, because the indirect, financial costs of tying up investment capital for years in research projects (which will not pay off until a marketable drug is developed) can be as large as a firm's actual R&D spending. Those financial costs—often called opportunity costs—reflect the returns that a firm could have earned from alternative investments if its capital had not been tied up in drug development. Opportunity costs exist in all industries and for all innovative products, but they are particularly large in the pharmaceutical industry because drugs have longer development times than many other types of products.

With the drug industry's R&D spending rapidly increasing but the number of new drugs approved each year showing little change, the average R&D cost per new drug has grown significantly. According to a widely cited estimate, that cost averages more than $800 million for innovative new drugs, including both direct and indirect costs. Possible reasons for the rise in R&D costs per drug include changes in the number and size of clinical trials that new drugs undergo. Some of those changes involve additional, postmarketing tests that firms conduct to try to distinguish their drug from products made by rival companies, and some of the changes reflect a possible shift in the focus of R&D toward drugs for chronic illnesses (which can require larger and longer trials). The development of complex new research technologies and advances in basic science may also have helped to drive up R&D costs.

Primary Determinants of R&D Costs

A frequently cited 2003 study by Joseph DiMasi, Ronald Hansen, and Henry Grabowski (DHG) estimated that the average cost of successfully developing a new molecular entity, including R&D spending on failed drug projects, was $802 million in 2000.[1] Although that estimate suggests that new drugs can be very costly to develop, it is an average that reflects the costs of successes and failures alike. It also reflects the research strategies and drug-development choices that firms make on the basis of their expectations about future revenue. If companies expected to earn less revenue from future drug sales, they would adjust their research strategies to reduce their average R&D spending per drug.

Research and development costs for new drugs are highly variable. Although the DHG study surveyed drugs from a representative set of therapeutic classes, it excluded some types of new drugs that have lower average R&D costs, such as those that do not introduce new active ingredients but rather are modifications of existing drugs. In addition, the estimate may not be representative of R&D costs for smaller pharmaceutical firms, which did not participate in the survey on which the study was based. However, by focusing on new molecular entities, the

1. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

Table 3-1.

DiMasi and Others' Estimate of Average Research Costs and Times for Successfully Developed New Molecular Entities

	Average Length of Research Phase		
	Preclinical Phase (4.3 years)[a]	Clinical Trials and FDA Approval (7.5 years)	Total (11.8 years)
Research and Development Costs (Millions of 2000 dollars)			
Direct costs	121	282	403
Opportunity costs[b]	214	185	399
Total Costs	**335**	**467**	**802**

Source: Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

Note: FDA = Food and Drug Administration.

a. The estimate for the duration of the preclinical phase is based on the comprehensive drug database maintained by the Tufts University Center for the Study of Drug Development.

b. Opportunity costs are the costs associated with keeping capital tied up in a specific drug-development project for a given period (that is, the forgone interest or earnings that a company might have gained from investing its capital in other ways). DiMasi and others assumed the forgone rate of return to be 11 percent per year.

DHG study did base its cost estimate on the types of drugs that have been the source of most pharmaceutical breakthroughs.[2]

The average successfully developed NME in the study's sample required 4.3 years for discovery and preclinical development and another 7.5 years for clinical trials and FDA approval.[3] (Approval itself took an average of 1.5 years.) Thus, developing an NME and bringing it to market required 11.8 years, on average (see Table 3-1).

For those various phases of research and development, the DHG study estimated average out-of-pocket (or direct) costs and fully capitalized costs (assuming a capital cost rate of 11 percent per year). The difference between the two represents opportunity costs. For the drug projects in the DHG survey, opportunity costs constitute about half of the total average cost of developing a drug. Those costs would make up a smaller percentage of the total cost for shorter projects. But in all cases, opportunity costs constitute a greater share in the preclinical phase than in the clinical-trial phase because investments made in the earlier phase are tied up longer.

The study's cost data are proprietary and cannot be independently verified. However, analysts at the Federal Trade Commission who sought to replicate the study's results found average research durations that were substantially

2. In some cases, however, breakthroughs have been achieved by enhancing existing drugs or by discovering important new uses for older drugs. For instance, new roles have been found for aspirin in reducing the risk of heart attacks, for antiepileptic drugs in treating bipolar disorder, and for antibiotics in treating peptic ulcers. See Iain M. Cockburn and Rebecca Henderson, *Public-Private Interaction and the Productivity of Pharmaceutical Research,* Working Paper No. 6018 (Cambridge, Mass.: National Bureau of Economic Research, April 1997), pp. 9-10.

3. In the DHG sample, the three phases of human clinical trials—tests for safety in a small sample of healthy human volunteers, efficacy and further safety testing in a larger sample of people with the condition that the drug is intended to treat, and large-scale clinical trials to establish efficacy and identify side effects—took an average of 2 to 2.5 years each. Elsewhere, DiMasi reported average phase lengths of 3.8 years (preclinical) and 10.4 years (clinical and FDA approval), or 14.2 years in all, for the 1990-1999 period. See Joseph A. DiMasi, "New Drug Development in the United States from 1963 to 1999," *Clinical Pharmacology & Therapeutics,* vol. 69, no. 5 (May 2001), pp. 286-296. For a different sample of drugs, Grabowski estimated an average of 3.5 years in discovery and preclinical testing (excluding basic research), more than 6 years in clinical trials, and 2.5 years for FDA review, or more than 12 years in total. See Henry Grabowski, *Health Reform and Pharmaceutical Innovation* (Washington, D.C.: AEI Press, 1994).

similar, for a much larger sample of drug projects.[4] They also found that average research lengths varied significantly for different therapeutic classes and different firms. The Office of Technology Assessment (OTA) evaluated an earlier survey by DiMasi and others that used a very similar methodology. OTA concluded that the average time profiles and rates of change in R&D spending reported by companies that responded to the survey were "congruent" with those firms' public, audited financial records.[5] And although OTA could not rule out that the survey responses might have overestimated actual research spending, it noted that the responses were "at least internally consistent with one another" from year to year.

An editorial in the *Journal of Health Economics* concluded that the DHG study's $802 million cost estimate was rigorously and carefully constructed.[6] However, it also argued that the average R&D cost of developing an incrementally modified drug was probably much lower than that amount. Available data indicate that, roughly speaking, spending to modify existing drugs accounts for less than one-third of total R&D expenditures, although modified versions of existing drugs make up about two-thirds of all new drug products.[7] Thus, the average direct R&D cost of an incrementally modified drug may be no more than one-fourth that of a new molecular entity. Its fully capitalized R&D costs may be an even smaller fraction—if, as seems likely, modifying a drug takes less time than discovering one.

Another analyst has asserted that the DHG estimate is representative only of research done by the type of large, leading pharmaceutical firms that participated in the survey.[8] Such firms are said to place more emphasis on treatments for cancer and chronic diseases than smaller firms do. Drugs for those kinds of illnesses can be costly to develop compared with drugs for acute illnesses because they often require larger and longer clinical trials.

In addition, the R&D costs that companies report may be somewhat inflated because the federal research and experimentation tax credit gives firms an incentive to be expansive in classifying expenses as R&D-related.[9] Thus, the DHG estimate may include some ancillary expenses not strictly for research and development. The Congressional Budget Office has no evidence, however, about whether that is or is not the case.

Ultimately, because the expected returns from individual drug projects depend as much on expected sales revenue as on R&D costs, an inexpensive drug project may be either more or less attractive to a company than an expensive one. As a result, an estimate of average R&D costs may be of little help to firms in deciding whether to undertake a particular new drug project. The main utility of studies such as the DHG survey lies in showing how long it takes and how expensive it is, on average, to develop the kinds of innovative drugs represented in those surveys, as well as how that duration and expense have grown over time as the industry has pursued different kinds of drug treatments using increasingly sophisticated research technologies.

Why Have R&D Costs Risen for Innovative New Drugs?

Various surveys conducted between 1976 and 2000 suggest that during that period, the average amount that surveyed firms reported spending on research and development of new molecular entities increased nearly sixfold in real terms (see Figure 3-1). DiMasi, Hansen, and Grabowski estimate that average R&D costs, including opportunity costs, rose at an annual rate that was 7.4 percent above inflation during the 1980s (the most recent decade for which they have made such an estimate) and

4. See Christopher P. Adams and Van V. Brantner, "Estimating the Cost of New Drug Development: Is It Really $802 Million?" *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 420-428.

5. See U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards,* OTA-H-522 (February 1993), pp. 61-62; and Joseph A. DiMasi and others, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics,* vol. 10, no. 2 (July 1991), pp. 107–142.

6. Richard G. Frank, "New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), p. 327.

7. Ibid., p. 327, citing CMR International's 2002 estimate that product-line extensions account for 30 percent of research and development and PhRMA's 1999 estimate that they account for "about 18 percent" of R&D expenditures.

8. F.M. Scherer, "The Pharmaceutical Industry—Prices and Progress," *New England Journal of Medicine,* vol. 351, no. 9 (August 26, 2004).

9. See Gary Guenther, *Federal Taxation of the Drug Industry: 1990 to 1999* (Congressional Research Service, July 22, 2002). See also Michael Kremer and Rachael Glennerster, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* (Princeton, N.J.: Princeton University Press, 2004), Chapter 9.

9.4 percent above inflation during the 1970s.[10] Observers attribute the continuing growth in R&D costs for innovative new drugs to several factors:

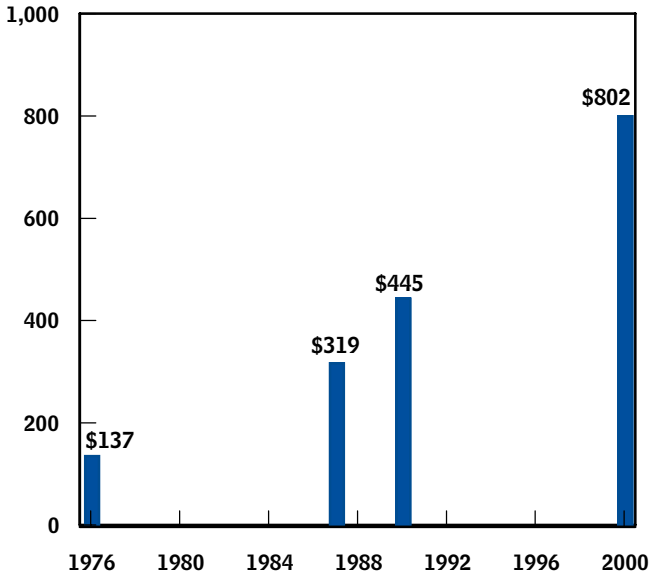
- An increase in the percentage of drug projects that fail in clinical trials;
- A trend toward bigger and lengthier clinical trials as well as a possible rise in the number of trials that firms are conducting (including trials for marketing purposes, such as to differentiate a product from its competitors);
- A shift in the types of drugs that companies work on, toward those intended to treat chronic and degenerative diseases;[11]
- Advances in research technology and in the scientific opportunities facing the pharmaceutical industry;
- The increased commercialization of basic research, as firms more often pay for access to basic research findings that in earlier years might have been freely available;[12] and
- A lengthening of the average time that drugs spend in preclinical research.

In the other direction, various developments—faster FDA reviews, regulatory changes, and speedier methods of identifying potential R&D failures—may have kept research and development costs from growing as quickly as they would have otherwise.

Figure 3-1.

Various Estimates of the Average R&D Cost of a Successfully Developed New Molecular Entity

(Millions of 2000 dollars)



Source: Congressional Budget Office based on R.W. Hansen, "The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes," in R.I. Chien, ed., *Issues in Pharmaceutical Economics* (Lexington, Mass.: Lexington Books, 1979), pp. 151-187; Joseph A. DiMasi and others, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics,* vol. 10, no. 2 (July 1991), pp. 107-142; U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards,* OTA-H-522 (February 1993); and Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

Notes: R&D = research and development.

The year shown for each estimate is the year in which the cost survey was performed, not the year in which the results were published.

Higher Failure Rates

To be approved by the FDA for use, a drug must undergo three phases of human clinical trials: tests for safety in a small sample of healthy human volunteers (phase I), effi-

10. DiMasi, Hansen, and Grabowski, "The Price of Innovation," pp. 167-168. OTA estimated a higher rate of increase over the first half of the 1970s, 12.4 percent above inflation. It attributed that rise largely to an increase in the size of clinical trials and to a lengthening of drug-development times (from 9.6 years to 11.8 years during that period) because of longer time spent in preclinical research and in gaining FDA approval. See Office of Technology Assessment, *Pharmaceutical R&D.*

11. Note that the earlier mention of chronic illnesses was in the context of the greater emphasis placed on them by larger firms. Here the context is the growth in that emphasis over time. For the industry's shift toward such illnesses, see DiMasi, Hansen, and Grabowski, "The Price of Innovation," p. 181; and Grabowski, *Health Reform and Pharmaceutical Innovation,* p. 12.

12. According to the Association of University Technology Managers, universities' total royalty income on patents has lately exceeded $1 billion per year. Much of that income is from biomedical patents. See Association of University Technology Managers, *AUTM U.S. Licensing Survey: FY 2004—Survey Summary* (Northbrook, Ill.: AUTM, 2005), p. 26, available at www.autm.net/events/File/FY04%20Licensing%20Survey/04AUTM-USLicSrvy-public.pdf.

cacy testing and further safety testing in a larger sample of people with the condition that the drug is intended to treat (phase II), and large-scale clinical trials to establish efficacy and identify side effects (phase III). According to the FDA, the proportion of all news drugs entering phase I trials that ultimately gain approval has fallen to 8 percent from a historical average of about 14 percent.[13] That decline could explain a significant part of the increase in average R&D costs per new drug—the more so the later those additional failures occur in the trial process.

