

Research and Development Expenditures 2

This chapter summarizes trends in pharmaceutical research and development (R&D) spending and compares estimates from available data sources. In short, the pharmaceutical industry invests more intensively in R&D than do most industries, and expenditures in constant dollars have risen at an astonishing rate of roughly 10 percent per year. Since 1980, pharmaceutical firms in the United States and abroad have devoted an increasing proportion of total sales to R&D. How much is spent? What does this record of increasing real investment in R&D say about the costs and returns to pharmaceutical R&D, both in the past and in the future? This chapter addresses these questions.

HOW TO MEASURE R&D SPENDING

There is no single comprehensive source of data on worldwide spending for pharmaceutical R&D. Because the research-intensive pharmaceutical industry is a mix of large multinational companies and small research-oriented firms, it is difficult to capture all R&D spending on human-use pharmaceuticals in one data source. R&D data come from three main sources: industry trade associations, governments, and companies themselves.

The Pharmaceutical Manufacturers Association (PMA) is the main source of industry trade data on R&D conducted in the United States by its member companies and abroad by its U.S.-based businesses.¹ PMA publishes an annual survey of its 60 corporate members, representing about 100 business entities.



¹ Domestic R&D data are for PMA members that are U.S.-based companies and U.S. subsidiaries of foreign companies. Data on foreign R&D expenditures reflect only PMA members that are U.S.-based companies.

In addition, in 1991, the Centre for Medicines Research, an arm of the Association of the British Pharmaceutical Industry, conducted a survey of pharmaceutical industry trade associations in nine European countries, Japan and the United States (172).

U.S. Government data on domestic R&D expenditures by industry are available from the National Science Foundation (NSF) Survey of Industrial Research and Development conducted routinely since 1956. Each firm in the sample is classified by a three-digit Standard Industrial Classification (SIC) Code.² The U.S. Census Bureau on behalf of NSF collects data on total companywide domestic R&D expenditures. The estimates for drug companies (SIC 283) include all R&D conducted in the United States in company-owned and -operated facilities. Unfortunately, nonpharmaceutical R&D may be included in the estimates.

Also, the composition of firms in the pharmaceutical industry changes as mergers and acquisitions alter SIC codes. For example, the acquisition in 1985 of G.D. Searle Company by Monsanto Corporation, a chemical firm, probably caused Searle's spending on R&D to be counted in SIC 281 (chemicals) in subsequent years. Because the SIC classifications change with merger and acquisition activity, NSF is probably a less reliable source of industrywide R&D growth rates than is PMA.

Company data are also available from annual reports and filings with the Securities and Exchange Commission (SEC). Compustat^{TM3} publishes audited company financial data for over 13,000 publicly traded companies in the United States. The data are organized by four-digit SIC code; firms are assigned to a primary SIC category by CompustatTM staff using industry definitions from the SIC manual, but there is no

guarantee that firms will be given the same SIC code as the NSF survey (387). Like the NSF survey, CompustatTM data on R&D spending include companywide estimates, including both pharmaceutical and nonpharmaceutical R&D. The CompustatTM estimates include both foreign and domestic R&D conducted by the reporting companies. Between 1971 and 1990, 133 firms were listed as pharmaceutical companies during at least 1 year of that period.⁴

Estimates of total industry R&D expenditures built from individual companies' financial records (i.e., PMA and Compustat) may be overstated because of certain accounting practices that can lead to double counting of such costs at the industry level. The purchase of the right to further develop a product is considered a purchase of "in-process R&D" for accounting purposes. If one company synthesizes a new drug, for example, and licenses it to another company for clinical development and marketing, the company purchasing the right in exchange for an upfront cash payment and future royalty payments may ac-



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The pharmaceutical industry's investment of approximately \$6 billion on R&D is one of the most intensive of all the R&D-oriented industries.

² The Standard Industrial Classification system is a method used to assign firms to industries according to the products or services they sell (126).

³ CompustatTM is a commercial on-line, time-series database service of Standard & Poor's, publisher of business reference books.

⁴ Prior to 1975, uniform accounting standards did not exist for reporting R&D spending; hence, data are reported in this study only for the period beginning with 1975.

count for the upfront cash payment as the purchase of “in-process R&D” (144). This cash payment may bear no relation to the actual incurred research expenditures; it is the purchase price of a valuable asset, whose cost of development was already accounted for (in earlier years) in the R&D expenses of the first company. The purchase price may include not only the payback for R&D performed by the first company but also a payment for the potential market value of the drug in the future. (A drug with a large potential market, for example, will have a high licensing price, even if the R&D costs to date have been low.)

