

**Rx R&D Myths:
The Case Against The Drug
Industry's R&D "Scare Card"**



**Congress Watch
July 2001**

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About Public Citizen

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Rx R&D Myths: The Case Against The Drug Industry's R&D "Scare Card"

Executive Summary

This new Public Citizen report reveals how major U.S. drug companies and their Washington, D.C. lobby group, the Pharmaceutical Research and Manufacturers of America (PhRMA), have carried out a misleading campaign to scare policy makers and the public. PhRMA's central claim is that the industry needs extraordinary profits to fund expensive, risky and innovative research and development (R&D) for new drugs. If anything is done to moderate prices or profits, R&D will suffer, and, as PhRMA's president recently claimed, "it's going to harm millions of Americans who have life-threatening conditions." But this R&D scare card – or canard – is built on myths, falsehoods and misunderstandings, all of which are made possible by the drug industry's staunch refusal to open its R&D records to congressional investigators or other independent auditors.

Using government studies, company filings with the U.S. Securities and Exchange Commission and documents obtained via the Freedom of Information Act, Public Citizen's report exposes the industry's R&D claims:

- The drug industry's claim that R&D costs total \$500 million for each new drug (including failures) is highly misleading. Extrapolated from an often-misunderstood 1991 study by economist Joseph DiMasi, the \$500 million figure includes significant expenses that are tax deductible and unrealistic scenarios of risks.
- The actual after-tax cash outlay – or what drug companies really spend on R&D – for each new drug (including failures) according to the DiMasi study is approximately \$110 million. (That's in year 2000 dollars, based on data provided by drug companies.) (See Section I)
- A simpler measure – also derived from data provided by the industry – suggests that after-tax R&D costs ranged from \$57 million to \$71 million for the average new drug brought to market in the 1990s, including failures. (See Section II)
- Industry R&D risks and costs are often significantly reduced by taxpayer-funded research, which has helped launch the most medically important drugs in recent years and many of the best-selling drugs, including all of the top five sellers in one recent year surveyed (1995).
- An internal National Institutes of Health (NIH) document, obtained by Public Citizen through the Freedom of Information Act, shows how crucial taxpayer-funded research is to top-selling drugs. According to the NIH, taxpayer-funded scientists conducted 55 percent of the research projects that led to the discovery and development of the top five selling drugs in 1995. (See Section III)

- The industry fought, and won, a nine-year legal battle to keep congressional investigators from the General Accounting Office from seeing the industry's complete R&D records. (See Section IV) Congress can subpoena the records but has failed to do so. That might owe to the fact that in 1999-2000 the drug industry spent \$262 million on federal lobbying, campaign contributions and ads for candidates thinly disguised as "issue" ads. (See accompanying report, "The Other Drug War: Big Pharma's 625 Washington Lobbyists")
- Drug industry R&D does not appear to be as risky as companies claim. In every year since 1982, the drug industry has been the most profitable in the United States, according to *Fortune* magazine's rankings. During this time, the drug industry's returns on revenue (profit as a percent of sales) have averaged about three times the average for all other industries represented in the Fortune 500. It defies logic that R&D investments are highly risky if the industry is consistently so profitable and returns on investments are so high. (See Section V)
- Drug industry R&D is made less risky by the fact that only about 22 percent of the new drugs brought to market in the last two decades were innovative drugs that represented important therapeutic gains over existing drugs. Most were "me-too" drugs, which often replicate existing successful drugs. (See Section VI)
- In addition to receiving research subsidies, the drug industry is lightly taxed, thanks to tax credits. The drug industry's effective tax rate is about 40 percent less than the average for all other industries. (See Section VII)
- Drug companies also receive a huge financial incentive for testing the effects of drugs on children. This incentive called pediatric exclusivity, which Congress may reauthorize this year, amounts to \$600 million *in additional profits* per year for the drug industry – and that's just to get companies to test the safety of several hundred drugs for children. It is estimated that the cost of such tests is less than \$100 million a year. (See Section VIII)
- The drug industry's top priority increasingly is advertising and marketing, more than R&D. Increases in drug industry advertising budgets have averaged almost 40 percent a year since the government relaxed rules on direct-to-consumer advertising in 1997. Moreover, the Fortune 500 drug companies dedicated 30 percent of their revenues to marketing and administration in the year 2000, and just 12 percent to R&D. (See Section X)

Rx R&D Myths: The Case Against The Drug Industry's R&D "Scare Card"

Introduction

Major U.S. drug companies and their trade association, the Pharmaceutical Research and Manufacturers of America (PhRMA), have carried out a campaign to scare policy makers and the public. The central claim of PhRMA's campaign is ominous: if anything is done to restrain high U.S. prescription drug prices, then research and development (R&D) to find new drugs for life-threatening diseases will suffer.

Alan Holmer, president of PhRMA, recently played this "R&D scare card" while on National Public Radio's "Talk of the Nation" program.

"Believe me," Holmer warned, "if we impose price controls on the pharmaceutical industry, and if you reduce the R&D that this industry is able to provide, it's going to harm my kids and it's going to harm those millions of other Americans who have life-threatening conditions."¹

Later in the program, to reinforce his argument, Holmer made the claim that research costs "\$500 million just to get one medicine to market."

The drug industry's "R&D scare card" is built on the premise that drug companies need extraordinary profits – about three times those of the average Fortune 500 company – in order to conduct expensive and risky research on innovative new drugs. But evidence shows the research isn't as expensive, risky or innovative as the industry claims.

Instead, the evidence shows that such research may cost far less than \$500 million for every new drug – and may be less than \$100 million for every new drug (including failed drugs). The evidence also shows that the drug industry isn't all that innovative, as it produces far more "me-too" or copycat drugs of little medical importance than life-saving medicines.² And, the evidence suggests that drug industry research isn't all that risky because the industry is awash in profits while lightly taxed and heavily subsidized. In fact, an internal National Institutes of Health (NIH) study obtained by Public Citizen shows that taxpayer-funded scientists and foreign universities conducted 85 percent of the published research studies, tests and trials leading to the discovery and development of five blockbuster drugs.³ It's no wonder the drug industry fought all the way to the Supreme Court to keep its R&D records hidden from congressional investigators.

In all, the evidence shows that the drug industry's R&D scare card is, in reality, an R&D "canard" – that is "an unfounded or false, deliberately misleading story."

I. Deconstructing the \$500 Million Myth

The story of PhRMA's R&D canard starts with the drug industry's repeated – and unchallenged – claim that it costs \$500 million to develop a new drug, including money spent on failures. The \$500 million figure has become ubiquitous and widely accepted. Unfortunately, it is misleading at best and inaccurate at worst.

Public Citizen calculated more realistic R&D costs using methodology modeled after that employed by the congressional Office of Technology Assessment (OTA) in its 354-page report, "Pharmaceutical R&D: Costs, Risks and Rewards," published in 1993. (See Appendix A)

These are our findings:

- As the OTA noted, "the industry's collective response to charges that drug prices are too high or are increasing too fast has been to point to the high and increasing cost of pharmaceutical R&D." Specifically, "industry representatives have pointed to academic studies of the average cost of bringing a new pharmaceutical compound to the market."⁴
- This decade, industry representatives have pointed to one academic study above all for the \$500 million figure. That is a 1991 study by Joseph DiMasi of the Tufts Center for the Study of Drug Development. PhRMA representatives have acknowledged that the \$500 million figure is an extrapolation, adjusted for inflation and changes in research and development, based on the Tufts Center study.⁵ DiMasi estimated the *pretax* cost of developing certain new drugs, including failures, at \$231 million in 1987.⁶
- OTA later revised DiMasi's \$231 million figure with significantly higher opportunity cost of capital. (Opportunity cost of capital is a calculation of what a R&D expenditure might be worth had the money been invested elsewhere. DiMasi used a 9 percent annual rate of return to calculate the cost of capital. OTA used a rate that went from 10 to 14 percent over time.) OTA put the "upper bound of the full capitalized cost" of R&D per new drug at \$359 million in 1990 dollars. Inflated to year 2000 dollars, this estimate becomes \$473 million, and it has been rounded up to \$500 million by the industry.⁷
- The Tufts Center for the Study of Drug Development is a self-described "independent research group affiliated with Tufts University." The center's sponsors include some of the world's largest drug companies such as Merck, Pfizer and Bayer.⁸ According to the Tufts Center, corporate sponsors get to "help shape strategic objectives" and "influence key Center activities."⁹
- DiMasi's study relied on data provided by 12 drug companies.¹⁰ This information has not been independently verified, nor checked for accuracy. The OTA issued this warning about DiMasi's data: "Any company that understood the study methods and the potential policy uses of the study's conclusions could overestimate costs without any potential for discovery. Thus, the motivation to overestimate costs cannot be discounted."¹¹

- It's important to note that DiMasi's study only focuses on the cost of developing "new chemical entities" (NCEs), which he defines as drugs that have never been tested before in humans.¹² (His definition of NCE differs only slightly from the Food and Drug Administration definition of a new molecular entity, or NME.¹³) Furthermore, DiMasi focuses only on "self-originating" NCEs, which are new entities developed by companies as opposed to those they acquire from other research organizations. Many new drugs approved for market are not NCEs, but are new dosage forms or new combinations of existing drugs.¹⁴ Thus, DiMasi focuses only on the most expensive new drugs, not *all* new drugs, resulting in a *higher* cost estimate.
- DiMasi's original \$231 million figure does not represent what companies *actually spend* to discover and develop new molecular entities. Rather, it includes the cost of all failed drugs and the expense of using money for drug research rather than other investments. It also *does not* account for huge tax deductions that companies get for R&D. Therefore, it substantially *overestimates* net expenditures on R&D.
- According to the OTA, "The net cost of every dollar spent on R&D must be reduced by the amount of tax avoided by that expenditure. Like all business expenses, R&D is deductible from a firm's taxable income."
- The OTA revised DiMasi's calculation, subtracting the expenses that are tax deductible under Section 174 of the federal tax code and the opportunity cost of capital.
- The tax deduction reduces the cost of R&D by the amount of the corporate marginal tax rate (currently 34 percent). This means, in effect, that every dollar spent on R&D costs \$0.66.¹⁵ The OTA concluded that DiMasi's original \$231 million figure (in 1987 dollars) was \$171 million (in 1990 dollars) after accounting for the R&D tax deduction.
- The opportunity cost of capital accounts for slightly more than half (51 percent) of DiMasi's total figure. After subtracting tax deductions and the opportunity cost of capital, OTA found that DiMasi's after-tax R&D cash outlay for a new NME was \$65.5 million (in 1990 dollars). That is the estimate of how much the drug companies in DiMasi's study actually spent on new chemical entities, including failures.
- It should be noted that five of the seven previous R&D cost studies that DiMasi references *did not* include opportunity cost of capital in their calculations.¹⁶
- Public Citizen inflated this figure to year 2000 dollars and found that actual after-tax cash outlay for NCEs (including failures) was \$110 million – based on DiMasi's data. (See Table 1)
- It's important to stress that this is the R&D cost for new chemical entities – which require the most expensive type of research – not all new drugs brought to market. The R&D

costs for all new drugs brought to market, based on PhRMA's own data, is detailed in Section II.

- Several additional points about DiMasi's estimate: First, it does not account for R&D tax credits available to the drug industry (these are different from the R&D deductions). DiMasi estimated that R&D tax credits amounted to a 6.8 percent subsidy for R&D expenditures from 1978 to 1986.
- Second, DiMasi assumes an FDA review time of 30 months in his calculations. FDA review time has dropped dramatically since 1991 and now averages 11 to 17 months. DiMasi said a one-year decrease in review time would cut his R&D estimate by \$19 million (in 1987 dollars, or \$29 million in year 2000 dollars).
- Third, evidence suggests that the time required to conduct clinical trials on new drugs is also decreasing – particularly for the most efficient companies. A January 2000 report by the Tufts Center for the Study of Drug Development stated that clinical testing time declined by 19 percent for drugs approved in 1996-1998 when compared with drugs approved in 1993-1995.¹⁷ In addition, the five quickest pharmaceutical companies shaved, on average, more than one-year off the industry-wide median time (5.7 years) for clinical research.¹⁸
- Fourth, the advent of new technologies such as genomics and combinatorial chemistry, has led, according to investment analysts at Lehman Brothers, “to a growing school of thought that the cost of discovering new biological targets and the cost of creating drug leads is falling.”¹⁹
- Finally, it should be stressed that DiMasi's estimate of R&D costs was far higher than in previous studies, including one published by the pharmaceutical industry in 1987. That study by S.N. Wiggins put the pre-tax cash outlay per NCE at \$65 million (in 1986 dollars).²⁰ After-taxes, the figure becomes \$67 million in year 2000 dollars.

Table 1

Comparative Analysis of Pharmaceutical R&D Costs (\$ millions per New Chemical Entity)

Study (Year)	Expressed in Dollars for Which Year	Pre-tax Including Cost of Capital (9%)	Pre-tax Excluding Cost of Capital	After-tax Actual Cash Outlay*
DiMasi Original (1991)	1987	\$231	\$114	\$61.6**
Office of Technology Assessment (1993)	1990	\$259	\$127	\$65.5
Public Citizen (2001)	2000	\$341	\$167	\$110.2***

* Excludes the opportunity cost of capital. **DiMasi did not calculate after-tax costs; the \$61.6 million figure was calculated by Public Citizen based on the 46 percent corporate tax rate in effect at the time of the expenditures

DiMasi studied. *** The \$110 million figure is calculated using the current corporate tax rate of 34 percent; this is the rate used to deduct R&D expenses from taxable income.

II. PhRMA's Own Data Contradicts the \$500 Million Claim

Not all R&D is created equal. DiMasi studied the most expensive of all new drugs. Only 36 percent of drugs the FDA approved for market in the 1990s were NMEs (similar to DiMasi's NCEs). The others were mostly new combinations of drugs or new formulations of existing drugs. (For example, from pill to syrup form.)

The drug industry's own data about this larger universe of new drugs reveal that the actual cash outlay for a new drug is far less than \$500 million – and perhaps as low as \$57 million per drug in recent years (including failures).

Here's how Public Citizen arrived at this conclusion:

PhRMA's annual survey lists aggregate R&D spending by year in two categories: domestic (spending in the U.S. by both foreign and domestic companies) and abroad (spending overseas by U.S.-based companies.)

Public Citizen uses PhRMA's domestic spending for its analysis, in part, because that's what DiMasi did when he ran a check on his study using aggregate data. His reasoning: "We include only domestic expenditures in our analysis under the assumption that the foreign expenditures of U.S.-owned firms will be directed primarily to non-U.S. introductions."²¹ (Public Citizen has calculated R&D costs with combined domestic-overseas spending in Appendix B. Spending in the last decade ranges between \$69 million and \$87 million per drug.)

According to PhRMA, U.S. and foreign drug companies spent \$139.8 billion on domestic R&D in the 1990s.²² During that same period, the U.S. Food and Drug Administration approved 857 new drugs for market.²³ Simple division suggests that drug companies spent \$163 million on R&D for every new drug approved for market in the U.S. in the 1990s (expressed in year 2000 *pre-tax* dollars).

This measure is very generous to the industry. It counts total R&D expenditures – which include salaries, equipment, overhead, lab tests (pre-clinical) and clinical trials.²⁴ And it counts all failed drugs as well as successful drugs. In addition, it uses PhRMA's own R&D figures, which have not been independently verified and may be inflated with marketing research costs.²⁵ Finally, it uses pre-tax figures; in fact, R&D expenses are tax deductible and every dollar spent on R&D has a net cost of only \$0.66.

A more accurate measure – according to pharmaceutical experts such as Stephen Schondelmeyer, director of the PRIME Institute at the University of Minnesota – would account for R&D tax deductions and the approximate seven-year lag between R&D spending and drug approval. (DiMasi said "approvals in one year should be associated with R&D expenditures lagged 2 to 12 years."²⁶) Therefore, a more accurate measure would compare R&D spending for 1994 to new drug approvals for the year 2000.

To be even more accurate, the measure should account for years in which R&D spending on new drugs was extraordinarily high or low. In other words, it should smooth out the peaks and valleys. Thus, this measure would compare R&D spending over seven-year periods with new drug applications (NDAs) approved over corresponding seven-year periods. An annual average should be calculated for each period, which has the effect of smoothing out peaks and valleys. (See Appendix B for more detailed methodology)

The results? From 1984-1990, PhRMA reported that R&D spending totaled \$32.8 billion. (That's domestic R&D spending by U.S. companies and foreign-based companies.)²⁷ Adjusted for inflation, that total is \$48.2 billion in year 2000 dollars. Divide that amount by the number of new drugs (563) approved from 1990-1996 and it appears that \$85.6 million was the average R&D cost for every new drug approved in that period (in pre-tax dollars). After subtracting tax deductions, worth 34 cents on the dollar, the actual cost plummets to \$56.5 million.