Rising failure rates could indicate that the stock of easily discoverable new drugs has been temporarily depleted, pending further advances in science. However, they could also result from growing consumer demand for new drugs. Firms are likely to invest first (if all else is equal) in projects with the highest expected returns, which are partly a function of how likely those projects are to succeed. Increases in demand induce firms to develop additional, less promising projects that they had held in reserve, including those less likely to succeed.

The average success rate for new molecular entities is much higher than for new-drug applications as a whole, but it still illustrates how relatively few drugs survive the clinical-trial process. Of the NMEs in the Tufts Center for the Study of Drug Development's database (from which the DHG sample was drawn), 71.0 percent survived phase I clinical trials to enter phase II, and 31.4 percent survived to phase III (see Figure 3-2). Because phase III trials are much larger and more expensive than earlier trials, the cost of failure rises disproportionately though the trial process. Overall, 21.5 percent of the NMEs completed phase III trials and were approved by the FDA, a rate nearly three times higher than for all new-drug applications.[14]

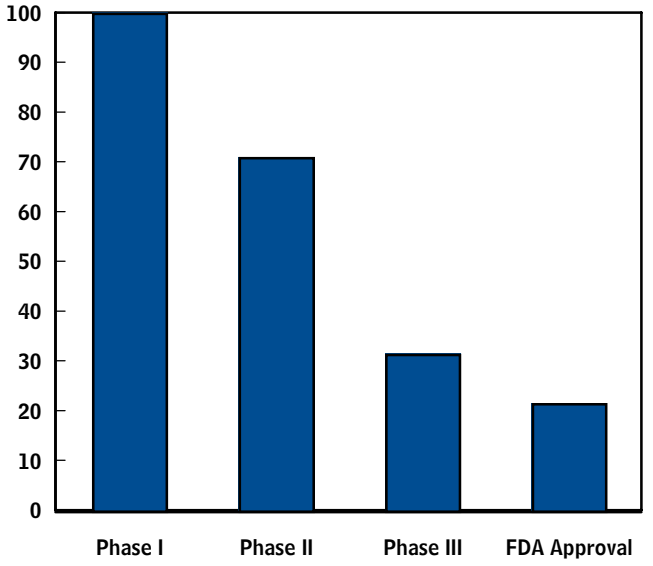
Changes in Clinical Trials

Contributing to the rise in R&D costs, average clinical-phase costs grew fivefold between 1987 and 2000, according to the DHG study—or at an average rate of more than 12 percent a year in real terms.[15] That growth resulted from increases in the size and duration of clinical trials. The DHG study estimates that the average number of people per trial grew by 7.5 percent annually, from about 2,300 in the 1980s to more than 5,600 by the early 2000s.[16] The average length of the clinical-trial phase increased by 27 percent over the 1980s and then declined by 4 percent over the 1990s.[17]

Companies may also be undertaking more clinical trials now than in the past, performing head-to-head trials for

Figure 3-2.

Percentage of New Molecular Entities Entering Each Phase of Clinical Trials



Source: Congressional Budget Office based on Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, vol. 22 (2003), pp. 151-185.

Note: FDA = Food and Drug Administration.

13. Food and Drug Administration, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004), p. 8.

14. DiMasi, Hansen, and Grabowski, "The Price of Innovation," p. 162.

15. Ibid., p. 162.

16. Ibid., p. 177. OTA agreed that clinical trials had grown larger in terms of number of subjects; see Office of Technology Assessment, *Pharmaceutical R&D,* pp. 144-146.

17. DiMasi, "New Drug Development in the United States from 1963 to 1999." Those estimates were based on a larger sample of NMEs than in the DHG study. Another study, using a different sample of drugs, found no evidence that the average length of clinical trials fell between 1992 and 2002; see Salomeh Keyhani, Mari Diener-West, and Neil Powe, "Are Development Times for Pharmaceuticals Increasing or Decreasing?" *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 461-468.

marketing and product-differentiation purposes.[18] (In the FDA approval process, a drug is compared with a placebo rather than with other drugs.) In some cases, a firm may sponsor clinical trials whose primary purpose is to familiarize participating doctors with the company's new drugs; such trials may not even be intended to be scientifically rigorous.[19] In other cases, firms may face pressure from health insurers to demonstrate their drugs' superiority with scientific rigor as a condition of being included in insurers' formularies of preferred drugs. To the extent that extra tests establish that a drug is superior to available substitutes, such tests can also allow firms to set higher prices.[20] However, quality differences between approved drugs are likely to be smaller than differences between a drug and a placebo, so showing that the differences are clinically and statistically significant requires larger and more costly clinical trials.

Changes in the Types of Drugs Being Developed

A shift in companies' R&D efforts toward drugs for chronic and degenerative illnesses rather than drugs for acute illnesses could also have contributed to higher R&D costs. Since chronic-illness drugs take longer to achieve measurable results, they may require bigger and more expensive trials. Also, because such drugs are meant to be taken for a long time, they must be tested for side effects over a longer period. Furthermore, their therapeutic effects may be subtle—reducing the severity of symptoms rather than curing a disease—and difficult to distinguish from the health effects of other, unrelated factors in the patient population. In such cases, a larger study with more participants may be necessary for statistical reasons. Finally, as the DHG study notes, therapies for chronic conditions typically require more-complex patient care and monitoring, further adding to the expense of clinical trials.[21]

Scientific Advances

Another change that may have played a role in boosting R&D costs is the retooling that the drug industry has undertaken in response to advances in basic science.[22] The sequencing of the human genome, which was completed in 2003, is expected ultimately to open productive new branches of drug research. However, that scientific milestone coincided with an unexpected slowdown in submissions of new-drug applications worldwide.[23] One explanation for the slowdown may be that new research technologies and capabilities—such as the industry's shift from traditional chemical methods in randomly screening for new drug compounds to computer-automated screening—have imposed learning costs that temporarily damped research output and raised firms' R&D costs.[24]

Factors Slowing the Growth of R&D Costs

Despite the overall increase in average research and development costs for new drugs, some changes have helped slow that growth. Additional review staff at the FDA, funded by revenue from the Prescription Drug User Fee Act of 1992, helped slow the growth rate of R&D costs by reducing the time required for FDA approval. The average development time for new drugs declined by about 10 percent over the 1990s, from nearly 99 months to about 90 months, according to the DHG study. Much

18. Scherer, "The Pharmaceutical Industry—Prices and Progress," p. 928.

19. David A. Kessler and others cite evidence that firms have conducted "seeding" clinical trials that lacked control groups, were not blinded, and appeared to be for marketing rather than scientific purposes; see Kessler and others, "Therapeutic-Class Wars—Drug Promotion in a Competitive Marketplace," *New England Journal of Medicine,* vol. 331, no. 20 (November 17, 1994), pp. 1350-1353. A recent study concludes that doctors who conduct clinical trials sponsored by a pharmaceutical company subsequently increase their prescribing of the sponsoring firm's drugs; see Morten Andersen, Jakob Kragstrup, and Jens Søndergaard, "How Conducting a Clinical Trial Affects Physicians' Guideline Adherence and Drug Preferences," *Journal of the American Medical Association,* vol. 295, no. 23 (June 21, 2006), pp. 2759-2764.

20. DiMasi, Hansen, and Grabowski, "The Price of Innovation," p. 181, citing F-D-C Reports, "NDA Submissions Are Shrinking in Size but Increasing in Complexity," *The Pink Sheet,* vol. 61 (1999), p. 28.

21. DiMasi, Hansen, and Grabowski, "The Price of Innovation," p. 181.

22. See Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs,* vol. 23, no. 1 (January/February 2004), p. 12.

23. Food and Drug Administration, *Innovation or Stagnation,* p. 3. In 2003, the National Human Genome Research Institute at the National Institutes of Health stated that "most new drugs based on the completed genome are still perhaps 10 to 15 years in the future, although more than 350 biotech products—many based on genetic research—are currently in clinical trials, according to the Biotechnology Industry Organization." See National Human Genome Research Institute, "The Human Genome Project Completion: Frequently Asked Questions" (November 2005), available at www.genome.gov/11006943.

24. See Peter Landers, "Drug Industry's Big Push into Technology Falls Short," *Wall Street Journal,* February 24, 2004, p. A1.

of that decline was attributable to the 1992 law, which is estimated to have reduced FDA review times by almost 10 months.[25] Other changes at the FDA—including a streamlining of the preclinical regulatory process, as called for in the FDA Modernization Act of 1997—may also have kept drug-development times shorter than they would have been otherwise.

The FDA asserts that methods to better predict the outcome of R&D and to demonstrate a drug's safety and efficacy more quickly hold promise as an important source of reductions in future R&D costs. According to the agency, research in the areas of prediction and demonstration has lagged behind advances in basic science. The FDA says that better predictive tools could reduce the number of drugs that enter clinical trials by more effectively identifying likely failures before clinical testing begins.[26] In any case, some evidence suggests that companies have become more adept at identifying failures earlier in the trial process: success rates for early-phase trials declined slightly between the 1991 study by DiMasi and others and the 2003 DHG study, while the likelihood of success in phase III trials rose by 5 percentage points.[27]

25. For the average new molecular entity in the DHG survey, that time savings would have reduced development costs by about $40 million (or about 5 percent of total costs), assuming that it eliminated 10 months of capital-cost accumulation on an average of $403 million in direct R&D costs, at an assumed capital-cost rate of 11 percent per year.

26. Food and Drug Administration, *Innovation or Stagnation*, p. 8.

27. DiMasi, Hansen, and Grabowski, "The Price of Innovation," p. 163.

CHAPTER

4

Does Federal R&D Spending Stimulate or Substitute for Private-Sector Spending?

Federally funded research plays a major role in the discovery of new pharmaceuticals. Most of the important new drugs introduced by the pharmaceutical industry over the past 40 years were developed with some contribution from public-sector research.[1] In the past decade, federal outlays on health-related research and development have totaled hundreds of billions of dollars at the National Institutes of Health (NIH) alone.[2] Although only some of that spending was explicitly related to pharmaceuticals, much of it was for the basic research on disease mechanisms that underlies the search for new drugs. Federally supported basic research in genomics, molecular biology, and other life sciences has greatly expanded the drug industry's technological opportunities, stimulating private investment in pharmaceutical R&D.

Given the extent of public R&D spending in the life sciences, however, there is a risk that such spending could "crowd out" (or discourage) private investment in some cases by substituting for it rather than complementing or stimulating it. The government's focus on basic research, while the drug industry concentrates on applied research and development, tends to minimize that risk. But the distinction between basic and applied research is not always clear—and it has blurred to some degree as drug development has become more dependent on scientific knowledge.

Aggregate statistical data suggest that, overall, private R&D spending responds positively to federal R&D. In specific cases, however, the government may have funded some research that the private sector otherwise would have paid for. Identifying where such direct crowding out has occurred is difficult, but it is probably more likely to happen in areas where potentially valuable commercial applications of government-funded research are more apparent.

In addition, an indirect form of crowding out may occur if increases in federal R&D spending cause total employment in the research field to rise. Higher demand for researchers could cause research salaries—and thus firms' labor costs—to increase. Salaries are more likely to be affected in that way when federal funding is growing rapidly. In general, however, federal funding trains many graduate students for research careers in the drug industry, contributing indirectly to the productivity and profitability of pharmaceutical R&D.

Public and Private R&D Spending

Health-related research receives the second largest amount of federal support for R&D (behind only defense-related research). That support has been steadily growing for several decades. Research spending by NIH—by far the primary recipient of government funding for health-related basic research—totaled $5.8 billion (in 2005 dollars) in 1970, more than doubled to $12.3 billion by 1990, and reached $28.5 billion by 2004 (see Figure 4-1). In comparison, R&D spending reported by the members of the Pharmaceutical Research and Manu-

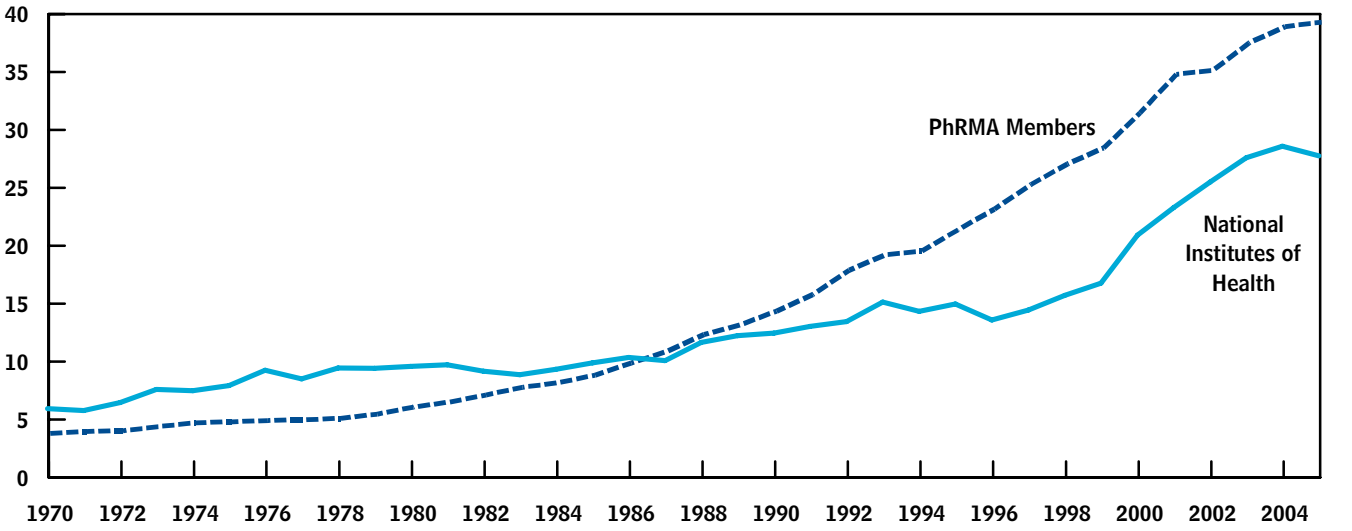
1. Out of 21 of the most influential drugs introduced between 1965 and 1992, only five were essentially developed entirely by the private sector. See Iain M. Cockburn and Rebecca M. Henderson, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," in Adam B. Jaffe, Josh Lerner, and Scott Stern, eds., *NBER Innovation Policy and the Economy,* vol. 1 (Cambridge, Mass.: National Bureau of Economic Research, 2000), pp. 20-21.