Conservative accounting practices require that such upfront payments be expensed, rather than capitalized as investments, because unapproved drugs are considered intangible assets of unproven value. Some companies, particularly small ones for which such payments are a substantial part of their R&D expenses, may separately identify such transactions as “purchase of in-process R&D.”⁶ Nevertheless, even when such transactions are separately identified in annual financial statements, it is unclear how the transactions are treated when companies report their expenditures through surveys such as those conducted by PMA.

The potential magnitude of the overstatement of industrywide R&D costs in databases using company financial statements is illustrated by a recently-announced strategic alliance between Centocor, a biotechnology firm, and Eli Lilly and Company, a large pharmaceutical company. Lilly acquired the right to collaborate with Centocor on the commercialization and marketing of Centocor’s promising anti-infective drug, CentoxinTM in exchange for purchase of Centocor stock and

\$50 million in cash (121). The \$50-million cash payment from Lilly to Centocor will probably be recorded as an R&D expense on Lilly’s financial statements because CentoxinTM is not yet approved for marketing.⁷ If Centocor uses the cash to fund continued R&D on the product, it, too, will report R&D expenses of \$50 million. Then, industrywide estimates of R&D expenditures that include both firms recorded R&D expenses would double count the actual R&D outlays associated with Centoxin.

The overestimate of R&D costs may have increased in the 1980s for two reasons. First, the percent of new chemical entities (NCEs) under development that are licensed from other companies increased in the 1980s (107). The increasing frequency of strategic alliances between pharmaceutical firms and small biotechnology firms in the late 1980s may have added to the trend. Second, between 1981 and 1987, the R&D limited partnership was an attractive financing vehicle for small biotechnology firms. Since the partnership actually owns the rights to the products of the research, purchase of in-process R&D by the company would be one way for the company to buy back the rights to products developed through the partnership before they are approved for marketing.

Despite these distortions, the Office of Technology Assessment believes that the overstatement in estimates based on company financial reports is still a small proportion of total industry R&D and does not account for much of the increase in the recorded rate of change of R&D in the 1980s, especially domestic R&D. First, PMA’s membership does not include many small biotechnology companies, so the potential for double counting of R&D expenditures is reduced. (For example,

⁵ Once a product is approved for marketing, however, the purchase of rights to market it can be treated as an investment. For example, when Genentech, Inc. purchased rights to market *Protropin* (its human growth hormone product) from the R&D limited partnership that owned rights, it accounted for the transaction as a “purchase of product technology” and amortized the cash outlay over a period of years (145).

⁶ For example, when Genzyme, Inc. purchased the rights to further develop the orphan product *alglucerase* from an R&D limited partnership, it showed the \$20-million price of buying out the partnership as a purchase of “in-process R&D” (141).

⁷ The Office of Technology Assessment requested Eli Lilly and Company to confirm or correct this interpretation but the company declined to respond to OTA’S inquiry.

Centocor is not a member of PMA and is also not included as a pharmaceutical firm in the Compustat database.) Second, although the R&D limited partnership grew in use over the 1980s, it represented a small proportion of the overall funding of pharmaceutical R&D, and few biotechnology based pharmaceutical products were actually marketed in the 1980s; therefore, few buy-outs would have occurred in the period. Third, a review of annual reports of nine large U.S. pharmaceutical companies over the period 1978-89 found no disclosure of unusual R&D expenditures (such as those involving a large cash payment to another firm), suggesting that such expenses were not material in these firms (29).

Nevertheless, the overestimation bias could grow in the 1990s as cross-licensing and strategic alliances among pharmaceutical companies increase in frequency. The NSF survey does not suffer from the double counting problem, although its estimates are sensitive to mergers and acquisitions that change industry classifications. Because the magnitude of the effect of the limitations of each database on the resulting estimates is unclear, it is best to examine all such estimates together.