For new drugs approved in the more recent seven-year NDA period 1994-2000, the average pre-tax cost of R&D was \$107.6 million. Adjusting for R&D tax deductions makes the figure \$71.0 million. (See Table 2)

Table 2
Average R&D Cost per New Drug Approved During the 1990s
(Rolling 7-Year Average with 7-Year Lag, \$ in millions, all in year 2000)

Domestic R&D Spending Only

7-Year R&D Period	Average Annual R&D Spending	7-Year NDA Period	Average Annual NDA's Approved	Pre-Tax R&D Spending per New Drug	After-Tax R&D Spending per New Drug
1988-1994	\$10,255.3	1994-2000	95.3	\$107.6	\$71.0
1987-1993	\$9,387.8	1993-1999	91.3	\$102.8	\$67.9
1986-1992	\$8,473.3	1992-1998	92.4	\$91.7	\$60.5
1985-1991	\$7,613.0	1991-1997	88.6	\$86.0	\$56.7
1984-1990	\$6,887.1	1990-1996	80.4	\$85.6	\$56.5

Source: Spending data comes from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2000; NDA data comes from U.S. Food and Drug Administration, Center for Drug Evaluation and Research, December 31, 2000. (All spending figures have been inflated to year 2000 dollars.)

Note: Domestic R&D includes expenditures within the United States by research-based pharmaceutical companies.

Two additional notes:

Some might quarrel with the seven-year lag, arguing that in accounting terms, today's R&D expenses are paid by today's revenue. Thus, R&D spending in any year ought to be compared with drugs brought to market that same year. This study rejects that argument. It doesn't reflect the reality that R&D spending invariably precedes the marketing of a drug and our purpose is to

understand what it costs to bring a drug to market, not how that R&D is paid for in accounting terms. In addition, as noted earlier, DiMasi agrees that spending should be lagged two to 12 years. Nevertheless, Public Citizen calculated R&D spending for current drug approvals and current research expenditures in Appendix B and found that spending remained close to \$100 million per drug, with costs in the 1990s ranging from \$99 million to \$118 million per drug.

Finally, it has also been suggested that our analysis should focus only on NCEs or NMEs because that's what DiMasi studied, and that's where the bulk of industry R&D is spent, and those new compounds are the drugs that make the industry risky. That analysis is below (see Table 3) although our intent was not to mirror DiMasi in this section. Rather, this section aims to point out that there are many kinds of drugs approved each year – not just the elite group in DiMasi's study. More important, PhRMA's R&D spending figures – the figures that it constantly touts – are for all drugs, not just NMEs or NCEs. So it's only fitting to compare PhRMA's spending for all drugs to all drugs approved for market. (That said, an all-NME analysis shows R&D spending of \$114 million to \$150 million per drug.)

Table 3
Average R&D Cost per New Molecular Entity During the 1990s
(Rolling 7-Year Average with 7-Year Lag, \$ in millions)

Domestic R&D Spending Only

7-Year R&D Period	Average Annual R&D Spending	7-Year NME Period	Average Annual NME's Approved	Pre-Tax R&D Spending per NME	After-Tax R&D Spending per NME
1988-1994	\$7,588.9	1994-2000	33.4	\$227.02	\$149.8
1987-1993	\$6,947.0	1993-1999	33.1	\$209.61	\$138.3
1986-1992	\$6,270.2	1992-1998	31.9	\$196.82	\$129.9
1985-1991	\$5,633.6	1991-1997	31.9	\$176.84	\$116.7
1984-1990	\$5,096.4	1990-1996	29.6	\$172.34	\$113.7

Source: Spending data comes from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2000; NDA data comes from U.S. Food and Drug Administration, Center for Drug Evaluation and Research, December 31, 2000. (All spending figures have been inflated to year 2000 dollars.)

Note: Domestic R&D includes expenditures within the United States by research-based pharmaceutical companies.

III. U.S. Taxpayers Play A Crucial Role in Pharmaceutical R&D

Drug companies stress how difficult it is to discover new drugs – particularly innovative life-saving drugs. But the evidence suggests it's not all that risky because the federal government is doing much of the crucial research. The National Institutes of Health (NIH) budget reached \$20.3 billion in fiscal year 2001 (a 14 percent increase over FY 2000) with much of that money going to research that ultimately helps with the discovery and development of pharmaceuticals - how much exactly is hard to say. The NIH admits it doesn't track its spending on drug development. NIH officials claim it's a tough task because so much NIH work is basic research

into diseases that is converted years later – often through several other related discoveries that build on one another – into a marketed drug.²⁸

What we do know is that several studies have shown that many important and popular drugs were developed with taxpayer support. That’s why publicly-funded researchers have 90 Nobel Prizes compared to just four by industry scientists, although the industry spends more on R&D.²⁹ For instance:

- A study by a Massachusetts Institute of Technology (MIT) scholar of the 21 most important drugs introduced between 1965 and 1992 found that publicly funded research played a part in discovering and developing 14 of the 21 drugs (67 percent).³⁰
- 45 of the 50 top-selling drugs from 1992-1997 received government funding for some phase of development, according to an investigation by *The Boston Globe*. In all, taxpayers spent at least \$175 million helping to develop these 50 drugs.³¹

Publicly-funded Researchers Conducted Most Studies Behind Blockbuster Drugs

An NIH internal document obtained by Public Citizen through the Freedom of Information Act (“NIH Contributions to Pharmaceutical Development,” February 2000, see Appendix C) reveals much more detail about the importance of taxpayer-funded research to drug companies.

The NIH report looked closely at the role of public research in developing the most popular drugs in the U.S. To avoid well-known NIH success stories, such as the agency’s work in developing treatments for cancer and AIDS, the NIH decided to examine the top five selling drugs in 1995, each of which had over \$1 billion in sales. Before scrutinizing the research behind these drugs, NIH did not know what, if any, role taxpayer-funded scientists played in bringing these drugs to market.

- NIH found that “NIH-funded research played a critical role in drug discovery in each of these cases.”³² In all, U.S. taxpayer-funded researchers conducted 55 percent of the published research projects leading to the discovery and development of these drugs (and foreign academic institutions 30 percent). “Researchers at U.S. universities and at NIH contributed by discovering basic phenomena and concepts, developing new techniques and assays, and participating in clinical applications of the drugs.”
- In the case of the hypertension drugs captopril and enalapril, the NIH concluded that the drugs were developed thanks to 14 public U.S. research projects and five foreign academic studies. Only three significant studies were conducted by the drugs’ patent holders, Squibb and Merck.
- Furthermore, four of the taxpayer-funded studies were deemed “key” and six of the studies were referenced in the industry’s work. The studies sponsored by the patent holders for these two drugs were of less consequence – none were considered “key” by

the NIH. In fact, for the five drugs it studied, the NIH deemed only one industry study “key.” (Public Citizen acknowledges the fact that academics generally have greater incentive to publish research than industry scientists.)

Table 4 shows the NIH findings on the top five selling drugs: ranitidine (better known as Zantac), which treats ulcers; acyclovir (Zovirax), which treats herpes simplex; captopril (Capoten) and enalapril (Vasotec – a slight alteration of captopril/Capoten) for hypertension; and fluoxetine (Prozac), an anti-depressant. The table reflects the NIH methodology, which was to count all the published research projects behind a drug’s discovery and development and classify them as U.S. taxpayer-funded studies, foreign academic studies, or industry studies (which are then divided into those done by the patent-holding company and those done by other companies).

The NIH study also attempted to weight the importance of the studies by identifying those that were “key” and those that were later referenced in industry studies.

Table 4
Who Contributed Most to Development of Top Five Selling Drugs (1995)

Importance of Research	Affiliation of Scientist	Ranitidine (Zantac)	Acyclovir (Zovirax)	Captopril (Capoten) and Enalapril (Vasotec)	Fluoxetine (Prozac)	Total
Key Contributions to Discovery and Development of Drug*	U.S. taxpayer studies	2	4	4	1	11
	Foreign academic studies	1	1	1	2	5
	Industry sponsored studies (excluding patent holder)	0	0	0	0	0
	Patent-holder sponsored studies	0	0	0	1	1
Referenced in Patent Holders' papers*	U.S. taxpayer studies	0	7	1	1	9
	Foreign academic studies	0	1	0	1	2
	Industry sponsored studies (excluding patent holder)	0	0	0	0	0
	Patent-holder sponsored studies	0	0	0	0	0
Other Contributions to Discovery and Development of Drug	U.S. taxpayer studies	6	21	9	16	52
	Foreign academic studies	15	8	4	6	33
	Industry sponsored studies (excluding patent holder)	4	0	0	3	7
	Patent-holder sponsored studies	2	2	3	4	11
Total		30	44	22	35	131
Percent of total research projects sponsored by U.S. taxpayer or foreign academic institutions		80%	95%	86%	77%	85%

Source: National Institutes of Health, “NIH Contributions to Pharmaceutical Development,” Administrative Document, February 2000. *As defined by the National Institutes of Health.

The NIH report also found:

- Public researchers often tackle the riskiest and most costly research, which is basic research, making it easier for industry to profit. The NIH report discovered that only 14 percent of the drug industry's total R&D spending went to basic research, while 38 percent went to applied research and 48 percent was spent on product development.³³
- This finding suggests that public researchers are doing the yeomen's work of identifying possible new medicines, while most drug industry R&D spending occurs after companies believe they have a marketable drug. The NIH report concluded: "To the extent that basic research into the underlying mechanisms of disease drive new medical advances, *the R&D in industry is not performing the role played by public research funding.*"³⁴
- Taxpayer-funded scientists do more than basic research. They also conduct clinical trials. NIH found that publicly-funded researchers either conducted or had their work cited in 61 percent of the clinical trials important to the development of the five blockbuster drugs it studied.
- NIH research enables drug companies to secure more lucrative monopoly patents. According to the study: "[P]harmaceutical companies that organize in ways that tap the results of publicly-funded science are those that are most successful. For example, they...obtained more patents per research dollar, on average, than firms whose scientists work less closely with the public sector."³⁵

IV. R&D Data Kept Secret – What Are They Hiding?

It's impossible to know what the drug industry really spends on research and what it counts as research spending. The industry has fiercely fought attempts to open its books on R&D. In fact, the industry waged a nine-year legal battle against the General Accounting Office (GAO) – the investigative arm of Congress – to keep GAO from obtaining information about R&D.³⁶

The battle eventually went all the way to the U.S. Supreme Court, where it hinged on two words ("directly pertinent"). In short, the GAO argued that it was entitled to examine all drug company financial records, because the companies had contracts with the U.S. Veteran's Administration, and the GAO wanted to know if the companies' high prices and profits were warranted by the costs of producing and selling the medicines. The drug companies countered that the law only allowed GAO access to records that were "directly pertinent" to those government contracts. Thus, interpreting these two words became the subject of litigation from 1974 to 1983.

Federal district courts were split on GAO's right of access to "indirect" product costs such as R&D and marketing. The companies argued that indirect costs were not *directly pertinent* because only a small portion of indirect costs could be allocated to the federal government's contracts. GAO reasoned that "direct" product costs were so small – only about 9 percent for a particular drug – that they were not meaningful.³⁷

In the end, the U.S. Supreme Court, in *Bowsher v. Merck & Co. Inc.*, did draw the line between direct and indirect costs. In addition, the court held that since Congress had drafted the limiting language (“directly pertinent”), arguments for change should be directed to Congress.

Of course, the long legal battle would not have been necessary had Congress been willing to exercise its subpoena power to obtain the data. In fact, Congress can get all the information it wants. But, as a congressional study noted, this route is “perhaps not politically feasible.”³⁸

Why not? It’s possible Congress has not acted because the industry has spent huge sums on political persuasion according to a new Public Citizen report (“The Other Drug War: Big Pharma’s 625 Washington Lobbyists”) including \$262 million in 1999-2000 on campaign contributions, lobbying and ads that benefited its congressional allies.³⁹ (The spending breaks down as \$177 million on lobbying, \$20 million on contributions to federal candidates and party committees, and \$65 million on issue ads.)

Opening the industry’s R&D books would be particularly useful because it’s not clear what the industry considers “R&D.” Claims have been made – by a U.S. Senate committee investigation⁴⁰ and the editor-in-chief of the New England Journal of Medicine⁴¹ – that the industry inflates its R&D records with the costs of administration and marketing. Making industry information more transparent could help to resolve questions and charges that now hang over the industry.

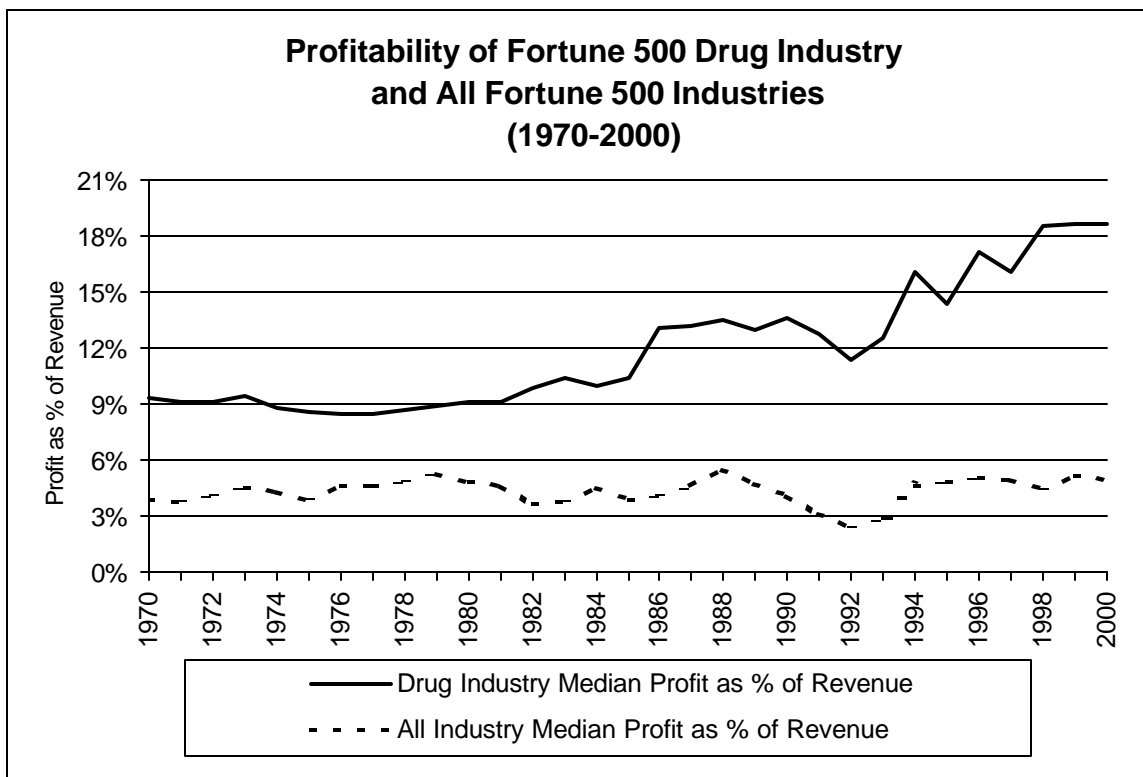
V. What Risk? The Druggernaut Consistently Ranks Tops in Profits

PhRMA and major drug companies attempt to justify high U.S. prescription drug prices by characterizing their business as a high-risk enterprise, which must therefore be rewarded with high returns. But where’s the risk in an industry that has consistently been rated the most profitable in America? Company reports to the federal Securities and Exchange Commission and *Fortune* magazine’s annual surveys of comparative industry profits show that:

- The drug industry was again ranked “more profitable than any other” by the Fortune 500 analysis of America’s largest companies in the year 2000. And the “druggernaut” walloped its competitors. The 11 drug companies that made the Fortune 500 enjoyed 19 percent return on revenues (in other words, 19 percent of revenues went to profits). The median for all other Fortune 500 companies was 5 percent return on revenues.⁴² (For a complete analysis of each company’s profitability, go to <http://www.citizen.org/congress/drugs/factsheets/mostprofitable.htm>.)
- The drug industry’s success in the Fortune 500 profitability rankings has become a rite of spring. Since 1982, the industry has topped *Fortune*’s rankings for return on revenue, and has been at or near the top for return on equity.⁴³

- The drug industry's profitability has grown in recent decades. On average, in the 1970s the profitability of Fortune 500 drug companies (measured by return on revenue) was two times greater than the median for all companies in the Fortune 500. In the 1980s it was three times. And in the 1990s, the drug companies' profitability was almost four times greater than the median for all companies in the Fortune 500.⁴⁴ (See Figure 1)
- The drug industry often thrives when other industries sag. Fortune 500 drug companies saw their year 2000 return on revenue increase 15 percent from 1999. That success came at a time when the American economy saw overall profit growth drop from 29 percent in 1999 to 8 percent last year.⁴⁵
- As consistent profit-generators, drug companies tend to outperform other industries during economic downturns, and investors know it. Not surprisingly, they boosted the stocks of Fortune 500 drug companies 38 percent while selling off other industries during last year's stock market turbulence.⁴⁶

Figure 1



Source: Public Citizen update of Stephen W. Schondelmeyer calculation, *Competition and Pricing Issues in the Pharmaceutical Market*, PRIME Institute, University of Minnesota based on data found in *Fortune* magazine, 1958 to 1999; *Fortune* magazine, April 2000, Fortune 500 (www.fortune.com).