2. NIH receives the majority of the government's funding for human life-sciences research. The rest goes to the National Science Foundation, the National Aeronautics and Space Administration, the Environmental Protection Agency, the Veterans Administration, and the Departments of Energy, Commerce, Defense, and Health and Human Services (of which NIH is a part). See National Science Foundation, *Federal Funds for Research and Development* (various years), available at www.nsf.gov/statistics/fedfunds/.

Figure 4-1.

Annual Spending on Research and Development by Drug Companies and the National Institutes of Health

(Billions of 2005 dollars)



Source: Congressional Budget Office based on Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006); and National Science Foundation, *Federal Funds for Research and Development* (various years), available at www.nsf.gov/statistics/fedfunds/.

Note: Spending was adjusted for inflation using the biomedical research and development price index from the Bureau of Economic Analysis.

facturers of America was just two-thirds the size of NIH's spending in 1980. PhRMA's R&D spending surpassed NIH's in 1987 and has remained higher since then, although both grew at similar rates in the late 1990s and early 2000s.[3]

Much of the government's R&D spending is for basic research, but a 1993 study by the Office of Technology Assessment found that some of it has funded applied research specifically related to the development of new drugs. OTA identified multiple federal programs, many of them at NIH, "whose specific mission [was] to conduct R&D involving actual or potential pharmaceutical products."[4] At that time (in the late 1980s), federal spending on such research amounted to slightly less than 10 percent of the government's total spending on health-related R&D.[5] However, much of the rest of that spending supports pharmaceutical R&D by improving the understanding of disease mechanisms. Although it is difficult to say exactly how much of the federal government's health-related R&D spending is relevant to the pharmaceutical industry, much of it probably is.

3. That comparison excludes R&D spending abroad by foreign PhRMA members. Domestic R&D by domestic PhRMA members has exceeded NIH outlays since 1991 (by $3 billion to $5 billion in most years).

4. U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards,* OTA-H-522 (February 1993), p. 211.

5. CBO calculation based on Office of Technology Assessment, *Pharmaceutical R&D,* Tables 9-4 and 9-6, pp. 214 and 215, and total government spending on health-related R&D of less than $10 billion a year. Since 2000, NIH has classified all of its R&D as research rather than development. See Ronald L. Meeks, *Proposed FY 2003 Budget Would Complete Plan to Double Health R&D Funding, Considerably Expand Defense R&D*, National Science Foundation InfoBrief (July 2002), footnote 3, available at www.nsf.gov/statistics/infbrief/nsf02326/. In NIH's 2007 R&D budget, basic research accounts for 58 percent of total spending, with applied or clinical research accounting for the rest. See American Association for the Advancement of Science, Intersociety Working Group, *AAAS Report XXXI: Research and Development, FY 2007* (Washington, D.C.: AAAS, 2006).

The rationale for government funding of basic scientific research is that if such research were left solely to the private sector, too little of it would be done, in the sense that the benefits to society from doing additional basic R&D (beyond what firms alone would conduct) would far outweigh the costs. A company's incentive to invest in R&D is limited to its own expected returns. In the case of basic research and development, those returns can be particularly low compared with the social benefits, because it can be difficult for private companies to capture more than a small fraction of the total social value of their basic research.[6] Although the distinction between basic and applied R&D is not always clear, it is useful to think of basic research as generating information or knowledge that is not readily embodied in physical products.[7] Companies can have trouble keeping the benefits of their basic R&D to themselves because the information can generally be communicated at very low cost.

Given the increasingly scientific basis of drug development, the pharmaceutical industry has come to view publicly funded basic R&D as a "critically important source of immediately useful knowledge and techniques."[8] Drug firms cite "immediate access to leading-edge publicly funded science" as an important competitive advantage.[9] Government funding for basic research also pays for the laboratory training that graduate students receive as they prepare for careers as professional researchers in the pharmaceutical industry.

Despite the difficulties of capturing more than a small part of its value, many drug companies perform some basic research themselves. In addition to supporting their applied R&D programs, such research helps to attract motivated scientists who might otherwise prefer to work in an academic setting. Doing its own basic research and publishing the findings may also enhance a firm's capacity to benefit from academic and government basic research.[10]

Does Government R&D Crowd Out Private R&D?

Even as it produces substantial social benefits, federal spending on basic research and development can also discourage private investment in R&D.[11] Such crowding out can occur directly, as when the government sponsors research that the private sector would otherwise have conducted. Or it may occur indirectly, as the government competes for trained scientists and other scarce resources and bids up their prices.

Government-sponsored R&D can also influence competitive interactions between firms. As a result of its own research and technical capabilities, one company may be better positioned than its rivals to take advantage of new scientific findings from government-sponsored basic research. Or the research may help competitors narrow a leading firm's advantage by expanding the scope of common scientific knowledge. In either case, public funding of basic research can affect private R&D spending by revising firms' expectations about profits.

Examples of Crowding Out

In the past, direct crowding out may have been relatively uncommon in the pharmaceutical industry because the public sector mainly focused on basic research and the private sector mainly concentrated on applied research and development. However, structural changes in the industry have increased the private sector's role in basic research. And advances in biological sciences have helped to blur the distinction between basic and applied research.

6. A basic research discovery cannot be patented unless the inventor can credibly describe the discovery's "specific and substantial" utility. See U.S. Patent and Trademark Office, "2107 Guidelines for Examination of Applications for Compliance with the Utility Requirement," available at www.uspto.gov/web/offices/pac/mpep/documents/2100_2107.htm.

7. See F.M. Scherer, *New Perspectives on Economic Growth and Technological Innovation* (Washington, D.C.: Brookings Institution Press, 1999), pp. 54-57; and Nathan Rosenberg, "Why Do Firms Do Basic Research (With Their Own Money)?" *Research Policy,* vol. 19 (1990), especially p. 170 for the distinction between basic and applied research in health and medicine.

8. Cockburn and Henderson, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," p. 17.

9. Ibid., p. 4.

10. Ibid.; and Rosenberg, "Why Do Firms Do Basic Research?"

11. Material in this and the following paragraph comes from Cockburn and Henderson, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," and from Iain Cockburn and Rebecca Henderson, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery," *Journal of Industrial Economics,* vol. 46, no. 2 (June 1998), pp. 157-182.

Box 4-1.

Do Private Firms Benefit Disproportionately from Taxpayer-Funded Basic Research?

Some observers have noted that companies can save significantly on research and development when they develop new drugs from chemical compounds that were discovered in government or academic laboratories. Such drugs should therefore be "reasonably" priced, according to those observers.

The Bayh-Dole Act of 1980 grants the government a royalty-free license to use inventions, such as new drugs, that it had a hand in developing, but that license is rarely exercised.[1] A chemical compound discovered through publicly funded research may be licensed to a private firm on terms specified by (or negotiated with) the institution where the compound was discovered. If the terms include royalty payments based on future sales revenue, restrictions on a drug's price are not in the best interest of either the institution or the licensed manufacturer.[2]

For U.S. taxpayers, the primary benefits of publicly funded research come from the therapeutic value of drugs that ultimately result from that research and the Treasury's receipt of corporate income taxes on profits from those drugs. Constraining the prices of such drugs would tend to weaken firms' incentives to develop government-funded research discoveries into new drugs, which is a primary rationale behind the Bayh-Dole Act.

The larger issue, however, is not how much firms charge for such drugs but on what terms the original research discoveries are licensed to them. Most of the costs involved in developing a new drug come not from the initial discovery research but from clinical testing and regulatory approval—costs that firms tend to bear themselves. Even so, unless licenses for taxpayer-funded research discoveries fully cover the costs of that initial research, the savings that firms gain by licensing under favorable terms may induce them to invest in developing taxpayer-funded discoveries in preference to other, more socially valuable R&D projects that they may have available. Such savings in research costs may also lead companies to invest more in R&D overall than they would otherwise. That added investment could broaden the types of drugs that firms tried to develop beyond what the market would otherwise demand or could cause drugs to be developed more quickly than the market demanded.

1. According to the Government Accountability Office (formerly the General Accounting Office), the license provision entitles the government to a discounted price only when a drug is actually produced under its license, which is rarely the case. See General Accounting Office, *Technology Transfer: Agencies' Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536 (July 2003), p. 7. For a broad discussion of the issue, see Wendy H. Schacht, *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology,* CRS Report for Congress RL32076 (Congressional Research Service, June 10, 2005).

2. For a specific example of development costs, licensing terms, revenues, and royalty payments for a particular drug, see Jeff Gerth and Sheryl Gay Stolberg, "Medicine Merchants: Birth of a Blockbuster; Drug Makers Reap Profits on Tax-Backed Research," *New York Times,* April 23, 2000, p. A1.

The mapping of the human genome in the 1990s and early 2000s developed into a race between a public agency (NIH) and a private firm (Celera) that saw potential commercial value in mapping human gene sequences. In that case, NIH's Human Genome Project supplanted some private R&D, but it did so intentionally: NIH scientists wanted to avoid delay in placing the sequenced human genome in the public domain, and they used a sequencing method that complemented Celera's method and arguably hastened the completion of the project.[12] The potential for overlap between the public and private sectors in that area continues, since both NIH and the pharmaceutical industry are said to be "funding work in structural genomics . . . the next step beyond mapping the human genome."[13]

In other cases, chemical compounds discovered in the public sector have sometimes provided the active ingredients for privately developed drugs (see Box 4-1). In general, the risk of crowding out seems likely to be greatest where the potential commercial applications of the government's research are most apparent.

Evidence of a Stimulus Effect

It is seldom possible to identify particular cases in which the private sector would have performed research if the government had not. Thus, most of the available empirical evidence is based on aggregate studies. On balance, that evidence suggests a positive relationship between public and private pharmaceutical R&D.

A 1995 study estimated that a 1 percent increase in NIH-funded research produced, on average, a 2.5 percent increase in private R&D spending (with a lag of about seven years while the basic research was conducted and its findings published).[14] Moreover, about two-thirds of the private response amounted to "spillovers"—new research outside the field in which the NIH research was conducted. Although those findings do not address whether the drug industry would eventually have done the original research itself, the study is suggestive because the private response is disproportionate: the federal spending appears to have stimulated total private investment rather than simply shifting it.

A more recent, unpublished study concludes that increases in public-sector spending for basic research are associated with eventual increases in approvals of new molecular entities (see Figure 4-2).[15] The aggregate evidence in that study suggests a lag of about 18 years between the initial funding for basic research and the Food and Drug Administration's approval of additional new drugs. That gap is approximately consistent with the seven-year lag noted above plus the time required for drug development, which averages about 12 years.[16] By implication, current federal funding for life-sciences research may broadly predict the number of NMEs that will be approved in the future. But the evidence in that study remains tentative, and the most recent data used in the study are now a dozen years old. The findings may not hold up when newer data are included.

In general, studies that compare different industries find that, on balance, increases in government R&D spending appear to complement private R&D investment.[17] Such comparisons, however, cannot rule out the possibility

12. The Human Genome Project was NIH's highest-priority R&D project during its race with Celera. In 2003, NIH and Celera were both credited with completing the map of the human genome. For the assertion that complementary sequencing approaches hastened that mapping, see National Institutes of Health, National Human Genome Research Institute, "International Human Genome Sequencing Consortium Announces 'Working Draft' of Human Genome" (news release, June 26, 2000), available at www.nih.gov/news/pr/jun2000/nhgri-26.htm. For the public-domain motivation and the characterization of the NIH/Celera genome mapping as a race, see Encyclopedia Britannica Online, "Human Genome Project: Road Map for Science and Medicine" (December 1, 2005), p. 4, available at www.britannica.com/eb/article-215220.

13. Richard E. Rowberg, *Pharmaceutical Research and Development: A Description and Analysis of the Process,* CRS Report for Congress RL30913 (Congressional Research Service, April 2, 2001), p. 23.

14. Michael R. Ward and David Dranove, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry,* vol. 33, no. 1 (January 1995), pp. 70-87.

15. Andrew A. Toole, *The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry,* Discussion Paper 00-07 (Stanford, Calif.: Stanford Institute for Economic Policy Research, November 2000).