TRENDS IN DOMESTIC R&D SPENDING

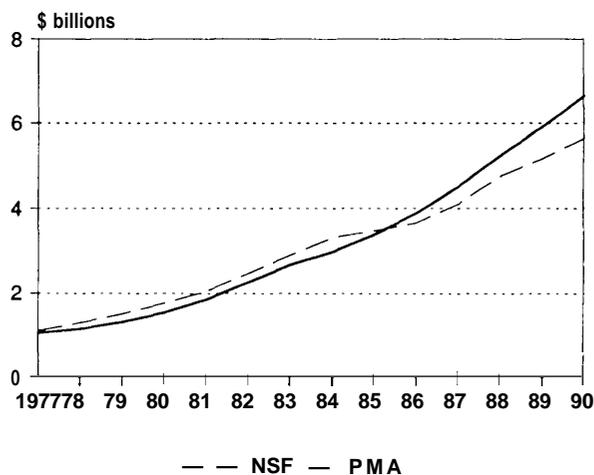
PMA and NSF each report on R&D performed by pharmaceutical firms in the United States. Between 1977 and 1990, domestic R&D spending increased at an annual rate of 13.3 percent in the NSF survey and 15.1 percent in the PMA series (see figure 2-1). After adjusting for inflation, the annual increases were 7.6 percent for the NSF series and 9.4 percent for the PMA series. Table 2-1 shows the estimated domestic expenditures from 1975 through 1990. R&D spending increased from \$1.1 billion in 1977 to between \$5.7 billion (NSF) and \$6.6 billion (PMA) in 1990.

Until 1986, the NSF estimates were higher than those of PMA. Because the NSF survey measures total company R&D, including R&D on both ethical pharmaceuticals and other lines of business, the difference is to be expected. Since 1986,

however, the PMA estimates have exceeded the NSF estimates. One possibility for this shift is the impact of mergers and acquisitions in the mid-1980s on industry classification in the NSF series.

Although the two data sources are not completely comparable, both reveal a shift in the speed of growth in domestic R&D spending by pharmaceutical companies beginning in the early 1980s. For example, according to NSF, inflation-adjusted R&D spending increased at about 7.7 percent per year between 1977 and 1980; between 1980 and 1985 it increased at 8.6 percent per year. However, between 1985 and 1990 real R&D spending in the NSF survey increased at only 6.5 percent. PMA data show more striking trends: between 1975 and 1980 real domestic R&D spending increased at a rate of 3.5 percent per year; between 1980 and 1985 it averaged 11 percent and between 1985 and 1990 it averaged 10.7 percent.

Figure 2-1—Domestic Pharmaceutical R&D Expenditures, 1977-90



KEY: NSF = National Science Foundation; PMA = Pharmaceutical Manufacturers Association.

SOURCES: Pharmaceutical Manufacturers Association, *Annual Survey Reports, 1975-91* (Washington, DC: PMA, 1978-91). National Science Foundation, *Surveys of Science Resources Series, Research and Development in Industry: 1987-7988, Detailed Statistical Tables, NSF 89-323* (Washington, DC: NSF, 1989, 1990). National Science Foundation, *Selected Data on Research and Development in Industry: 1990, NSF 92-317, Selected Data Tables* (Washington, DC: NSF, 1992).

Table 2-1—Aggregate Domestic R&D Expenditures,^a 1975-90 (\$ billions)

| | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 ^b |
|---|------|------|------|------|------|------------------|------------------|------------------|------------------|------------------|------|------|------|------|------|-------------------|
| National Science Foundation | | | | | | | | | | | | | | | | |
| Current dollars. | NA | NA | 1.1 | 1.3 | 1.5 | 1.8 ^c | 2.1 ^c | 2.5 ^c | 2.9 ^c | 3.3 ^c | 3.5 | 3.7 | 4.1 | 4.7 | 5.2 | 5.7 |
| Constant 1990 dollars ^d | NA | NA | 2.2 | 2.4 | 2.5 | 2.7 | 2.9 | 3.3 | 3.7 | 4.0 | 4.1 | 4.2 | 4.6 | 5.1 | 5.4 | 5.7 |
| Pharmaceutical Manufacturers Association | | | | | | | | | | | | | | | | |
| Current dollars. | .9 | 1.0 | 1.1 | 1.2 | 1.3 | 1.5 | 1.9 | 2.2 | 2.7 | 3.0 | 3.3 | 3.9 | 4.5 | 5.2 | 6.0 | 6.6 |
| Constant 1990 dollars ^d | 2.0 | 2.0 | 2.1 | 2.1 | 2.2 | 2.4 | 2.6 | 3.0 | 3.4 | 3.6 | 4.0 | 4.5 | 5.0 | 5.7 | 6.3 | 6.6 |

^aIncludes company, Federal and other funds for R&D.
^bBudgeted amounts.
^cFederal sources of R&D funds to companies are excluded in this year.
^dAdjusted by GNP implicit price deflator.

