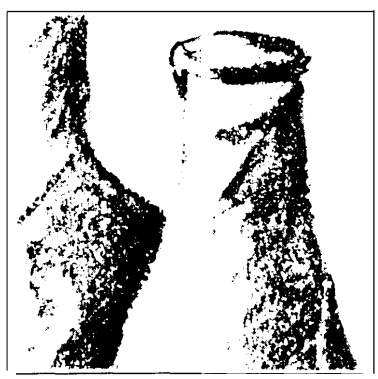
Returns on Pharmaceutical R&D

4

The cash outlays spent in bringing a new product to the point of approval for marketing in the United States increased in the 1970s and early 1980s. These cash outlays occurred over a substantial period of time, an average of 12 or more years.

A company makes these investments expecting that the financial returns from successful drugs will be high enough to justify the money, time, and risk involved. If the expected financial returns are too low to repay investors, then research and development (R&D) will decline as fewer projects are pursued. On the other hand, if overall returns on drugs introduced in the past are more than enough to repay investors for the cost, time, and risk involved, then consumers are paying too much. Evidence of long-run persistence of higher returns for new drugs over what is necessary to justify the cost and risk of R&D would imply unnecessary pricing power for new drugs [366). [1]

In an industry with active competition, pharmaceutical R&D investment will follow expected returns on new products. The introduction of a ‘‘pioneer’ drug, the first product introduced within a family of compounds, should and often does lead to R&D by rival firms intent on introducing a similar therapeutic alternative, or ‘ ‘me-too’ drug (158, 298), which can share the market with the leader. Box 4-A describes the intense competition among rival firms for the development of compounds in an important new class of drugs for the treatment of high cholesterol.



[1]The rationale for patent protection is based on the need for providing a return on the R&D necessary to bring an innovation to the market (366). In the absence of patent protection (or some other form of protection from imitation), competitors would copy the innovation at a fraction of the cost to the innovator and sell the product at prices that arc insufficient to recover the initial R&D investment. Thus, incentives to invest in innovation would be compromised (242).

Box 4-A--HMG-CoA Reductase Inhibitors

In August 1987, the first of a newly discovered class of cholesterol-lowering drug compounds known as HMG-CoA reductase inhibitors was approved for marketing in the United States. The drug, lovastatin, developed by Merck & Company, generated higher first-year sales than any previously introduced prescription medicine. Today, lovastatin has annual sales exceeding $1 billion and maintains a 60 percent share of the U.S. market for all cholesterol-lowering drugs.

The competitive drive to bring the first HMG-CoA reductase inhibitor to market highlights the intense research and development (R&D) rivalry that frequently precedes the debut of an innovative new drug. Although Merck was the first company to win U.S. marketing approval for a drug in that class, Merck was not the first to synthesize and clinically test such an agent. The prototype HMG-CoA reductase inhibitor, mevastatin, was isolated in 1976 by researchers at Japan's Sankyo. Mevastatin entered phase I clinical trials in Japan and other countries in 1978. At that time, Mevastatin showed much promise in significantly reducing low-density lipoprotein (LDL) cholesterol levels with few side effects. Meanwhile, scientists at Merck isolated a related compound, lovastatin, early in 1979. Merck filed for a U.S. patent on lovastatin just months after Sankyo filed for a Japanese patent on mevastatin.

Foreign clinical trials with lovastatin began in April 1980 but were suspended just 5 months later because, according to a Merck spokesman, "a similar compound had caused a toxic reaction in animals at another lab. " Although it was not announced at the time, the "similar compound" was Sankyo's mevastatin, which had been quickly withdrawn after intestinal lymphomas were found in 50 percent of laboratory dogs undergoing tests with the drug.

In 1982, Merck allowed several clinicians to file individually sponsored investigational new drug applications (INDs) for lovastatin in order to treat patients with severely high cholesterol unresponsive to existing therapies. The drug dramatically lowered LDL cholesterol with very few observed side effects. The results prompted Merck to reinstitute animal studies, and in May 1984 the company filed a commercial IND, allowing lovastatin to enter phase I clinical trials.

HMG-CoA reductase inhibitors drew more attention in 1985, as Dr. Michael S. Brown and Dr. Joseph S. Goldstein of the University of Texas won the Nobel prize for medicine for their work on LDL receptors. By November 14, 1986, Merck had finished its clinical and long-term animal studies and sent its new drug application (NDA) to the Food and Drug Administration (FDA). Lovastatin, with a IND/NDA classification of 1A, was approved within 9 months, bringing its total review time (from IND to NDA approval) to 1,204 days, making it one of the most rapidly approved drugs in the history of the FDA.

Meanwhile, the industry's R&D race produced additional HMG-CoA reductase agents. Sankyo's second HMG-CoA reductase inhibitor, pravastatin, licensed to Bristol-Myers Squibb, entered phase III clinical trials in Japan at the same time lovastatin entered phase III clinical trials in the United States. In October 1990, 21 months after Bristol-Myers Squibb submitted the NDA on January 31, 1989, FDA's Endocrinologic and Metabolic Advisory Committee unanimously recommended pravastatin be approved On October 31, 1991, 3 years after approval in Japan, the FDA approved pravastatin with a "lC" rating, a new molecular entity (NME) with little or no therapeutic gain over existing therapies. Bristol-Myers Squibb initially offered pravastatin at a direct price discount of 5 percent and a 10 percent discount to wholesalers of lovastatin. By 1993, pravastatin's sales are estimated to reach $500 million.

Simvastatin, Merck's successor product to lovastatin, was recommended for approval by FDA's Endocrinologic and Metabolic Advisory Committee in February 1991 and was approved for marketing on December 21, 1991. As with pravastatin, the FDA gave simvastatin a " 1C" rating, and it has been offered at a 5 to 10 percent discount to lovastatin. Unlike the breakthrough compound lovastatin, simvastatin has worldwide patent protection. Marketed outside the United States since 1988, simvastatin has been prescribed to over 1 million patients in 30 countries, and already ranks among the world's 50 top-selling drugs.

A list of HMG-CoA reductase inhibitors currently or formerly under development follows.

Compound	Sponsor	Approval Status
lovastatin	Merck	IND: April 1984. NDA: November 1986. Approval: August 1987.
pravastatin	Sankyo, Bristol-Myers Squibb	Launched in Canada, Europe, Japan, and Mexico. U.S. NDA: January 31,1989. U.S. approval: November 31, 1991.
simvastatin	Merck	Launched in at least 17 countries worldwide, including most of Europe. U.S. NDA: November 1986. U.S. approval: December 1991.
colestolone	American Cyanamid	Entered U.S. clinical trials in 1987.
fluvastatin	Sandoz	U.S. NDA filed March 1992.
Crilvastain	Pan Medica	Phase II clinical trials.
dalvastatin	Rhone-Poulenc Rorer	Phase III clinical trials.
BAYW6228	Bayer	Phase II clinical trials.
HR780	Hoeschst	Phase II clinical trials.
CI 981	Warner-Lambert	Phase I clinical trials.
BB-476	British Bio-technology	Series of compounds under development; preclinical.
BMY-22566	Bristol-Myers Squibb	Preclinical Studies.
SQ-33600	Bristol-Myers Squibb	Preclinical studies, discontinued
BMY-21950	Bristol-Myers Squibb	Phase I clinical trials.
GR-95030	Glaxo	Preclinical studies, discontinued
SC-45355	Searle	Preclinical studies, discontinued
L-659699	Merck	Preclinical studies,
L-669262	Merck	Preclinical studies.
CP-83101	Pfizer	Preclinical Studies.

Safety issues may lengthen the review period for successor products. As it considered pravastatin, the FDA's Endocrinologic and Metabolic Advisory Committee weighed increasing general concerns over the potential carcinogenicity of HMG-CoA reductase inhibitors against the need to maintain equitable review criteria for competing products. One FDA reviewer noted that too much emphasis on carcinogenicity data in pravastatin's review would "prevent a level playing field" with lovastatin. The approval of pravastatin and simvastatin suggest that comparable safety criteria continue to be used for successor HMG-CoA reductase agents.

The market potential for HMG-CoA reductase inhibitors is vast. In the United States alone, as many as 60 million people are estimated to have high cholesterol, but fewer than 1 million people currently receive drug therapy. As a result, the pharmaceutical industry continues to devote substantial R&D expenditures toward cholesterol-lowering drugs.

SOURCES: J. De Pass, 'The World's Top 50 Prescription Drugs," *Medical Marketing &Media,* 26:21, August 1991. *F-D-C Reports: Health News Daily,* "Bristol-Myers Squibb Launching Pravachol in Mid-November," *F-D-C Reports: Health News Daily, Nov. 4,* 1991, p. 4-5. *F-D-C Reports: Prescription and OTC Pharmaceuticals,* "Rep. Weiss' Subcommittee Investigating Regulation of Merck's Mevacor, Roche's Versed, W-L's THA; Dec. 1 Subpoena Deadline Set for FDA, OMB Documents," *F-D-C Reports: Prescription and OTC Pharmaceuticals, Nov. 23, 1987,* p. 6-7. *F-D-C Reports: Prescription and OTC Pharmaceuticals,* "FDA Approves 15 of 21 New Molecular Entities in December; Commissioner Young Says Approvals Will Be More Evenly Distributed in Coming Years," *F-D-C Reports: Prescription and OTC Pharmaceuticals,* Jan. 11, 1988, p. 10-13. *F-D-C Reports: Prescription and OTC Pharmaceuticals,* "Bristol-Myers Squibb Pravachol (Pravastatin) Recommended for Approval by FDA Advisory Committee," *F-D-C Reports: Prescription and OTC Pharmaceuticals,* Oct. *29,* 1990, p. 8-10. *F-D-C Reports: Prescription and OTC Pharmaceuticals,* "Cholesterol-Lowering Trials for New Classes of Drugs Should Include Clinical Endpoints," *F-D-C Reports: Prescription and OTC Pharmaceuticals, Mar.* 11, 1991, p. 7. *F-D-C Reports: Prescription and OTC Pharmaceuticals,* "Merck's Zocor (Simvastatin) Will Be Promoted by 1,230 Sales Reps Jointly With Smithkline Beecham," *F-D-C Reports: Prescription and OTC Pharmaceuticals,* Jan. *6, 1992,* A. Garber, Assistant Professor, School of Medicine, Stanford University, Palo Alto, CA, personal communication% Jan. 5, 1993. N. Ishida, Finance Manager, Sankyo USA, New York, NY, personal communication, Oct. 17, 1991. M. Malkin, Merck & Company,Inc., Rahway, NJ, personal communication, Oct. 21, 1991. *Pharmaprojects (Surrey,* United Kingdom: P.J.B. Publications Ltd., 1991). R.L. Pierce, Food and Drug Administration, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD, personal communication% Jul. 18, 1991. *Scrip World Pharmaceutical News, "Sankyo's* Compaction Effective in Familial Hypercholesterolaemia," *Scrip World Pharmaceutical News* 624:13, *1981. Scrip World Pharmaceutical News,* "Blockbusters in R&D," *Scrip World Pharmaceutical News* 1104:24, 1986. *Scrip World Pharmaceutical News,* "Merck & Co. Products Lead World Markets," *Scrip World Pharmaceutical News* 1397:16-17, *1989.* P.R. Vagelos, "Are Prescription Drug Prices High?" Science 252:1080-1084, 1991. M. Waldholz, "FDA Clears Sale of Bristol-Myers Cholesterol Drug,' New *York Times, Nov. 4, 1991,* p. B5.

New drugs need not be very similar in molecular structure to compete in a therapeutic category. For example, new medicinal approaches to the treatment of hypertension proliferated during the 1980s, as calcium channel blockers and angiotensin converting enzyme inhibitors have competed with beta-blockers and diuretics (4). Thus, the opportunities for competitive R&D are numerous, and in an industry with a large number of competing research-intensive fins, this competition should reduce industrywide returns on pharmaceutical R&D as competing products are introduced to share existing markets.

This chapter examines the returns on pharmaceutical R&D. It provides two kinds of evidence on returns: the present value of dollar returns on new chemical entities (NCEs) introduced during a selected time interval (which can be compared with the present value of the R&D costs required to produce the NCEs); and the net internal rate of return (IRR), or economic profit, from all business activities of firms whose primary line of business is the development, manufacture, and sale of ethical pharmaceuticals.