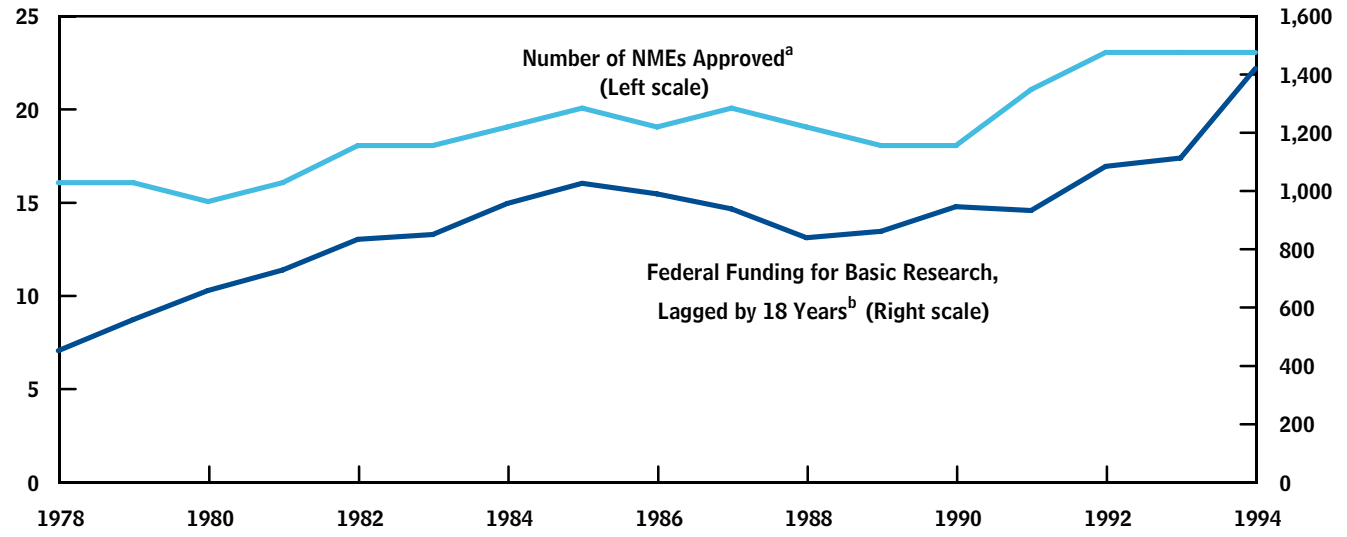
16. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

17. See Paul A. David, Bronwyn H. Hall, and Andrew A. Toole, "Is Public R&D a Complement or Substitute for Private R&D? A Review of the Econometric Evidence," *Research Policy,* vol. 29, nos. 4-5 (April 2000), pp. 497-529. The review covers studies of crowding out conducted over the past 35 years.

Figure 4-2.

NME Approvals and Public-Sector Spending on Basic Research

(Millions of 1986 dollars)



Source: Congressional Budget Office based on Andrew A. Toole, *The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry*, Discussion Paper 00-07 (Stanford, Calif.: Stanford Institute for Economic Policy Research, November 2000).

Note: NME = new molecular entity.

a. Four-year moving average (for example, the number of NMEs shown for 1978 is the average of the numbers approved in 1975, 1976, 1977, and 1978, to smooth the variation in the pattern of approvals).

b. Research and development grants by the National Institutes of Health and other agencies of the Public Health Service. Excludes intramural research and extramural grants for activities that Andrew Toole judged not to be relevant to pharmaceutical research. Such excluded grants include training, education, construction, demonstration, and institutional block grants, as well as grants to organizations considered to do little basic science relevant to pharmaceuticals (such as the National Institute on Dental Research, the National Institute on Environmental Health Sciences, and several others). The data for research funding were plotted 18 years ahead (for example, the 1972 number was plotted onto 1990) to show the correlation between the pattern for NME approvals and the pattern for federal funding of basic research.

that changes in public and private R&D spending may simply reflect similar responses to underlying shifts in available technological opportunities rather than having any causal link. Firm-level studies avoid that possibility by including companies that conduct research in different areas of technology; those studies have been somewhat more likely than cross-industry studies to conclude that government spending for R&D displaces private-sector spending.

In the end, the prevalence of crowding out or stimulus probably depends on the industry in question. For pharmaceuticals, the importance of advances in basic science to the search for new drugs, and the ease with which the benefits of basic research flow beyond the researcher's control, provide rationales for a government role in basic R&D, even if such R&D can directly displace private investment in some circumstances.

Impact on Salaries and Other Research Costs

Government spending on research and development can also indirectly crowd out private investment by causing R&D costs to rise. Pharmaceutical research requires highly trained scientists, and the supply of those researchers cannot adjust quickly to changes in demand. Rapid increases in government (or private) R&D spending may cause salaries for researchers to rise in both public- and private-sector organizations.[18] The supply of researchers

18. See Austan Goolsbee, "Does Government R&D Policy Mainly Benefit Scientists and Engineers?" *American Economic Review*, vol. 88, no. 2 (May 1998), pp. 298-302.

eventually increases in response to higher salaries. But that response takes several years, because new workers drawn to the field by higher pay must first receive graduate training.

When additional researchers enter the labor force, real salaries tend to decline to reflect the increase in supply. Until that adjustment occurs, however, increases in government R&D spending can push private R&D costs higher, which may discourage or delay some private-sector investment. That form of indirect crowding out is more likely to occur when federal R&D spending is growing more quickly. In addition, it may have a greater effect on firms' decisions about whether to undertake specific future projects (or cancel specific current projects) that are of marginal expected profitability than on projects with higher expected payoffs. Public and private spending levels on R&D have been growing rapidly in recent years; during that time, both total employment in biomedical research and researchers' real salaries have also risen.

A Changing Role for Public-Sector Research

The role of the public sector in the development of new drugs has evolved with changes in science and public policy. The potential returns to the private sector from academic and government-sponsored biomedical research have increased dramatically over the past generation, raising the issue of how best to maximize the benefits from publicly funded research. In 1980, lawmakers enacted the Bayh-Dole Act to address concerns that only a small fraction of government patents were being developed commercially.[19] The law gave universities, nonprofit organizations, and small businesses the property rights to inventions stemming from government-funded research they conducted. As a result, the marketing of such research discoveries has greatly increased, generating significant royalty income for those institutions and perhaps substantial benefits for society as well.

Basic research discoveries tend not to be patentable, so the assignment of property rights has less effect on the social value that results from basic research than it would have otherwise. Much of that value instead derives from academic traditions of scientific openness and the free flow of ideas. As the Supreme Court's decision in *Diamond v. Chakrabarty* illustrates, however, the scope of what is patentable can shift over time—and thus the balance between the social benefits of "open science" and of property rights and commercial development can change as well.

Some analysts argue that in addressing such issues, it may be counterproductive in the long run to further weaken the institutions of open science, increase the market orientation of public-sector researchers, or give taxpayers a greater share of the benefits that private companies derive from developing ideas generated in the public sector.[20] For example, gaining price concessions from drug firms that benefit from publicly funded research would increase taxpayers' current benefits but could reduce their future benefits. Such concessions would reduce firms' expected profits from licensing and developing taxpayer-funded research and thus would affect their future decisions about R&D (see Box 4-1).

Moreover, benefits can also flow the other way: academic and government researchers have sometimes made valuable discoveries that built on research done in the private sector. For example, public-sector researchers have discovered new approved uses for aspirin, antiepileptics, and antibiotics—drugs that were originally developed in the private sector.[21]

19. The Bayh-Dole Act (officially called the Patent and Trademark Law Amendments Act of 1980) was enacted as Public Law 96-517. Amendments to it were enacted in 1984 as P.L. 98-620. For the rationale behind the Bayh-Dole Act, see Wendy H. Schacht, *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology*, CRS Report for Congress RL32076 (Congressional Research Service, June 10, 2005).

20. Cockburn and Henderson, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery," p. 180.

21. See Iain M. Cockburn and Rebecca Henderson, *Public-Private Interaction and the Productivity of Pharmaceutical Research*, Working Paper No. 6018 (Cambridge, Mass.: National Bureau of Economic Research, April 1997).

CHAPTER

5

Has the Drug Industry's Innovative Performance Declined?

The number of new drugs introduced each year has not kept pace with research and development spending in the drug industry. Over the past three decades, the number of new molecular entities per annual dollar of research spending on such drugs—a conventional, if incomplete, measure of R&D performance—has declined significantly. Although that decline may result solely from higher R&D costs, concerns persist that rising technological complexity and structural changes (such as from mergers) have hurt the real research productivity of the pharmaceutical industry.

Conventional measures of R&D performance—such as annual approvals of new-drug applications or NMEs, either in total or per dollar of R&D spending—are misleading, however, and do not adequately summarize the industry's R&D performance. Carefully conducted studies of specific drug markets indicate that major gains have been achieved in a number of therapeutic areas, albeit at a growing cost per innovation. The difficulty and expense of such studies are obstacles to developing a comprehensive measure of R&D performance in the pharmaceutical industry.

Recent Innovative Performance

From the 1970s into the 1990s, the number of new molecular entities approved by the Food and Drug Administration each year generally increased (with some variability). At the same time, the drug industry's real R&D spending also grew, at first gradually and then more quickly. After the mid-1990s, however, NME approvals dropped sharply although R&D spending continued to rise (see Figure 5-1). Worldwide, the number of drugs with new active substances approved in major international markets also fell by half during the 1990s, while private-sector spending on drug R&D tripled.[1] Measures of R&D performance based on numbers of patents or new-drug applications show similar patterns of decline.

Whether that decline indicates a decrease in the industry's actual R&D productivity is uncertain, since the quality of NMEs and their value to consumers are not directly observable (and have been estimated only for selected drugs). Given the nearly 12-year average lag between initial R&D spending and NME approval that has been estimated, it is too soon to know how the sharp rise in R&D spending in the 2000s will affect future approvals of NMEs. However, growth in R&D spending during the 1990s resulted in a lower average number of annual approvals in the 2000s than in the 1980s and early 1990s (even including 1980, when an unusually low number of NMEs were approved). Thus, current growth in R&D expenditures does not necessarily portend an increase in the number of new drugs.

The industry's innovative performance depends not only on the number of those drugs but also on their characteristics. Thus, if fewer NMEs were approved but they included enough important, pioneering, or more effective drug therapies, the industry's actual R&D productivity would not necessarily be lower. For that to be the case, however, increases in quality would have to at least match the increases in R&D spending.

Shortcomings of the Usual Measures of Performance

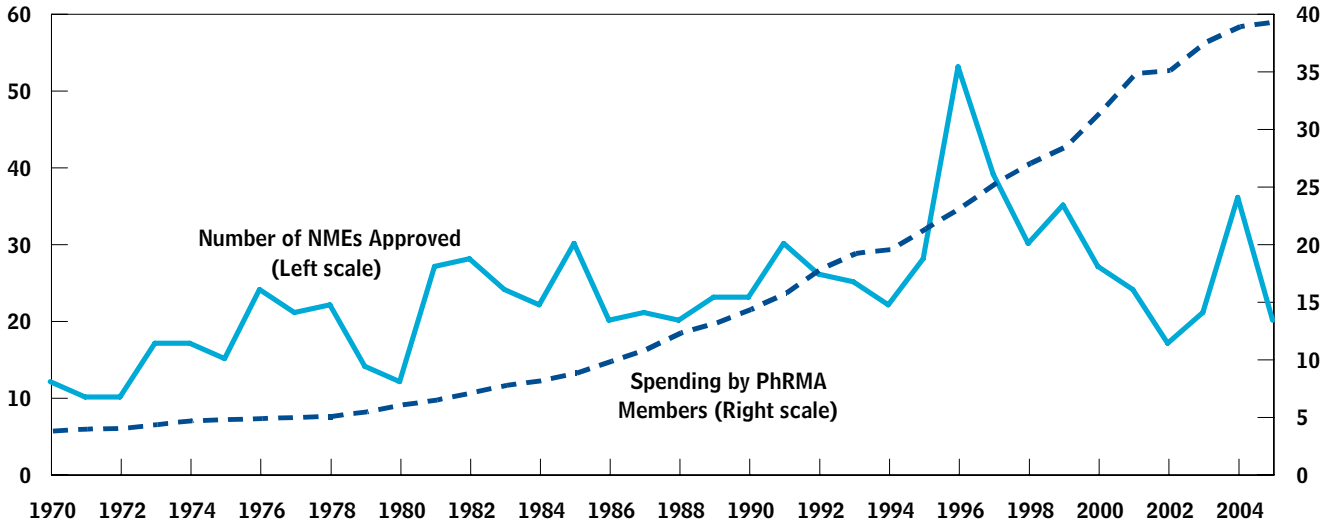
Conventional and readily accessible measures of innovative performance—which are based on the number of

1. See European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures—2003 Update* (Brussels: EFPIA, 2003).

Figure 5-1.

NME Approvals and Drug Companies' Spending on Research and Development

(Billions of 2005 dollars)



Source: Congressional Budget Office based on Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006); and Food and Drug Administration, Center for Drugs and Biologics, *New Drug Evaluation Statistical Report* (1985), Table III-1, Graph III-2, and Appendix B, and *New Drug Evaluation Statistical Report* (March 1986 and April 1987), Table II-1 and Graph II-2; Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management, *Offices of Drug Evaluation Statistical Report* (1987-1989), Table II-1, Graph II-1, and Graph II-2; Food and Drug Administration, "CDER NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type" (March 22, 2005), available at www.fda.gov/cder/rdmt/pstable.htm; and Food and Drug Administration, "FDA Facts: The Center for Drug Evaluation and Research," available at www.fda.gov/bbs/topics/news/2006/NEW01342/Fact_Sheet_CDER.pdf.

Note: Spending was adjusted for inflation using the biomedical research and development price index from the Bureau of Economic Analysis.

new molecular entities approved per year—are incomplete because they do not count all of the output from research and development. They exclude incremental modifications to existing drugs, which (as described in Chapter 2) can sometimes benefit consumers significantly by reducing side effects, being more convenient to take, or treating additional conditions.[2] Since a growing share of the drug industry's R&D has been directed toward product improvements—which now account for about one-third of the industry's R&D spending—failing to consider those drugs along with NMEs is a significant omission. If the benefits of product improvements are smaller than the benefits of the original new drugs (which is not always the case), they are often achieved at a lower R&D cost too. But although the number of product improvements per year has increased since 1990, that rise has been slight compared with the growth in R&D spending during that time.