KEY: NA = not available.

SOURCE: Office of Technology Assessment, 1993, based on Pharmaceutical Manufacturers Association, *Annual Survey Reports, 1975-91* (Washington, DC: PMA, 1976-91). National Science Foundation, *Surveys of Science Resources Series, Research and Development in Industry: 1987-1988*, Detailed Statistical Tables, NSF 89-323 (Washington, DC: National Science Foundation, 1989, 1990).

TRENDS IN WORLDWIDE PHARMACEUTICAL R&D EXPENDITURES

Data on worldwide R&D expenditures by U.S.-based firms are available both from CompustatTM and PMA. Despite the difference between the two sources in coverage of R&D expenditures, total R&D conducted by U. S.-based pharmaceutical companies in 1975 was estimated at \$1.1 billion by both PMA and CompustatTM (table 2-2). By 1990, this spending had grown to between \$7.9 billion (CompustatTM)

and \$8.1 billion (PMA). These data suggest that after adjusting for inflation, foreign and domestic R&D spending by U.S.-based companies increased at approximately 8 to 8.5 percent per year between 1975 and 1990. The rate of increase appears to have accelerated, however. Before 1980, real worldwide R&D expenditures of U.S. firms increased only by 5 to 6 percent per year (table 2-2). Between 1985 and 1990, PMA data show a 10.9 percent annual rate of increase in real spending.⁷ CompustatTM data show a rate of

Table 2-2—Aggregate Pharmaceutical Foreign and Domestic R&D, Selected Years (\$ billions)

| | 1975 | 1980 | 1985 | 1987 | 1990 | Annual percent rate of change | | |
|---|--------|--------|--------|--------|--------|-------------------------------|---------|---------|
| | | | | | | 1975-80 | 1980-85 | 1985-90 |
| <i>CompustatTM</i> | | | | | | | | |
| Current dollars. | \$1.10 | \$2.08 | \$4.20 | \$5.53 | \$7.90 | 13.6% | 15.1% | 13.5% |
| Constant 1990 dollars ^b | 2.44 | 3.19 | 4.98 | 6.19 | 7.90 | 5.5 | 9.3 | 9.7 |
| <i>Pharmaceutical Manufacturers Association^c</i> | | | | | | | | |
| Current dollars. | 1.06 | 1.98 | 4.08 | 5.51 | 8.13 | 13.2 | 15.6 | 14.8 |
| Constant 1990 dollars. | 2.36 | 3.03 | 4.83 | 6.17 | 8.13 | 5.2 | 9.8 | 10.9 |

^a Figures are based on a total of 133 firms listed in the Compustat file under Standard industrial Code (SIC) code 2834 in at least 1 year between 1971 and 1990. The number of firms vary from year to year due to firms' entry and exit from SIC 2834.
^b Adjusted by GNP implicit price deflator.
^c R&D expenditures reported by Pharmaceutical Manufacturers Association member firms.

SOURCE: Office of Technology Assessment, 1993, based on unpublished data provided by S.H.Kang, School of Industrial Administration, Carnegie-Mellon University, Pittsburgh, PA; Pharmaceutical Manufacturers Association, *Annual Survey Reports, 1975-91* (Washington, DC: PMA, 1976-91).

⁷ Because spending in various countries must be converted into a common currency, exchange rate changes can affect reported spending. The devaluation of the dollar after 1985 may be responsible for some of the unusually high increase in total spending reported in recent years.

growth in real spending of 9.2 percent per year between 1985 and 1990.

The Centre for Medicines Research estimates total expenditure on pharmaceutical R&D in 11 industrialized countries increased from \$5.4 billion in 1981 to \$15 billion in 1988 (172). Estimated spending (in current dollars) accelerated after 1985, increasing 22 percent per year between 1985 and 1988, compared with 10.5 percent per year between 1981 and 1985.

Thus, although a comprehensive source of data on worldwide R&D spending is unavailable, the existing data sources point to an accelerating rate of increase in real spending on R&D throughout the 1980s.