RETURNS ON R&D: THE EVIDENCE

Overview of Methods

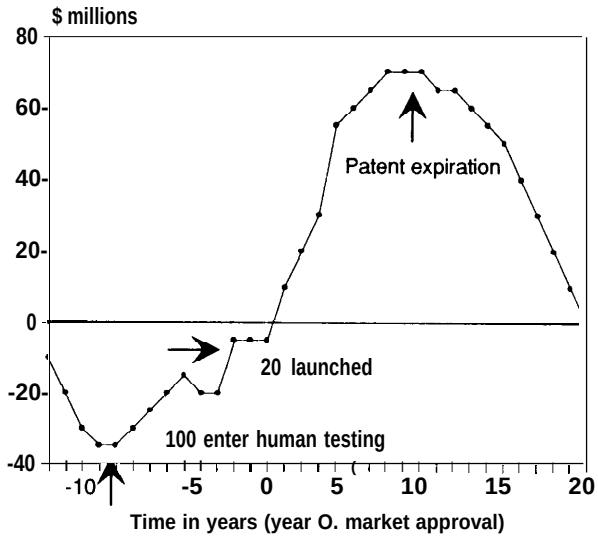
In chapter 3, the Office of Technology Assessment (OTA) reviewed the evidence on the full (or capitalized) cost of R&D at the point of market approval for drugs first entering clinical testing in the 1970s and early 1980s. The full cost of R&D can be thought of as the average value on the day the products are launched that successful drugs must have if they are to provide investors an adequate payback for the cash outlays, risk, and time spent in bringing the drugs to market.

The value of the potential income from successful drugs on the day of product launch depends on the complete product life cycle expected for these compounds. Figure 4-1 shows a hypothetical life cycle of R&D investment and revenues for an industry.

Suppose the industry starts from scratch with new companies 15 years before marketable products can be expected. The firms build or rent research facilities, then embark on programs to discover a group of candidate compounds for further research. Further laboratory and animal testing of these lead compounds over the next 3 to 4 years results in, say, 100 drug candidates that merit clinical testing. These 100 candidates then undergo rigorous testing to determine their safety and effectiveness in humans. More money is invested to fund the testing required to bring these drug candidates to market. As the testing process continues over the next 9 years, some compounds are found to be unsafe or ineffective and are abandoned. Ultimately, suppose only 20 of the 100 candidates jump all the hurdles and reach the market.

As the originators of the winning 20 compounds prepare for market entry, the firms developing them must invest again, this time in plant and equipment to manufacture the products. Once they are approved and launched, the new drugs start earning revenues (minus the costs of producing, marketing, and distributing them). Net revenues grow over the next few years and then flatten out. After 10 years or so, patents expire, and net revenues begin to decline as generic copies of the drugs are introduced. Ultimately, perhaps after 20

Figure 4-l-Cash-Flow Profile of 100 Drug Candidates



SOURCE: Office of Technology Assessment, 1993.

years, new generations of medical technology render the products obsolete, and they are removed from the market,

As figure 4-1 illustrates, in the early years of industry operation, cash flows out of the firms in the industry in the form of expenditures on R&D and manufacturing capacity. Years later, cash flows back into the firms as some of the investments paid off. Whether the NCEs pay off enough in revenues to justify the investment requires a comparison of the outflows of cash with their inflows, taking into account the timing of those cash flows.

The issue for this section is how to measure the net cash flows from the point of market approval to the end of the product's life cycle, taking account of the fact that revenues are uncertain, that costs must be incurred to manufacture, market and distribute the products, and that income delayed is worth less to investors than income today. Once the net income from the sale of successful drugs over their lifetime is appropriately measured, it must be compared with the fully capitalized cost of the R&D spent to bring them to market.

Just as the R&D investments in various years were compounded to their full net present value (NPV) in the year of market approval at an interest rate equal to the opportunity cost of capital, the future revenues (net of costs) must be discounted back to their NPV at the time of market approval, using an appropriate opportunity cost of capital. After that is done, the NPV of the fully capitalized costs of R&D can be subtracted from the NPV of the net revenues. If the difference is greater than zero, then the overall investment in R&D returned more than was necessary to repay the investors for the time their money was tied up and the risk they took. If the NPV of the investment as a whole was less than zero, then investors did not, on average, recover their cost of capital and could have done better by investing their funds in other industries.

Ideally, analysis of NPV should be based on actual cash flows, not on what financial accounting statements report. For example, when it builds a $50-million manufacturing facility, a company spends the money at the time of construction, but the fro's income statements will recognize the expense only gradually through depreciation charges. The actual investment in the facility was made at the time it was built, not as it was recognized in depreciation expenses. At the end of the product's life, the firm may "sell' the facility to a new group of projects at its current (or salvage) value. The salvage value of the facility should be reflected as a positive cash flow at the end of the product's life.

The analysis should also reflect the effect of taxes on cash flows. R&D expenses result in tax deductions and other credits that reduce taxes, while the net revenues from sales must be reduced by the taxes they cause to be paid.

Sales are highly uneven across drugs, with a few very successful drugs providing the bulk of the revenues (160). Some firms in the industry may not have any winners; others may be highly successful. At the industry level, analysis of returns on R&D is blind to the distribution of revenues across R&D projects or firms. Indeed, investors in startup firms or R&D projects expect many ventures to fail. It is the promise of the occasional big success that attracts the investment dollars. Nevertheless, across a large number of R&D projects, when winners and losers are averaged together, the NPV of the investment, at the appropriate cost of capital, should be in the neighborhood of zero.

Past Studies

Several researchers have tried to measure the net returns on R&D for new chemical entities by predicting the shape of the cash-flow profile (as illustrated in figure 4-1) for a group of drugs reaching the market in a given period. The researchers piece together information from a variety of sources about R&D outlays, the shape of the cash flow curve for new drugs, and the costs of producing and selling the products over the course of their life in the market.

These estimates are necessarily imprecise, because information on the full life cycle of a

group of drugs introduced in the study period may not yet be available, and data on production, marketing, and distribution costs are typically available only for the company as a whole, not for individual products or even lines of business.

Three such studies are reviewed here.[2] Joglekar and Paterson (215), Grabowski and Vernon (160) and Virts and Weston (500) estimated the NPV of returns on R&D investment in different samples of NCEs. Table 4-1 summarizes the main assumptions and findings of each study.

Joglekar and Paterson used the sales histories of 218 NCEs introduced in the United States between 1962 and 1977 (adjusted for inflation) as the basis for predicting the revenues to an "average" NCE expected to be introduced in 1988. The researchers made assumptions about the cost of producing and distributing the NCEs over their product lives. R&D cash outlays were based on Hansen's study of R&D costs (175), adjusted for inflation.[3] Joglekar and Paterson calculated the NPV of the investment using a 6 percent cost of capital; the estimated average after-tax NPV was $75 million per NCE (in 1976 dollars).

Grabowski and Vernon used the sales history of NCEs introduced between 1970 and 1979 to estimate the returns on this group of NCEs. The researchers estimated the total R&D cost (capitalized to the point of market approval at 9 percent) for this group of NCEs at $125 million (in 1986 dollars). Grabowski and Vernon's assumptions about production and distribution costs are similar in many respects to those of Joglekar and Paterson's, but Grabowski and Vernon included substantial extra costs in the early years of product life to cover expenditures for facilities, equipment, advertising, and promotion associated with the launch of a new product. Using a 9 percent cost of capital, the estimated after-tax NPV of overall investment in NCEs was just $1.3 million (in 1986 dollars).

Virts and Weston (500) multiplied U.S. hospital and drugstore prescription volume data on 119 NCEs introduced between 1967 and 1976, by the average selling price of the drugs and a prescription volume growth factor of 2 percent per year to estimate the revenue curve for these drugs. The market life was assumed to be 10 years, after which revenues would decline immediately to zero. Tax effects were not considered. The costs of R&D were based on Hansen's study (175), and all costs and revenues were discounted at 8 percent per year. The pretax NPV of the investment was negative: -$16 million per drug (in 1978 dollars).

The differences among the three studies in net returns on R&D illustrate the importance of assumptions about the level and the timing of revenues and expenditures as well as the cost of capital. Table 4-1 summarizes the main assumptions and finding of each study.

The Virts and Weston study underestimated lifetime revenues by limiting the product life to 10 years, clearly much below the actual experience of drugs introduced throughout the period covered by their study. Grabowski and Vernon used more realistic estimates of revenues for the cohort of drugs introduced in the 1970s, but they assumed revenues would decline sharply after the loss of patent protection and foreign sales of new drugs would be in the same ratio to U.S. sales as are foreign sales of all pharmaceuticals. Joglekar and Paterson, on the other hand, may have overestimated worldwide revenues and underestimated the cost of capital.

---

[2] Earlier studies by Baily (32), Schwartzman (372), and Statman (401) also examined returns on R&D, but these studies used industry-level data on R&D expenditures, production of NCEs, and sales. These studies also cover an earlier period; consequently, they are not reviewed in this report. Another study by Grabowski and Vernon (157) is essentially an early version of their study reviewed here.

[3] Joglekar and Paterson spread the total R&D period out longer than Hansen's analysis projected. Between the discovery phase and the clinical testing phase, Joglekar and Paterson inserted time for preclinical animal tests and Investigational New Drug application filing time (a total of 14 months), Hansen had included the cost of preclinical animal tests, but his analysis assumed such tests would be undertaken concurrently with the last part of the discovery phase. Thus, Joglekar's and Paterson's capitalized R&D costs are higher than Hansen's study implied.

Table 4-I—Three Studies of Returns on Pharmaceutical R&D

	G rabowski & Vernon (1990)	Joglekar & Paterson (1986)	Virts & Weston (1980)
Assumptions			
Revenues			
U.S. revenues	■ IMS[a] drugstore and hospital sales for NCEs introduced 1970-79 ■ Postpatent loss of sales 600/0 over 5 years.	IMS[a] drugstore and hospital sales for 218 NCEs introduced in U.S. 1962-77—extrapolated with regression out to 24 years after introduction; expressed in 1976 dollars.	■ IMS[a] outpatient prescriptions for 119 NCE's introduced 1967-76. Muitiplied by average selling price. ■ Revenues = O after year 10. ■ 6% per year inflation in drug price over cost.
Worldwide sales (as a multiple of U.S. hospital and drugstore sales)	1.9	increasing from 1.86 to 2.44 over the life of the drug (extrapolated from PMA data for 1954 -78.)	1.6
Tax rate	*35%*	35%	0
Production and distribution costs	(see below)	(see below)	Cost per unit = 60% of selling price.
Contribution margin (operating profit + R&D as a percent of sales)[b]	Varied: 33%-40% (400/. in 1980s) + 4% adjustment for depreciation.	45% (excludes depreciation and interest on working capital).	
Plant and equipment expenditures	50% of 10th year Sales, 2/3 spent evenly in 2 years prior to product launch. Remainder spent evenly over years 2 to 10 after product launch.	240/. of 5th year sales, spent evenly 4, 3, and 2 years prior to market launch. (investment depreciates over time and remaining book value is written off in the last year of analysis.)	
Working capital	12.5% of annual sales, recovered in final year of product life.	24% of fifth year sales, invested evenly 3,2, and 1 years prior to market launch. Withdrawn in last year of analysis.	
inventories	41.6% of annual sales, valued at manufacturing cost.	[included in working capital]	
Promotion & advertising costs	1OO% of year 1 sales 50% of year 2 sales 25% of year 3 sales	[included in contribution margin]	[included in cost percentage]
R&D costs	$125 million (1986 dollars)	$32 million (1976 dollars) distributed according to Hansen, 1979.	$59 million (1978 dollars) based on Hansen, 1979

(Continued on next page)

Table 4-l—Three Studies of Returns on Pharmaceutical R&D--(Continued)

	Grabowski & Vernon (1990)	Joglekar & Paterson (1986)	Virts & Weston (1980)
Discount rate: (cost of capital)	90/o	6%	8%
Results			
NPV of investment	+ $1.5 million (1986 dollars)	+ $75 million (1976 dollars)	-$16 million (1978 dollars)
	+ $1.73 million (1990 dollars)	+ $168 million (1990 dollars)	-$29 million (1990 dollars)

a IMS America, I.e., is a market research firm that conducts ongoing surveys of hospital and drugstore purchases of pharmaceuticals in the United States.
b Variable costs:1=contribution margin. The contribution margin as defined in these studies equals operating profit and R&D as a percent of sales.

KEY: NCES = new chemical entities; NPV = net present value.

SOURCE: Office of Technology Assessment, 1993. Based on data from H.G. Grabowski and J.M. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R& D," Management *Science* 36(7):804821, July 1990; P. Joglekar and M.L. Paterson, "A Closer Look at the Returns and Risks of Pharmaceutical R& D," *Journal of Health Economics* 5:153-177, 1986; J.R. Virts and J.F. Weston, "Returns to Research and Development in the U.S. Pharmaceutical Industry," *Managerial and Decision Economics* 1(3):103-111, 1980.