VI. What Risk? A High Percentage of New Drugs Are “Me-Too” Drugs

Evidence also suggests that a significant amount of industry R&D does not concern new treatments for serious and life-threatening conditions, but instead goes into “me-too” drugs. These are drugs that have little or no therapeutic gain over drugs that already exist; also known as “copycat” drugs.

Until 1992, the U.S. Food and Drug Administration classified every new drug approved according to its significance for human health. The ranking system:

1A = Important therapeutic gain: a breakthrough drug

1B = Modest therapeutic gain: e.g., change in formulation so that the drug can be taken once instead of three or four times a day

1C = Little or no therapeutic gain: “me-too” or “copycat” drug – for all practical purposes a duplicate of products already available

Table 5
More than Half of New Drugs Approved from 1982-1991 Were “Me-Too” Drugs

FDA Category	Number	Percent
1A - Important Therapeutic Gain	41	16%
1B - Modest Therapeutic Gain	80	31%
1C - Little or No Therapeutic Gain	137	53%
Total New Drugs Approved 1982-91	258	100%

Source: Donald Drake and Marian Uhlman, *Making Medicine, Making Money* (1993), p. 72.

As seen in Table 5, more than one-half (53%) of the newly discovered drugs had “little or no therapeutic gain” compared to drugs already on the market – and only 16 percent of new drugs represented an “important therapeutic gain.”

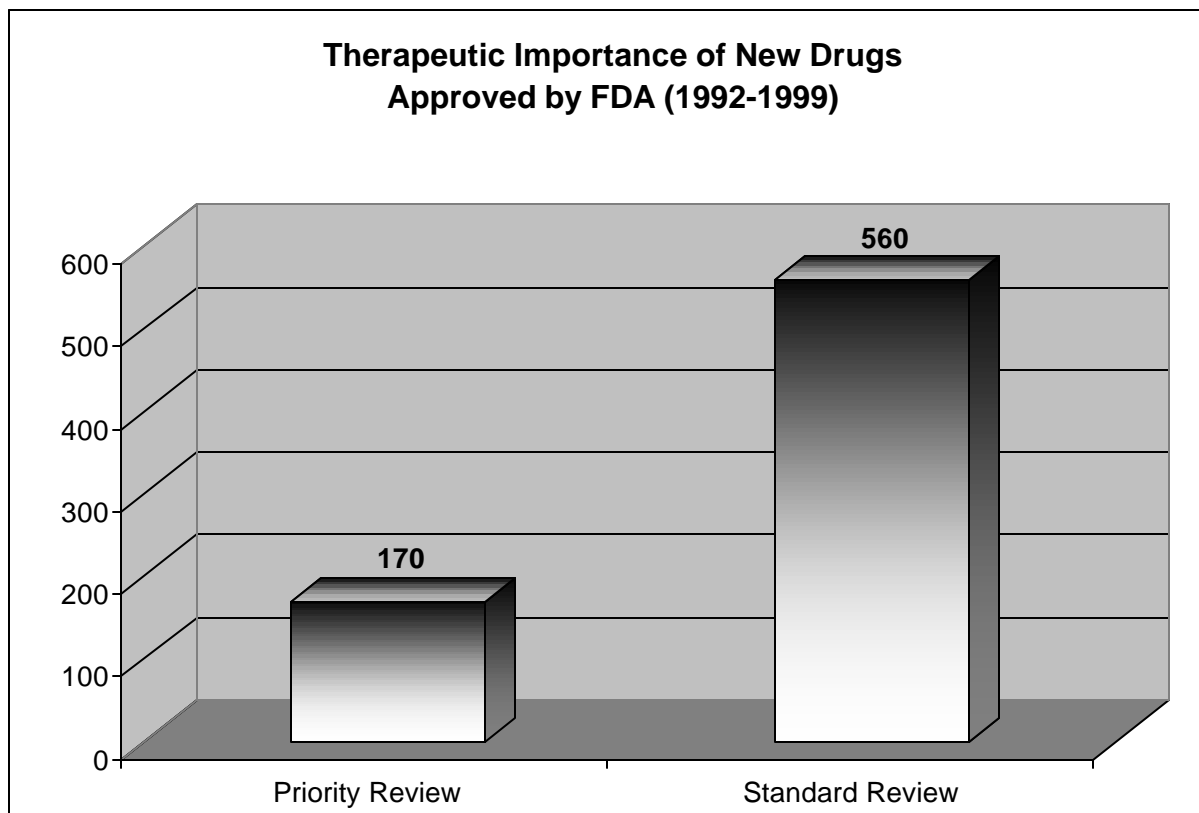
The pharmaceutical industry abhorred this system, because it provided objective information to the public and medical practitioners about the true value of a majority of their products. In response to industry pressure, the Bush I Administration eliminated these rankings in 1992.⁴⁷ Industry executives were grateful and glad. “To put [the 1A-1B-1C system] into well-deserved oblivion was a PMA priority for a very long time,” said John R. Stafford, chief executive officer of American Home Products at the 1992 annual convention of the Pharmaceutical Manufacturers Association (PhRMA’s former name). “Now it is accomplished.”⁴⁸

Although our ability to track the exact proportion of “me-too” drugs ceased with the demise of this ranking system, more recent evidence still confirms that a relatively small proportion of the

drug industry's claimed R&D expenditures are directed at the discovery of innovative treatments for serious and life-threatening illnesses:

- While the FDA dumped the 1A-1B-1C rankings, its new system still shows that the vast majority of new drugs did not represent significant therapeutic improvements. From 1992 through 1999, the FDA rated 170 drug approval applications for “priority review” and 560 for “standard review.” (See Figure 2) “Priority review” is for drugs that represent “significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease.” “Standard review” is for drugs that “appear to have therapeutic qualities similar to those of one or more already marketed drugs.”⁴⁹ (Critics claim that the FDA's “priority” category is far too liberal, giving drugs like Celebrex – which is no more effective than naproxen at relieving arthritis pain – priority status. Nevertheless, if the results from Figure 2 are combined with those in Table 5, only 22 percent of the drugs approved by the FDA from 1982-1999 represented important therapeutic gains.)

Figure 2



Source: FDA/Center for Drug Evaluation and Research, “NDAs Approved in Calendar Years 1990-1999,” December 31, 1999.

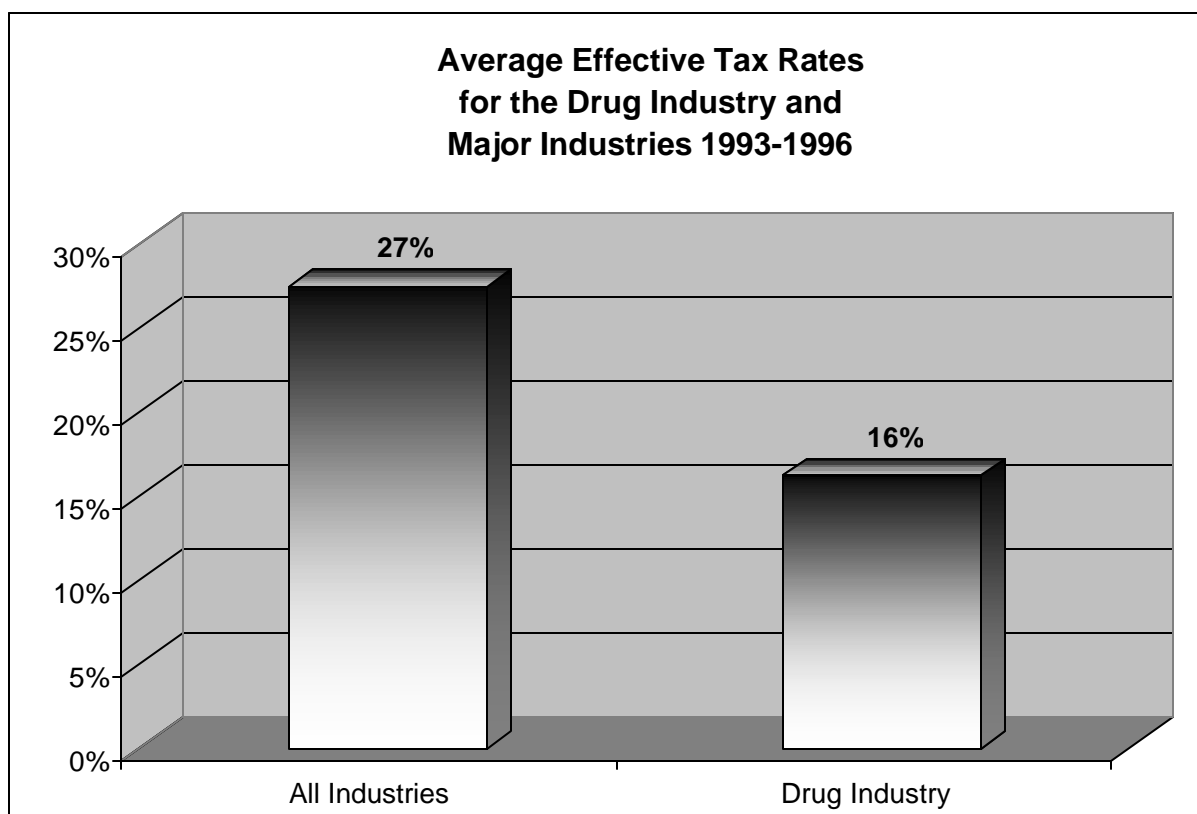
Note: According to the FDA, “priority review” is for drugs that represent a “significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease.” “Standard review” is for drugs that “appear to have therapeutic qualities similar to those of one or more already marketed drugs.”

VII. What Tax Burden? The Drug Industry Is Lightly Taxed

The drug industry has historically realized significant savings from four tax credit provisions: the foreign tax credit, possessions tax credit, research and experimentation tax credit, and the orphan drug tax credit (all of these are in addition to deductions for research expenditures which are worth 34 cents on the dollar). Combined, these tax credits have allowed the drug industry to save \$4 billion a year in taxes, according to the Congressional Research Service.⁵⁰

- In all, the industry used tax credits to save almost \$28 billion from 1990 through 1996.⁵¹
- The drug industry has also taken advantage of a tax break for companies that build factories in Puerto Rico. From 1980 through 1990, the GAO estimated that 26 pharmaceutical companies had tax savings of \$10.1 billion thanks to this tax credit.⁵²
- The drug industry's effective tax rate has been lower – much lower in some cases – than that of almost every major industry, despite its very high profitability. The drug industry's effective tax rate averaged 16 percent from 1993 through 1996 compared to 27 percent for all major industries over the same period.⁵³ (See Figure 3)

Figure 3



Source: Congressional Research Service Memorandum, "Federal Taxation of the Drug Industry from 1990 to 1996," December 1999.

Note: An industry's effective tax rate differs from its statutory corporate tax rate. Hence, the industry deducts R&D expenses at the 34 percent corporate tax rate, yet also pays at the same time an effective tax rate of 16 percent. This is not inconsistent in any way. It's very similar to what many Americans experience when they itemize their personal taxes. The 34 percent deduction is on a firm's taxable income and it reduces a firm's taxable income. The effective tax rate is a calculation based on tax credits, which are applied to reduce the tax liability, or taxes owed, after determining taxable income. For more details, see Appendix D.

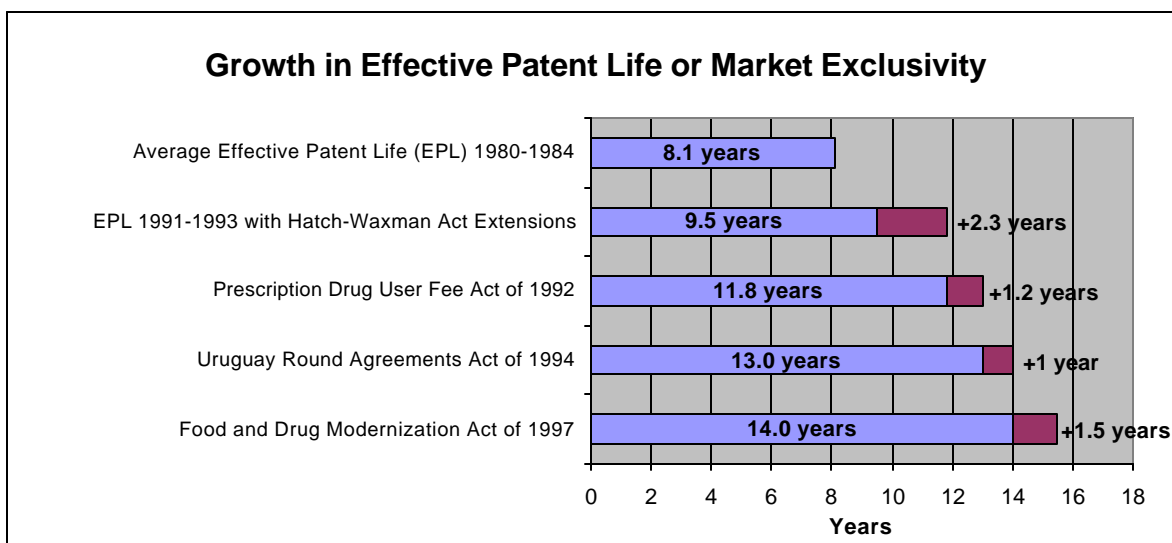
VIII. More Public Aid: Monopoly Patents and Research Incentives

In addition to research subsidies and tax credits, the drug industry enjoys other forms of government assistance, including patent extensions and lucrative incentives for testing the safety of drugs in children.

The federal government grants drug companies monopoly patents on new products that last 20 years, from date of patent application to expiration. More important is the "effective patent life" of a drug, which is the number of years remaining in a drug's patent term after the U.S. Food and Drug Administration approves the drug for market.

Starting in the mid-1980s, the federal government adopted several laws that extended the effective lives of drug patents. Combined, various laws of the 1980s and 1990s (Hatch-Waxman Act of 1984, Prescription Drug User Fee Act of 1992, the Uruguay Round Agreements Act of 1994, and the Food and Drug Modernization Act of 1997) have added 4.4 to 5.9 years of effective patent life. Effective patent life now averages 13.9 to 15.4 years.⁵⁴ (See Figure 4)

Figure 4



Source: National Institute for Health Care Management, "Prescription Drugs and Property Rights," 2000.

These patent extensions create a windfall for drug companies. For example, a pediatric exclusivity provision contained in the Food and Drug Modernization Act of 1997 gives six months of extra monopoly patent protection, or exclusivity, to a drug in return for the manufacturer conducting studies on the safety of the drug for children. Critics of the provision complain that it creates a lucrative incentive for companies to test their most valuable drugs on children, rather than those drugs most needed by children.

Indeed, drug companies are gaining the six-month bonus by testing some drugs that treat conditions uncommon in children, such as arthritis, ulcers and hypertension. For instance, pediatricians wrote less than 1 percent of the prescriptions for Glucophage, an adult-onset diabetes drug, and Vasotec, a hypertension medicine. The six months of extra exclusivity won by these drugs is worth nearly \$1 billion in sales.⁵⁵

Because the pediatric incentive delays the introduction of lower-priced generic drugs, the FDA estimates that it will reward drug companies with \$592 million per year in additional profit and cause consumers to pay an additional \$14 billion over 20 years in higher prices.⁵⁶ (For more complete analysis of pediatric exclusivity, see <http://www.citizen.org/congress/drugs/pediatricexclusivity.html>)

IX. High U.S. Drug Prices Don't Necessarily Mean More R&D

The pharmaceutical industry is a global industry dominated by large multinational companies. Since the 1980s, U.S. pharmaceutical companies have merged with or acquired significant stakes in European firms, and vice versa. All drug companies, regardless of where their national headquarters are located, charge higher prices in the U.S. market. That doesn't mean, however, that R&D will diminish if U.S. prices are moderated, as PhRMA President Alan Holmer has declared.

There are several reasons why. For one, profit margins are large enough that reducing them will still leave plenty of money for research. For another, cutting research is anathema to a drug company. It means walking away from new and potentially lucrative drugs. And that seems an odd course to take at a time when research is becoming quicker because of advances in technology and thus, cheaper.