Even performance measures that include modifications to existing pharmaceuticals are limited because they give every new drug or drug product equal weight, despite sometimes large differences in quality or value. For example, a pioneering drug treatment that benefited a large

2. For example, demand for selective serotonin reuptake inhibitors and proton pump inhibitors (PPIs) comes primarily from patients with conditions other than those drugs' original primary approved uses. Some PPIs, such as Prilosec and Zantac, can now be purchased over the counter for heartburn, further expanding the demand for nonprimary uses. Drug treatments for HIV illustrate the potentially large value to be gained from simplified dosing regimens. Zidovudine, or AZT, the first FDA-approved drug for HIV, originally required a dosing regimen of six times per day (every four hours around the clock). The required dosage of AZT is now just two or three times per day, often in combination with other drugs (see AIDS Education Global Information System, "So Little Time . . . An AIDS History," available at www.aegis.com/topics/timeline). Moreover, the FDA recently approved a once-per-day combination drug for treating HIV.

patient population would count the same toward a firm's R&D performance as a drug for a less prevalent condition for which other effective drugs were available.

The reason that conventional measures of R&D output do not account for drug quality is that quality can be very difficult to estimate. Doing so may require collecting large amounts of field data and using carefully designed statistical analyses, and the results of such studies are not always conclusive. Nevertheless, many examples exist of major therapeutic gains achieved by the industry in recent years.[3] Statins, which reduce cholesterol levels, did not exist a generation ago; now they are by far the best-selling class of drugs in the United States.[4] Selective serotonin reuptake inhibitors, which unlike earlier drugs for depression can be prescribed by nonspecialists, have "enormously" expanded the market for antidepressants and are credited with creating a sharp decline in the prevalence of untreated depression.[5] Significant gains have been made in the diagnosis and treatment of many types of cancer.[6] And new antiulcer drugs have drastically reduced ulcer surgeries.[7] One analysis finds that although annual approvals of NMEs have declined over the past 20 years, approvals of "high-quality" NMEs have risen slightly over that period.[8] Thus, anecdotal and statistical evidence suggests that the rapid increases that have been observed in drug-related R&D spending have been accompanied by major therapeutic gains in available drug treatments. There is not enough detailed evidence about how drug quality has changed over time to support a rigorous analysis of the productivity of pharmaceutical research. However, the evidence suggests that looking at the number of new drugs without considering their therapeutic value omits an important factor in that analysis.

Another problem with using a traditional productivity measure—output per unit of input—to assess R&D performance is that it treats the new drugs approved in a given year as if they were produced by the R&D dollars spent that year (rather than over the preceding 12 years or so). It is difficult to know whether such a measure overstates or understates actual productivity in any particular year. But it will be accurate only by chance.

Factors That Could Diminish Innovative Performance

In the absence of accurate, comprehensive statistical measures, the drug industry's R&D performance can be considered qualitatively. Even if drug quality has been increasing, the industry's performance may still have declined, for several reasons.

First, the supply of not-yet-discovered innovations ebbs and flows. Major scientific advances can generate a fresh supply of "easier" discoveries with lower development costs. Those discoveries would be exploited before costlier ones with comparable expected revenues. Because science does not advance at a steady pace, the pool of undeveloped discoveries will at times be smaller and more expensive to exploit. At those times, real research productivity will be lower. Indeed, the currently feasible opportunities for biomedical research have been described as tending toward diseases that are more complex or with drug targets that are more difficult to treat.[9]

3. See W.S. Comanor, "Pharmaceutical Prices and Expenditures," in R.M. Andersen, T.H. Rice, and G.F. Kominski, eds., *Changing the U.S. Health Care System* (San Francisco: Jossey Bass, 2001). For a more comprehensive perspective going back to the 1950s, when the industry offered few effective drugs beyond broad-spectrum antibiotics, see Frederic M. Scherer, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), Chapter 9.

4. IMS Health, "20 Leading Therapeutic Classes by U.S. Sales, 2005" (January 2006), available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_73915261_77140565,00.html.

5. Ernst R. Berndt, Iain Cockburn, and Zvi Griliches, "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressants," *Brookings Papers on Economic Activity: Microeconomics* (1996), pp. 149-150.

6. Frank Lichtenberg credits new cancer drugs with adding about one year to the life expectancy of people diagnosed with cancer between 1975 and 1995; see Frank R. Lichtenberg, *The Expanding Pharmaceutical Arsenal in the War on Cancer,* Working Paper No. 10328 (Cambridge, Mass.: National Bureau of Economic Research, February 2004).

7. Comanor, "Pharmaceutical Prices and Expenditures," p. 2.

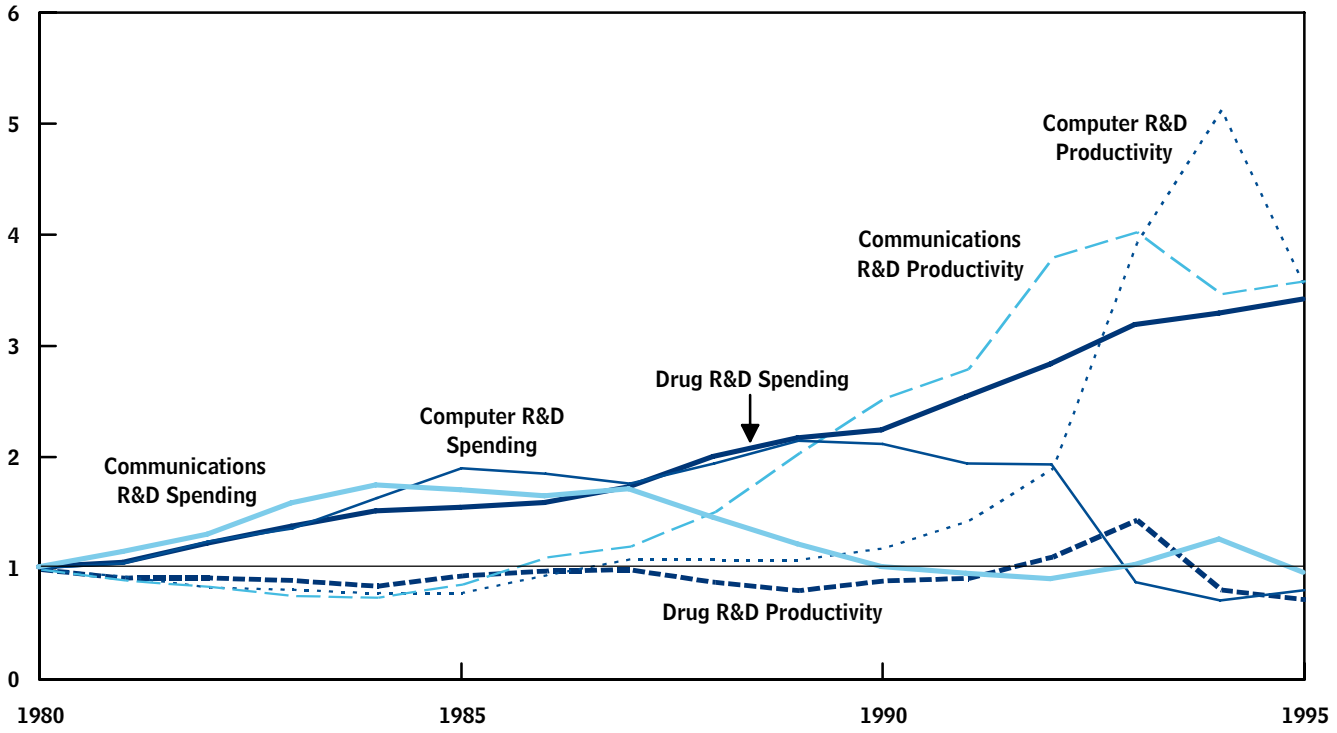
8. See Henry Grabowski and Richard Wang, "The Quantity and Quality of Worldwide New Drug Introductions, 1982-2003," *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 452-460. The authors defined high-quality NMEs as those that have been introduced in at least four of the world's seven largest pharmaceutical markets (Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States) or that represent the first NME launched in a particular therapeutic class in the United States.

9. Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs,* vol. 23, no. 1 (January/February 2004), p. 12.

Figure 5-2.

Research and Development Spending and Productivity for Various U.S. Industries

(Index, 1980 = 1.0)



Source: Congressional Budget Office based on National Science Foundation table "Company and Other (Except Federal) Funds for Industrial R&D Performance, by Industry and by Size of Company: 1953-98," available at www.nsf.gov/statistics/iris/search_hist.cfm?indx=10; and Bronwyn H. Hall, Adam B. Jaffe, and Manuel Tratjenberg, *The NBER Patent Citation Data File: Lessons, Insights, and Methodological Tools,* Working Paper No. 8498 (Cambridge, Mass.: National Bureau of Economic Research, October 2001).

Notes: This figure measures productivity as the number of patents granted in an industry per dollar of research and development spending. R&D spending in one year is compared with successful patents two years later, reflecting the lag with which such spending leads to patent applications.

The figure stops at 1995 (including patents applied for through 1997) because most patent applications filed after 1997 had not yet been approved by 1999, when the data set for patents ended. Thus, successful patent applications for 1998 and 1999 are underrepresented in the data and would provide an artificially low measure of R&D productivity for those years.

Second, growing technological complexity could dampen the industry's R&D performance, unless the new technologies boosted drug quality by enough to offset the effects of higher research costs.

Third, rising real wages would have the same effect if they were not accompanied by an increase in real research output (that is, in the annual number of new drugs approved, adjusted for quality). Both scientific employment and real wages have been growing in the pharmaceutical industry. Between 1980 and 2000, total R&D employment in the drug industry grew at an average rate of 5.4 percent a year (employment among scientific and professional staff grew by 7.4 percent annually). The industry's labor costs rose at an even faster rate during that period: by an average of 9.3 percent a year, adjusted for inflation.[10] If R&D output has not increased by at least that much, then (unless capital costs are lower) R&D productivity will have declined.

10. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), p. 178

Fourth, an empirical study of various industries suggests that decreases in R&D output per dollar may, in part, merely indicate strong consumer demand for an industry's new products.[11] Such demand would cause firms to invest more in research and development, in some cases to the point of diminishing marginal returns.[12] The study looked at differences between industries in growth of R&D spending and concluded that such growth was negatively associated over time with an industry's number of patents per dollar. During the past quarter century, it concluded, the number of patents per R&D dollar has declined in industries in which R&D spending has risen the most—but has recovered when an industry's rate of spending growth has slowed. If that pattern was the outcome of profit-maximizing behavior in a well-functioning market, a decline in patents per dollar (or drugs per dollar) would not necessarily be a problem. Higher demand could lead to diminishing returns on R&D for two reasons: because increased R&D spending could put upward pressure on researchers' wages, and because higher demand could encourage companies to reach more deeply into their inventories of potential R&D projects to ones with lower expected returns.

The pharmaceutical industry provides a good illustration of that study's conclusions. The growth of R&D spending has been particularly high in the drug industry compared with other industries, and the drop in patents per dollar has been greater (see Figure 5-2). Declines in R&D output per dollar have not been confined to the pharmaceutical industry, however, or to industries in the United States. Patents per research dollar have fallen in many industries in the United States and around the world. (For the computer and communications industries, patents per dollar rebounded when the growth of R&D spending slowed.)

11. Jean O. Lanjouw and Mark Schankermann, *Research Productivity and Patent Quality: Measurement with Multiple Indicators,* Discussion Paper EI/32 (London: London School of Economics and Political Sciences, Toyota Centre, December 2002), available at sticerd.lse.ac.uk/dps/ei/ei32.pdf. To allow for comparisons among industries, the study measured R&D output by counting patents rather than new products.

12. "Diminishing marginal returns" refers to a situation in which each additional unit of investment produces a smaller return than the one before it.

Did Changes in the Size of Drug Companies Affect Research Productivity?

In the 1990s, a wave of mergers of large, traditional pharmaceutical companies transformed the structure of the drug industry. By 2002, the 10 largest drug firms accounted for 48 percent of pharmaceutical sales worldwide, up from about 20 percent in 1985.[13] Currently, eight of the top 10 firms are the products of horizontal mergers between two or more large drug companies, all of which occurred since 1989 (see Table 5-1).[14]

Consolidation in the pharmaceutical industry may have been motivated by several factors. With the rise of generic drugs, the rapid loss in sales that now occurs when a drug's patent expires can leave firms with excess capacity in production and marketing. Merging with another company can help fill that capacity. Firms may also merge to exploit potential economies of scale or scope in research and development.[15]

To many observers, however, the decline in the introduction of new drugs indicates that the industry has become less innovative. The popular press has sometimes suggested that large drug firms are less innovative than small firms or that mergers have reduced R&D productivity by

13. Patricia M. Danzon, Andrew Epstein, and Sean Nicholson, *Mergers and Acquisitions in the Pharmaceutical and Biotechnology Industries,* Working Paper No. 10536 (Cambridge, Mass.: National Bureau of Economic Research, June 2004), p. 2.

14. "Horizontal" here refers to mergers between drug manufacturers, even if they do not compete directly in the marketplace. In the Federal Trade Commission's analyses of mergers, pharmaceutical markets are usually defined narrowly in terms of drugs for specific illnesses and conditions. Antitrust concerns arise when merging firms compete directly and together would represent a large share of a given market or would perform much of the R&D in that market. In such cases, the FTC can require the companies to divest themselves of products, intellectual-property rights, or R&D projects in order to make it harder for them to raise prices or block the development of potentially competing drugs. A merger between two large pharmaceutical firms need not reduce competition in individual markets, although many of the mergers in Table 5-1 required some divestitures.

15. Economies of scale are decreases in average R&D costs from, for instance, having larger laboratories (which could allow expensive equipment to be shared among projects); economies of scope are decreases in average R&D costs from researching a wider variety of products (because knowledge gained in one product area can benefit researchers in other areas).

Table 5-1.