Assumptions about the cost of production, distribution, and marketing differed widely among the studies. Virts and Weston simply assumed that on average the full cost of producing and selling the drugs in any year is 60 percent of their selling price. Grabowski and Vernon and Joglekar and Patterson used a modified ‘ ‘contribution margin’ to estimate these costs. The ‘ ‘contribution margin’ is formally defined as the percent of a company’s sales that contributes to paying off the fixed costs (such as investments in facilities, plant and equipment) and profits of the enterprise after the direct costs of producing, marketing and distributing the product are deducted (205). Fixed costs do not vary with the amount of drug that is sold. The contribution margin is the percent of sales left over after the direct variable costs have been deducted. The direct cost of production and distribution as a percent of sales (the estimate required to determine net cash flows) is therefore one minus the contribution margin.[4]

The fro’s operating profit is calculated net of the costs of advertising and promotion, but these costs reflect the full line of products that the firm sells. Expenditures for promotion and advertising are heavier in the years immediately following product launch, so the contribution margin based on pharmaceutical companies’ operating profits underestimates new products’ share of advertising and promotion expenses and overestimates such expenditures for products as they age. Joglekar and Paterson did not account for the difference in timing of this major component of expenses but assumed the contribution margin was an accurate reflection of the expenses for new NCEs. Grabowski and Vernon, on the other hand, added a substantial expense in the first 3 years of product sales to cover the additional advertising and promotion expenditures associated with product launch, but adjusted the contribution margin to reflect lower expenses in later years (154).

Finally, assumptions about actual cash outlays for manufacturing plant and equipment vary widely among the studies. Grabowski and Vernon effectively assumed a much higher total investment than did the authors of either of the other studies.

OTA Analysis of Returns on R&D

OTA estimated the return on R&D for NCEs approved for marketing in the United States in the years 1981-83. OTA chose this relatively brief period for analysis because we had access to U.S. sales data only for these years. These NCEs include all newly introduced compounds regardless of their country of origin or licensing status within the sponsoring company.

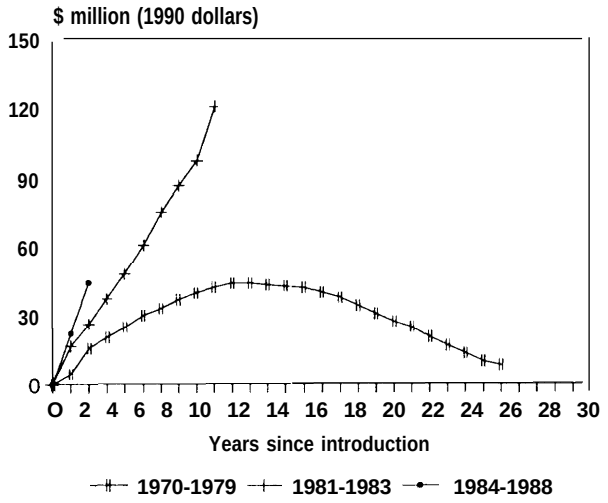
OTA’s approach is similar to Grabowski and Vernon’s (160), but OTA’s assumptions vary in important respects. Where the available data are imprecise or scant, OTA used a range of estimates reflecting the best available evidence. In addition, when uncertainty was high, OTA used conservative assumptions that would tend to understate returns on R&D.

THE SALES CURVE

Figure 4-2 shows U.S. sales to hospitals and drugstores in constant 1990 dollars for NCEs introduced in 1981-83 and, for the sake of

[4]In theory, the contribution margin should be calculated gross of charges for depreciation on facilities and equipment, R&D and other investments. These investments should be recognized separately at the time they are made. Information on product-specific direct production, distribution and marketing costs is hard to come by, however, and the closest approximation to the contribution margin that is available from companies’ financial statements is operating profit plus R&D expenditures. Joglekar and Paterson explicitly recognized expenditures for plant and equipment as cash outlays in the year they would be expended and adjusted the contribution margin accordingly (215). Grabowski and Vernon also adjusted after-tax income for depreciation expenses, which had the effect of raising the contribution margin by about 4 percentage points (154).

Figure 4-2—Average Sales of New Chemical Entities Introduced, 1970-79, 1981-83, and 1984-88



SOURCES: 1970-79: H.G. Grabowski and M. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R& D," *Management Science* 36(7):804-821, July 1990.1981 -83: Coppinger, P., "Overview of the Competitiveness of the U.S. Pharmaceutical Industry," presentation to the Council in Competitiveness Working Group on the Drug Approval Process, Washington, DC, Dec. 12, 1990. 1984-88: IMS America, Inc., unpublished data prepared for the Office of Technology Assessment, 1991.

comparison, in earlier and later years as wells Although OTA had only 1 year of data for NCEs introduced in 1984-88, that one data point suggests that, after adjusting for inflation, U.S. sales of new NCEs in the early years after approval continued to steepen throughout the 1980s.

Sales to hospitals and drugstores account for the majority of, but not all, ethical pharmaceutical sales in the United States. Staff-model health maintenance organizations (HMOs) and mail-order pharmacies account for a growing proportion (2.4 percent and 5.9 percent in 1991 respectively) of total pharmaceutical sales. Sales to clinics and nursing homes account for another 6 percent of pharmaceutical sales (128). Together, sales to these other distribution channels were 14 percent of total sales, or 19 percent of sales to drugstores and hospitals.[6] Therefore, OTA increased domestic hospital and drugstore sales in each year by 19 percent to account for these additional channels of distribution.

Hospital and drugstore sales data are based on retail invoices and therefore do not reflect the amount manufacturers actually receive. About 71 percent of ethical pharmaceutical sales were distributed through wholesalers in 1991 (320). For these drugs, the manufacturer received approximately 6.3 percent less revenue than the invoice price.[7] OTA therefore reduced the sales estimates by 4.5 percent to reflect the difference between sales at the wholesale level and manufacturers' revenues.

OTA had access to data on U.S. sales revenue only for the first 9 years of marketing for the 1981-83 drugs. To predict the revenue curve beyond those years, OTA examined trends in effective patent lives and in the loss of revenue after patent expiration.

Effective Patent Life--The effective patent life is defined here as the elapsed time between the U.S. Food and Drug Administration (FDA) approval for marketing of a new drug and the expiration of the last patentor market exclusivity provision that effectively protects the original compound from competition from bioequivalent

[5] Data on mean annual hospital and drugstore sales per NCE introduced in 1981-83 were supplied by the Food and Drug Administration (97). Data for the 1970s are taken from Grabowski's and Vernon's study (159), and OTA obtained 1 year's worth of data for the 1984-88 NCEs from IMS America Inc., a market research firm that conducts ongoing surveys of hospital and drugstore sales.

The data on sales for the 1984-88 cohort of drugs are for NCEs approved in the period, not necessarily introduced; the data for the 1970s cohort are for NCEs both approved and introduced in the period; and the data for the 1981-83 cohort are for NCEs introduced in the period. Of the 60 therapeutic NMEs first introduced to the U.S. market in 1981-83, 54 were approved during the same period. Three others were approved in 1979 arid 1980 and are included in the analysis. Six therapeutic NMEs approved during 1981-83 were excluded from the analysis because one was never marketed and the other five were not introduced to the market until at least 5 years after 1983.

[6] Data supplied to OTA by Medco Containment Services, Inc., showed that new drugs constituted the same percentage of total sales (in physical units) in the mail-order business as in community pharmacies (255),

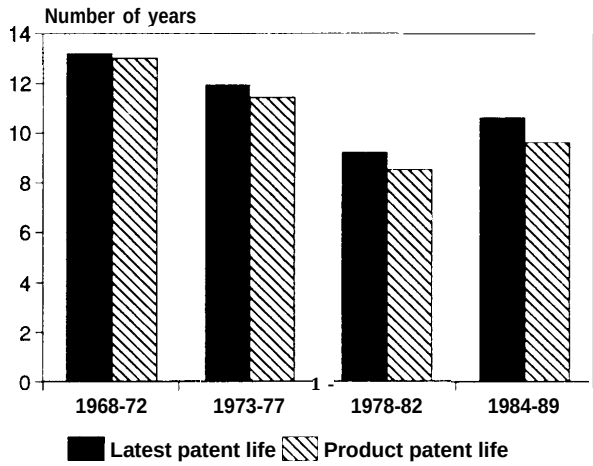
[7] The 1991 average wholesalers' gross margins were approximately 6.8 percent of net sales. Income obtained from interest, payment for direct services to retailers, and other sources accounted for 0.63 percent of sales (362).

generic products.[8] The longer this period, the more years the firm has a monopoly over its product. Though this monopoly is imperfect because close substitutes exist for many patented drug products, generic competition has the potential for rapidly transforming the originating company's brand-name product into a standardized commodity with consequent rapid declines in market revenues.

The greatest threat to the effective U.S. patent life of a new compound is the delay between patent issuance and FDA's approval to market the product, Since the passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417), new drugs have been eligible to receive patent term extensions of up to 5 years (with total patent life not to exceed 14 years as a result of the extensions) to compensate for regulatory delays. In addition, the Orphan Drug Act of 1983 (Public Law 97-414) granted 7 years of exclusive marketing rights for new drug products designed to treat rare conditions.

OTA analyzed the effective patent life of NCEs approved for marketing between 1984 and 1989 and compared the results with an analysis of effective patent life conducted in 1983 for the U.S. House of Representatives as part of the legislative debate over the Drug Price Competition and Patent Term Restoration Act (440). OTA calculated two measures of effective patent life: the life of the patent protecting the product itself, and the longest period of protection indicated by any exclusivity provision or any patent covering a drug and listed in FDA's "Orange Book" (473).[9] Data from the U.S. Patent Office were used to update patent extension information not yet published in the most recent supplement to the Orange Book. The results are shown in figure 4-3.

Figure 4-3—Effective Patent Life for Drugs Approved, 1968-89



SOURCES: Office of Technology Assessment, 1993. Based on U.S. Congress, House of Representatives, Committee on Energy and Commerce, unpublished data, 1993; U.S. Department of Health and Human Services, Food and Drug Administration, unpublished data, 1991; U.S. Department of Commerce, Patent and Trademark Office, unpublished data, 1991.

After declining steadily throughout the 1970s and early 1980s, effective patent life has rebounded somewhat in the years since 1984.

The simple average patent life data shown in figure 4-3 may actually understate the effective period of market exclusivity for originator compounds first marketed in 1981-83 and beyond. Firms may manage the patent period more carefully when the potential revenues from a drug are greater.[10]

To test this hypothesis, OTA obtained data on hospital and community pharmacy sales of all 1984-88 NCEs 2 calendar years after the calendar year of FDA approval (201). Table 4-2 shows the relationship between sales and effective patent life for NCEs by sales volume in the second year

[8] The term "effective patent life' may be a misnomer, since it refers to all kinds of market exclusivities. In this report it is used merely to indicate how long after entry to the market the compound in its original dosage form is formally protected from generic competition.

[9] Any patent listed in the Orange Book series as a barrier to the approval of a generic version Of the listed product. Under the '98 Act, a generic manufacturer must provide a certification of patent invalidity or noninfringement as to any listed patent. The cost of researching such claims is high, and litigation is always a threat for a potential generic competitor (124).

[10] patent terns in other industrialized countries run for 20 years from the date of application. In the United States, patent terms 11111 fOr 17 years from the date of issuance. Firms have substantial opportunities to delay the date of issuance, and anecdotal evidence suggests pharmaceutical firms have taken advantage of those opportunities in the past (123).

Table 4-2—Mean and Median Effective Patent Life as a Function 01 Sales for New Chemical Entities Approved 1985-89

	Latest patent	NCE patent
Mean, total sample (113 drugs)	10.6	9.6
Mean, nonorphans (94 drugs)	10.7	9.5
Breakdown by sales[a]		
Mean for drugs with sales data available (69 drugs)	10.5	9.2
Standard deviation	4.0	3.8
$0-20 million (43 drugs)	9.8	8.4
Standard deviation	4.0	3.6
$20-$50 million (9 drugs)	10.6	8.4
Standard deviation	2.9	3.2
$50-$100 million (8 drugs)	11.9	11.2
Standard deviation	3.4	2.7
>$100 million (9 drugs)	13.1	11.7
Standard deviation	4.0	4.2
Median effective patent life	10.7	10.0

a Sales are measured in the second calender year after the calendar year of approval. Sales data are in 1989 dollars, converted using GNP implicit price deflator.

KEY: NCE = new chemical entity.

SOURCE: Office of Technology Assessment, 1993. Sales data obtained from IMS America, Inc.

after approval (in 1989 dollars). A pattern of longer patent life for drugs with higher sales is evident in the table and was found to be statistically significant in a regression analysis.[11] This analysis suggests that, on average, each additional $100 million in sales is associated with 400 additional days of effective patent life.