“A decade ago, a good research chemist could produce 50-100 new compounds a year. Today with standard combinatorial chemistry, the same chemist can turn out a couple of thousand compounds a year,” according to industry analysts at PricewaterhouseCoopers. “Meanwhile, high-throughput screening has massively accelerated the speed at which compounds can be tested to identify the most promising molecules.”⁵⁷

The upshot of this move towards “e-R&D”? New technologies “will enable drug manufacturers to accelerate the selection process, reduce the costs of preclinical and clinical studies, and increase their overall chance of success. We estimate that they could collectively save at least \$200 million and two to three years per drug.”⁵⁸

In addition, the drug industry will soon enjoy a “demographic tailwind” as the Baby Boom generation hits retirement age and consumes more prescription drugs. “The fundamentals are massively positive,” said Tom McKillop, head of AstraZeneca, the company that makes the world’s best-selling drug, Prilosec. “We’ve got huge increases in the number of elderly. And we’re at a new phase of pharmaceuticals. Discoveries now involve the chronic degenerative diseases like Alzheimer’s...The science has never been more exciting.”⁵⁹

Price and profit controls – which exist in virtually all European countries – haven’t hurt the thriving drug industry in Europe where companies such as Glaxo Wellcome, Novartis, Aventis, AstraZeneca and Roche all have revenues that put them in the top 10 companies in global drug sales. (There are five American and five European companies in the top 10.)⁶⁰

While it is true that many European companies have substantial sales in the U.S., they still maintain robust R&D activities, despite the price controls in the European market.

A recent study by the Tufts Center for the Study of Drug Development notes that 49 percent of 107 new chemical entities it reviewed were first approved for market in the U.S.⁶¹ This suggests that a majority of new NCEs are developed outside the U.S. If that’s the case, then it appears that R&D operations of European companies are indeed healthy despite price controls.

This conclusion is supported by data concerning new drugs and the home-base of the companies that are bringing them to market. As Figure 5 shows, European-based companies have produced more new molecular entities (NMEs, which are similar to NCEs) in the last decade than American companies. While some important facts are not reflected in this data – such as where the European companies actually conducted their research and sold these drugs – the numbers do support the assertion that European companies have strong R&D activities, while operating under price controls.

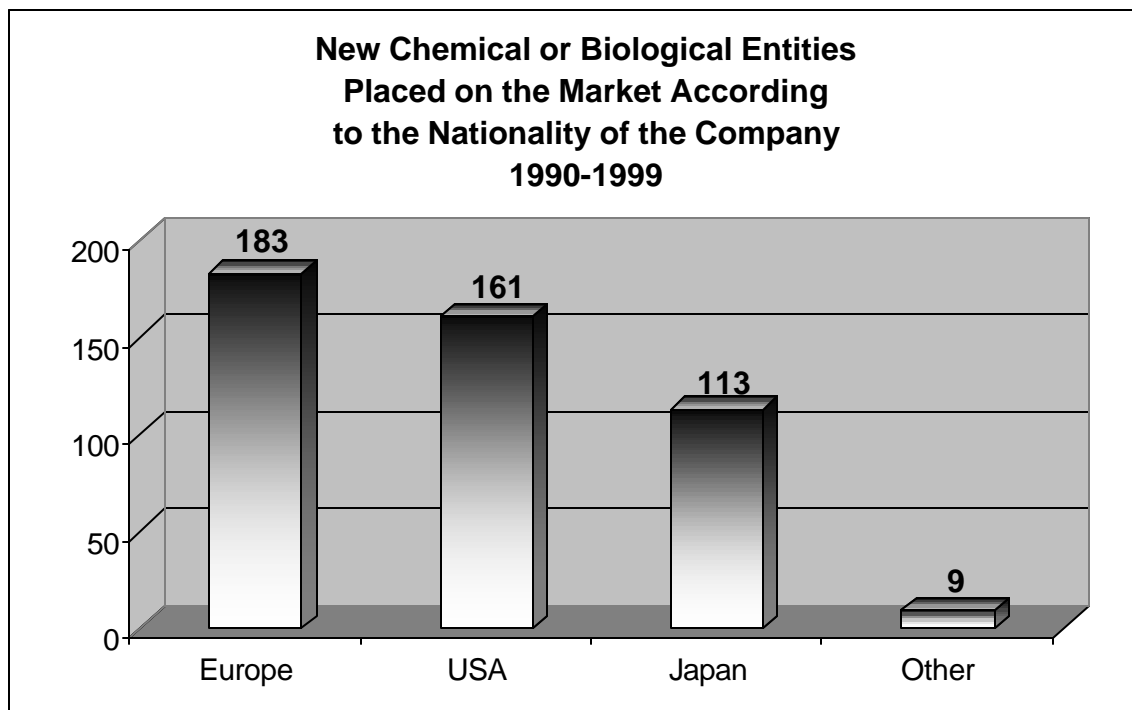
There are many factors that shape R&D and government regulation of prices is just one of them. As a GAO report concluded: “[D]rug prices are only one of many factors that influence pharmaceutical R&D. Therefore, pharmaceutical spending control policies can coexist with a strong research-based industry, even though by themselves such policies would decrease R&D spending.”⁶²

Any debate about prices and R&D must address not just the average cost of R&D per drug, but also the more important question of whether prices are already too high or are increasing too fast. In addition, any debate should look at whether dollar returns on R&D investments are more than enough to continue to induce investment in drug research.

On this last point, the OTA study was clear and unequivocal – returns were more than enough to stimulate investment. Specifically, the OTA found: “Each new drug introduced to the U.S. market between 1981 and 1983 returned, net of taxes, at least \$36 million more to its investors than was needed to pay off the R&D investment.”⁶³

Furthermore, the OTA said, “The long-run persistence of higher dollar returns... than the amount needed to justify the cost and risk of R&D is evidence of unnecessary pricing power for ethical pharmaceuticals.”⁶⁴

Figure 5



Source: European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures*, 2000. A drug is defined as a new chemical or biological entity if it has never before been marketed regardless of dosage form.

Finally, the OTA said it’s not clear whether a reduction in R&D spending would necessarily be harmful. “Whether a decrease in R&D would be good or bad for the public interest is hard to judge. It is impossible to know whether today’s level of pharmaceutical R&D is unquestionably worth its cost to society [in high prices].”⁶⁵

It could very well be that some research can wither without significant consequence. Section VI showed that the majority of drugs that companies bring to market are not drugs that represent important therapeutic advances. Rather, most are me-too drugs that replicate already successful drugs so that different companies can gain a cut of a burgeoning market. Some industry critics argue that less research on me-too drugs would improve the overall quality of industry research and decrease clutter in the market.

X. Advertising, Not R&D, Is the Drug Industry’s Fastest Growing Expenditure

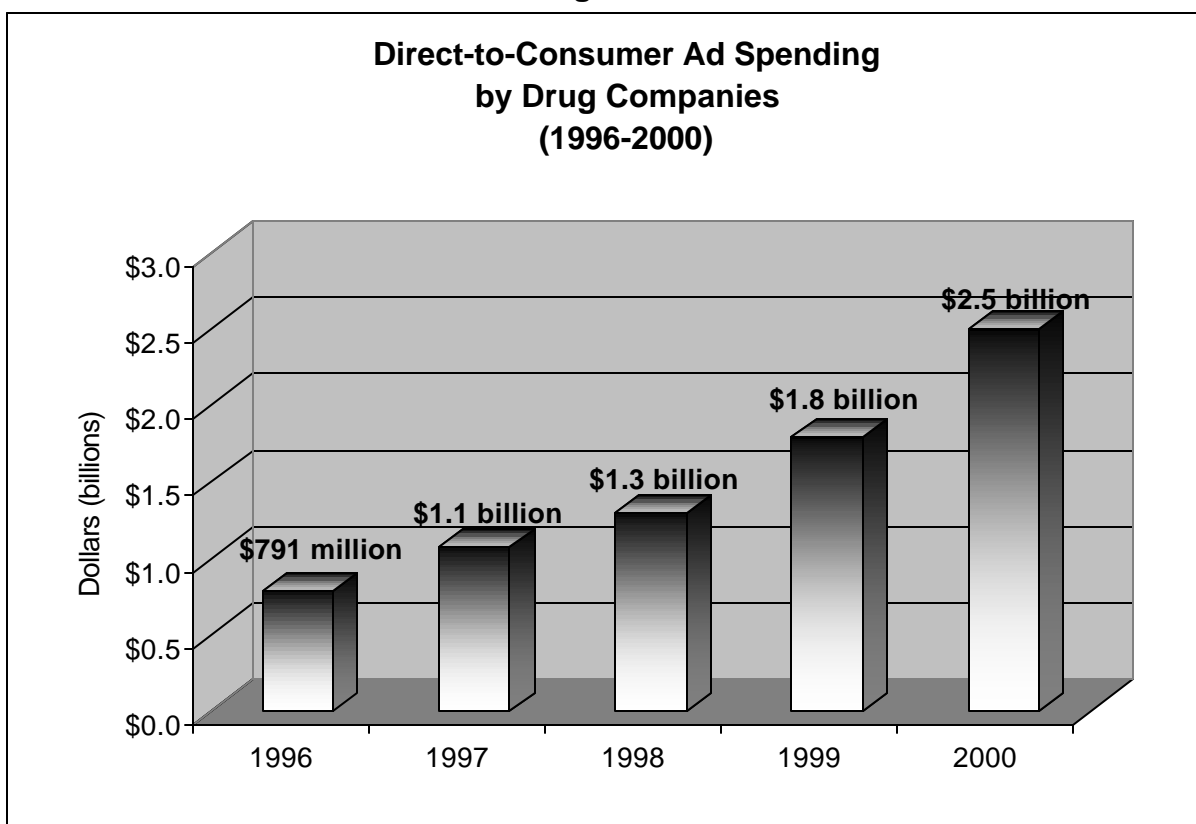
Since Senator Estes Kefauver’s groundbreaking hearings into the business practices of U.S. pharmaceutical companies in the late 1950s, the industry’s investment in marketing to gain and

maintain market share has been well documented. Public Citizen's Health Research Group has exposed the negative impact on consumer and patient health that the industry's slick and all-but-unregulated marketing practices produce (see www.citizen.org/hrg/publications/drugs.htm then scroll down to "promotion" for a list of publications). Since the FDA relaxed standards for Direct-to-Consumer (DTC) TV ads in 1997, drug advertising – and its negative consequences – have escalated rapidly.

As a result, promotion and advertising have driven drug expenditures higher and higher. And while it's impossible to pinpoint (because of industry secrecy) how much of the industry's R&D costs are actually market research, we do know the following:

- In 2000, the 11 Fortune 500 drug companies devoted nearly three times as much of their revenue to marketing and administrative costs (30 percent of revenue) as to research and development (12 percent of revenue).⁶⁶
- Drug industry spending on DTC advertising increased at a far greater rate (38 percent) in 1999 than spending on research and development (14 percent).⁶⁷
- One blockbuster drug was hyped more than Coke and Bud: After the FDA relaxed its rules on TV advertising in 1997, Schering-Plough spent \$136 million in 1998 advertising its allergy drug Claritin. That's more than Coca-Cola Co. spent advertising Coke, or Anheuser-Busch spent advertising Budweiser that year.⁶⁸
- Prior to the FDA's relaxation of the DTC standards the drug industry spent \$791 million on advertising in 1996. It is estimated that DTC spending totaled \$2.5 billion for the year 2000, an increase of 216 percent over 1996 and 39 percent over 1999.⁶⁹ (See Figure 6)
- Increased advertising seems to be playing a big part in increased spending on drugs. The 25 most-advertised drugs accounted for 41 percent of the increase in overall 1999 drug spending.⁷⁰
- It's clear why drug companies are spending more and more on advertising – it works. In a 1998 IMS Health survey of physicians, 97 percent of allergists said their patients were influenced by DTC advertising.⁷¹
- In a UCLA survey, 92 percent of consumers said they had heard of Claritin; 25 percent said that if their doctor advised against prescribing a particular drug they would switch doctors.⁷²
- Advertising is becoming more important to drug companies: The drug industry is shifting the core of its business away from the often unpredictable task of creating drugs and toward the steadier business of marketing them. Marketing of Viagra to healthy young men is an example of how the industry is pinning its future less on new products and more on persuading people to buy the pills already being sold.⁷³

Figure 6



Source: IMS Health figures made available to Public Citizen on April 18, 2001.

Note: 2000 figure estimate based on DTC spending through October.

XI. Conclusion and Recommendations

The prescription drug industry is arguably America's most government-coddled industry. It receives a 20-year monopoly patent on the drugs it develops, permitting companies to charge whatever the market will bear for life-saving drugs. The industry is one of the least taxed in America, yet it has the highest profit margin of all industries – three times the average of all industries. It claims to be a high-risk industry, yet for almost two decades it has topped the profit charts by a factor of two and more recently three. Taxpayers fund significant amounts of the research that results in new drug discoveries, but demand next to nothing in return – not even a simple accounting of our investment. It is time to form a new relationship on behalf of America's consumers between our government and the drug industry.

The financial outlook for the prescription drug industry has never been healthier. In 2000, the 11 largest drug companies netted \$28 billion in profits – a 15 percent increase in their return on revenue over 1999. (See Public Citizen's report at: <http://www.citizen.org/congress/drugs/factsheets/mostprofitable.htm>). The profits of one drug company, Merck (\$6.8 billion), were larger than the combined profits of all the Fortune 500

companies in each of the following industries: airline, entertainment, metals, food production and hotel/casino/resort industries.

And the picture looks just as rosy, if not rosier, for the future. As Fortune magazine noted in a recent issue, “Never has an industry had brighter long-term prospects...pharma is highly likely to match or exceed the past decade’s performance, in which it generated average annual returns of 25 percent. In a queasy economy, that’s powerful medicine indeed.”

Public Citizen believes that it is essential that America maintain a strong and vibrant prescription drug industry – one that provides healthy but reasonable profits to attract investors. However, this report shows that there is no essential connection between high prices and revenues for the industry and the invention of new medications. The industry has massively overstated the amount it spends inventing new drugs. It devotes much more of the revenue it takes in to paying dividends to its stockholders and to promoting drugs it has already created than it does to inventing new drugs. It leaves much of the truly pioneering research into deadly diseases to publicly funded researchers at the National Institutes of Health and universities around the world. And the drugs the industry “invents” are more likely to be knock-offs of drugs already on the market than they are to be new cures for a deadly disease.

In light of this situation, Public Citizen makes the following recommendations to Congress:

A. Drug Price Cost Containment

- 1. Medicare cost containment:** As Congress debates enacting Medicare prescription drug coverage there is a deafening silence about giving Medicare the authority to negotiate drug prices as it already negotiates hospital and physician payments. If the Departments of Defense and Veterans’ Affairs can negotiate deep price cuts there is no rationale for prohibiting Medicare from doing the same. Yet no major bill proposes such authority because of the power of the drug industry over lawmakers. As recent Congressional Budget Office projections show, given the rising cost of drugs and the budgetary limits placed on a drug benefit, it will be very difficult to construct a benefit that is generous enough along with premiums and cost sharing that are low enough to attract a sufficient number of Medicare beneficiaries to make the program viable. The logical solution is to reduce the cost of drugs. There are different ways to allow for Medicare negotiated prices – the bottom line could be a savings that is 30 percent to 40 percent greater than that anticipated under current Democratic reform proposals using a pharmacy benefit manager model. The Merrill Lynch investment company noted in a 1999 report that such savings would result in a net revenue loss to the drug industry of only 3.3 percent because lower prices would stimulate greater demand.⁷⁴
- 2. Reasonable pricing of drugs developed with taxpayer support:** Drug companies should be required to sell drugs that have benefited from taxpayer-funded research at reasonable prices to all, including the Medicare program.

Reasonable prices would be determined in a fashion similar to that used in other advanced industrialized countries. Drug companies would be required to submit price applications in which they would propose a price at which they planned to sell their drug along with a justification for that price. The justification would include a listing of the research and development expenses by the company, a detailed accounting of the role of federally-funded research in the development of the drug, and the anticipated therapeutic benefit of the drug. The reasonable price would be set such that the company would receive a healthy but reasonable profit above and beyond its expenses. In determining a reasonable price for a drug, an examination would also be made of the price of drugs in the same therapeutic class in the U.S. and other advanced industrialized countries. The reason that taxpayers fund government research through the National Institutes of Health (NIH) is to develop cures for dread diseases. Clearly, NIH research does little good if consumers cannot afford the drugs that were developed with our tax dollars. This proposal would benefit all those who rely on essential medications, not just Medicare beneficiaries.

3. **Payment based on the value of drugs:** As discussed in this report, much of the research and development and advertising by the drug industry is for the production and marketing of me-too drugs, which represent little or no therapeutic improvement over existing drugs. FDA should require studies of the comparative efficacy and safety of drugs as a condition of their approval. Medicare should not cover new drugs unless there is scientific documentation of a therapeutic advantage over older approved drugs. For drugs that show a genuine therapeutic advance, Medicare would cover the drug and negotiate a fair price based on the new innovation. If Medicare were to do this, then a Medicare drug benefit would not hinder genuine innovation, as the drug industry has asserted, but might act as an inspiration to innovation. In the event that Medicare were unable to create a system of negotiated payments based on a drug's value, then studies of drugs' comparative value could be conducted through the Centers for Education Research and Training (CERT) created under Food and Drug Administration Modernization Act of 1997 (FDAMA). CERT sites are independent, academic centers that given adequate funding could evaluate the comparative value of drugs. Private payers should use the work of the CERT sites to set their coverage policies for new drugs as a way of controlling costs in the private sector and creating an incentive for innovative research.