Merger History of the Top Ten Pharmaceutical Companies in 2004 by Global Sales

Ranking/Firm	Large Entities That Have Merged Since 1989 to Create Current Firm
1. Pfizer	Pfizer, Warner-Lambert, Pharmacia, Upjohn, Monsanto
2. GlaxoSmithKline	Glaxo, Wellcome, SmithKline Beckman, Beecham
3. Sanofi-Aventis	Rhone-Poulenc, Rorer, Hoechst, Marion Merrell Dow, Sanofi
4. Johnson & Johnson	
5. Merck	
6. Novartis	Ciba-Geigy, Sandoz
7. Astrazeneca	Astra, Zeneca
8. Roche	Roche, Syntex, Genentech
9. Bristol-Myers Squibb	Bristol-Myers, Squibb, DuPont Pharmaceuticals
10. Wyeth	American Cyanamid, American Home Products, Genetics Institute

Source: Congressional Budget Office based on information from IMS Health and the companies listed above.

distracting companies' research scientists.[16] The economic evidence for those assertions is ambiguous.

Direct empirical evidence about the effects of mergers on the performance of drug companies is scarce. Given the length of the drug-development process, assessing R&D performance requires more years of postmerger data than yet exist. But an analysis of how mergers have affected other aspects of performance concluded that the recent mergers in the drug industry have had, on average, no initial effect on a range of measures of firms' inputs and outputs.[17] Companies' propensity to merge appears to be associated with factors such as low expected growth in earnings and approaching patent expirations. Adjusting for that propensity, the study found no significant changes during the first three years after a merger in the growth rates of a firm's sales, number of employees, R&D expenditures, or market value. However, such firms' R&D expenditures grew more slowly than those of comparable firms that did not merge, suggesting that mergers may initially divert resources away from R&D.

Comparisons of the performance of large and small pharmaceutical firms from the 1960s to the early 1990s suggest that larger companies had an advantage in being able to sustain a broader range of research programs of a given size—and thus could capture more of the resulting knowledge than if the programs were housed in separate, smaller firms. Those economies of scope boosted research productivity at the drug-discovery phase.[18] (Firm-specific factors such as experience and managerial ability were even more important.)[19]

Since the early 1990s, however, biotechnology and genomics have changed the research landscape. Numerous small, research-oriented companies have arisen to specialize in new-drug discovery. In theory, with firms increasingly focused on either early- or late-stage R&D, the potential gains from alliances between specialized companies may also have grown: small firms could license their drug discoveries to larger companies to gain access to greater resources and expertise for conducting large, complex clinical trials. But recent evidence suggests that a company's likelihood of succeeding in later-stage trials may be greater the more focused (less broad) its research

16. See, for example, James Surowiecki, "The Pipeline Problem," *New Yorker,* February 16, 2004; and Gardiner Harris, "Where Are All the New Drugs?" *New York Times,* October 5, 2003, Section 3, p. 1.

17. See Danzon, Epstein, and Nicholson, *Mergers and Acquisitions in the Pharmaceutical and Biotechnology Industries*.

18. See Rebecca Henderson and Iain Cockburn, "Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery," *RAND Journal of Economics,* vol. 27, no. 1 (Spring 1996), pp. 32-59. That study examined the R&D programs of 10 large pharmaceutical firms between 1961 and the early 1990s.

19. See Iain M. Cockburn and Rebecca Henderson, "Scale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research," *Journal of Health Economics,* vol. 20, no. 6 (November 2001), pp. 1033-1057.

experience has been.[20] Thus, in the current environment, hosting a wide range of research activities within one firm may have become a disadvantage in drug development.

The rise of small, specialized biotechnology companies has blurred the once-clear division between basic science conducted "upstream" in university and government labs and applied research performed "downstream" in the commercial sector. A generation ago, the pharmaceutical industry essentially consisted of a moderate number of large drug companies doing their own applied R&D on the basis of publicly available basic research discoveries. Now, small firms perform some of that basic research. That change may lead to a more efficient allocation of research resources, to the extent that well-defined property rights exist for basic research discoveries that have commercial value and that markets for those discoveries are competitive.[21]

Some analysts believe that smaller biotechnology firms tend to be more agile and more willing to take risks than larger pharmaceutical firms and thus innovate more quickly and cost-effectively. But greater specialization in drug research—as, for instance, with smaller companies focusing more on drug discovery and larger ones emphasizing drug development and clinical trials—requires greater effort to work out licensing agreements between firms, diverting resources that more highly integrated companies could use on R&D or other productive activities. A larger number of small firms can also mean more competition and more racing to patent and license discoveries, which (beyond a certain point) can lead to a less efficient use of resources.

On balance, increased specialization could improve R&D productivity in the drug industry. But the commercialization of research relationships that formerly existed outside the marketplace makes those relationships—and the industry's R&D productivity—potentially vulnerable to a decline in profits.

20. See Patricia M. Danzon, Sean Nicholson, and Nuno Sousa Pereira, "Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances," *Journal of Health Economics,* vol. 24, no. 2 (March 2005), pp. 317-339.

21. For a more detailed discussion of the ideas in this and the two following paragraphs, see Cockburn, "The Changing Structure of the Pharmaceutical Industry," p. 14.

CHAPTER

6

Profitability and R&D Investment in the Drug Industry

People place a great deal of value on their health. Since most of the demand for pharmaceutical products comes from consumers who are not at full health, their willingness to pay for some kinds of drugs may be quite high (not only in absolute terms but also in relation to the cost of manufacturing and supplying those drugs). Moreover, health insurance insulates many consumers from the full cost of their prescription drug choices. When few competing drugs are available, demand may be particularly insensitive to price. For all of those reasons, many brand-name drugs are sold at a sizable markup over their unit cost of production.

The pricing of brand-name drugs highlights multiple tensions. One is between the high long-run cost of developing a new drug and the much lower short-run cost of producing it. Another tension is between shareholders' expectations that drug firms will maximize their profits and consumers' notions of fairness. The perception that drug prices are high—combined with rapid growth in total U.S. spending on prescription drugs—has frequently focused attention on the sensitive issue of the drug industry's profitability.

Recent Estimates of Profitability

On paper, the pharmaceutical industry has consistently ranked as one of the most profitable industries in the United States. In 2005, pharmaceutical firms in the *Fortune* 500 averaged a 10.3 percent return on assets, compared with a median return of 4.7 percent for all industries (see Figure 6-1). That return put the drug industry ninth out of the 50 industries ranked that year (it ranked second in 2003 and 12th in 2004).[1]

However, those figures misrepresent the industry's actual profits. The reason is that the standard accounting measure of profits overstates true returns to R&D-intensive industries, such as pharmaceuticals, and makes it difficult to meaningfully compare profit levels among industries. Accounting measures treat most R&D spending (except for capital equipment) as a deductible business expense rather than as a capitalized investment.[2] But the intangible assets that research and development generate—such as accumulated knowledge, new research capabilities, and patents—increase the value of a company's asset base. Not accounting for that value overstates a firm's true return on its assets.[3]

By standard accounting measures, the pharmaceutical industry's return on assets (even with a recent decline)

1. In 2005, the industry also ranked fifth in return on revenues (15.7 percent versus a median value of 5.9 percent for all firms) and fifth in return on shareholder equity (23.4 percent compared with a median of 14.9 percent).

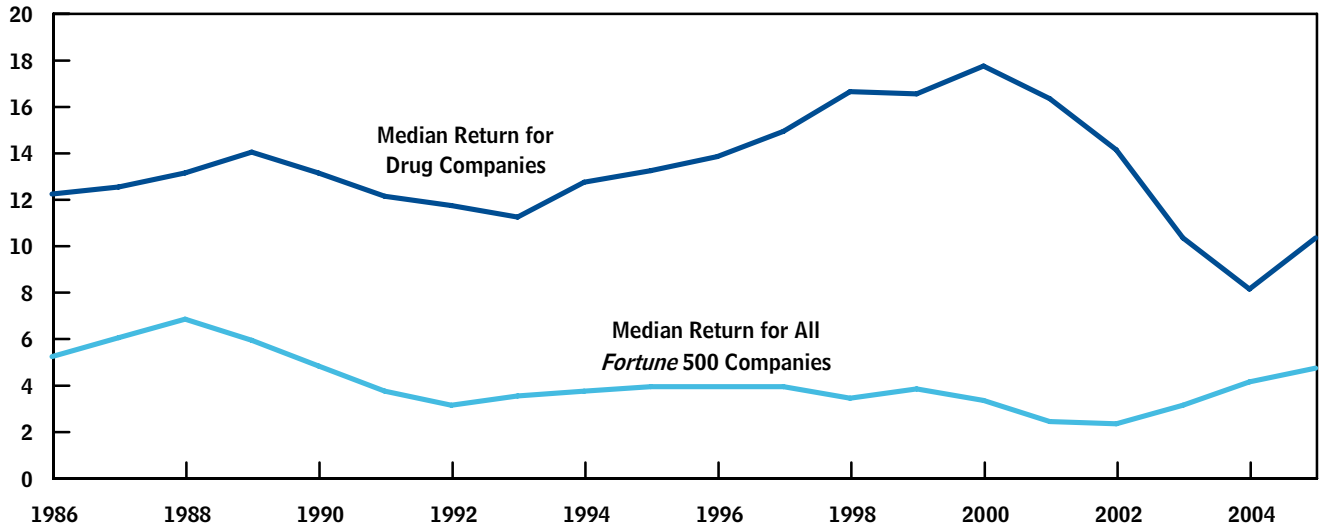
2. The federal tax code also encourages firms to report their R&D investments as business expenses, since noncapitalized ("expensed") R&D spending qualifies for R&D tax credits, but capitalized spending does not. See U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards,* OTA-H-522 (February 1993), pp. 184-185. For a discussion of several other differences between accounting and economic measures of profit, see ibid., p. 96.

3. Return on assets is defined as earnings divided by assets; thus, the smaller the measured assets, the larger the return. The accounting treatment of R&D expenses also overstates returns by ignoring the opportunity costs of capital, which are larger than average in the pharmaceutical industry because of the longer-than-average lag between investment in R&D and introduction of new products. See Frederic M. Scherer, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), p. 336. Uwe Reinhardt notes, however, that expensing R&D investments could also *under*state returns by overstating expenses, and that when R&D spending is growing rapidly, the net effect of expensing on returns is uncertain. See Uwe E. Reinhardt, "Perspectives on the Pharmaceutical Industry," *Health Affairs,* vol. 20, no. 5 (September/October 2001), p. 143.

Figure 6-1.

Return on Assets for Drug Companies Versus for All Major Companies, by Standard Accounting Methods

(Percent)



Source: Congressional Budget Office based on *Fortune* magazine (various issues).

has consistently been two to three times higher than the median for *Fortune* 500 firms.[4] Adjusted for intangible R&D assets, the industry's actual profitability is still somewhat above average, but by less than shown in Figure 6-1. The Office of Technology Assessment estimated that in the early 1990s, standard accounting rates of return were overstating the drug industry's profits by 20 percent to 25 percent.[5] OTA found that adjusting for firms' intangible assets halved the gap between the drug industry's average returns and those of a matched sample of nondrug firms with similar financial characteristics.

Allowing for differences in capital costs between industries, which largely reflect differences in the riskiness of investing in a particular industry, companies should achieve comparable returns, on average, in the long run. Differences in returns between industries will tend to be minimized as investors pursue the highest available returns: capital will flow into an industry with above-average returns on R&D until the industry reaches the point of diminishing marginal returns, at which point, investors will seek higher returns in other industries. Thus, the persistently above-average returns on pharmaceutical R&D in Figure 6-1 could simply reflect a greater cost of capital for the drug industry, commensurate with its riskier investment environment.

In the short run, industries' rates of return need not reflect differences in capital costs. One study found that the average rate of return on innovation for new drugs in the 1990s modestly exceeded the industry's cost of capi-

4. A 1998 CBO study found that increased competition from generic drugs had begun to reduce the drug industry's profitability. See Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998), p. 47.

5. See Office of Technology Assessment, *Pharmaceutical R&D,* pp. 96-101. By standard accounting measures, the drug industry's profits would have amounted to about 1.4 percent of U.S. health care spending in 2001, according to one analyst. See Reinhardt, "Perspectives on the Pharmaceutical Industry," pp. 143-144. That year, the share of total health care spending in the United States that was attributable to prescription drugs was 9.4 percent (it is currently about 10 percent). See Centers for Medicare & Medicaid Services, "National Health Care Expenditures Projections: 2005-2015," available at www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2005.pdf.

tal.[6] OTA ruled out capital-cost differences as a reason for the pharmaceutical industry's higher returns, concluding that "R&D drives profitability in the industry and has produced returns over reasonably long periods of time that may exceed the cost of capital."[7] Consistent with the notion that investors pursue the highest returns, one analyst has suggested that if the pharmaceutical industry was actually earning significantly higher returns than average (adjusted for differences in risk), outside firms would have sought to merge with drug companies.[8] Economists broadly agree that a reduction in profits would cause private-sector investment in drug R&D to grow more slowly or to decline.[9]

Expected Profits as a Signal for Performing Drug R&D

The profitability of the drug industry is an important issue not only because of its connection to rising U.S. spending on prescription drugs but also because profits provide a way for pharmaceutical firms to gauge what types of products consumers value most. If profits do not accurately reflect that value, however, they may induce the drug industry to perform too much or too little R&D, either on specific kinds of drugs or as a whole.

Various factors may reduce the accuracy of profits as an indicator of social value. In the case of drugs to treat or prevent illnesses (such as tuberculosis, malaria, and other diseases of the developing world) that disproportionately affect lower-income populations, potential profits are often too low for market forces alone to encourage private-sector R&D, despite the high social value of treating such illnesses.[10] Even when higher-income populations are the likely market, the ability of profits to guide firms toward the most socially valuable kinds of R&D is highly dependent on three factors:

- How well informed health care professionals and consumers are about the attributes of existing drugs,
- How patents and health insurance coverage of prescription drugs affect pharmaceutical companies' revenues and returns on R&D, and
- How strong incentives are for doctors and patients to consider price when choosing among prescription drugs.