The estimated period. of effective patent protection reflects only the period during which the original compound is formally protected from competition by patent or other laws. The expiration of patent protection on the original compound may not mark the end of exclusive marketing, however. Some compounds may not experience generic competition for several years after the patent expires, either because of delays in FDA approval of generic copies or because the total market for the drug is too small to induce generic manufacturers to enter the market. Even more important, process patents that are issued after the original patents sometimes may be effective in keeping generic products out of the market (see box 4-B). And, other product-line extensions occurring late in the original patent life may partly protect the originator compound from competition. The 1984 Drug Price Competition and Patent Term Restoration Act granted a 3-year period of exclusivity, regardless of patent status, to any existing product for which an additional full NDA or supplemental NDA requiring new clinical research is approved by the FDA[12] (83). Thus, if a new dosage form, such as a sustained release formulation, is developed and approved for the originator product, the new dosage form has a 3-year period of market exclusivity from the date of its FDA approval regardless of the patent status of the product itself.[13]

As box 4-C illustrates, companies can and do use the terms of the provision to extend the effective period of exclusivity for the compound by managing the introduction of new dosage forms to coincide with the expiration of patents on earlier generations of a compound. Originator companies have a natural advantage in developing new dosage forms prior to the expiration of the original compound patents, because the patent

11 The estimated regression model is = 3684.589+ .000004S,, where P_I is effective patent life for drug i expressed in days and S_I is sales for drug i expressed in dollars, The estimated coefficient on sales has a t-statistic of 2.0 with 67 degrees of freedom which is significant at the 5-percent level in a two-tailed test. The proportion of variation in effective patent life explained by this model (R^2) is .05.

12 Generic companies can apply for a full NDA (undertaking all of the preclinical and clinical research required of the originator company) to avoid the exclusivity provision, provided the patent on the originator drug has expired, but they cannot receive approval under abbreviated new drug applications (ANDAs) to market the drug. The time and cost involved with full NDA submission effectively eliminates this avenue of competition.

13 Supplemental NDAs also can be submitted for new indications or new dosing regimens, resulting in a new label for the originator product, but under FDA's current interpretation of the law, the sponsor of a generic drug can still submit an ANDA for the original label. Some legal experts claim this interpretation is potentially subject to court challenge, because FDA would be treating the generic drug and the newly labelled originator drug as completely interchangeable, thus impairing the exclusivity right (83).

Box 4-B–Postpatent Generic Competition: Opportunities and Obstacles

"Generic Erosion for Ceclor?"

"When Lilly's Ceclor (cefaclor) comes off patent in the U.S. in 1992, unit sales of the antibiotic, which account for roughly 15 percent of the company's total sales, could be eroded by 70-80 percent by generic competition in the first 18 months, according to Kidder, Peabody analyst James Flynn.

This erosion will take place despite the fact that Lilly holds process patent for Ceclor which expire between 1994 and 2006, and plans to introduce a sustained-release formulation, Ceclor AF, the analyst predicts.

Recent legal action in Japan, where Lilly has filed suit against ten companies for alleged infringement of its cefaclor patent, suggests that the company intends to defend its patents vigorously... However, Mr. Flynn argues that Lilly's process patents will not be recognized in a number of countries (e.g. Italy) which are likely to be used as manufacturing sites for generic companies planning to import formulations of cefaclor on expiration of the product patent.

Barr and Biocraft, which have valid cephalosporin manufacturing facilities in the U. S., may also try to ''skirt' Lilly's process patents, Mr. Flynn says. Such a strategy would give these companies a' 'meaningful cost advantage" over importing firms, he adds.

Ceclor AF is unlikely to be introduced in the United States much before the cefaclor product patent expires, Mr. Flynn says. A preferred dosing regimen is the only benefit he is aware Ceclor AF would have over generic competition. The analyst notes that Lilly's Keftabs formulation of Keflex (cefalexin) gained less than 15 percent of Keflex' sales after the 1987 product patent expire. '

''[6]Ceclor Market Dominance Will Continue Past Dec. 1992 Patent Expiration, Lilly Contends: Process Protection Thru 1994"

' 'Lilly's dominant position in the oral antibiotic market will survive the expiration of the U.S. patent on Ceclor in December 1992, the company maintained at a meeting with financial analysts in New York on Feb. 28. Based on a process protection for cefaclor and a pending NDA application for the follow-up compound loracarbef, Lilly is forcefully declaring its intention to hold its place in the oral antibiotic field...

Asked to comment on the impact of the upcoming patent expiration on Ceclor sales, Lilly Pharmaceutical President Gene Step said the relevant questions should be what will be Lilly's overall position in the oral antibiotic market and what is the likelihood of generic versions of cefaclor reaching the market.

''You really have to [ask] what is our participation in the oral antibiotic market and to what extent will **that be** affected" by generic cefaclor or "by other products that we mayor may not be selling" in the future, Step said.

> Lilly is emphasizing the ***de facto*** protection of a difficult production process and a patent position on a late-stage intermediate . . . Step declared that when all factors are considered Ceclor should ''remain a viable product for Eli Lilly beyond expiration of the patent. "

As the company often has been pointing out recently, Step told the Feb. 28 meeting that Ceclor has yet to face generic competition outside the U. S., even in markets where there is no patent protection. ' 'While we cannot know what the actions of everybody else in the world will be," Step said, ''it is very interesting to observe that while there isn't patent coverage in a large part of the world for Ceclor, there isn't any generic Ceclor. "

Lilly Research Labs President Mel Perelman, Phd, explained the process protection during question-and-answer. "The Ceclor synthetic route is so long and so complex," that it will be difficult to duplicate, Perelman said...

> A producer of cefaclor can take a number of different routes to get to the intermediate, Perelman explained, "but they can't go through it without violating our patent. So an ethical or legal end-run seems extremely improbable. The patent on the intermediate runs until December 1994. Step further pointed out that establishing a cefaclor manufacturing process ''will require very considerable capital investment...we have haven't seen that yet '.,,

SOURCES: Generic erosion: Quote from "Generic Erosion for Ceder, " ***Scrip World Pharmaceutical News*** 1594:25,1991. Ceclor market: Quoted from ''Ceclor Market Dominance Will Continue Past Dec. 1992 Patent Expiration, Lilly Contends: Process Protection Thru 1994, Lorabid NDA Filed as Backup, " ***F-D-C Reports: Prescription and OTC Pharmaceuticals, Mar. 4, 1991,*** p. 15.

Box 4-C--Cardizem QD 1991 Approval Is Key to Successful Cardizem Switch Before Patent Expiry in 1992"

"Marion Merrell Dow is counting on a late 1991 approval of Cardizem QD to give it time to convert patents from the immediate-release form of the diltiazem calcium channel blocker before the patent expires Nov. 5,1992, company management indicated at a Feb. 27 meeting with securities analysts in Kansas City, Missouri.

Calling the approval of Cardizem QD Marion Merrel1 Dow's "number one new product priority," MMD President Fred Lyons said: "I think it's possible that QD could be approved this year and introduced by the first of next year."

The Cardizem QD NDA for hypertension was filed in February 1990 and is scheduled to go before FDA's Cardiovascular and Renal Drugs Advisory Committee on March 14.

To protect its $745 roil. *Cardizem franchise,* Marion Merrell Dow apparently intends to follow a strategy similar to the one Pfizer used to protect its nifedipine franchise from generics with sustained-release *Procardia XL. Pfizer's* strategy called for discounting the new generation product by 25 percent and promoting the price savings directly to consumers. Pfizer told analysts last fail that Procardia XL accounted for nearly two-thirds of all Procardia scripts one year after its launch in October 1989 ("The Pink Sheet" Nov. 5, p. 8).

Marion Merrell Dow Prescription Products Division President David Roche outlined his company's strategy to convert patents from immediate-release Cardizem to the once-a-day formulation by pointing to his own experience in Canada as head of MMD's Nordic Labs subsidiary. Cardizem went off-patent in July 1988, the same time that *Cardizem* SR twice-a-day was approved. By discounting the sustained-release product by 5 percent and aggressively promoting it, Roche said, Nordic was able to maintain the total number of Cardizem prescriptions through 1990.

Roche also said that like Pfizer, Marion Merrell Dow would seek to "build patent brand loyalty" to its Cardizem products. In addition, Roche said, Cardizem products will constitute "50 percent plus" of the combined 1,100-person sales force's detail time in 1991.

Cardizem QD initially will be indicated only for hypertension, while Cardizem is approved for both hypertension and angina. However, Cardizem SR, which has been available since early 1989, is indicated for angina only, so the two products combined may replace the original.. "

SOURCE: Quoted from "Cardizem QD 1991 Approval Is Key to Successful Cardizem Switch Before Patent Expiry in 1992," *F-D-C Reports: Prescription and OX Pharmaceuticals, Mar. 4,* 1991, p. 12.

laws prohibit other companies from conducting research with commercial value using a patented product. (Appendix E contains a summary of the patent protection available to pharmaceutical products, including biotechnology drugs.)

New dosage forms typically offer important medical benefits to patients by making compliance easier or making dosing more convenient and sometimes less uncomfortable. Increasing company incentives to develop products with these benefits is the rationale for the 3-year exclusivity provision of the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417). The issue raised here is not whether such provisions are good public policy, but what the magnitude of their potential impact on the complete life cycle of revenues may be for an originator NCE.

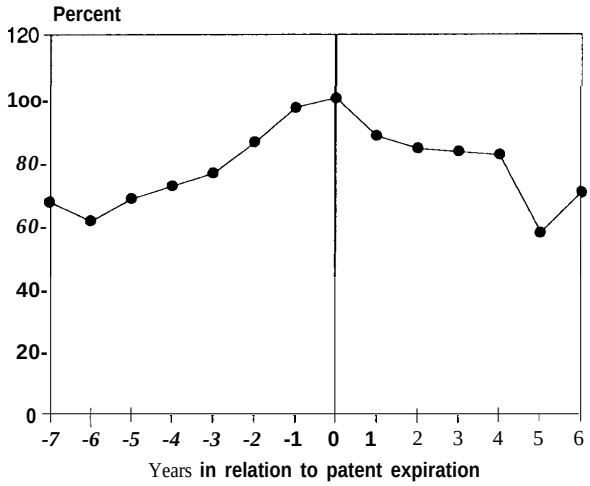
For NCEs approved in the 1981-83 period, OTA assumed that the average effective patent life is 9 years. As figure 4-3 shows, the simple average effective patent life for drugs approved in

the period 1978-82 was between 8 and 9 years. Because patent life is positively correlated with sales revenue, it is appropriate to slightly increase the patent life for total revenues from the new drugs approved between 1981 and 1983. This estimate of patent life does not include any additional market exclusivity granted for new dosage forms.

Postpatent Revenues-After a drug loses patent protection, it becomes vulnerable to competition from generic copies. The Drug Price Competition and Patent Term Restoration Act of 1984 made FDA approval relatively easy for makers of generic copies of originator drugs.[14] It is widely held that this law has led to rapid decline in the originator drug's market share following patent expiration. In their analysis of returns on R&D for NCEs approved between 1970 and 1979, Grabowski and Vernon assumed that the originator drug would hold only 40 percent of total revenue in the market 5 years after patent expiration, but they predicted that increased generic competition in future years could reduce the originator's market share to 20 percent of the total domestic market revenue within 6 years of loss of patent or exclusive marketing protection (160).

OTA analyzed changes in the U.S. market for therapeutic compounds losing patent protection in the years 1984-87. An OTA contractor obtained data for the years 1980-90 on hospital and drugstore sales for 35 noninjectable, noninfusible, therapeutic molecular compounds that lost patent protection in the period 1984-87 (368,369). Details of sample selection, methods, and results are presented in appendix F. Sales (in revenue and physical units) were recorded for all strengths and dosage forms of the compound. (Sales volume for each form of the compound was converted into a standardized physical volume measure, the defined daily dose (DDD)).

Figure 4-4-Originator Revenue[a] as a Percent of Originator Revenue in Year of Patent Expiration



[a] *Based* on 1990 dollars.

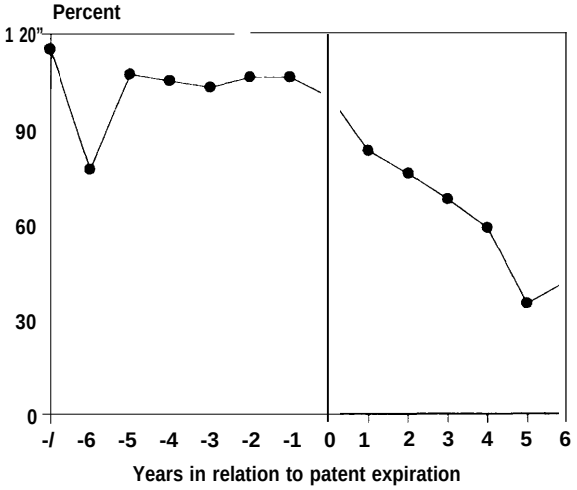
SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, "Economic Products," contract paper prepared for Office of Technology Assessment, December 1991.