B. Industry Transparency & Preventing Conflicts of Interest

1. **Better tracking of taxpayer developed drugs:** Legislation must be enacted that requires the NIH to maintain a public record detailing the extent of federally-funded support towards the research and development of new drugs. By forcing the NIH to formally track the role of research it funds in the creation of new drugs, the public will be better able to hold the industry accountable for how it

uses the research it is given and be able to seek compensation for such public assistance in the form of reasonable prices for drugs.

2. **Require disclosure of the cost of R&D:** Since drug industry claims about the cost of R&D play such a prominent role in its campaign to oppose Medicare drug coverage and Medicare-negotiated drug prices it would be very valuable for the government and private sector to be able to determine how much it costs for the industry to develop new medicines. Currently, only Congress may subpoena drug company financial records to determine what the industry spends on R&D – authority it has not used. The General Accounting Office also should be given such authority in order to determine if the numerous government programs that purchase drugs are being defrauded.
3. **Require disclosure of best prices:** The public debate over what can be done about the high price of prescription drugs for U.S. seniors and other consumers has been stymied by a lack of information about the discounts that the industry offers its most favored domestic and foreign purchasers. Legislation should be enacted that would force the industry to reveal to policy makers the lowest prices it charges to purchasers here and abroad.
4. **Prohibit drug researcher conflicts of interest:** Oftentimes, researchers use non-profit institutions to apply for government research grants, but then enrich themselves by funneling the results of that research to for-profit companies that they control or are employed by. Congress should enact legislation to prevent such abuse of the taxpayer trust. Or, if Congress is unwilling to prohibit such conflicts of interest, it should require grant recipients to fully disclose them.

C. Ending Corporate Welfare

1. **End the pediatric incentive for all new drugs:** Pediatric exclusivity is a provision in current law that gives drug companies an additional six months of monopoly marketing protection for testing drugs in children. If this provision is reauthorized this year it will mean \$29 billion in additional revenue for the brand-name drug industry over the next 20 years. This provision should not be reauthorized. Instead, Congress should grant the FDA authority to require that all new drugs likely to be used in children be studied for safety and efficacy in children as a pre-condition of marketing approval. The FDA has estimated the annual cost of conducting those studies if they had been required between 1993 and 1997 at \$80 million.⁷⁵ This is a modest cost in exchange for lucrative monopolies granting the rights to market a prescription drug. The amount represents less than one-half-of-one-percent of the \$28 billion in profits earned by the top 11 drug companies in 2000. For more on this go to: <http://www.citizen.org/congress/drugs/pedexclusivityfactsheet.html>.

2. **No patent extensions/no patent abuses:** The Hatch-Waxman Act, which was passed in 1984, has been described as legislation that balanced the public's need for access to lower-priced generic drugs and the brand name drug industry's need for adequate revenues to fund the research and development it uses to invent medications. However, in the years since the Act was passed the drug industry has exploited loopholes in the law to extend their lucrative patents on drugs in ways that were not intended by the Act. One of the loopholes in the law is a provision that prevents a generic from coming to market for 30 months after a lawsuit for patent infringement has been filed against them by a brand name company. The industry exploits this loophole by filing frivolous lawsuits against generics -- thus delaying the entry of competing products by at least 30 months. This provision in the Hatch-Waxman Act should be revised so that brand name drug companies can only receive protection from competition if they can prove in a court of law that there is a good reason that a competing generic ought to be kept off of the market. This change is contained in legislation pending before the U.S. House and Senate, the Greater Access to Affordable Pharmaceuticals Act, Schumer-McCain/Brown-Emerson, S. 812/H.R.1862.

C. Comparative Drug Information

1. **Require the FDA to estimate the therapeutic value of new drugs:** In order for the public and private sectors to be better equipped to negotiate lower drug prices, better information is needed about whether new products may offer a therapeutic advantage over older drugs or are simply me-too drugs. This would be similar to the system used by the FDA prior to 1992 in which it distinguished between drugs that represented an "important therapeutic gain, a "modest therapeutic gain," and "little or no therapeutic gain."
2. **Analyze the comparative value of all currently-approved prescription drugs:** Congress should require the FDA or else establish a private entity to study the comparative value of all prescription drugs so that consumers, payers, and doctors can be better informed. If funding for the Centers for Education, Research and Training (CERT) established under FDAMA were increased, they could do this research. As a condition of federal support, academic medical centers could be required to use this unbiased information in educating medical students and in continuing medical education so that doctors can make distinctions between "me-too" and breakthrough drugs in their prescribing decisions. Also, such information would be made available to medical insurance payers so that they could make better decisions about which drugs to cover.

E. Regulate Drug Company Advertising and Promotion

1. **Require FDA to promulgate regulations for direct-to-consumer (DTC) advertising:** As this report shows, drug company advertising to consumers plays

a role in rising prescription drug costs. But currently there is limited FDA authority to regulate such advertising. Congress should require the FDA to issue regulations concerning DTC advertising by a date certain. These regulations should require that drug companies provide consumers with scientifically accurate, useful, comparative information about the value of drugs in their advertisements and in the packaging of the drugs they manufacture.

2. **Assure adequate FDA funding to monitor both professional and DTC advertising:** The FDA office charged with overseeing drug advertising, the Division of Drug Marketing Advertising and Communication (DDMAC), is woefully understaffed. While the dollar value of DTC advertising and promotion has more than tripled from \$791 million in 1996 to \$2.5 billion in 2000, and other advertising, to professionals, also increased, the number of FDA staff assigned to review and investigate all prescription drug advertising during this same period has increased from 11 to only 14. Clearly, in order for FDA to protect consumers from misleading claims in advertisements by the drug industry that help to fuel double-digit spending increases, additional staff for DDMAC is essential.
3. **Strengthen FDA enforcement:** To give FDA stronger enforcement powers, Congress should give the agency the authority to level civil monetary fines for misleading drug advertising. The FDA has asked for such authority in the past. (See *American Journal of Law and Medicine*, 1999, p. 149.).

Appendix A

Chapters on R&D Costs for New Drugs from the Office of Technology Assessment Report “Pharmaceutical R&D: Costs, Risks and Rewards”

See attached

Chapter One: Summary

Chapter Three: The Costs of Pharmaceutical R&D

Summary | 1

In this assessment, the Office of Technology Assessment examined the costs of pharmaceutical research and development (R&D), the economic rewards from that investment, and the impact of public policies on both costs and returns. Below is a brief synopsis of the study's major conclusions:

SUMMARY OF FINDINGS

- Pharmaceutical R&D is a costly and risky business, but in recent years the financial rewards from R&D have more than offset its costs and risks.
- The average aftertax R&D cash outlay for each new drug that reached the market in the 1980s was about \$65 million (in 1990 dollars). The R&D process took 12 years on average. The full aftertax cost of these outlays, compounded to their value on the day of market approval, was roughly \$194 million (1990 dollars).
- The cost of bringing a new drug to market is very sensitive to changes in science and technology, shifts in the kinds of drugs under development and changes in the regulatory environment. All of these changes are occurring fast. Consequently, it is impossible to predict the cost of bringing a new drug to market today from estimated costs for drugs whose development began more than a decade ago.
- Each new drug introduced to the U.S. market between 1981 and 1983 returned, net of taxes, at least \$36 million more to its investors than was needed to pay off the R&D investment. This surplus return amounts to about 4.3 percent of the price of each drug over its product life.



2 | Pharmaceutical R&D: Costs, Risks and Rewards

- . Dollar returns on R&D are highly volatile over time. Changes in R&D costs, tax rates, and revenues from new drugs are the most important factors influencing net returns. Drugs approved for marketing in 1984-88 had much higher sales revenues (in constant dollars) in the early years after approval than did drugs approved in 1981-83. On the other hand, R&D costs may be increasing and generic competition could be much stiffer for these drugs after they lose patent protection.
 - Over a longer span of time, economic returns to the pharmaceutical industry as whole exceeded returns to corporations in other industries by about 2 to 3 percentage points per year from 1976 to 1987, after adjusting for differences in risk among industries. A risk-adjusted difference of this magnitude is sufficient to induce substantial new investment in the pharmaceutical industry.
 - . The rapid increase in revenues for new drugs throughout the 1980s sent signals that more investment would be rewarded handsomely. The pharmaceutical industry responded as expected, by increasing its investment in R&D. Industrywide investment in R&D accelerated in the 1980s, rising at a rate of 10 percent per year (in constant dollars).
 - . The rapid increase in new drug revenues was made possible in part by expanding health insurance coverage for prescription drugs in the United States through most of the 1980s. Health insurance makes patients and their prescribing physicians relatively insensitive to the price of a drug. The number of people with prescription drug coverage increased, and the quality of coverage improved.
 - . Almost all private health insurance plans covering prescription drugs are obligated to pay their share of the price of virtually any FDA-approved use of a prescription drug. FDA approval acts as a *de facto* coverage guideline for prescription drugs. Most health insurers have almost no power to influence prescribing behavior or to control the prices they pay for patented drugs.
 - Manufacturers of drugs that are therapeutically similar to one another compete for business primarily on quality factors, such as ease of use, side-effect profiles and therapeutic effect. With price-conscious buyers such as health maintenance organizations (HMOs) and hospitals, however, they have engaged in more vigorous price competition.
 - . If price competition among therapeutically similar compounds became more common, the directions of R&D would change and the total amount of R&D would probably decline. Whether a decrease in R&D would be good or bad for the public interest is hard to judge. It is impossible to know whether today level of pharmaceutical R&D is unquestionably worth its costs to society.
 - The National Institutes of Health (NIH) and other Public Health Service laboratories have no mechanism to protect the public's investment in drug discovery, development and evaluation. These agencies lack the expertise and sufficient legal authority to negotiate limits on prices to be charged for drugs discovered or developed with Federal funds.
-

INTRODUCTION

Pharmaceutical R&D is the process of discovering, developing, and bringing to market new ethical drug products. Most pharmaceutical R&D is undertaken by private industrial firms, and this report is about how and why industrial pharmaceutical companies make decisions to undertake R&D, what they stand to gain from such investments, and how they are helped or hindered by public policies that influence the process.

Industrial R&D is a scientific and an economic process. R&D decisions are always made with both considerations in mind. Science defines the opportunities and constraints, but economics determines which opportunities and scientific challenges will be addressed through industrial research.

This report focuses mainly, but not entirely, on the economic side of the R&D process. In this perspective, pharmaceutical R&D is an **investment**. The principal characteristic of an investment is that money is spent today in the hope that even more money will be returned to the investors sometime in the future. If investors (or the corporate R&D managers who act on their behalf) believe that the potential profits from R&D are worth the investment's cost and risks, then they will invest in it. Otherwise, they will not.

ORIGINS AND SCOPE OF OTA'S STUDY

OTA's study of pharmaceutical R&D grew out of a long-standing congressional debate over the prices of ethical drugs. Increases in real (inflation-adjusted) drug prices and perceived high prices for new drugs have been a concern of congressional committees for more than 30 years.

The industry's collective response to charges that drug prices are too high or are increasing too fast has been to point to the high and increasing cost of pharmaceutical R&D and their need to repay investors for their substantial and risky investments (325,326,505). Industry representatives have pointed to academic studies of the



Photo credit: ELI LILLY AND COMPANY

Pharmaceutical research and development is both a scientific and an economic process. Personnel, equipment and facilities come together in sophisticated organizations required for R&D.

average cost of bringing a new pharmaceutical compound to the market (324,326). One objective of OTA's report is to evaluate the accuracy of the industry's claims by examining the data and methods used to reach such conclusions.

By itself, the average cost of pharmaceutical R&D tells little about whether drug prices are too high or are increasing too fast. A more important question is whether the dollar returns on R&D investments are higher or lower than what is needed to induce investors to make these investments. The long-run persistence of higher dollar returns in the industry as a whole than the amount needed to justify the cost and risk of R&D is evidence of unnecessary pricing power for ethical pharmaceuticals (366). OTA examined the economic returns to investors in pharmaceutical R&D.

The U.S. Federal Government is anything but a passive observer of the industrial pharmaceutical R&D process. The Federal Government subsidizes private R&D, regulates the introduction and

¹ Ethical drugs are biological and medicinal chemicals advertised and promoted primarily to the medical, pharmacy, and allied professions. Ethical drugs include products available only by prescription as well as some over-the-counter drugs (320). Strictly speaking, ethical drugs include diagnostic as well as therapeutic products, but this report concentrates on R&D for therapeutic ethical drugs.

Box I-A—The Content of Pharmaceutical R&D

Synthesis and Extraction—The process of identifying new molecules with the potential to produce a desired change in a biological system (e.g., to inhibit or stimulate an important enzyme, to alter a metabolic pathway, or to change cellular structure). The process may require: 1) research on the fundamental mechanisms of disease or biological processes; 2) research on the action of known therapeutic agents; or 3) random selection and broad biological screening. New molecules can be produced through artificial synthesis or extracted from natural sources (plant, mineral, or animal). The number of compounds that can be produced based on the same general chemical structure runs into the hundreds of millions.

Biological Screening and Pharmacological Testing—studies to explore the pharmacological activity and therapeutic potential of compounds. These tests involve the use of animals, isolated cell cultures and tissues, enzymes and cloned receptor sites as well as computer models. If the results of the tests suggest potential beneficial activity, related compounds—each a unique structural modification of the original—are tested to see which version of the molecule produces the highest level of pharmacological activity and demonstrates the most therapeutic promise, with the smallest number of potentially harmful biological properties.

Pharmaceutical Dosage Formulation and Stability Testing—The process of turning an active compound into a form and strength suitable for human use. A pharmaceutical product can take any one of a number of dosage forms (i.e., liquid, tablets, capsules, ointments, sprays, patches) and dosage strengths (i.e., 50, 100, 250, 500 mg). The final formulation will include substances other than the active ingredient, called excipients. Excipients are added to improve the taste of an oral product, to allow the active ingredient to be compounded into stable tablets, to delay the drug's absorption into

marketing of new drugs, and pays for many drugs through Federal health care programs. Federal tax policies also alter R&D costs and returns. OTA assessed how Federal policies affect R&D costs and returns and how well Federal agencies protect the direct and indirect Federal investment in pharmaceutical R&D.

ISSUES BEYOND THE SCOPE OF THIS STUDY

OTA did not examine the implications for the competitiveness of the U.S.-based pharmaceutical industry of Federal policies affecting pharmaceutical R&D. The U.S.-based industry is a leader in the discovery and development of new drugs, particularly important new drugs with global markets. The U.S.-based industry has introduced roughly one out of every four new compounds introduced to the world market since 1961 (68,342) and is so far unchallenged as the leader

in biotechnology-based drugs and vaccines. All of the 15 biotechnology-based drugs and vaccines approved in the United States as of August 1991 were developed by U.S.-based firms (453).

Federal policies affecting R&D obviously affect the U. S.-based industry, but their influence on the relative competitiveness of the U.S.-based industry is much more difficult to predict. Most of the U.S. Federal policies in place today that affect drug R&D are neutral with respect to the drug's country of origin. Whether the United States should adopt policies that explicitly encourage U.S.-based R&D or manufacturing is beyond the scope of this project.²

THE NATURE OF PHARMACEUTICAL R&D INVESTMENTS

■ Pharmaceutical R&D's Two Objectives: New Drugs and New Markets

Pharmaceutical R&D includes many different scientific and clinical activities (see box I-A).

² For an examination of the competitiveness of U.S.-based dedicated biotechnology companies, see OTA's recent report on the subject (453).

the body, or to prevent bacterial growth in liquid or cream preparations. The impact of each on the human body must be tested

Toxicology and Safety Testing—Tests to determine the potential risk a compound poses to man and the environment. These studies involve the use of animals, tissue cultures, and other test systems to examine the relationship between factors such as dose level, frequency of administration, and duration of exposure to both the short- and long-term survival of living organisms. Tests provide information on the dose-response pattern of the compound and its toxic effects. Most toxicology and safety testing is conducted on new molecular entities prior to their human introduction, but companies can choose to delay long-term toxicity testing until after the therapeutic potential of the product is established.

Regulatory Review: Investigational New Drug (IND) Application—An application filed with the U.S. FDA prior to human testing. The IND application is a compilation of all known information about the compound. It also includes a description of the clinical research plan for the product and the specific protocol for phase I study. Unless the FDA says no, the IND is automatically approved after 30 days and clinical tests can begin.

Phase I Clinical Evaluation—The first testing of a new compound in human subjects, for the purpose of establishing the tolerance of healthy human subjects at different doses, defining its pharmacologic effects at anticipated therapeutic levels, and studying its absorption, distribution, metabolism, and excretion patterns in humans.