DIRECTIONS OF PHARMACEUTICAL R&D

Where have the increasing funds devoted to pharmaceutical R&D been applied? Have they been used increasingly for the advancement of scientific knowledge within companies? Have they been increasingly targeted to discovery and development of drugs that treat diseases through

entirely new modes of action (“breakthrough” drugs) or have they been targeted to new drugs similar in structure and mode of action to products already on the market (so-called “me-too” drugs)? To what extent have they been used to support the development of product extensions or to research new uses of existing drugs?

The data available on trends in R&D do not provide answers to these questions. PMA is the only source of data on the allocation of R&D across different kinds of functions, and the PMA fictional classification system is not germane to these questions (table 2-3). Unfortunately, these categories cut across all kinds of research and cannot even be used very accurately to estimate the proportion of R&D that is for drug discovery versus clinical testing. Spending by fictional category has remained relatively stable over time. Companies reporting to PMA also provide estimates of the percent of R&D devoted to “the advancement of scientific knowledge and development of new products” versus “significant improvements and/or modifications of existing

Table 2-3-Distribution of R&D Expenditures by Function, Selected Years 1976-89a (\$ millions)

| Function | 1976 | 1977 | 1978 | 1980 | 1982 | 1985 | 1987 | 1988 | 1989 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Clinical evaluation: phases I, II, III ... | \$20.2 | \$17.8 | \$16.5 | \$19.8 | \$19.9 | \$21.0 | \$24.0 | \$26.4 | \$26.7 |
| Biological screening and pharmacological testing. | 19.5 | 18.7 | 18.8 | 18.6 | 17.9 | 16.6 | 16.8 | 16.7 | 16.9 |
| Synthesis and extraction. | 16.6 | 17.2 | 16.3 | 15.4 | 11.6 | 11.6 | 10.3 | 10.3 | 9.8 |
| Pharmaceutical dosage formulation and stability testing. | 9.1 | 9.7 | 10.1 | 9.2 | 10.4 | 9.3 | 9.1 | 9.1 | 9.4 |
| Toxicology and safety testing. | 8.9 | 9.2 | 10.0 | 9.7 | 8.9 | 8.9 | 8.3 | 7.8 | 7.0 |
| Process development for manufacturing and quality control. | 9.5 | 8.8 | 9.2 | 9.0 | 9.5 | 9.4 | 9.4 | 9.1 | 7.3 |
| Clinical evaluation: phase IV. | 3.2 | 4.7 | 4.8 | 3.7 | 3.2 | 5.0 | 4.4 | 3.5 | 4.0 |
| Regulatory, IND and NDA preparation, submission and processing. | 3.3 | 3.3 | 3.6 | 4.1 | 3.9 | 4.4 | 3.6 | 3.0 | 3.3 |
| Bioavailability studies. | 2.2 | 2.3 | 2.2 | 2.1 | 2.8 | 2.9 | 3.0 | 2.8 | 2.6 |
| Other. | 7.5 | 8.3 | 8.5 | 8.4 | 11.9 | 10.9 | 11.1 | 11.3 | 13.0 |
| Percent of pharmaceutical R&D devoted developing new products. | 79% | 80% | 80% | 81% | 79% | 82% | 83% | 82% | 82% |

a Based on R&D conducted in the United States by all PMA members.

KEY: IND = investigational new drug application; NA = not available; NDA = new drug application.

SOURCE: Pharmaceutical Manufacturers Association, *Annual Survey Reports, 1975-91* (Washington, DC: PMA, 1976-91).

products" (320). How firms define new products or modifications of existing products is unclear, however, and the reliability of these estimates cannot be verified. Nevertheless, the data do suggest a relatively stable mix of R&D over time—about 80 percent devoted to new-product R&D (table 2-3).

There is only sketchy information on trends in the allocation of new-product R&D between discovery research and clinical trials. DiMasi and colleagues asked 12 U.S. companies to estimate R&D expenditures for clinical and preclinical research on self-originated NCEs for the period 1970-86 (107). Over the entire period, 66.1 percent of research on self-originated drugs was reported as devoted to the preclinical phase. No clear trends were evident in the ratio over time (106), suggesting the allocation of R&D dollars has remained stable over time.