Figures 4-4 and 4-5 show how the annual sales in 1990 dollars and in physical units of the originator compound changed before and after the year in which the patent expired. Three years after patent expiration, the originator's annual dollar sales (in 1990 dollars) were 83 percent of sales in the year of patent expiration, while the originator's unit sales were 68 percent of its sales in the year of patent expiration.[15]

[14] Manufacturers seeking to market a generic version of an originator product could file an ANDA, showing only bioequivalence with the originator product, and not needing to prove anew that the generic copy is effective.

15 A recent analysis of generic competition by Grabowski and Vernon reported different results (161). Grabowski and Vernon examined 18 compounds with annual sales of $50 million dollars or more, 16 of whose patents expired in the 1984-87 period. (Two drugs had patent expiration dates in the early 1980s.) They then examined the originator product's market share for *the most commonly prescribed dosage form. They* did not report market share data on revenues, but they did report on market shares unphysical units of the most frequently prescribed dosage form. Within 2 years of the first generic entry, the originator's market share in physical units had fallen to 49 percent. (In OTA's sample of compounds, the originator's market share in physical units 2 years *after patent expiration was* 65 percent.) The difference in market shares can be explained in part by: 1) the inclusion in OTA's sample of compounds with lower annual sales, which may draw less competition from generics; 2) OTA's inclusion of sales of all strengths and dosage forms; and 3) delays between patent expiration and the entry of generic competition during which the originator product maintains an exclusive marketing position.

Figure 4-5-Originator Unit Volume as a Percent of Originator Volume in Year of Patent Expiration



SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, "Economic Products," contract paper prepared for Office of Technology Assessment, December 1991.

The slower decline of the originator's dollar sales than of physical units following patent expiration means that the price of originator products increased after patents expired. This finding is surprising to many people who would expect brand-name prices to decline in the face of active competition from generic competitors. Yet it makes sense for the manufacturer of an originator product to raise its price as generic competitors enter if a high enough proportion of the people who prescribe and buy the drug do not care very much about price when they choose between brand-name and generic products (136).

The sample excluded drugs not generally distributed through drugstores. Products sold exclusively to hospitals or other institutional settings, such as infusible or injectable drugs, would be likely to lose revenue more quickly after entry by generic competitors than products offered through drugstores (158), (See chapter 10 for a discussion.) OTA estimated that these drugs constitute roughly 14 percent of market sales (in dollars) in the year of patent expiration (see appendix F).

The data on the U.S. postpatent sales decline also do not include sales made to several kinds of purchasers that can be expected to switch to generic versions of drugs very soon after they are available. First, sales made through mail-order pharmacies, a small but growing channel of distribution comprising 5.9 percent of domestic pharmaceutical sales in 1991 (128) are not included. Generic versions of multisource drugs[16] constitute a somewhat higher proportion of dollar sales to mail-order pharmacies than to community-based pharmacies (see appendix F).

Second, sales to Federal Government purchasers, such as the Department of Veterans Affairs and the Military, are not included in these data. These purchasers can be expected to switch to generic versions of compounds soon after they are available. The Department of Veterans Affairs spent approximately $500 million for outpatient prescription drugs in 1991 (312). This sum is approximately 1 percent of total domestic pharmaceutical sales (128,320).

Third, staff-model HMOs, which represented about 2.4 percent of ethical pharmaceutical sales in 1991, switch to generics relatively quickly (5 15). Thus, the rate of decline in revenues after patent expiration is understated in these data. OTA adjusted the rate of decline in sales after patent expiration to take account of these and other limitations of the data (see appendix F for details).

For the analysis of the returns on NCEs approved in the 1981-83 period, OTA assumed that the originator drug's revenues would decline after patent expiration at annual rates shown in table 4-3. The generics data available to OTA gave no guidance on losses after the 6th year following patent expiration. OTA assumed that revenues would fall by 20 percent per year in the 8th to 1lth year after patent expiration. Sales would fall to zero after 12 years following patent expiration or after 20 years following the original approval of the NCE.

16 Multisource drugs are those with generic competition on the market.

Table 4-3-OTA'S Assumptions About Changes in Sales of Originator Drugs After Patent Expiration

Year after patent expiration	Percent change in dollar sales
1	-18%
2	-8.5
3	-6.0
4	-6.0
5	-5.0
6	-5.0
7	-5.0
8	-20.0
9	-20.0
10	-100.0

SOURCE: Office of Technology Assessment, 1993; based on sources and assumptions outlined in appendix F.

Future changes in the health care system may increase the speed with which purchasers switch to generic products.[17] For illustrative purposes, OTA examined the sensitivity of measured returns on R&D to a decline in revenues at an annual rate of 20 percent from the date of patent expiration until the 20th year following approval of the drug.

Worldwide Sales—Revenues come from sales in other countries as well as in the United States, so the revenue curve must be adjusted accordingly. Although data on worldwide sales of pharmaceutical products are collected by IMS International, Inc., OTA did not have access to its data.[18] The only data available to OTA are aggregate estimates of the U.S. and foreign markets for all ethical pharmaceuticals (or for all pharmaceuticals). These aggregate estimates are available from industry trade organizations and from the annual reports of individual Fins.

Glaxo, a British pharmaceutical company, estimates the total world market and the share of each country in its annual report. Glaxo bases its estimates on data from IMS International and other sources. According to Glaxo the United States accounts for 27 percent of world sales, and 10 other industrialized and newly industrialized countries account for 54 percent of world sales. The rest of the world accounts for 19 percent. Japan comprises the second largest national market, with an 18-percent share. These aggregate industry sales figures suggest a ratio of total world sales to U.S. sales of approximately 3.7 to 1. If only the top 10 countries are included (on the assumption that the ''rest of the world' does not constitute a large market for new chemical entities), the ratio of total to U.S. sales is 3 to 1. Many of the drugs sold in other countries are never launched in the United States, so it is difficult to draw conclusions from these worldwide aggregate sales figures about how new chemical entities that are medically important enough to seek and receive U.S. FDA approval would fare.

The Pharmaceutical Manufacturers Association (PMA) collects sales data of its member firms in an annual survey. U.S.-owned PMA member firms reported that the ratio of total worldwide sales to domestic sales was 1.765 to 1 in 1990 (317). These companies are likely to have a lower percent of sales outside the United States than are foreign-owned firms that launch new products in the United States, and the ratio is based on drugs that have lost patent protection as well as those that are covered by patents. Thus, this ratio is too conservative.

Grabowski and Vernon, using estimates based on IMS International data, assumed that the ratio of total world revenues to U.S. revenues for drugs introduced in the 1970s, was 1.9 to 1 throughout the life of the NCE (160). Joglekar and Paterson estimated the trend in the global sales ratio over the period 1954-78 based on IMS data and predicted that the ratio for drugs introduced

[17] For example, HMOS and other managed care plans with comprehensive pharmaceutical benefits typically either mandate generic prescribing or offer incentives to users for purchase of generic brands (5 15). If managed care grows in the United States in the future, the speed with which generic substitution occurs may increase. See chapter 10 for a discussion of trends in insurance and payment.

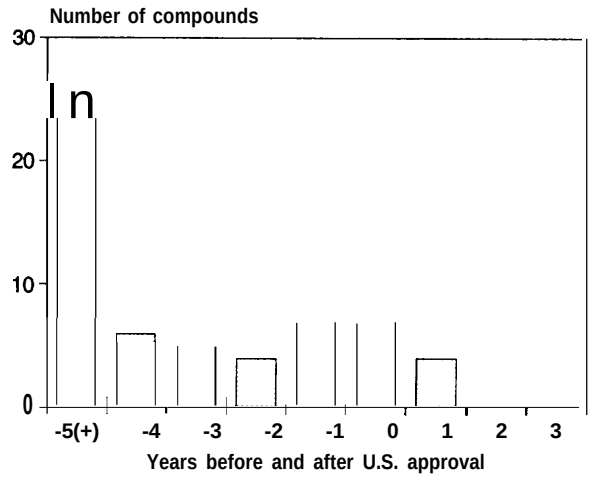
[18] IMS International, Inc. indicated the cost to OTA of obtaining worldwide sales data for these drugs would be between $75,000 and $150,000 (339).

between 1962 and 1977 would increase from 1.86 to 1 to 2.44 to 1 between 1985 and 2044.

Lacking more detailed data on the ratio of total world sales for specific NCEs over their product life cycle, OTA assumed that the ratio is 2 to 1. OTA has reason to believe that this ratio is on the low side, based on informal discussions with researchers who have access to unpublished data.

Application of a worldwide sales ratio beginning with FDA approval ignores the revenues that accrue when products are launched in other countries before the FDA approves them.[19] Figure 4-6 charts the frequency of early approval in other countries for the NCEs approved by FDA in 1981-83. Over 25 percent of drugs approved in the United States in this period were first approved at least 5 years earlier in another country. The revenues realized in the years before FDA approval are potentially very significant in terms of the present value of revenues, but without access to foreign sales data it is impossible to estimate their size. To be conservative, OTA excluded early foreign sales from the analysis.

Figure 4-6--Year of First Entry to the Market for New Molecular Entities Approved in the United States, 1981-83



SOURCE: Office of Technology Assessment, 1993, based on unpublished data from the Office of Planning and Evaluation, Office of the Commissioner, U.S Food and Drug Administration.

COST OF MANUFACTURING, MARKETING, AND DISTRIBUTING NCES

Sales revenues from new products must be reduced by the cash outlays required to make and sell them. Accurate measurement of product-specific costs of manufacture, marketing, distribution, and administration is difficult for multiproduct companies, and publicly available financial statements offer only rough estimates of the magnitude of these costs.

OTA estimated manufacturing, distribution, marketing and administrative costs from a variety of sources, including the existing literature and annual reports of six U.S.-owned companies with pharmaceutical sales comprising at least 65 percent of total company sales.[20] The method and estimates are described in detail in appendix G.

Marketing costs were assumed to be higher in the early years of product life and low after patent expiration, but over the lifetime of the product they average 22.5 percent of total sales.

OTA also accounted for high initial cash outlays for capital expenditures on manufacturing capacity as well as ongoing manufacturing costs. Initial expenditures for plant and equipment for each compound were assumed to be $25 million, spread evenly across the 2 years before and the year of product approval.[21] The sensitivity of the results to an increase in this cost to $35 million was also tested.

OTA assumed that the full value of plant and equipment would be consumed in the production of the single product and that at the end of the 20 years of product life, the salvage value would be

19 OTA's analysis also ignores the revenues from products that remained unapproved in the United States but were accepted and launched in other countries. The foreign revenues from these drugs that are never approved in the United States help offset the R&D costs associated with each successful U.S. entry,

20 The six firms are Merck, Eli Lilly, Syntex, Schering-Plough, Upjohn and Pfizer.

21 In addition to this initial capital expenditure, OTA included all ongoing depreciation expense-s for manufacturing facilities (which are embedded in cost-of-sales ratios) in excess of the depreciation that could be taken on the $25-million capital expenditure.

Table 4-4-Cost Assumptions in OTA's Analysis of Returns on R&D

Cost component	Year after product launch	Base case
Capital expenditures for plant and equipment	Total over life cycle	$25 million
	2 years before approval	$8.33 million
	1 year before approval	$6.33 million
	Year of approval	$6.33 million
Manufacturing and distribution (as a percent of sales)	1-20	25.5% of sales less adjustment for depreciation charges on plant and equipment (20-year life)
General and administrative costs as percent of sates	1-20	11.1% of sales
Marketing costs as percent of sales	Average over life cycle	22.6% of sales
	1	1 OO.O°/' of sales
	2	50.0% of sales
	3-9	40.9% of sales
	10-20	6.5% of sales
Value of inventory as percent of sales	1-20	12.7% of sales
Working capital as percent of sales	1-20	1 7.0% of sales
Ongoing R&D rests	Total over life cycle	$31.2 million
	1-9	$3.46 million

SOURCE: Office of Technology Assessment, 1993.

zero, also a conservative assumption. Table 4-4 contains a summary of OTA's base case assumptions regarding costs of production, distribution, administration and marketing.

R&D COSTS

The NCEs introduced in the period from 1981 to 1983 began clinical testing roughly 8 years earlier (1973-75), the midpoint of the study years in DiMasi's R&D cost study (109). OTA assumed that DiMasi's cash outlays (in constant 1990 dollars), success rates, and development time profile represent the experience of the NCEs approved between 1981 and 1983.

In addition to the costs required to bring a compound to market, OTA's analysis also explicitly recognized ongoing R&D costs after the product is launched. These R&D expenditures may be intended to explore the usefulness of the drug in new conditions or to develop new dosing strengths, formulations, or dosage forms. OTA's method for estimating the ongoing costs of R&D is outlined in appendix G. Total ongoing R&D expenditure was assumed to be $31.7 million per compound (in 1990 dollars), evenly distributed over the first 9 years of product life.