Phase II Clinical Evaluation—Controlled clinical trials of a compound's potential usefulness and short term risks. A relatively small number of patients, usually no more than several hundred subjects, enrolled in phase II studies.

Phase III Clinical Evaluation—Controlled and uncontrolled clinical trials of a drug's safety and effectiveness in hospital and outpatient settings. Phase III studies gather precise information on the drug's effectiveness for specific indications, determine whether the drug produces a broader range of adverse effects than those exhibited in the smaller study populations of phase I and II studies, and identify the best way of administering and using the drug for the purpose intended. If the drug is approved, this information forms the basis for deciding the content of the product label. Phase III studies can involve several hundred to several thousand subjects.

Process Development for Manufacturing and Quality Control—Engineering and manufacturing design activities to establish a company's capacity to produce a product in large volume and development of procedures to ensure chemical stability, batch-to-batch uniformity, and overall product quality.

Bioavailability Studies: The use of healthy volunteers to document the rate of absorption and excretion from the body of a compound's active ingredients. Companies conduct bioavailability studies both at the beginning of human testing and just prior to marketing to show that the formulation used to demonstrate safety and efficacy in clinical trials is equivalent to the product that will be distributed for sale. Companies also conduct bioavailability studies on marketed products whenever they change the method used to administer the drug (e.g., from injection to oral dose form), the composition of the drug, the concentration of the active ingredient, or the manufacturing process used to produce the drug.

Regulatory Review: New Drug Application (NDA)—An application to the FDA for approval to market a new drug. All information about the drug gathered during the drug discovery and development process is assembled in the NDA. During the review period, the FDA may ask the company for additional information about the product or seek clarification of the data contained in the application.

Postapproval Research—Experimental studies and surveillance activities undertaken after a drug is approved for marketing. Clinical trials conducted after a drug is marketed (referred to as phase IV Studies in the United States) are an important source of information on as yet undetected adverse outcomes, especially in populations that may not have been involved in the premarketing trials (i.e., children, elderly, pregnant women) and the drug's long-term morbidity and mortality profile. Regulatory authorities can require companies to conduct Phase IV studies as a condition of market approval. Companies often conduct post-marketing studies in the absence of a regulatory mandate.

SOURCE: Office of Technology Assessment, 1993; based on Pharmaceutical Manufacturers Association Annual Survey Reports.

6 | Pharmaceutical R&D: Costs, Risks and Rewards

Before any new therapeutic ethical pharmaceutical product can be introduced to the market in the United States and most other industrialized countries, some R&D must be undertaken, but the specific activities and required R&D expenditures vary enormously with the kind of product under development. New therapeutic ethical pharmaceutical products fall into four broad categories:

- New chemical entities (NCEs)—new therapeutic molecular compounds that have never before been used or tested in humans.³
- Drug delivery mechanisms—new approaches to delivering therapeutic agents at the desired dose to the desired site in the body.
- Follow-on products—new combinations, formulations, dosing forms, or dosing strengths of existing compounds that must be tested in humans before market introduction.
- Generic products—copies of drugs that are not protected by patents or other exclusive marketing rights.

R&D is needed to bring all of these products to the market. National regulatory policies determine some of the required R&D, but some R&D would be undertaken even if there were no new drug regulation.

NCEs are discovered either through screening existing compounds or designing new molecules; once synthesized, they must undergo rigorous preclinical testing in laboratories and animals and clinical testing in humans to establish safety and effectiveness. The same is true for novel drug delivery mechanisms, such as monoclonal antibodies or implantable drug infusion pumps. Follow-on products also must undergo preclinical and clinical testing before they can be marketed, but the amount of R&D required to prove safety

and effectiveness is usually less than for the original compound.

Even after a new drug has been approved and introduced to the market, clinical R&D may continue. Some of this postapproval clinical evaluation is required by regulatory agencies as a condition of approval, but other clinical research projects are designed to expand the market for the drug. For example, much clinical research is done to test new therapeutic uses for a drug already on the market or to compare its effectiveness with that of a competing product.

The research required on a generic product is typically much less than on the original compound it copies. In the United States, the makers of generic products must show the U.S. Food and Drug Administration (FDA) that the drug is therapeutically equivalent to the original compound, not that the compound itself is effective against the disease. This involves much less R&D than is necessary to introduce either NCEs or follow-on products.

The discovery and development of NCEs is the heart of pharmaceutical R&D, because the developers of follow-on or generic products build on the knowledge produced in the course of developing them. The market for the compound and all its follow-on products or generic copies in future years rests on the R&D that led to its initial introduction to the market. Most of the money spent on pharmaceutical R&D goes to the discovery and development of NCEs. Companies responding to the Pharmaceutical Manufacturers Association's (PMA) annual survey estimated that 83 percent of total U.S. R&D dollars in 1989 were spent in "the advancement of scientific knowledge and development of new products" versus "significant improvements and/or modifications of existing products" (320).⁴

³Another term frequently used to refer to newly developed compounds is "new molecular entity" (NME). The U.S. Food and Drug Administration (FDA) coined the term for use in its published statistical reports (474). The FDA includes some diagnostic agents and excludes therapeutic biologicals in data they present on NMEs, whereas in this report the term NCE is used to refer to therapeutic drugs and biologicals but not to diagnostic products. OTA uses the term NME only when discussing work that specifically employs FDA's definition of that term.

⁴How responding firms defined new products or modifications of existing products is unclear, however, and the accuracy or reliability of these estimates cannot be verified.

A patent on an NCE gives its owner the right to invest in further R&D to test new therapeutic uses or produce follow-on products. This continuing R&D may extend the compound's life in the market or increase its market size. Therefore, a complete analysis of returns on R&D for NCEs should encompass the costs of and returns on these subsequent investments as well.

NCEs comprise two poorly-defined sub-categories: pioneer drugs and "me-too" drugs. Pioneer NCEs have molecular structures or mechanisms of action that are very different from all previously existing drugs in a therapeutic area. The first compound to inhibit the action of a specific enzyme, for example, is a pioneer drug. Me-too drugs are introduced after the pioneer and are similar but not identical to pioneer compounds in molecular structure and mechanism of action. Many me-too drugs are developed through deliberate imitation of the pioneer compound and have a shorter and more certain discovery period (158). But, the R&D cost advantage gained by imitation is typically met by a reduction in potential dollar returns from being a late entrant to the market (55,158).

The distinction between pioneers and me-toos is fuzzy, and not all me-too drugs are imitative. Although it is rational for pharmaceutical firms to imitate an existing product in order to share in a potentially lucrative market (102,298,346,363,418), much of the R&D on me-too drugs is not imitative but competitive. Companies race to be first to the market. The race has one winner and often a field of followers. The R&D costs of those who lose the race but manage ultimately to produce a product may be as high as or even higher than the costs of developing the pioneer compound.

For example, substantial R&D activity is currently underway in several pharmaceutical companies to develop new asthma therapies based on leukotriene inhibitors (403). A total of 25 compounds are now under investigation. How the research will proceed, which research programs will yield products that can be tested in

humans, and which of those products will ultimately meet the tests of efficacy and safety required for market approval are anyone's guess. Already, research has been discontinued on at least three such products because of unanticipated safety problems in animal or clinical studies (378,379).

■ The Three Most Important Components of R&D Investment: Money, Time, and Risk

Investors spend money today to make more money in the future. The less money required for the investment and the more that is expected in the future, the better the investment is. But money is only the first component of the R&D investment. Not only do investors care about how much money is required and the potential dollar returns that may result, but they also care about the second component: the timing of money outflows and inflows. The longer the investor must wait to get money back, the more he or she expects to get. Stated another way, money that will come in tomorrow, even with complete certainty, is not worth as much as the same amount in hand today.⁵

For risk-free investments, such as U.S. Treasury bills, the required return (as a percent of the capital invested) is determined by supply and demand in the money markets. If the going risk-free interest rate is 5 percent per year, for example, an investor who puts up \$100 expects to get at least \$105 back next year. From another point of view, \$100 promised for delivery next year is worth only \$95.23 today, because the investor could take that \$95.23, invest it in a risk-free security, and have the \$100 a year hence. Not having access to the \$95.23 today essentially deprives the investor of the opportunity to invest at the going interest rate.

The interest rate required to induce the investor to permit his or her money to be used is referred to as the opportunity cost of capital. The value today (e.g., \$95.23) of money promised for delivery sometime in the future (e.g., \$100), evaluated at the opportunity cost of capital (e.g.,

⁵ This principle lies behind the payment of interest on safe investments like insured bank deposits or U.S. Treasury bills.

5 percent), is referred to as the present value of money.

Like all investments, R&D investments must return enough money in the future so that the present value of those returns (evaluated at the investment's cost of capital) is at least as great as the amount of the investment.

Risk is the third component of the R&D investment. Riskier investments require higher dollar returns; otherwise investors would put their money in safe investments like U.S. Treasury bills. Thus, the opportunity cost of capital for R&D investments must be higher than the cost of capital for risk-free investments. And, the present value of \$100 that is expected next year but with a great deal of uncertainty is even lower than the present value of a risk-free investment. How much higher the opportunity cost of capital for an R&D investment is, and how much lower the present value of future expected returns is, depends on the riskiness of the R&D investment.

Pharmaceutical industry executives often emphasize the particular riskiness of R&D. Analogies to drilling for oil are common: R&D involves many dry holes and a few gushers. According to one industry executive, pharmaceutical R&D is like "wildcatting in Texas (188)." Data on the dropout rate for drugs under development support these notions that R&D is, indeed, an uncertain and risky undertaking.

The risk that is accounted for in the opportunity cost of capital is different from these conventional notions about the risks of R&D. Modern finance theory distinguishes between two different kinds of investor risk: diversifiable risk and undiversifiable risk (59). The "wildcatting" risks of drug R&D are diversifiable: the investor can invest in a large diversified portfolio of R&D projects (or firms undertaking such projects) and obtain, on average, an expected dollar return that is very predictable,



Photo credit: BRISTOL-MYERS SQUIBB COMPANY

Pharmaceutical R&D is risky business. Clinical testing of thousands of patients can result in the failure of a new compound to reach the market. Company scientists review detailed clinical data on many patients to determine the therapeutic benefit of a new agent.

For example, suppose the average NCE entering clinical testing has a 1-in-5 chance of ultimately reaching the market. If it does, it will make on average \$100 million for the company. The expected dollar return, then, is \$20 million.* If investors diversify their portfolios across a large enough number of R&D projects, they can be fairly certain that they will make, on average, about \$20 million per project. Thus, the variation in returns due to the low probability of successful drug development can be eliminated by diversify-

*The expected value is the average return weighted by the probability of each potential outcome: $\$100(0.20) + \$0(0.80) = \$20$.

ing the investment portfolio across a large number of projects.⁷

Some kinds of risk cannot be diversified away. Suppose, for example, prescription drug sales were closely linked to the state of the economy, perhaps because high unemployment produces more people who are uninsured and cannot afford prescription drugs. Pharmaceutical R&D would then have a great deal of undiversifiable risk because returns on R&D would depend on the state of the economy as a whole, and investors cannot diversify away these economywide risks.

The central finding of modern finance theory is that the cost of capital for a given investment must be adjusted only for the portion of risk that is undiversifiable. (See appendix C for an explanation.) The technical risks of project failure that weigh so heavily on the minds of R&D managers and executives do not raise the opportunity cost of capital.

OTA used standard financial techniques to obtain estimates of the cost of capital in the pharmaceutical industry as a whole and the cost of capital for pharmaceutical R&D investments in particular. We relied on techniques and data provided in a contract report by Stuart Myers and Lakshmi Shyam-Sunder (285). The cost of capital varies over time and across firms, but over the past 15 years the cost of capital in the pharmaceutical industry as a whole varied in the neighborhood of roughly 10 percent after adjusting for investors' inflation expectations (see appendix C).

Pharmaceutical firms are collections of investments, some very risky and others much less so. The undiversifiable risks of R&D projects are higher than those of other investments that drug companies must make, for reasons that are outlined in appendix C. R&D investments are riskier the earlier in the R&D process they are. How much riskier is difficult to assess, but OTA concluded that the cost of capital for the earliest stages of R&D may be up to 4 percentage points higher than the cost of capital for pharmaceutical companies as a whole.

■ Investors Look Ahead

In making R&D decisions, investors try to predict the possible future outcomes as accurately as they can. They assess the present value of their investments based on these predictions, not on the basis of past performance or profits.⁸ An industry's past performance is informative to an investor only to the extent that technology and market conditions remain stable.

If investors always look ahead, then profits from today's drugs (which were developed with yesterday's R&D) do not determine how much will be invested in R&D. R&D managers do not invest in R&D simply because they have the cash on hand; they invest when the prospects for future returns look promising.

This conclusion seems to contradict the industry's contention that today's profits are needed to fund today's R&D (356). The success of the health-care oriented biotechnology industry in raising external capital proves that companies can

⁷ The portfolio diversification need not occur within each individual company; investors can just as easily hold a diverse portfolio of companies in the industry. Within-company diversification may be important for managers whose professional and financial futures may rest with their own firm's performance, however. To the extent that managers seek to diversify their company's investments for their own purposes, they are not representing the interests of the firm's owners.

⁸ In interviews with executives and R&D directors of eight pharmaceutical firms, OTA learned that few companies do formal present value analyses to select R&D projects or to determine how much R&D should be conducted in any year. What is true for the pharmaceutical industry may be true more generally. Seiberer surveyed executives of Fortune 100 companies about their investment decisions and found that only about 30 percent of the responding companies used present value analysis in decisions regarding R&D (364). The high level of technical uncertainty may lead to other decision rules for R&D. Total R&D budgets appear to be based on current and recent earnings, managers' intuitive assessments of technical opportunities, and constraints on the rate of growth of R&D operations.

Despite the fact that formal investment analysis is infrequently used in R&D decisions, the present value of dollar returns to R&D across the entire industry should approximate the present value of R&D costs. Although R&D managers may not follow strict rules, companies whose investments do not return enough to cover the cost of capital will ultimately fail, while those whose investments return more than enough to cover the cost of capital will gradually expand their investments.

raise substantial R&D capital in external capital markets when future prospects look promising. Between July 1990 and July 1991, over \$2.6 billion was raised by the biotechnology industry from external financing sources, almost all of it for health care applications (65).⁹

Established pharmaceutical firms do not fire almost all of their investment needs, not just R&D, with internal cash flows from current operations (285). Internal funds may carry a lower cost of capital for complex investments like R&D, because outside investors are at a disadvantage in being able to assess the potential returns on R&D projects and will therefore demand a higher expected return on their money to cover the risk of being misled by company managers (170,189). The more complex the R&D, the more these information disparities are likely to raise the cost of external sources of capital.

A higher cost of external capital than of internal funds would explain companies' clear preference for internally generated cash flows when they have access to them. If the effective cost of capital is lower for firms that have high cash flows, more R&D projects would pass the present value test and be undertaken. Thus, the availability of internally generated funds may increase the amount of R&D that is performed over what the R&D levels would be if all such funds had to be raised in external capital markets.

How much more R&D is conducted because established pharmaceutical firms use cash flows to fund their investments depends on how much higher the cost of capital for outside funds is. The size of external capital market investments in the biotechnology industry (which has low current operating cash flows) suggests that much of the R&D currently financed in established firms through internally generated cash would be undertaken even if these cash flows were unavailable.

R&D COSTS: THE EVIDENCE

Although the investor always looks ahead in making R&D decisions, R&D cost estimates are retrospective. R&D costs can change quickly as underlying scientific, technical or regulatory conditions change, so it is dangerous to predict much about the future, or even about the costs of projects under way today, from studies of past R&D costs. OTA looked at the existing studies of R&D costs and also at recent trends in some critical components of the cost of bringing new drugs to market.

The costs of bringing a new drug to market rightly include those for projects that were abandoned along the way. Since investors could not have known beforehand which projects would succeed and would not knowingly have invested in the losers, these 'dead-end' costs are unavoidable costs of R&D.

The full cost of bringing a new drug to market can be thought of as the minimal payoff required from the drugs that successfully reach the market required to induce investors to lay out the money at each step of the way. To measure the full cost of past R&D projects, all outlays required to achieve the successes must be compounded (or capitalized) to their present value on the day of market approval at an interest rate equal to the cost of capital.

The full cost of bringing a new drug to market calculated in this way is much higher than the amount of money companies must actually raise to fund R&D projects. To pursue R&D, companies must raise only enough money to cover the actual outlays for successful and unsuccessful projects. Estimating the full cost of bringing a new drug to market, by contrast, provides a way of gauging how much money must be earned from the successful drugs, once they reach the market, to justify the research outlays.

⁹ The sources of external financing used by biotechnology firms change from year to year. In the past, R&D Limited Partnerships were an attractive financing mechanism, but changes in federal tax law took away their advantage. In 1991, initial public offerings were the major source of funds. Venture capital was less important than in previous years. Small biotechnology companies look to strategic alliances with traditional pharmaceutical firms for sources of financing when other sources are unavailable (65).