Early signs are emerging that the output of R&D--new products—is increasing modestly. Though the number of new molecular entities (NMEs)⁹ approved by the U.S. Food and Drug Administration (FDA) remained fairly constant throughout the 1980s—at a mean of 22.5 per year, the number of commercial investigational new drug (IND) applications for initiation of clinical testing of NMEs has increased over the decade. From 1980 to 1982, the Center for Drug Evaluation and Research (CDER) of the FDA issued an average of 271 commercial INDs annually while during the 1988-90 period, the average rose to 349 per year (475). Because more than one IND can be filed for each compound, a better indicator of trends in productivity of research, especially early research, is the number of NCEs entering testing. Data from a sample of over 40 companies indicate that the number of INDs for NCEs increased from 210 per year between 1975 and 1978 to 299 per year between 1983 and 1986 (107).¹⁰ The total



Photo credit ELI LILLY AND COMPANY

The introduction of biotechnology-derived drugs has increased rapidly since the first FDA approval in 1982 of Lilly's recombinant DNA product, Humlin.

number of NCEs entering human testing in U.S.-based firms grew from 58 per year in the late 1970s to 67 per year between 1983 and 1986. Although INDs for NCEs originated in U. S.-based firms grew by 25 percent between the periods, the percent of all NCE INDs for self-originated U.S. drugs declined from 60 to 53 percent between the two periods. Licensed-in drugs and INDs submitted by foreign firms grew as a proportion of total NCE INDs submitted to the FDA.

The number of biotechnology drugs in development increased dramatically over the period. Between 1982—the year the FDA approved the first biotechnology-derived drug (Eli Lilly's recombinant human insulin j-and 1991, the FDA had approved a total of seven biotechnology drugs; however, as of October 1991 21 biotechnology drugs were awaiting FDA marketing approval (146). Chapter 6 discusses the potential backlog of approvals for biotechnology drugs in greater detail.

⁹ The terms 'new chemical entity' (NCE) and 'new molecular entity' (NME) both refer to new drugs, although their precise definitions are somewhat different. DiMasi et al. define NCE as 'a new molecular compound not previously tested in humans.' NME is a term used by the FDA that, unlike NCE, includes some diagnostic agents and excludes therapeutic biological (109,474). In keeping with DiMasi's definition, this report uses the term NCE to refer to both therapeutic drugs and biological. OTA uses the term NME only when discussing work that specifically employs FDA's definition of that term.

¹⁰ DiMasi and colleagues also give information on the 1979-82 period. See chapter 6 for more detail.

INTERPRETING AGGREGATE TRENDS

Each new dollar spent on pharmaceutical R&D is an investment in a potential stream of future revenues. Although investors make mistakes, their decisions are a true reflection of expectations about the future. The rapid increase in total industrywide pharmaceutical R&D in constant dollars in the 1980s means that investors expected aggregate net revenues over the lifetimes of the new products would be sufficient to justify the additional investment with its attendant risks.

Little more can be concluded from an examination of R&D spending trends. For example, investors might or might not expect the number of drugs approved for marketing to increase in the future. The R&D could be directed toward fewer products with more lucrative markets, or it could be directed to the introduction of a large number of products, each with more modest market potential.

Some of the R&D might be directed to the development of “me-too” drugs that do not

substantially enlarge the overall market but share an existing market with close therapeutic substitutes. The pursuit of “me-too” drugs is an attempt by rival firms to shave off part of the monopoly profits enjoyed by the maker of the pioneer drug in a therapeutic class.¹¹ The higher the initial monopoly profits, the more incentive rivals have to develop a similar competing drug (102,346,363,418). Thus, the increased R&D in the 1980s could in part be a response to high returns to pioneer drugs developed in the 1970s.

R&D dollars pursue returns, and the risks investors will take to obtain those returns depend on how great they promise to be. To understand the drivers behind the pharmaceutical R&D phenomenon of the 1980s, it is necessary to examine closely how the returns to these investments have been changing over time. Subsequent chapters of this report examine trends in the average cost of discovering and developing new ethical pharmaceuticals and the net returns to bringing these products to market.

¹¹ Pioneer and “me-too” drugs are granted monopolies by the United States and other countries’ patent systems, which protect patented pharmaceutical compounds (or their manufacturing processes or uses) from copy for specific periods from the date of application or issue. Even with a strong patent, the monopoly may be limited by the availability of similar drugs in the therapeutic class, of competing classes of drugs, or of nonpharmaceutical therapies.