TAXES

To measure the net after-tax returns on R&D, the cash flows generated by the sale of each product in the years following market launch must be reduced by the amount of taxes they cause to be paid. Ideally, the reduction in cash flows would be equal to the extra tax paid in each year of the product's life as a direct result of manufacturing and selling the product.

Precise measurement of these extra tax payments is difficult for three reasons. First, taxes owed or payable are based not only on cash flows from the product but on rules in tax codes governing what can be deducted, and when. Expenditures to build manufacturing facilities, for example, cannot be deducted in full in the year they are made for U.S. income tax purposes; they must be depreciated over a specified number of years. (OTA assumed that investments in plant

and equipment would be depreciated for tax purposes on a straight-line basis over 10 years.)

Second, taxes owed or payable depend not only on what is manufactured and sold but also on where it is manufactured. Drug companies can and do make decisions to manufacture products in jurisdictions that will afford them the best profile of after-tax cash flows. The availability of tax credits for locating manufacturing operations in U.S. possessions, such as Puerto Rico, substantially reduces the tax liability of pharmaceutical companies. (See chapter 8 for more detail.) Thus, the opportunity to make a new product in a low-tax jurisdiction means that the extra taxes incurred as a result of the introduction of a new group of products will certainly fall short of the statutory marginal corporate tax rate.

Third, tax payments in any year depend not only on taxable income in that year but also on the profit and loss history of the company. Some current tax liabilities can be applied to previous years if the company lost money in the past. Similarly, payment of some taxes can be deferred to future years. Income tax expenses can remain higher or lower than actual payments over a long period of time if an industry as a whole is, or has been, in a period of eligibility for tax deferments.

Taken together, these measurement problems imply that the U.S. marginal corporate tax rate is too high a rate to apply to the cash flows associated with a new product after it is introduced to the market. A better approximation of the tax burden would be based on the ratio of taxes paid to income from ongoing pharmaceutical operations. [22]

Three estimates of this ratio are available for the pharmaceutical industry. All of them were made at the firm level and therefore include nonpharmaceutical operations. Also, each estimate is based on: 1) a different sample of fins, 2) a different definition of tax liability, and 3) a different definition of income.

- The General Accounting Office and the congressional Joint Committee on Taxation calculated taxes payable each year as a percent of firms' pretax net income (net of extraordinary income) in that year. (Tax liabilities that are deferred to future years were not included, but payments made as a result of past deferments were.) For five U.S.-based pharmaceutical firms in the sample, the effective worldwide tax rate on worldwide income was 34.3 percent in 1987 (438). The rate varied between 1981 and 1987, starting higher (41.3 percent) in 1981 and reaching a low in 1983 (32.1 percent), but climbing again to a high of 37.1 percent in 1986.
- Baber and Kang calculated worldwide income taxes paid as a percent of net income before depreciation and taxes (as reported in financial statements) between 1975 and 1987 for 54 U.S. pharmaceutical firms with R&D expenses greater than 5 percent of sales (24,224). Table 4-5 shows the income tax rates from 1981-87. Taxes paid for this sample of firms was in the range of 29 to 34 percent of income until 1987, when taxes paid jumped to 39.7 percent of income.

Table 4-5-Taxes Paid as a Percent of Net Income for 54 R&D-Intensive Pharmaceutical Companies

Year	Tax rate (percent)
1981	31.8%
1982	31.0
1983	31.7
1984	32.5
1985	29.1
1986	33.7
1987	39.1

SOURCE: The Office of Technology Assessment, 1993, based on unpublished computations by S-H. Kang for pharmaceutical firms in W.R. Baber and S.-H. Kang, "Accounting-Based Measure as Estimates of Economic Rates of Return: An Empirical Study of the U.S. Pharmaceutical Industry 1976-87, draft report prepared for the Office of Technology Assessment, March 1991.

22 This ratio is also referred to as the effective tax rate (see chapter 8 for details).

- Tax Analysts, Inc., a tax research group, calculated current taxes payable, not including paybacks of past deferments but including a proportion of incurred tax liability that will be paid in future years,[23] as a percent of income from ongoing operations (257). The effective worldwide tax rate for 15 U. S.-based pharmaceutical firms under these criteria was 32 percent in 1987 (257,258).

The average effective tax rate for the industry after 1987 is likely to decline because the Tax Reform Act of 1986 reduced the U.S. corporate marginal tax rate after 1986. In 1987, the top Federal statutory marginal tax rate was 40 percent, compared with 46 percent in 1986, and it dropped to 34 percent in 1988. Therefore, when the effect of tax credits and deferments is taken into account, the average effective tax rate is likely to be even lower than 32 percent in years after 1987. For the drugs approved in 1981-83, the lower tax rate would have gone into effect in the 4th to 7th year after product launch.[24]

After taking into account the information summarized above, OTA assumed that taxes would constitute 32 percent of net pretax cash flows throughout the life of new drugs introduced between 1981 and 1983.

THE COST OF CAPITAL

The real (inflation-adjusted) weighted average company cost of capital for pharmaceutical firms varied roughly in the neighborhood of 10 percent in the 1980s (285). OTA assumed that the real cost of capital for investments made after product approval is 9.8 percent, because 10 percent is too high for investments made on existing products. The cost of capital for investments in ongoing operations is lower than the cost of capital for investments in R&D (285), and the weighted average cost of capital for the firm as a whole strikes a balance among different kinds of investments. OTA therefore adjusted the cost of capital for investments in ongoing operations slightly downward from 10 percent.

RESULTS

Table 4-6 shows the NPV of the net returns in the years following market approval (in 1990 dollars) under the base case. The NCEs of 1981-83 deliver cash flows equal to net present value of $341 million per compound. After taxes, the present value in the year of FDA approval of this net revenue is reduced to approximately $230 million. These net revenues must be compared with the present value of the investment in R&D required to discover and develop the compounds. An upper bound on the fully capitalized R&D costs is about $359 million before tax savings, or $194 million after tax savings are considered (see table 3-10 in chapter 3). Thus, under the base-case scenario, on average, each compound can be expected to return a net present value of at least $36 million more (after taxes) than would be required to bring forth the investment in the R&D.

The results are somewhat sensitive to the global sales multiplier, which is in turn very uncertain but likely to be higher than the ratio used in the base case. If the ratio were much higher than 2 to 1, the net present value of the

Table 4-6-Net Present Value[a] of Postlaunch Returns to R&D for NCEs Approved 1981-83 (1990 $ millions)

Pretax	$341
After tax	$230

[a] Net present value is calculated with a 9.9 percent cost of capital.
KEY: NCE = new chemical entity.
SOURCE: Office of Technology Assessment, 1993.

23 According to Tax Analysts, Inc., a proportion of deferred taxes are never likely to be paid. This portion of deferred taxes is not counted in the tax rate.

24 The reduction in U.S. corporate income taxes resulting from the Tax Reform Act represents a one-time windfall for returns on drugs discovered and developed before 1987. While taxes on net income from the manufacture and sale of new products will continue to stay as they are unless a new law changes them, the after-tax cost of R&D conducted after 1987 increased from approximately 54 percent of cash R&D outlays to 66 percent. Thus in the future the increased after-tax income from successful new drugs resulting from the Tax Reform Act of 1986 will be offset to some extent by increased after-tax costs of R&D.

investment would be even greater than the base case indicates.

Changes in the initial investment in plant and equipment slightly affect estimated returns. A $35-million investment in plant and equipment reduces the net present value of pretax net revenues to $336 million and the NPV of after-tax net revenues to $225 million.[25] The average capital expenditures for plant and equipment would have to be as high as $100 million for the NPV of after-tax cash flows to equal the NPV of after-tax R&D costs.

The results are not very sensitive to changes in the speed with which the originator's brand sales decline after patent expiration. If the average sales per compound were to decline by 20 percent per year beginning with the year of patent expiration (instead of according to the schedule shown in table 4-3), the present value of dollar returns would be $311 million before taxes and $209 million after taxes. The after-tax return still lies above the upper bound on R&D costs.

A decline of 20 percent per year in originator revenues from the date of patent loss would mean that within 3 years tier patent expiration, originator sales revenue would be just51 percent of its sales in the year of patent expiration. Fully 6 years after the passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) there is no evidence that the rate of revenue loss for originator compounds is approaching this rate. For the NPV of returns on R&D to equal zero, the postpatent decline in revenues would have to be over 30 percent per year from the year of patent expiration.

What does it mean to have the average revenue per compound deliver $36 million more in NPV than was needed to bring forth the research on the drugs introduced in 1981-83? This excess would be eliminated if the annual revenue per compound was reduced by 4.3 percent. If demand for the drugs is totally insensitive to changes in price, then the average price could be reduced throughout the product life cycle by 4.3 percent without reducing returns below the amounts necessary to repay R&D investors. To the extent that demand for a compound increases as its price decreases, prices could have been reduced more than 4.3 percent in each year.

These estimates are rough approximations of the actual returns that the 1981-83 class of NCEs will earn. OTA attempted to be conservative in measuring returns, but the estimate is subject to measurement error whose magnitude is not easily assessed. They illustrate how volatile net returns can be over time and how sensitive they are to:

1. The cost of R&D, which in turn depends on the assumed cost of capital and the productivity of the research process; and
2. The worldwide revenues that can be expected from the drugs that result from that process.

As this and other chapters in this report illustrate, both worldwide revenues and the cost of R&D for each new NCE can change rapidly. If firms devote increasing resources to basic research, then the cost per success can increase dramatically, not only because of the actual outlays, but also because these expenditures are made early in the process and carry a high cost of capital. At the same time, worldwide revenues per NCE can also change dramatically over short periods of time, as figure 4-2 clearly demonstrates. The second-year U.S. sales of compounds that the FDA approved in the period 1984-88 were substantially higher than the sales of the drugs introduced in the 1981-83 period. Yet, future changes in methods of paying for prescription drugs, brought about by health insurance reform or health care cost containment in the United States and abroad, could adversely affect the sales curve for drugs introduced in the 1990s.

[25] The pretax net cash flows are reduced by only $5 million because higher initial capital expenditure means that a higher proportion of the cost of sales is devoted to depreciation expenses, which are subtracted from the estimate of direct manufacturing cost.%

TOTAL PHARMACEUTICAL INDUSTRY RETURNS

The previous section described an analysis of investments in a specific group of new drugs, from their very beginning as R&D projects to their ultimate obsolescence and removal from the market. Although the analyses reviewed and presented above are imprecise, because some data on revenues and costs can be estimated only roughly, within the limits of data accuracy the analyses appropriately measure the net present value of investments in R&D.

Another more indirect way to assess returns on R&D is to estimate the profitability of research-intensive pharmaceutical companies. Audited financial data are available to estimate profitability at the company level for public corporations. Pharmaceutical firms invest in the discovery, development, production, marketing, and distribution of many products, including some that are not ethical pharmaceuticals. The total profit or return on a company's investment in a given period is a mixture of returns on past investments made over many previous years on many different projects.

At the company level, the return on investment is defined by the internal rate of return (RR), the interest rate at which the net present value of all cashflows into and out of the firm equals zero. If the IRR across all companies in an industry is greater than the industry's cost of capital, then the industry returned more to its investors than was necessary to bring forth the investment dollars, and one would suspect that barriers to entry or other forms of monopoly power (perhaps obtained through patent protection) might exist in the industry (86). On the other hand, a low IRR relative to the cost of capital would, if companies invest efficiently, lead to disinvestment in the industry, including R&D.[26] Over the entire life of the industry (from its start to its dissolution), the IRR should be in the neighborhood of its cost of capital.

The annual financial reports of public companies contain estimates of total firm profit rates based on accounting records. For example, the net income as a percent of the total ''book value' of assets[27] is a commonly used benchmark of firm profitability (301). Companies themselves report this ratio in their annual financial statements and compare their performance in specific years with that in previous years. Other commonly used profit ratios, such as net income as a percent of sales, are also easily computed from company financial statements.

It is not surprising, then, that analysts would compare the accounting profit rates of firms in the pharmaceutical industry with those of firms in other industries (301 ,457).[28] The ready availability of publicly reported and independently audited data, and the widespread use of these measures by companies themselves, invites such comparisons. But they are limited in two important ways. First, accounting-based profit measures can be poor approximations of firms true IRRs. Second, comparing returns of the pharmaceutical industry with those of other industries is not a perfect substitute for comparing its returns with the industry's cost of capital. Risk differs among industries, so even if accounting-based profits were good proxies for IRRs, simple interindustry comparisons, without consideration of the riskiness of industries, would be misleading.

Accounting profits are poor measures of IRR for several reasons:

---

26 Another possible explanation for persistently low IRRs in an industry is that the managers of firms in the industry do not adequately represent the interests of their shareholders (39,155,282).