Product Information

To the degree that available information about drugs' true therapeutic benefits is incomplete, health insurers and consumers may be willing to pay too much for one drug and not enough for another. Clinical trials for FDA approval compare prospective drugs with a placebo, not with other drugs. Thus, postmarketing clinical trials and field studies that compare multiple drugs may add valuable information to what is learned from the FDA approval process. Currently, however, no systematic pro-

6. See Henry Grabowski, John Vernon, and Joseph DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *PharmacoEconomics,* vol. 20, supplement 3 (2002), pp. 11-29. The authors estimated an 11.5 percent rate of return on R&D, compared with a real cost of capital of 11 percent. (The standard accounting measure of profitability implies a gap of 2 to 3 percentage points.) A 1994 study reached very similar conclusions; see Henry G. Grabowski and John M. Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics*, vol. 13, no. 4 (December 1994), pp. 383-406. It also estimated a gap of about 0.5 percentage points between the rate of return on R&D and the annual cost of capital.

7. Office of Technology Assessment, *Pharmaceutical R&D,* p. 103. OTA noted that over an industry's lifetime, average returns must exactly reflect the cost of capital, but it is when returns exceed capital costs that industries attract investment capital and grow.

8. Ernst R. Berndt, "Pharmaceuticals in U.S. Health Care: Determinants of Q and P," *Journal of Economic Perspectives,* vol. 16, no. 4 (Fall 2002), p. 62.

9. See, for example, Frederic M. Scherer, "Pricing, Profits, and Technological Progress in the Pharmaceutical Industry," *Journal of Economic Perspectives,* vol. 7, no. 3 (Summer 1993), p. 105.

10. That problem has led some governments and nongovernmental organizations to take steps to stimulate research and development in such cases. For example, in 2004, the United Kingdom committed to buy between 200 million and 300 million doses of a yet-to-be-developed malaria vaccine at a price intended to encourage the vaccine's development. In addition, the Gates Foundation and the World Bank have each pledged several hundred million dollars toward malaria research or drug purchases. The potential for such efforts to spur increased R&D on malaria is discussed in Jean O. Lanjouw and Iain M. Cockburn, "New Pills for Poor People? Empirical Evidence After GATT," *World Development,* vol. 29, no. 2 (February 2001), pp. 265-289. The authors conclude that private R&D spending on malaria rose after policy shifts increased its potential returns (the General Agreement on Tariffs and Trade was amended to address intellectual-property concerns, and some developing countries strengthened their protection for intellectual property in drug innovations).

Box 6-1.

Drug Prices and Consumer Value in R&D Spending

Higher prices for new drugs imply higher returns on research and development (if everything else, such as the level of consumer demand, is unchanged). In turn, higher returns attract more investment in R&D. To the extent that drug prices reflect the value that consumers receive from different drugs, prices will encourage pharmaceutical companies to try to develop more of the kinds of drug products that consumers value most.

Drug prices do not necessarily provide an accurate signal of consumers' preferences in all cases, however. For example, it is not always clear why the market sustains high prices for some new drugs when cheaper alternatives of seemingly comparable quality are available. One possibility is that because drugs function in ways that are complex and often not fully understood, it can take a long time to assess how well they actually perform relative to the available alternatives.

Antipsychotic drugs are a case in point. In the 1990s, an expensive new class of "atypical" antipsychotic drugs was introduced that avoided the often debilitating neurological side effects of older antipsychotics. When state Medicaid programs switched to the new drugs, their total spending on antipsychotics increased significantly. California's Medicaid program, for instance, spent seven times more on antipsychotic drugs in 2001 than it did in 1993, although the number of claims it processed for schizophrenia (one of the primary illnesses for which those drugs are prescribed) rose by only 10 percent during that period.[1] Some observers expected that the new drugs would lower California's other Medicaid costs by reducing hospital stays. However, no such savings materialized.[2] In addition, a large, federally funded study that compared several of the new drugs with a much cheaper antipsychotic drug dating from the 1950s found little difference between them in terms of tolerability or effectiveness.[3] Such findings could cause consumers to revise how much they value the

1. See Mark Duggan, "Do New Prescription Drugs Pay for Themselves? The Case of Second-Generation Antipsychotics," *Journal of Health Economics,* vol. 24, no. 1 (January 2005), pp. 1-31.
2. Ibid.
3. See Jeffrey A. Lieberman and others, "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia," *New England Journal of Medicine,* vol. 353, no. 12 (September 22, 2005), pp. 1209-1223. The new atypical antipsychotics have side effects of their own (notably, an increased risk of diabetes because of weight gain). The neurological side effects of the older drug, perphenazine, were avoided by administering it at lower dosages.

cess exists for generating that information. Firms often conduct their own head-to-head drug comparisons in clinical trials, but those studies may have little value for consumers. With antipsychotic drugs, for example, a recent analysis found that in 90 percent of firm-sponsored trials, the results favored the drug made by the sponsoring firm.[11] Many doctors depend at least partly on pharmaceutical companies' sales representatives for information about the drugs they prescribe.

11. See Stephan Heres and others, "Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics," *American Journal of Psychiatry,* vol. 163, no. 2 (February 2006), pp. 185-194.

If better information caused drugs' prices to align more closely with their therapeutic value—and especially if doctors used that information in choosing which drugs to prescribe—companies would have an incentive to reallocate their R&D resources (in search of higher returns) toward drugs with relatively greater social value. (See Box 6-1 for a discussion of pricing and value of new antipsychotic drugs.) In cases where drug prices fell as a result of improved information, firms would perform less R&D; in cases where drug prices rose, firms would conduct more research and development.

There are limits, however, to how much could be gained from more-extensive study of drug quality. The information is costly to produce, underlying scientific complexi-

Box 6-1.

Continued

new antipsychotics (subject, as always, to revision on the basis of future studies) and could influence the industry's R&D spending on that class of drugs.

In the case of drugs (such as the new antipsychotics) that have strong Medicaid sales, prices may be higher than they would be if Medicaid constituted a smaller share of the total demand for those drugs. The price that Medicaid pays for a drug depends on the average price that the manufacturer earns on sales to retail pharmacies. Thus, the manufacturer may be able to make more profit on a drug with large Medicaid sales by setting higher prices for its retail customers, who are fewer in number in such cases. The company will lose some sales as a result, but it can make up for them with increased revenue from Medicaid sales (which tend to be less sensitive to price, because Medicaid patients tend to have much lower copayments than people with private health insurance do).[4] The resulting higher profits—although not an intended consequence of the Medicaid program—encourage additional private-sector investment in R&D on such drugs. That outcome is a distortion of the decisions about R&D that firms would make in the absence of the program. However, it does help low-income Medicaid patients, whose below-average ability to pay would not, on its own, attract as much R&D on drugs for illnesses that affect Medicaid patients at greater rates than the general population.

4. In the first quarter of 2005, the maximum Medicaid copayment required by any state was $3, and in most states, that payment was the same regardless of the price of the drug. See Mark Duggan and Fiona Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," *Quarterly Journal of Economics*, vol. 71, no. 1 (February 2006), p. 4, footnote 3. The authors found that for every increase of 10 percentage points in Medicaid's share of a drug's total sales, the average prescription price of that drug was 7 percent to 10 percent higher than it would be otherwise. As a result, non-Medicaid customers also paid more: an average of 13.3 percent more for drugs of all types in 2002.

ties limit how precisely quality can be determined, and the benefits of generating more information will be greater for some kinds of drugs than for others. The potential gains from additional information are likely to be greater in markets that have many competing drugs, widely varying prices, and high sales than in smaller markets with fewer drugs or lower prices.

The Role of Health Insurance and Patents

The interaction of health insurance—Medicaid, Medicare, and private plans—with strong patent protection of pharmaceutical innovations can create particularly large incentives for drug companies to invest in R&D. Patents provide stronger intellectual-property protection in the pharmaceutical industry than in many other industries.[12] Firms' expectations of being able to set prices for new drugs above competitive levels and thus recoup their R&D investment are crucial to their decisions to innovate. Strong patent protection supports those expectations.

Because health insurance insulates many consumers from the full effects of high prices, however, the demand for a new drug—and firms' resulting revenue—are higher at any given price than they would be otherwise.[13] Moreover, much of the health insurance in the United States is provided as an employment benefit that is not subject to

12. See Edwin Mansfield, "Patents and Innovation: An Empirical Study," *Management Science,* vol. 32 (February 1986), pp. 173-181. See also Scherer, *Industry Structure, Strategy, and Public Policy.*

13. Although this discussion focuses on the long-term impact of health insurance on R&D investment, insurance has another important effect. By covering consumers' prescription drug purchases, it lessens the primary cost of the patent system—that is, the potentially significant loss of social benefits when consumers who would purchase a new drug at a lower price are dissuaded by its higher price under patent. See Alan M. Garber, Charles I. Jones, and Paul M. Romer, *Insurance and Incentives for Medical Innovation,* Working Paper No. 12080 (Cambridge, Mass.: National Bureau of Economic Research, March 2006).

income or payroll taxes.[14] By reducing the cost of health insurance to consumers, that tax subsidy encourages more people to obtain coverage, and induces some of them to purchase more coverage, than they would otherwise.[15] The additional revenue that results from the effect of insurance on the demand for prescription drugs—combined with strong patent protection—can give companies excessive incentives to invest in drug R&D.[16] (Incentives are excessive if they draw additional resources toward drug research and development and away from other, more socially valuable uses.)

Incentives to Consider Drug Prices

The effects of insurance and market power from strong patents can be tempered through greater exercise of buyers' power to reduce drug prices, as well as through increased incentives for consumers and doctors to consider price differences between drugs. Large insurance and retail buyers often can negotiate lower prices for the drugs they purchase. For example, health insurance plans have increasingly gained price reductions from manufacturers as a condition of including a drug in a plan's formulary of preferred products.

Health plans have also expanded their use of multitiered copayment price structures, which give consumers a stronger incentive to use less expensive drugs. In 2004, more than two-thirds of U.S. workers with employment-based health insurance faced a three-tiered structure of prescription drug prices (with low, medium, and high prices for generic, formulary brand-name, and non-formulary brand-name drugs, respectively). Use of such copayment structures has more than doubled since 2000.[17] To the extent that multitiered systems still do not charge consumers the full difference in price if they prefer a more costly drug, room exists to strengthen price incentives further.[18]

Doctors' prescription-writing practices heavily influence which drugs consumers use. Insurers, therefore, have also been exercising greater control over prescription drug spending by giving doctors stronger incentives to know about the various drugs they may prescribe and the prices of those drugs.[19]

Implications of Improved Profit Signals

The average returns to society from past drug research and development appear to have been large.[20] However, because of the various sources of inefficiency in the allocation of R&D resources described above, the marginal return (the benefit from the "last" dollar of R&D) could be less than the marginal cost (that last dollar) in some areas of drug research. Overinvestment in specific areas of R&D could be tempered through better information about product quality or copayment prices that more fully reflected differences in what insurers pay for different drugs. Those changes would provide pharmaceutical

14. According to the Congressional Research Service, "more than 60 percent of the non-institutionalized population under age 65 is insured through employment-based plans. On average, large employers pay about 80 percent of the cost of this insurance, though some pay all and others none." See Bob Lyke, *Tax Benefits for Health Insurance and Expenses: Overview of Current Law and Legislation,* CRS Report for Congress RL33505 (Congressional Research Service, June 30, 2006), p. CRS-2.

15. The demand for insurance has also expanded with the number and variety of prescription drugs on the market. In 1961 (when far fewer prescription drugs existed, and Medicare and Medicaid had not yet been created), less than 0.5 percent of consumer spending on prescription drugs was covered by health insurance. That figure rose to more than 30 percent by 1980, nearly 50 percent by 1990, and 70 percent by 2005. For recent figures, see Centers for Medicare & Medicaid Services, "National Health Care Expenditures Projections, 2005-2015," Table 11, available at www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2005.pdf. For earlier figures, see Department of Health and Human Services, *Report to the President: Prescription Drug Coverage, Spending, Utilization, and Prices* (April 2000), Table 2-30.

16. On the relationship between innovation and insurance coverage, see Burton Weisbrod, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature,* vol. 29, no. 2 (June 1991), pp. 523-552.

17. See Henry J. Kaiser Family Foundation, *Prescription Drug Trends,* Fact Sheet No. 3057-03 (June 2006), available at www.kff.org/rxdrugs/upload/3057-05.pdf.

18. See Reinhardt, "Perspectives on the Pharmaceutical Industry," pp. 140-146.

19. See Scherer, "Pricing, Profits and Technological Progress in the Pharmaceutical Industry."

20. See, for example, discussions of antidepressants and several other important health care technologies in David M. Cutler and Mark McClellan, "Is Technological Change in Medicine Worth It?" *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 11-29, and of cancer drugs in Frank R. Lichtenberg, *The Expanding Pharmaceutical Arsenal in the War on Cancer,* Working Paper No. 10328 (Cambridge, Mass.: National Bureau of Economic Research, February 2004).

companies with more-accurate signals about the relative value of different drug treatments.

By itself, the rapid growth that has occurred in spending on prescription drugs is not necessarily a sign of inefficiency in drug utilization or R&D. Health care innovations have often caused consumer spending to rise, just as the introduction of any new or improved product can cause spending on that type of product to increase. (For example, total spending on computers increased for many years as their attributes—such as speed, storage, and memory—improved.)[21] Prescription drugs that offer new therapies or that substitute for other forms of treatment are particularly likely to cause total drug spending to rise. Thus, even if better profit signals induced drug firms to shift their R&D resources toward new treatments with higher social value, it might not follow that total spending on prescription drugs would decline, or even grow more slowly. Better signals would, however, lead to greater efficiency in the use of drug treatments as well as in the research and development of new treatments.