The present value of full R&D costs has three components:

- Cash outlays required to produce the successes (and to pay for the abandoned projects along the way),
- Timing of the cash outlays, and
- Opportunity cost of capital for each specific R&D investment.

There is only one way to get information on both the amount and timing of cash outlays required to produce a successful NCE: take a large and representative sample of R&D projects and, for each project, record incurred costs month-by-month until the project is either abandoned or approved for marketing. Then, outlays over time can be converted to their present value in a particular reference year at the appropriate cost of capital. The present value of outlays per approved NCE is the average cost of bringing an NCE to market.

This project-level approach was used in a pair of studies pioneered by Ronald Hansen (175) and updated and extended by Joseph DiMasi and colleagues (109). The frequent contention by industry spokesmen that it costs \$231 million (in 1987 constant dollars) to bring an NCE to market (326) is the central result of the DiMasi study (109). In 1990 constant dollars, the cost would be \$259 million.¹⁰

The main problem with this approach is that accurate data on the costs and time required to reach specific milestones in the R&D process, and rates of success or abandonment along the way, are proprietary. Researchers must depend on the ability and willingness of companies to supply detailed data on R&D project costs and histories. Hansen and DiMasi relied on surveys of 14 and 12 U.S.-based pharmaceutical firms, respectively, that were willing to provide estimates of R&D outlays and timing for the samples of newly synthesized NCEs. The researchers could not

audit these estimates for accuracy or consistency across companies.

Early in this assessment, OTA determined that it would be infeasible to mount an independent project-level study of R&D costs. Although Congress has the power to subpoena company data, pharmaceutical companies have actively resisted providing it to congressional agencies. In the past, the U.S. General Accounting Office (GAO) tried to obtain data on pharmaceutical R&D (and other) costs but was ultimately foiled after many years of effort that involved decisions in the U.S. Supreme Court. (See appendix D for a legal analysis of congressional access to financial data.) Although business confidentiality arguments are not sufficient to block a congressional subpoena (423), such arguments can result in protracted negotiations over whether or not the information will be kept confidential and the scope of the documents that must be turned over. The pursuit of data from a number of companies would be very costly and take many years.

OTA's approach to R&D cost assessment relied on a detailed analysis of the validity of the Hansen and DiMasi studies. First, OTA examined the validity of the methods used to estimate each component of R&D costs (cash outlays, project time profiles, and success rates). Second, OTA tested the consistency of the resulting estimates with corroborative studies. Third, OTA examined whether the rate of increase in real (i.e., inflation-adjusted) R&D cost implied by the two studies is consistent with data on trends in major cost drivers, such as the number of subjects of clinical trials, biomedical research personnel costs, and animal research costs.

■ Cash Costs Per Success

Hansen examined a probability sample of about 67 NCEs originated by U.S.-based pharmaceutical companies first entering human clinical trials from 1963 through 1975. DiMasi and colleagues studied a sample of 93 such NCEs first entering human trials from 1970 through 1982.

¹⁰ In this OTA report, all estimates of R&D costs and returns are expressed in 1990 constant dollars and were calculated by OTA using the GNP implicit price deflator.

Total cash outlays per successful new NCE were estimated at \$65.5 million (in 1990 dollars) by Hansen and at \$127.2 million by DiMasi, a 94 percent increase in estimated outlays per successful new drug over the period of the two studies. The two studies suggest that real (inflation-adjusted) R&D cash outlays per successful NCE increased at an annual rate of about 9.5 percent.

The increase in cash outlays per success was moderated by an improvement in the success rate of NCEs over time. Whereas Hansen projected only 12.5 percent of the NCEs would ultimately get FDA approval for marketing, DiMasi and colleagues estimated that about 23 percent of the projects would be successful. Without this improvement, the reported increase in cash outlays per success would have been even higher.

OTA found two principal threats to validity of the methods used to estimate cash outlays per success: 1) the small number of NCEs in the samples, especially in the Hansen study; and 2) the reliance on unverifiable cost data that responding companies supplied. Although most companies were capable of estimating the costs associated with discovery and development of particular NCEs with reasonable accuracy, inherent differences in the structure of cost-accounting systems across companies introduce potential inconsistency and bias. More importantly, any company that understood the study methods and the potential policy uses of the study's conclusions could overestimate costs without any potential for discovery. Thus, the motivation to overestimate costs cannot be discounted.

Because of these threats to validity, OTA looked for corroborative evidence on cash outlays per success. Aggregate annual data on industry R&D spending and NCE approvals in the United States are readily available and reasonably verifiable. In a study using industry-level spending data, Wiggins estimated R&D cash outlays per successful NCE at \$75 million (in 1990 dollars) (\$20).

Wiggins' sample of approved NCEs corresponds roughly in time to Hansen's sample of NCEs first entering clinical testing, but for

technical reasons Wiggins' sample may be somewhat more recent and therefore more costly to develop than the drugs in Hansen's study. (See chapter 3 for an explanation.) On the other hand, Wiggins studied the costs of producing all NCEs, not just those originated by U.S.-based firms. NCEs licensed from other firms probably cost the firm that acquires them less to develop. Thus, Wiggins' estimate of R&D costs maybe too low for self-originated drugs. OTA concluded, therefore, that Hansen's estimate of \$65.5 million in cash outlays per successful drug is reasonably accurate and perhaps even slightly low.

A similar analysis was not available to cover the time period of DiMasi's study, but OTA checked the results of the DiMasi study against data on aggregate R&D spending by the U.S. industry and the total number of self-originated NCEs introduced by these companies. OTA's check revealed a substantial consistency between aggregate R&D spending estimates and the cash outlays per NCE estimated by DiMasi study (see chapter 3 for details).

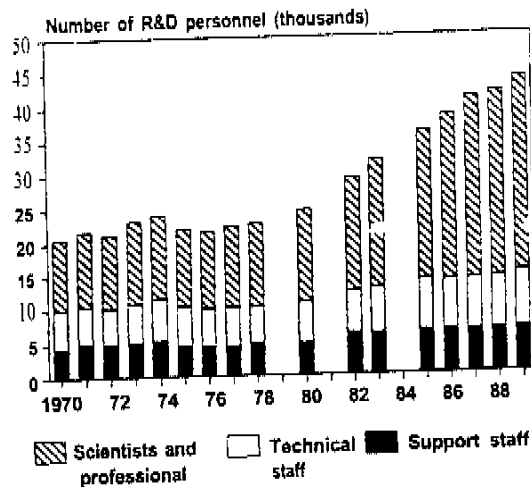
OTA also examined whether trends in three R&D cost drivers—the costs of research personnel, the size of clinical trials, and the cost of animal research—were consistent with the estimated increases in cash R&D outlays per successful NCE between the periods that Hansen and DiMasi studied.

R&D PERSONNEL

The number of R&D personnel employed by PMA-member firms remained fairly constant throughout the 1970s but grew rapidly beginning in 1980 (figure 1-1). Most of this growth was in scientific and professional personnel, which numbered about 12,000 in 1977, but increased to almost 29,000 by 1989. At the same time, inflation-adjusted salaries of biological scientists did not increase.

How much of the increase in employment in the 1980s reflects increased labor inputs per successful NCE, versus adjustments for a larger field of NCEs entering each phase of clinical testing or a greater commitment to basic research,

Figure 1-1—Research and Development Personnel in Pharmaceutical Companies, 1970-89



SOURCE: Office of Technology Assessment, 1993, based on Pharmaceutical Manufacturers Association Annual Survey Reports.

cannot be answered with available data. The most that can be said is that trends in employment of research personnel are consistent with a substantial increase in R&D cash outlays per NCE for those NCEs first entering clinical research in the

late 1970s and early 1980s, the later part of the period covered by the DiMasi study.

ANIMAL RESEARCH

Trends in the cost of animal research are even more difficult to gauge. Some tentative evidence suggests that the number of animals used in pharmaceutical research may have declined between the 1970s and the 1980s, especially in the earliest stages of pharmaceutical R&D, when compounds are being screened for their pharmacologic activity. Any decline in the use of animals was accompanied by a dramatic increase in the cost of conducting animal tests, however. Table 1-1 shows the inflation-adjusted cost of conducting specific animal studies in 1980 and 1990 in eight animal testing laboratories. The costs of virtually all kinds of animal studies increased dramatically over the period. These data suggest that the cost of studies involving animal subjects has increased dramatically, but the ultimate impact on the cash costs per successful NCE cannot be gauged because of uncertainties about trends in the volume of testing, about which there is little information.

Table 1-1—Price of Animal Studies^a (\$ 1990 thousands)^b

Study	Estimated price in 1980	Price range in 1990	Fold Increase	Number of Labs providing information
Acute rats.	\$0.8	\$ 4-5	5-6.25	8
28-day toxicity in rats.	15	30-65	2-4.3	8
Subchronic rats.	38	55-143	1.4- 3.8	8
2-year rat bioassay.	384	250-575	.7- 1.5	5
Teratology rats.	23	52-70	2.3- 3.0	5
Acute monkey.	14	39-62	2.8- 4.4	6
Subchronic monkey.	74	108-184	1.5- 2.5	6
Acute dog.	2.3	22-51	9.6- 22.1	7
Subchronic dog.	46	72-147	1.6- 3.2	7

^a Each laboratory surveyed was given an identical protocol on which the price is based. The "cost" includes profit as well as all direct and indirect costs. Laboratories surveyed were Hazleton, Bioresearch, IIT, TSI Mason, Biodynamics, Pharmakon, PRI, and IRDC.

^b All prices were adjusted to 1990 dollars using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, based on W.G. Flamm and M. Farrow, "Recent Trends in the Use and Cost of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, DC, April 1991.

CLINICAL TRIAL SIZES

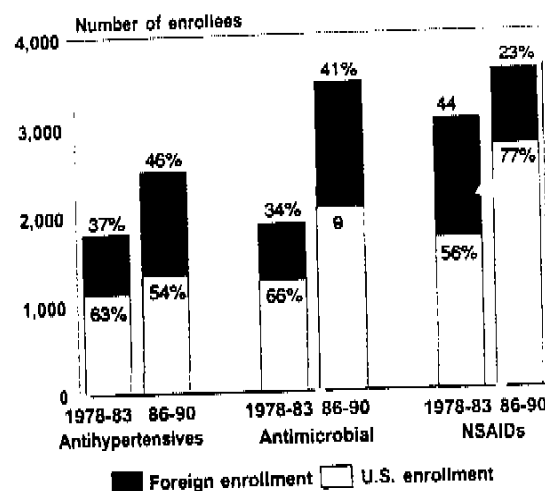
Pharmaceutical executives claim that the number of people enrolled in clinical trials has increased dramatically over time. A rapid increase in trial sizes would be consistent with an increase in the estimated cost of phase III clinical trials from \$5.7 million for each NCE entering the phase in Hansen's study to \$14.3 million in DiMasi's study (in 1990 dollars). Part of the explanation for such an increase may be a change in the mix of drugs under testing from those for acute illness to those for chronic illness. Drugs for long-term use often require larger trial sizes.

Even within specific categories of drugs, however, the number of people enrolled in trials seems to have increased. OTA surveyed pharmaceutical companies for the size of clinical trials conducted prior to FDA approval for NCEs in three classes with a large number of approved drugs: antihypertensives, antimicrobial, and nonsteroidal anti-inflammatory drugs (NSAIDs). We compared NCEs approved for marketing 1978-83 with those approved between 1986 and 1990. Figure 1-2 shows the average number of subjects entered in trials up to the point of NDA submission.

Although the time periods covered in the clinical trial survey do not correspond exactly to the Hansen and DiMasi research periods,¹¹ the survey results do show that the number of subjects in clinical trials increased in the period between the later years of the Hansen study and the later years of the DiMasi study, even within reasonably homogeneous therapeutic categories.

That the number of subjects in foreign countries increased faster than did the number of U.S. subjects in two categories suggests that part of the observed increase in research costs is due to the globalization of research strategies over time. Other industrialized countries increased their requirements for premarket approval during the 1970s, and U.S. firms may have become more aggressive in seeking early approval for NCEs in other countries. These forces would gradually

Figure 1-2—Mean Number of Subjects Enrolled in Clinical Trials Prior to Submission of NDA for NCEs Approved in 1978-83 and 1986-90



KEY: NCE = new chemical entity; NDA = new drug application;
NSAIDs = nonsteroidal anti-inflammatory drugs

SOURCE: Office of Technology Assessment, 1993.

compress total R&D expenditures into the pre-NDA period.

The increase in clinical trial sizes within the therapeutic categories that OTA studied is not big enough to explain the almost three fold increase in the average cash outlay for NCEs that entered phase III clinical trials between the Hansen and DiMasi studies. Trial sizes were not very different across categories, even though antimicrobial drugs are more frequently for acute conditions, while antihypertensive drugs and NSAIDs are more frequently for chronic conditions. The per-patient cost of conducting trials must have increased dramatically. OTA could not independently verify whether this cost increased as fast as the Hansen and DiMasi studies imply.

OTA FINDINGS ON THE VALIDITY OF ESTIMATED CASH COSTS

OTA concluded from the corroborative evidence available at the aggregate spending level

¹¹ Hansen's study years (NCEs first entering testing between 1963-75) correspond roughly with introductions in 1970-81. DiMasi and colleagues' study years (1970-82) correspond roughly with introductions in 1978-90.

that the estimates of cash outlays per successful NCE made by DiMasi are reasonably accurate. Hansen's early estimate may have been too low, suggesting that the rate of increase in costs between the periods covered by the two studies may have been overstated. Data on rates of change in three illustrative components of R&D-- personnel, animal research costs, and clinical trial size--are consistent with a substantial increase over the period covered by the studies in the real cash outlays required to bring a new drug to market.

■ Present Value of Cash Outlays

The present value of the R&D cost at the point of market approval depends on the timing of R&D expenditures over the life of projects and the cost of capital for the investments over time. R&D outlays occur over a long and, according to the Hansen and DiMasi studies, lengthening period of time. Hansen estimated the total R&D time was 9.6 years; DiMasi, 11.8 years.

OTA concluded from a review of study methods that the length of the clinical research and the regulatory review periods estimated by Hansen and DiMasi are very accurate. Estimates of the length of the preclinical period (the time required to discover and prepare a compound for testing in humans) are much less precise and might even be a bit too short, especially in DiMasi's study.

Neither Hansen nor DiMasi adjusted the cost of capital for the greater risk of R&D projects. Both studies took the weighted average company cost of capital in established pharmaceutical firms as their basis for calculating the fully capitalized cost of R&D. Hansen assumed a real cost of capital of 8 percent; DiMasi, 9 percent. As discussed above, the average inflation-adjusted cost of capital for pharmaceutical firms as a whole varied throughout the period but was probably closer to 10 percent. The cost of capital for R&D projects is even higher and increases the earlier the stage of R&D.

OTA estimated that the cost of capital for early R&D may be up to 4 percent higher than the cost of capital for manufacturing plant and equipment. OTA recalculated the fully capitalized cost of R&D at the point of market approval with a cost of capital that decreases linearly from 14 to 10 percent from the beginning to the end of R&D projects.¹² The estimate for the DiMasi study increased from \$259 million (in 1990 dollars) to \$359 million. Thus, a reasonable upper bound on the fully capitalized cost of R&D for a successful NCE at the time of market approval is \$359 million.

■ After-Tax Costs of R&D

The effective cost to a company of bringing a new drug to market is substantially less than the cost estimates discussed above because they do not account for the taxes the company is relieved of paying when it invests in R&D. The net cost of every dollar spent on research must be reduced by the amount of tax avoided by that expenditure. These tax savings result from both deductions and tax credits. (When R&D is successful and produces marketable products, the company will pay extra taxes as a result, and these dollar returns must also be reduced by the amount of the extra taxes.)

Like all business expenses, R&D is deductible from a firm's taxable income. This tax deduction reduces the cost of R&D by the amount of the company marginal tax rate. Because of the size and sales of most major pharmaceutical firms, the bulk of their taxable income would fall into the highest tax bracket. This marginal tax rate fell from 48 to 46 percent between 1971 and 1986. At 46 percent, every dollar spent on R&D would cost the company only \$0.54. With the passage of the Tax Reform Act of 1986 (Public Law 99-514), the marginal rate fell to 34 percent, thus effectively raising the cost of each dollar of R&D to \$0.66. Corporations also pay State income taxes which also can be reduced with business deductions.

¹² Because 10 percent is a weighted average cost of capital across all of the company's investments, investments in manufacturing facilities probably have a cost of capital below 10 percent. Therefore, this estimate may overestimate the cost of capital for R&D at each stage.

Pharmaceutical firms can also use special tax credits available only for firms that perform certain kinds of R&D. Since 1981, the tax code has included a tax credit for increases in qualifying R&D expenses. This credit carried a statutory rate of 25 percent until 1986, when it was reduced to 20 percent. Quantifying the extent to which this credit reduces the cost of R&D for pharmaceutical firms is impossible for two reasons: 1) the credit depends on the amount that a firm increases R&D expenditures, not on the level of those expenses; and 2) expenditures on supervisory activities or overhead do not qualify for the credit.