27 Book value refers to the end-of-the-year value of capital assets after depreciation expenses. Strict accounting convention determine what kinds of investments create a capital asset. R&D, for example, is not recorded as an investment but is fully expensed in the year in which expenditures are made. This accounting convention required since 1975 by the Federal Accounting Standards Board, is equivalent to depreciating the investment 100 percent in the year it is made.

28 By these conventional measures the pharmaceutical industry would appear to be substantially more profitable than other industries.

- Accounting standards require firms to record as current expenditures all outlays for R&D, advertising, and promotion when in reality these expenditures are investments whose payoffs may be delayed or extended into future accounting periods. The value of the ''intangible assets' produced by these investments is too uncertain for use in accounting statements. Thus, the book value of assets in a company's financial statement underestimates the true value of assets, especially when these investments are important components of the company's activities, as in the pharmaceutical industry (62,78,80).
- Financial statements often report income and expenses as they are accrued in accounting records, not as they are actually realized in cash flows. These differences between accrual accounting and cash flows can distort the timing of investments and revenues and therefore misrepresent the rate of return in a given period (27)
- Even if the above distortions are corrected, the accounting rate of return could still depart from the IRR because accounting profits do not adjust properly for the time profile of cash flows from various investments and are further distorted by growth or decline in investment overtime (132,398,402).

Past Studies

OTA found six studies of pharmaceutical industry profits in which accounting rates of return to pharmaceutical firms were corrected by treating R&D (and sometimes advertising) as investments rather than as current expenditures. Each study makes assumptions about the useful life of these intangible investments and the rate at which their value depreciates. See table 4-7 for a summary of these studies. These studies are limited by small numbers of fins, virtually all successful and therefore likely to be more profitable than the industry as a whole, and few years of data. Nevertheless, they consistently find that correcting pharmaceutical industry profit rates for investment in intangible capital reduces rates of return by roughly 20 to 25 percent (214).

Three research studies compared adjusted pharmaceutical industry profits with similarly adjusted profits in other industries. Table 4-8 summarizes the methods and results of these studies. Once again, these studies include a small number of pharmaceutical and nonpharmaceutical firms, virtually all successful, and examine a short time period. Nevertheless, these studies show that adjusting accounting rates of return for investments in R&D and advertising does not completely erase differences in computed profits between pharmaceuticals and the comparison industries.

Even if the corrections to accounting rates of return in these studies were sufficient to approximate IRRs (which they do only imperfectly), the differences in the rates of return might reflect differences in the riskiness (and, hence, the cost of capital) among industries. Thus, little can be said about the rate of return on investments in the pharmaceutical industry from these studies.

OTA's Contractor Report on Comparative Profits

OTA asked William Baber and Sok-Hyon Kang to compare the IRR of a sample of firms in the pharmaceutical industry with IRRs of nonpharmaceutical companies using a new technique that adjusts accounting data to obtain a closer approximation of IRRs. (27). The method, pioneered by Ijiri (199,200) and Salamon (359,360), calculates a "cash flow recovery rate' from accounting data, which can then be combined with assumptions about the time profile of cash flows to imply an IRR for the industry.

The time profile of cash flows (including the total life of investments and the shape of cash flows over time) is itself an unknown both for the pharmaceutical industry and for other firms. Consequently, Baber and Kang examined several alternative assumptions about the life of investments (including R&D as well as tangible capital facilities and equipment) and the shape of the cash flow curve in both pharmaceutical and nonphar-

Table 4-7—Accounting Rates of Return Corrected for Investment in R&D and Advertising

Researcher(s)	Sample	Time period	Data source(s)	Major assumptions	Accounting rate of return	Corrected rate of return	*Corrected ROR+* Accounting ROR
Stauffer, 1975	6 major pharmaceutical firms	Varying across firms from 1953-72 to 1963-72	Compustat	1. No correction for inflation. 2. 4-year R&D gestation period with constant expenditures per unit of time. 3. Product sales reach constant level first year after introduction, remaining at that level for 15 years. 4. Sales decay rate = 0.7.	Varied across firms	Varied across firms; less than accounting rate of return for 5 out of 6 firms	Ranged from 0.72-1.23
Clarkson, 1977	1 pharmaceutical firm (Eli Lilly and Co.) (out of 69 firms in cross-sectional sample)	1965-74	Eli Lilly and Co. *Annual Reports*	1. Corrected for inflation using wholesale price index. 2. 3-year life for advertising. 3. Basic research = 16% of total R&D. 4. Basic research accumulates at 10?40 per year for 11 years and depreciates for 15 years. 5. Development accumulates at 10% per year for 6 years and depreciates for 11 years.	17.3% (average over time)	11 .I°/o (average over time)	0.64
Grabowski and Mueller, 1978	7 pharmaceutical firms (out of 86 firms in cross-sectional sample)	1968	Compustat; previously collected R&D data for 1959-69; advertising expenditures for five major media "from individual media information sources."	1. Corrected for inflation using GNP price index. 2. Removed cyclical effects and financing effects. 3. R&D depreciates at constant proportional rate of either 5 or 10?40. 4. Advertising depredates at constant proportional rate of 30%	14.1 % (average over firms)	10.80/0 (using 10°/. R&D depreciation rate) *10.5%* (using 5% R&D depreciation rate)	0.77 0.74
Bloch, 1973	4 pharmaceutical firms	1969	Annual reports	1. R&D depreciation schedule estimated by regression of sales on lagged R&D. 2. Advertising not capitalized. 3. After-tax returns.	Varied across firms 9.7-22.1%	7.6-16.1 '/o	Ranged from 0.70-0.80
Ayanian, 1975	6 major pharmaceutical firms	1973 (for ROR)	Data on advertising and R&D expenditures provided by firms; Moody's *Industrial Reports.*	1. No correction for inflation. 2. R&D and advertising depreciated at same rate, assumed at either 9 or 13% per year.	17.7°/0 (average over firms)	14.060/' (average) (using 13"/. depreciation rate) 13.690/. (using 9% depreciation rate)	0.79 0.77

(Continued on next page)

Table 4-7—Accounting Rates of Return Corrected for Investment in R&D and Advertising--(Continued)

Researcher(s)	Sample	Time period	Data source(s)	Major assumptions	Accounting rate of return	Corrected rate of return	*Corrected ROR+* Accounting ROR
Megna and Mueller, 1991	10 major pharmaceutical firms	1975-85	Compustat	1. No correction for inflation. 2. Estimated firm-specific rates of depreciation of R&D and advertising by regression of sales on lagged R&D and advertising expenditures (assumed binomial lag functions).	14.81%	12.1 5% (average over time)	0.82

KEY: ROR = rate of return.

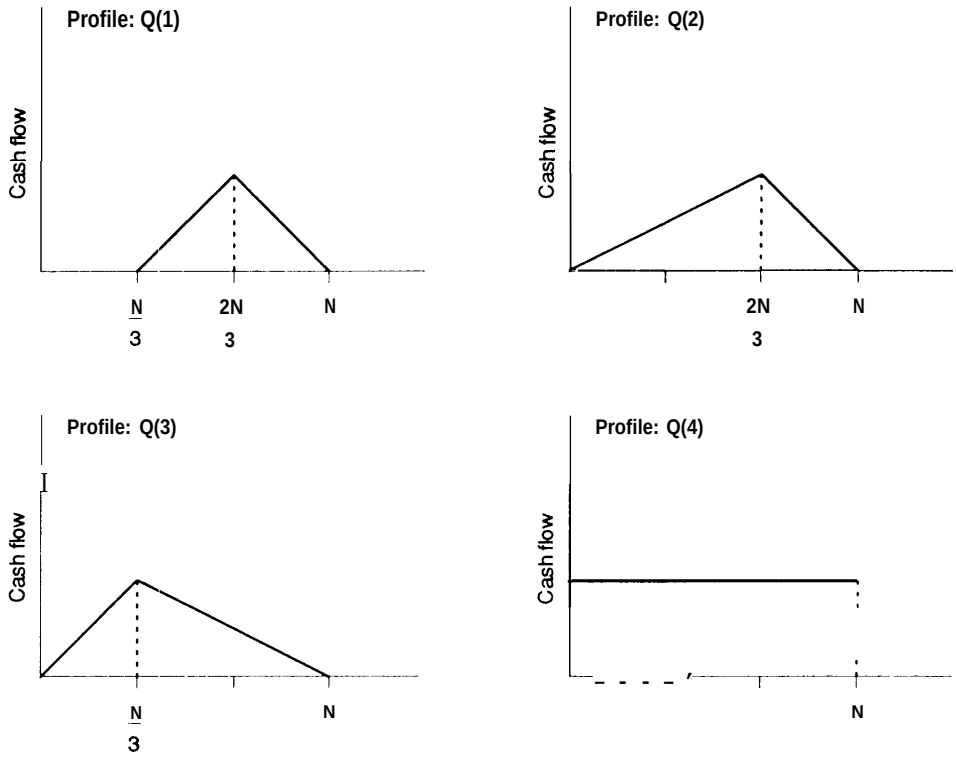
SOURCE: Office of Technology Assessment, 1993, based on E.J. Jensen, "Rates of Return to Investment in the Pharmaceutical Industry: A Survey," contract paper prepared for the Office of Technology Assessment, September 1990.

Table-4-8--Results of Studies Comparing Adjusted Pharmaceutical Industry Profits With Profits in Other Industries

Study	Pharmaceutical industry sample	Other industries sample	R&D capitalization assumptions		Advertising capitalization met hod		Results		Comments
			Pharmaceuticals	Other	Pharmaceuticals	Others	Pharmaceuticals	Other firms	
Grabowski and Mueller, 1978	7 companies 1968	79 firms in a national sample of industries performing R&D.	R&D depreciates in value at constant proportional rate of 5%.	R&D depreciates at constant proportional rate of 10%.	Depreciates at 30% per year	Depreciatesat 30% per year	10.8%	7.2%	■ 1968 profits smoothed for cyclical effects ■ After-tax profits ■ Inflation adjusted
Clarkson, 1977	1 company 1959-73	68 firms in a national sample.	*'Basic'' research: 16% of* R&D. Basic research has 26-year life, accumulatesfor11 years (growing in value at 10 % per year); then depreciates for 15 years. *Development 84% of* R&D. Development has a 17-year life, accumulates for 6 years (growing in value at 10 0/o per year) then depreciates for 15 years.	Development life and depreciation schedule estimated from industry sources. Varies across industries. Basic research assumed to accumulate for the development life plus 5 years.	3-year life	3-year life	12.9%	9.6%	■ After-tax profits ■ Inflation adjusted
Megna and Mueller, 1991	10 major firms 1975-88	Selected firms in advertising or R&D-intensive industries. 6 firms in toy industry; 4 distilled beverage firms; 9 cosmetic firms.	R&D depreciation rates estimated for each firm by regressing sales on lagged R&D. Maximum 8-year life.	R&D depreciation rates estimated for each firm by regressing sales on lagged R&D. Maximum 8-year life.	Same depreciation estimation technique as R&D with a maximum 4 year life.	Same depreciation estimation technique as R&D with a maximum 4 year life.	12.15%	■ Toys = 6.66°/0. ~ Distilled beverages = 11.44%. ● Cosmetics = 11.51%.	■ After-tax profits ■ Not inflation adjusted

SOURCE: Office of Technology Assessment, 1993.

Figure 4-7—Cash-Flow Profiles Used in Internal Rate of Return Computations



KEY: N = Life of investment project; Q = Cash flow profile

KEY: N = Life of Investment Project; Q = Cash-flow profile.

SOURCE: W.R.Baber and S-H. Kang, "Accounting-Based Measure as Estimates of Economic Rates of Return: An Empirical Study of the U.S. Pharmaceutical Industry 1976-87, draft report prepared for the Office of Technology Assessment, March 1991.

maceutical firms, Figure 4-7 shows four different cash flow profiles. Q1, an inverted v-shape profile with a substantial delay before revenues begin to accrue from an investment, has often been viewed as the most appropriate shape for an R&D-intensive industry like pharmaceuticals (160). (This profile is similar to the cashflow profile for new drugs shown in figure 4-1,) Other profiles may be more realistic for nonpharmaceutical fins. Because the productive life of investments may also be longer in the pharmaceutical industry, the contractors estimated IRRs for 20-year and 30-year investment lives.[29]

The contractors compared 54 research-intensive pharmaceutical firms listed at least once in the Compustat™ database between 1975 and 1987[30] with two ''control' samples, each with 54 firms having financial characteristics similar to

---

29 Other, shorter, investment lives were also considered, but the resulting calculated IRRs were unrealistically low for all samples and are not reproduced here. The difference in IRRs between pharmaceutical and nonpharmaceutical firms is even greater for shorter investment lives (27).

30 Study of years prior to 1976 is infeasible because accounting practices for R&D were not standardized until 1975 with the publication of a Federal Accounting Standards Board rule on the treatment of R&D (29,74).