21. See Congressional Budget Office, *The Role of Computer Technology in the Growth of Productivity* (May 2002), pp. 9-11.

References

Acemoglu, Daron, and Joshua Linn, "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," *Quarterly Journal of Economics* (August 2004), pp. 1049-1090.

Adams, Christopher P., and Van V. Brantner, "Estimating the Cost of New Drug Development: Is It Really $802 Million?" *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 420-428.

American Association for the Advancement of Science, Intersociety Working Group, *AAAS Report XXXI: Research and Development, FY 2007* (Washington, D.C.: AAAS, 2006).

Andersen, Morten, Jakob Kragstrup, and Jens Søndergaard, "How Conducting a Clinical Trial Affects Physicians' Guideline Adherence and Drug Preferences," *Journal of the American Medical Association,* vol. 295, no. 23 (June 21, 2006), pp. 2759-2764.

Berndt, Ernst R., "Pharmaceuticals in U.S. Health Care: Determinants of Q and P," *Journal of Economic Perspectives,* vol. 16, no. 4 (Fall 2002), pp. 45-66.

Berndt, Ernst R., Iain M. Cockburn, and Karen A. Grépin, "The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilization in Original and Supplemental Indications," *PharmacoEconomics* (forthcoming, 2006).

Berndt, Ernst R., Iain Cockburn, and Zvi Griliches, "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressants," *Brookings Papers on Economic Activity: Microeconomics* (1996), pp. 133-199.

Berndt, Ernst R., and others, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews: Drug Discovery,* vol. 4, no. 7 (July 2005), pp. 545-554.

Boston Consulting Group, *The Contribution of Pharmaceutical Companies: What's at Stake for America* (Boston, Mass.: Boston Consulting Group, September 1993).

Cockburn, Iain M., "The Changing Structure of the Pharmaceutical Industry," *Health Affairs,* vol. 23, no. 1 (January/February 2004), pp. 10-22.

——, "Is the Pharmaceutical Industry in a Productivity Crisis?" (paper prepared for the National Bureau of Economic Research's Innovation Policy and the Economy Conference, Washington, D.C., April 19, 2006), available at www.nber.org/books/innovation7/cockburn4-29-06.pdf.

Cockburn, Iain M., and Rebecca Henderson, "Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery," *RAND Journal of Economics,* vol. 27, no. 1 (Spring 1996), pp. 32-59.

——, *Public-Private Interaction and the Productivity of Pharmaceutical Research,* Working Paper No. 6018 (Cambridge, Mass.: National Bureau of Economic Research, April 1997).

——, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery," *Journal of Industrial Economics,* vol. 46, no. 2 (June 1998), pp. 157-182.

——, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," in Adam B. Jaffe, Josh Lerner, and Scott Stern, eds., *NBER Innovation Policy and the Economy,* vol. 1 (Cambridge, Mass.: National Bureau of Economic Research, 2000), pp. 1-34.

——, "Scale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research," *Journal of Health Economics,* vol. 20, no. 6 (November 2001), pp. 1033-1057.

Comanor, W.S., "Pharmaceutical Prices and Expenditures," in R.M. Andersen, T.H. Rice, and G.F. Kominski, eds., *Changing the U.S. Health Care System* (San Francisco: Jossey Bass, 2001).

Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998).

——, *Prices for Brand-Name Drugs Under Selected Federal Programs* (June 2005).

Cutler, David M., and Mark McClellan, "Is Technological Change in Medicine Worth It?" *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 11-29.

Danzon, Patricia M., Andrew Epstein, and Sean Nicholson, *Mergers and Acquisitions in the Pharmaceutical and Biotechnology Industries,* Working Paper No. 10536 (Cambridge, Mass.: National Bureau of Economic Research, June 2004).

Danzon, Patricia M., Sean Nicholson, and Nuno Sousa Pereira, "Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances," *Journal of Health Economics,* vol. 24, no. 2 (March 2005), pp. 317-339.

David, Paul A., Bronwyn H. Hall, and Andrew A. Toole, "Is Public R&D a Complement or Substitute for Private R&D? A Review of the Econometric Evidence," *Research Policy,* vol. 29, nos. 4-5 (April 2000), pp. 497-529.

DiMasi, Joseph A., "New Drug Development in the United States from 1963 to 1999," *Clinical Pharmacology & Therapeutics,* vol. 69, no. 5 (May 2001), pp. 286-296.

DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151-185.

DiMasi, Joseph A., and Cherie Paquette, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development," *PharmacoEconomics,* vol. 22, supplement 2 (2004), pp. 1-14.

DiMasi, Joseph A., and others, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics,* vol. 10, no. 2 (July 1991), pp. 107–142.

Duggan, Mark, "Do New Prescription Drugs Pay for Themselves? The Case of Second-Generation Antipsychotics," *Journal of Health Economics,* vol. 24, no. 1 (January 2005), pp. 1-31.

Duggan, Mark, and Fiona Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," *Quarterly Journal of Economics,* vol. 71, no. 1 (February 2006), pp. 1-30.

Dyer, Geoff, "Debate Is Raging over Whether Nexium, a Widely Used Ulcer Drug, Is Really a Worthwhile Improvement for Most Patients over an Earlier Treatment—Especially with Healthcare Budgets Under Growing Pressure," *Financial Times* (London Edition), October 22, 2003, p. 25.

Finkelstein, Amy, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* (May 2004), pp. 527-564.

Food and Drug Administration, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

Frank, Richard G., "New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 325-330.

Garber, Alan M., Charles I. Jones, and Paul M. Romer, *Insurance and Incentives for Medical Innovation,* Working Paper No. 12080 (Cambridge, Mass.: National Bureau of Economic Research, March 2006).

General Accounting Office, *Technology Transfer: Agencies' Rights to Federally Sponsored Biomedical Inventions,* GAO-03-536 (July 2003).

Gerth, Jeff, and Sheryl Gay Stolberg, "Medicine Merchants: Birth of a Blockbuster; Drug Makers Reap Profits on Tax-Backed Research," *New York Times,* April 23, 2000, p. A1.

Giaccotto, Carmelo, Rexford Santerre, and John Vernon, *Explaining Pharmaceutical R&D Growth Rates at the Industry Level: New Perspectives and Insights,* Publication 03-31 (Washington, D.C.: AEI-Brookings Joint Center for Regulatory Studies, December 2003).

Goolsbee, Austan, "Does Government R&D Policy Mainly Benefit Scientists and Engineers?" *American Economic Review,* vol. 88, no. 2 (May 1998), pp. 298-302.

Gordon, Robert J., "Recent Productivity Puzzles in the Context of Zvi Griliches' Research" (paper presented to the American Economic Association, January 2002), available at http://faculty-web.at.northwestern.edu/economics/gordon/Aeazg.pdf.

Grabowski, Henry, *Health Reform and Pharmaceutical Innovation* (Washington, D.C.: AEI Press, 1994).

——, "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," in John V. Duca, ed., *Science and Cents: Exploring the Economics of Biotechnology* (Dallas: Federal Reserve Bank of Dallas, September 2003), pp. 87-104.

Grabowski, Henry G., and John M. Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics,* vol. 13, no. 4 (December 1994), pp. 383-406.

Grabowski, Henry, John Vernon, and Joseph DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *PharmacoEconomics,* vol. 20, supplement 3 (2002), pp. 11-29.

Grabowski, Henry, and Richard Wang, "The Quantity and Quality of Worldwide New Drug Introductions, 1982-2003," *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 452-460.

Griliches, Zvi, "Productivity, R&D, and the Data Constraint," *American Economic Review,* vol. 84, no. 1 (March 1994), pp. 1-23.

Guenther, Gary, *Federal Taxation of the Drug Industry: 1990 to 1999* (Congressional Research Service, July 22, 2002).

Hall, Bronwyn H., Adam B. Jaffe, and Manuel Tratjenberg, *The NBER Patent Citation Data File: Lessons, Insights, and Methodological Tools,* Working Paper No. 8498 (Cambridge, Mass.: National Bureau of Economic Research, October 2001).

Hansen, R.W., "The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes," in R.I. Chien, ed., *Issues in Pharmaceutical Economics* (Lexington, Mass.: Lexington Books, 1979), pp. 151–187.

Harris, Gardiner, "Where Are All the New Drugs?" *New York Times,* October 5, 2003, Section 3, p. 1

Henderson, Rebecca, and Iain Cockburn, "Scale, Scope and Spillovers: The Determinants of Research Productivity in Drug Discovery," *RAND Journal of Economics,* vol. 27, no. 1 (Spring 1996), pp. 32-59.

Heres, Stephan, and others, "Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics," *American Journal of Psychiatry,* vol. 163, no. 2 (February 2006), pp. 185-194.

Jones, Charles I., and John C. Williams, "Measuring the Social Return to R&D," *Quarterly Journal of Economics,* vol. 113, no. 4 (November 1998), pp. 1119-1135.

Kessler, David A., and others, "Therapeutic-Class Wars—Drug Promotion in a Competitive Marketplace," *New England Journal of Medicine,* vol. 331, no. 20 (November 17, 1994), pp. 1350-1353.

Keyhani, Salomeh, Mari Diener-West, and Neil Powe, "Are Development Times for Pharmaceuticals Increasing or Decreasing?" *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 461-468.

Kremer, Michael, "Patent Buyouts: A Mechanism for Encouraging Innovation," *Quarterly Journal of Economics,* vol. 113, no. 4 (November 1998), pp. 1137-1167.

——, "Pharmaceuticals and the Developing World," *Journal of Economic Perspectives,* vol. 16, no. 4 (Fall 2002), pp. 67-90.

Kremer, Michael, and Rachael Glennerster, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* (Princeton, N.J.: Princeton University Press, 2004).

Landers, Peter, "Drug Industry's Big Push into Technology Falls Short," *Wall Street Journal,* February 24, 2004, p. A1.

Lanjouw, Jean O., and Iain M. Cockburn, "New Pills for Poor People? Empirical Evidence After GATT," *World Development,* vol. 29, no. 2 (February 2001), pp. 265-289.

Lanjouw, Jean O., and Mark Schankermann, *Research Productivity and Patent Quality: Measurement with Multiple Indicators,* Discussion Paper EI/32 (London: London School of Economics and Political Sciences, Toyota Centre, December 2002).

Lichtenberg, Frank R., *The Expanding Pharmaceutical Arsenal in the War on Cancer,* Working Paper No. 10328 (Cambridge, Mass.: National Bureau of Economic Research, February 2004).

Lieberman, Jeffrey A., and others, "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia," *New England Journal of Medicine,* vol. 353, no. 12 (September 22, 2005), pp. 1209-1223.

Lu, Z. John, and William S. Comanor, "Strategic Pricing of New Pharmaceuticals," *Review of Economics and Statistics,* vol. 80, no. 1 (February 1998), pp. 108-118.

Lyke, Bob, *Tax Benefits for Health Insurance and Expenses: Overview of Current Law and Legislation,* CRS Report for Congress RL33505 (Congressional Research Service, June 30, 2006).

Mansfield, Edwin, "Patents and Innovation: An Empirical Study," *Management Science,* vol. 32 (February 1986), pp. 173-181.

National Science Foundation, Division of Science Resources Statistics, *Federal Funds for Research and Development* (various years).

Offit, Paul A., "Why Are Pharmaceutical Companies Gradually Abandoning Vaccines?" *Health Affairs,* vol. 24, no. 3 (May/June 2005), pp. 622-630.

Peck, Carl C., "Drug Development: Improving the Process," *Food and Drug Law Journal,* vol. 52, no. 2 (1997), pp. 163-167.

Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006).

Porter, Eduardo, "Do New Drugs Always Have to Cost So Much?" *New York Times,* November 14, 2004, Section 3, p. 5.

Reinhardt, Uwe E., "Perspectives on the Pharmaceutical Industry," *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 136-149.

Rosenberg, Nathan, "Why Do Firms Do Basic Research (With Their Own Money)?" *Research Policy,* vol. 19 (1990), pp. 165-174.

Rowberg, Richard E., *Pharmaceutical Research and Development: A Description and Analysis of the Process,* CRS Report for Congress RL30913 (Congressional Research Service, April 2, 2001).

Schacht, Wendy H., *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology,* CRS Report for Congress RL32076 (Congressional Research Service, June 10, 2005).

Scherer, Frederic M., "Pricing, Profits, and Technological Progress in the Pharmaceutical Industry," *Journal of Economic Perspectives,* vol. 7, no. 3 (Summer 1993), pp. 97-115.

——, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), Chapter 9.

——, *New Perspectives on Economic Growth and Technological Innovation* (Washington, D.C.: Brookings Institution Press, 1999).

——, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs,* vol. 20, no. 5 (September/October 2001), pp. 216-220.

——, "The Pharmaceutical Industry—Prices and Progress," *New England Journal of Medicine,* vol. 351, no. 9 (August 26, 2004), pp. 927-932.

Surowiecki, James, "The Pipeline Problem," *New Yorker,* February 16, 2004.

Toole, Andrew A., *The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry,* Discussion Paper 00-07 (Stanford, Calif.: Stanford Institute for Economic Policy Research, November 2000).

U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards,* OTA-H-522 (February 1993).

Ward, Michael R., and David Dranove, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry,* vol. 33, no. 1 (January 1995), pp. 70-87.

Weisbrod, Burton, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature,* vol. 29, no. 2 (June 1991), pp. 523-552.

Weisbrod, Burton A., and Craig L. LaMay, "Mixed Signals: Public Policy and the Future of Health Care R&D," *Health Affairs,* vol. 18, no. 2 (March/April 1999), pp. 112-125.