31 The first control sample was obtained by matching nonpharmaceutical firms with pharmaceutical firms on the basis of sales and sales growth; the second control sample was obtained by matching nonpharmaceutical firms with p harmaceutical firms on the basis of sales and R&D intensity.

the pharmaceutical firms.[31] Table 4-9 shows the weighted mean IRRs between 1976 and 1987 for the pharmaceutical firms and each of the control samples under alternative assumptions about investment life and cash-flow profiles.

Differences in weighted mean annual IRRs between pharmaceutical and nonpharmaceutical firms of about 2 to 3 percentage points per year persist and were statistically significant regardless of assumptions made about investment life or cash-flow profile.[32] The same analysis for a sample of 88 pharmaceutical firms (including firms with ratios of R&D to sales lower than 5 percent) and their matched control firms showed differences of the same magnitude (27). Thus, while the differences in uncorrected accounting profits between research-intensive pharmaceutical companies and non-pharmaceutical companies over the period were as high as 4 to 6 percentage points per year, the IRRs implied by the contractors' study differ by much less, 2 to 3 percentage points per year.[33]

Baber and Kang's method for estimating industry-level IRRs is itself subject to measurement error, so the reliability of the measured rates of return for each industry group (pharmaceuticals and controls) is uncertain. Nevertheless, Baber and Kang applied the estimation method consistently across all firms in the three groups, so the **differences** in profit rates between pharmaceuticals and controls, which were stable across a wide range assumptions about their investments, are, in OTA's judgment, reliably estimated.

The contractor's comparative profit study is silent on the question of whether a 2 to 3 percentage point difference in rates of return is due to differences in the cost of capital between

Table 4-9—Mean Estimated Internal Rates of Return for Pharmaceutical Industry and Control Groups[a]

	Investment life (years) 30	20
Pharmaceuticals		
Mean accounting return on assets. ..	0.1432	0.1432
Implied IRR[b]		
Q(I).	...0.1382	0.1361
Q(2).	...0.1413	0.1374
Q(3).	...0.1434	0.1389
Q(4).	...0.1460	0.1393
Control Group I (sales)[c]		
Mean accounting return on assets. ..	0.1029	0.1029
Implied IRR[b]		
Q(I).	...0.1143	0.1076
Q(2).	...0.1147	0.1058
Q(3).	...0.1150	0.1036
Q(4).	...0.1155	0.1041
Control Group II (R&D)[d]		
Mean accounting return on assets. ..	0.0875	0.0875
Implied IRR[b]		
Q(I).	...0.1163	0.1117
Q(2).	...0.1178	0.1113
Q(3).	...0.1190	0.1109
Q(4).	...0.1200	0.1111

a Based on a sample of 54 pharmaceutical companies listed in Compustat™ database at least once in the period 1975-87 with R&D-to-sales ratios of 5% or more. Constant growth rates of invested capital equal to the geometric mean sample growth rates from 1975-87 were used to calculate IRR estimates. Estimates based on actual growth rates in each sample are comparable.
b Cash flow Profiles, Q1 through Q4, are shown in figure 4-7.
c Firms matched with pharmaceuticals on the basis of sales and sales growth,
d Firms matched with pharmaceutics on the basis of sales and R&D intensity.

KEY: IRR = internal rate of return; Q = cash flow profile.
SOURCE: Office of Technology Assessment, 1993, based on W.R. Baber and S.-H. Kang, 'Accounting-Based Measures as Estimates of Economic Rates of Return: An Empirical Study of the U.S. Pharmaceutical Industry 1976-87," contract paper prepared for the Office of Technology Assessment, March 1991.

32 The estimates shown in table 4-9 are based on constant growth rates. In an extension of their study, Baber and Kang estimated IRRs with actual investment growth **rates. The** results were substantially the same (28).

33 Because the study used new analytical techniques that are unfamiliar to many analysts, OTA solicited independent review and comment on the validity of its methods and findings from both its advisory panel and a selected group of academic experts in economics and accounting. The paper evoked considerable criticism from one outside reviewer, who questioned the validity of assumptions underlying the use of the method. OTA then submitted the detailed critique to the study authors, and both the critique and the authors' response were sent to two independent outside experts for further review. The results of the review process reinforced the conclusion that pharmaceutical industry IRRs were **2 to 3** percent higher than the returns on the control samples in the 12-year period under study. (A copy of the history of written reviews and comments is available upon request from OTA.)

pharmaceuticals and the control firms. If investment in the pharmaceutical industry is riskier than in the control fins, then the cost of capital will be higher. OTA examined differences in the cost of capital between the pharmaceutical industry and the two control samples.

The cost of capital is the rate of return investors require to induce them to invest in a company with a given level of risk. The weighted average cost of capital is the blended cost of the fro's debt and equity capital (285,409).

OTA estimated the weighted average cost of capital for the pharmaceutical industry and the two control groups. The cost of capital varies over time with changes in underlying interest rates; consequently, precise measurement of the cost of capital over the 12-year period of this study is impossible. In addition, OTA's method may be subject to biases in measurement. We used the same approach consistently across all samples, however, so the biases would tend to cancel themselves out when examining differences in the cost of capital between pharmaceuticals and controls. OTA is therefore confident that the measured differences in the cost of capital among the samples are reasonably precise. (The method and assumptions underlying the estimates are described in appendix C.)

The cost of capital for the pharmaceutical industry was slightly higher than that for control sample I (matched by sales and sales growth) but lower than that for the control sample II (matched by sales and R&D). (See table 4-10). Thus, it appears that the higher estimated IRRs of the research-intensive pharmaceutical industry cannot be explained by a higher cost of capital in the pharmaceutical industry.

Another possible explanation for the difference in estimated IRRs is the investment character of advertising and promotion. Baber and Kang did not convert advertising expenditures to investments, but the pharmaceutical industry is characterized by high advertising and promotional expenditures that generate intangible capital. The life of these investments may be longer than the life of advertising in other industries, and longer than 1 year, although there is virtually no evidence to support this contention and some evidence against it (87,280).[34] In preliminary analyses, the contractors investigated the effect of capitalizing advertising expenses over a 3-year period for all fins; this action widened even further the gap in implied IRR between the pharmaceutical industry and the control firms (26).[35]

Table 4-10-Cost of Capital Difference Between Pharmaceutical Industry and Control Firms (15 Largest Pharmaceutical Firms)

Pharmaceuticals - Control 1.	+.007
Pharmaceuticals - Control II.	-.016

Control I: Firms similar to pharmaceutical industry in sales and sales growth.

Control II: Firms similar to pharmaceutical industry in sales and R&D intensity.

SOURCE: Office of Technology Assessment, 1993, based on data provided by S.-H. Kang, unpublished computations for firms listed in W.R. Baber and S.-H. Kang, "Accounting-Based Measure as Estimates of Economic Rates of Return: An Empirical Study of the U.S. Pharmaceutical Industry 1976-87," contract paper prepared for the Office of Technology Assessment, March 1991.

Other Studies

Another way of examining returns on pharmaceutical firms is to study the response of companies' stock and bond values to investments in tangible and intangible (i.e., R&D and marketing) assets. If the securities markets are efficient and accurately predict the future value of firms (at least over a long time frame), then the potential returns from new investments by a firm should, with random error, immediately be reflected in the market value of the firm.

Two unpublished research studies have used the relationship between investments and compa-

~ Hurwitz and Caves (195)1 have suggested that advertising and promotion outlays may serve to realize the goodwill inherent in an innovation. The value lies in the innovation itself; promotion, like production and distribution is necessary to unlock that value.

35 Grossly longer investment lives for advertising in the pharmaceutical industry, such as 10 years or more would be required for the differences in implied IRRs between pharmaceuticals and the control firms to disappear.

nies' market values to estimate returns on different kinds of investments across industries. Results pertaining only to the pharmaceutical industry are reported here.

Thomas (422) estimated the relationship between market values and R&D, advertising, and working capital in 23 large pharmaceutical firms in 1984. Pharmaceutical industry stock market values rose with higher ratios of R&D to investment in plant and equipment, but pharmaceutical industry market values were unrelated to advertising expenditures.[36] Thomas used the estimated relationship between R&D intensity and the fro's market value to correct accounting rates of return for the value of the intangible capital built up from past R&D investments. The accounting rate of return declined from 20 to about 11 percent when the estimated value of the intangible R&D capital is added to the asset base.

As Comanor has observed, studies of stock market rates of return ''indicate little about competition or monopoly in the pharmaceutical industry, [because] stock market values typically capitalize future returns into the value of the firm, which includes any prospective effects of monopoly power as well as other factors' (86). Thus, a high value of intangible R&D capital may reflect the monopoly-creating effect of R&D in an industry with relatively strong patent protection.

Mueller and Reardon (282) estimated the excess market rate of return for a sample of 21 pharmaceutical firms over their cost of capital in the period 1971-88. Mueller and Reardon observed changes in market prices from one period to the next can be related to changes in different kinds of investment. They found that investments in pharmaceutical R&D led to changes in market value that were more than twice as high as the cost of capital, while advertising did not raise market values at all, and investments in plant and equipment raised market values less than the cost of capital. High market returns on R&D relative to the cost of capital suggest that over the 18-year period of the study, pharmaceutical R&D paid off in the aggregate more than was necessary to bring forth the investment.

Mueller's and Reardon's conclusion that returns on R&D are well above the cost of capital in the pharmaceutical industry must be considered suggestive at best, because the method for estimating changes in market values required the researchers to estimate a rate of depreciation on existing assets (both tangible and intangible) that is the same across all kinds of assets. Yet, plant and equipment are likely to depreciate according to rates that differ greatly from those governing R&D and other intangible investments.

Other problems also cloud Mueller's and Reardon's findings. The benefits of R&D cannot be obtained without investments in plant and equipment that produce the products and, in the current market, without the advertising and promotion necessary to sell them. While R&D may be a necessary condition for obtaining high returns, firms must invest in those seemingly less profitable activities as well. Analysis of the market returns on investment as a whole in the seven largest pharmaceutical companies in Mueller's and Reardon's study found only three of the companies with stock market returns greater than the cost of capital.[37]

To summarize, studies of the impact of pharmaceutical investments on returns in the stock and bond markets do not prove, but are consistent with, the finding 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.

---

36 Market values actually declined with the ratio of advertising expenditures to investment in plant and equipment, but the relationship was statistically insignificant. The failure to find a significant relationship could be due to very small variation among pharmaceutical firms in the advertising/plant and equipment ratio, but the paper did not provide information necessary to test this possibility.

37 T. calculate these returns, however, the authors had to assume that the market value of the firm's capital would decline at a rate Of 10 percent per year in the absence of new investment. The validity of this assumption is questionable.

FINDINGS AND CONCLUSIONS

OTA's review of the evidence on the returns on R&D indicates that these returns were higher than was required to reward investors for the time and risks incurred. The net returns on NCEs introduced to the U.S. market between 1981 and 1983 are likely to exceed the cost of capital by an amount that would allow annual revenues from these drugs to be reduced across the board by about 4.3 percent.

These results conflict with findings of earlier studies, largely because the realized revenues from this cohort of new drugs were so much higher in real terms than the revenues from new drugs introduced in previous years. Very preliminary sales data on drugs approved between 1984 and 1988 suggest that the revenue curve from new drugs continues to steepen in real terms. OTA's assumptions about other key elements of revenues and costs also differed from those of previous studies but not consistently in ways that would increase returns. For example, OTA assumed a much higher cost of capital for R&D than did other studies and therefore used a relatively high cost of R&D against which to judge returns.

Estimates of returns on R&D are highly sensitive to changes in market conditions for drugs throughout their product life cycle. Actions by governments or insurers to control prices paid for new drugs or to encourage price competition among different drugs with similar therapeutic effects could rapidly reduce worldwide sales revenues. (See chapter 10 for a description of prescription drug pricing policies in the United States and selected foreign countries.) There is, however, no evidence that these effects have yet occurred at a scale that would seriously jeopardize the market for new drugs.

Evidence on the economic rate of return to the pharmaceutical industry as a whole over a relatively long period (1976-87) shows returns that were higher than returns on nonpharmaceutical firms by about 2 to 3 percentage points per year after adjustment for differences in risk among fins. This is a much lower differential than is suggested by conventional comparisons of profit ratios, but it is still high enough to have made the industry a relatively lucrative investment.

Together, the findings on returns on pharmaceutical R&D and to the industry as a whole explain why R&D expenditures have risen so dramatically in real terms throughout the 1980s. Investors have followed the promise of high returns on future innovations. Ultimately investment in research is determined by expected revenues. The dramatic increase in real revenues to new drugs throughout the 1980s has sent signals to the industry that more investment will be rewarded handsomely. The industry has responded as expected, by increasing its commitment to investment, including investment in R&D. The resulting rise in R&D investment may have dampened internal rates of return as more money is poured into projects that, if successful, must share revenues with other competing products on the market.