When it can be used, the most powerful tax credit affecting pharmaceutical R&D is the Orphan Drug credit. The Orphan Drug Act of 1983 (Public Law 97-414) provides a 50-percent tax credit for qualifying clinical R&D on drugs that have received an orphan designation. An important limitation of the Orphan Drug credit, in addition to its being limited only to clinical R&D and orphan drugs, is that the credit cannot be saved and used in future years if the company has no current taxable income. Thus, small startup companies, often the developers of orphan drugs, cannot use it.

OTA recalculated DiMasi's estimate of R&D cost per NCE taking account of tax savings. The sample of NCEs that DiMasi studied underwent the great bulk of discovery and development at a time when the marginal tax rate was 48 or 46 percent. Adjusting for tax savings (using a 46 percent rate) without any other changes reduces the net cash outlays per NCE from \$127.2 million to \$65.5 million, and adjusting for tax savings reduces the total costs capitalized to the point of market approval at a 10 percent cost of capital from \$259 million to \$140 million (table 1-2). When the cost of capital is permitted to decrease linearly from 14 to 10 percent over the life of the R&D projects, the net after tax cost is \$194 million. OTA concluded that for NCEs whose clinical research began in the period 1970-82—the time period of the DiMasi study—the upper bound on after-tax capitalized cost of

Table 1-2—After-Tax R&D Costs Estimated by DiMasi Under Different Assumptions About the Cost of Capital (\$ 1990 millions)

Cost of capital (%)	Before-tax savings	After-tax savings (46%)
9	\$258,650	\$139,671
10	279,112	151,045
Variable (10 - 14)	359,313	194,029

a All assumptions, given in 1990 dollars, were adjusted for inflation using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, estimates adapted from J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

R&D required to bring an NCE to market is \$194 million. The effect of the R&D tax credit, the U.S. investment tax credit and the orphan drug tax credit was not taken into account.

Had today's marginal corporate tax rate (34 percent) been in effect at the time the NCEs in DiMasi's study were developed, the net after-tax cash outlay per successful NCE would have been no more than \$80.1 million, and the full cost capitalized at a 10 percent cost of capital would be \$171 million. At today's tax rate, with a cost of capital decreasing from 14 to 10 percent over the life of the project, the average cost of developing a new drug would be no more than \$237 million.

■ R&D Costs Today and in the Future

The fully capitalized cost of bringing a new drug to market is very sensitive to four components of the R&D process:

1. The preclinical cash outlays required to discover or design a potential therapeutic compound and then to determine whether it is worth testing in humans;
2. The success rate at which compounds move from phase to phase of clinical research and ultimately to the market;
3. The scope and size of clinical trials; and
4. The time a drug spends in regulatory review.

The studies of R&D costs that OTA reviewed were for compounds that entered human clinical testing in the 1960s and 1970s. Much has changed since then in the technical and regulatory conditions governing pharmaceutical R&D, making inappropriate any extrapolation from the experience of that generation of drugs to those entering clinical testing today.

The technology of drug discovery and design has changed enormously. Whereas researchers used to screen a large number of chemicals for the few that cause a desired chemical or biological reaction, they now frequently engage in a more deliberate process based on knowledge of biological function. (See chapter 5 for a description of trends in the science and technology of drug discovery.)

For example, many drugs are discovered today through analysis of drug receptors, molecules that bind with specific agents to change cellular function. Agents that can bind with the receptor or that inhibit the binding of a naturally occurring substance become potential drug candidates. The process of finding such molecules involves determining the shape of a receptor and designing the agents that will affect its function.

Understanding the structure of receptor molecules has become the key to many areas of drug discovery. Most receptors are large proteins with multiple regions of interest. Expensive analytic instruments and computers are necessary to define the shape of these molecules. Companies have justified investments in nuclear magnetic resonance spectroscopy and x-ray crystallography, two techniques for analyzing the shape of large molecules, as tools to determine the three-dimensional structure of receptor sites, a process that will improve the prospects for developing drugs that fit into the desired sites. These and other techniques of structure-activity analysis require massive computer power to analyze data and construct three-dimensional molecular images.

One outgrowth of the expanding base of knowledge about disease mechanisms is the endless supply of possible research directions that



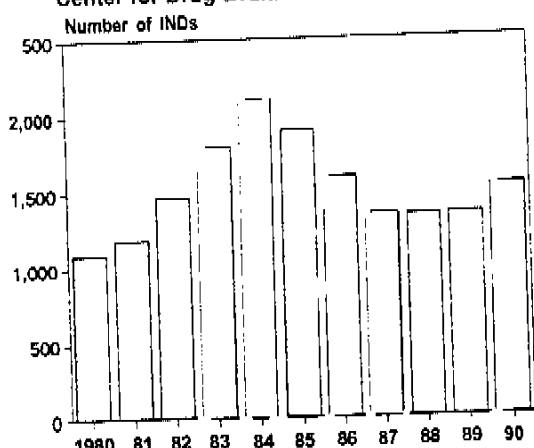
Photo credit: BRISTOL-MYERS SQUIBB COMPANY

Computers facilitate the design of new enzyme inhibitors by enabling scientists to graphically visualize the structure of targeted molecules.

this knowledge creates. For example, drug receptors that reside on the surface of cells mediate many of the most important functions in the body and are extremely promising targets for future drug development. Enzymes that mediate biochemical reactions and genetic materials also offer up a plethora of drug development targets. There are too many possible targets, however, for scientists to understand the structure and function of each. Thus, at the same time that new research technology advances understanding, it expands the choices and increases the chances of dry holes in the discovery phase.

The impact of the rapid advances in the science and technology of drug discovery on the costs of R&D is impossible to predict. While investment in instrumentation and computers has clearly increased, the impact on the cost of R&D depends largely on what these advances do to the productivity of the discovery phase of R&D. If, dollar-for-dollar, the new drug discovery techniques produce more new drugs worthy of clinical testing, and if these new drugs are more likely to successfully jump the hurdles in each phase and

Figure 1-3—IND Applications Received by the Center for Drug Evaluation and Research



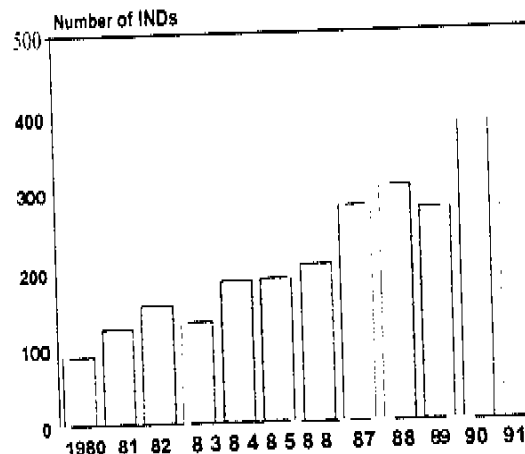
KEY: IND = investigational new drug.

SOURCE: Office of Technology Assessment, 1993 based on U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistical Report: 1991*, U.S. Department of Health and Human Services, Rockville, MD, 1992.

reach the market, then the costs of R&D per successful drug could decline. On the other hand, if the explosion of possible research avenues makes the discovery process even more chancy, then the cost of bringing a new drug to market could increase. Both trends could occur at the same time, with unpredictable consequences for overall R&D costs.

The results of the changes under way in the process of drug discovery are evident in the number of investigational new drug (IND) applications submitted to the FDA in recent years. INDs increased throughout the 1980s, with the highest rate of growth coming in the investigation of biological (biotechnology drugs and other biological products) (figure 1-3 and figure 1-4). The shift in drug development toward biotechnology-based drugs means that discovery and development costs may be very different from those that

Figure 1-4—IND Applications Received by the Center for Biologics Evaluation and Research



SOURCE: Federal Coordinating Council for Science, Engineering, and Technology, Office of Science and Technology Policy, Executive Office of the President, *Biotechnology for the 21st Century: A Report by the FCCSET Committee on Life Sciences and Health* (Washington, DC: U.S. Government Printing Office, February 1992), and data provided by the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration.

came before, but without better data on clinical trial sizes, regulatory delays, and other regulatory requirements, it is impossible to say whether on the whole the shift toward biotechnology-based drugs will increase or decrease the costs of R&D.

The most recently available data on the success rate from first filing of an IND application to FDA approval shows an improvement over time. At OTA's request, the FDA compiled information on INDs filed for new molecular entities (NMEs) in the periods 1976-78 and 1984-86.¹³ The percent of NMEs that reached the NDA filing stage within 54 months of the first filing of a commercial IND increased from 6.8 to 11 percent, and although few drugs filing INDs in the later period have yet been approved, the percent reaching approval within 54 months is also higher for drugs entering testing in the later period. Improvements in

¹³ FDA staff were very helpful to OTA and provided staff to collect and analyze IND data according to OTA's specifications. The amount of effort that FDA staff were required to spend on this analysis revealed some of the limitations of FDA's electronic databases for tracking trends in drug development. FDA's automated information system does not link applications for INDs with applications for NDAs, so any tracking of drugs from IND to approval, rejection or discontinuation of the project must be done by manual search of the IND and NDA files.

success rates can have a substantial moderating effect on realized R&D costs per success, but the data available so far are too limited to conclude much about ultimate success rates for drugs that recently entered testing.

OTA's data on the length of the regulatory period (from the NDA filing to approval) show no improvement in recent years, but efforts to harmonize the regulatory review process across countries and recently passed legislation that will increase FDA staff available for new drug review in return for "user fees" from sponsors (Public Law 102-571) could shorten the period overall. If the ultimate success rate for NCEs does not improve, getting successful drugs through the FDA regulatory period faster will only modestly reduce the capitalized cost of R&D.

In short, OTA cannot predict how R&D costs will change in the future. The rapid advances in science and technology, the shift in the nature of drugs under development, and the new FDA regulatory initiatives all promise to influence R&D costs, but the net direction of the effect of all of these influences together is beyond predicting.

RETURNS ON R&D: THE EVIDENCE

The costs of R&D are most meaningful in comparison with the dollar returns they produce. Measuring dollar returns accurately is difficult because the life of a new NCE maybe 20 years or longer and the costs of producing, distributing and marketing the NCE can be estimated only imprecisely. Nevertheless, several authors have tried to measure the present value on the day of market approval of dollar returns on NCEs (\$159,215,500). The studies produced widely differing findings, ranging from high present values of dollar returns to present values that lie below the fully capitalized cost of R&D. The studies

differ widely because they each examined NCEs that came to market in different periods and made different assumptions about the value of product sales over the product life cycle and the cost of manufacturing, distribution and marketing.

OTA conducted an independent analysis of the dollar returns on R&D using recent data on annual revenues from NCEs and the costs of producing, marketing and distributing these products. OTA analyzed the return on NCEs introduced to the U.S. market in the years 1981-83. OTA chose this relatively brief period for two reasons. First, the period corresponds in time to the R&D period studied by DiMasi and colleagues. Second, we had access to data on drugstores and hospital sales only for this particular set of NCEs (97).¹⁴

■ The Sales Curve

Figure 1-5 shows U.S. sales to hospitals and drugstores in constant 1990 dollars in each year after market introduction for NCEs introduced in the years 1981-83 and, for the sake of comparison, in earlier and later periods as well. Although OTA had access to only 1 year of data on NCEs introduced from 1984 through 1988, that one data point suggests that, after adjusting for inflation, U.S. sales of NCEs in the early years after approval continued to steepen throughout the 1980s.

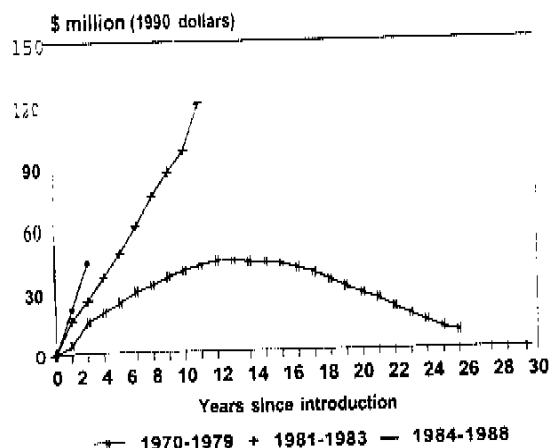
To predict the sales curve for the 1981-83 NCEs beyond the 9th year, OTA examined trends in effective patent lives and in the loss of revenue after patent expiration.

EFFECTIVE PATENT LIFE

The effective patent life is the elapsed time between FDA approval for marketing of a new drug and expiration of the last patent or market exclusivity provision that effectively protects the original compound from generic competition. Two new Federal laws passed in the 1980s, the

¹⁴ Gaining access to sales data on NCEs was a major problem for OTA throughout the course of this study. Detailed data are collected by proprietary organizations on U.S. and worldwide sales of NCEs, and these data are sold to subscribers. IMS America, Inc. and IMS International, Inc. are market research firms that, among other activities, conduct ongoing surveys of pharmaceutical product sales and prescriptions for sale to subscribers. The cost to OTA would have been prohibitive, however. For example, IMS International, Inc. quoted a preliminary price to OTA for estimates of the total non-U.S. sales between 1981 and 1990 for NCEs introduced between 1981-83 at \$75,000 to \$125,000 (\$39).

Figure 1-5-Average U.S. Sales of New Chemical Entities Introduced in 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):804-82, 1, 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.

Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Orphan Drug Act of 1983 (Public Law 97-414), increased the effective patent life for new compounds.

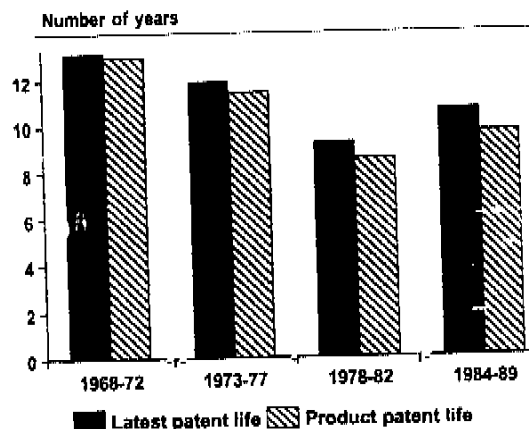
Figure 1-6 shows recent trends in the average effective patent life for NCEs. As expected, after declining steadily throughout the 1970s and early 1980s, effective patent life rebounded somewhat in the years since 1984.

The end of the effective patent life does not always mark the end of exclusive marketing for the NCE. Some compounds may not have generic competitors for several years after the patent expires, either because of delays in FDA approval of generic versions or because the total market for the drug is too small to induce generic manufacturers to enter the market. Occasionally a process patent issued after the original patents will protect a product for some time.

Product line extensions, such as new once-a-day dosage forms, have become increasingly important in protecting the original compound's market against generic competition. The 1984 Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) granted a 3-year period of market exclusivity, regardless of patent status, to any product for which new clinical research is required. Thus, if a new sustained release formulation is developed and approved for the originator compound, 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 compound itself.

Companies use the terms of the provision to extend the effective exclusivity period by managing the introduction of new dosage forms to coincide with the expiration of the patent on earlier generations of the compound. Physicians almost always prefer extended-release dosage forms because they increase patients' adherence to the prescription. Increasing company incentives to develop products with these benefits is the rationale for the 3-year exclusivity provision in

Figure 1-6-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.

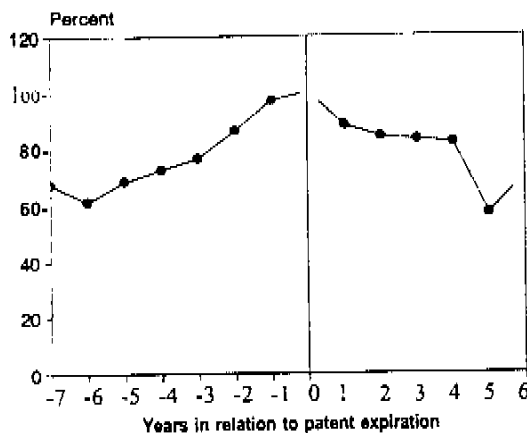
the Drug Price Competition Act. Nevertheless, the introduction of these new products can keep the compound's revenues high for years after the effective patent life ends.

POSTPATENT REVENUES

The Drug Price Competition and Patent Term Restoration Act made FDA approval relatively easy for makers of generic copies of originator drugs after patents or market exclusivities expire. It is widely held that this law led to rapid decline in the originator drug's market share following patent expiration.

OTA analyzed changes in the U.S. market for 35 therapeutic compounds that lost patent protection in from 1984 through 1987 and found that the sales decline is not nearly as steep as is commonly thought—at least not yet. Figures 1-7 and 1-8 show how the compounds' hospital and drugstore sales (in 1990 dollars) and physical units changed before and after the year in which patents expired. Three years after patent expiration, the mean annual dollar sales of the original compound were 83 percent of mean sales revenue in the year of

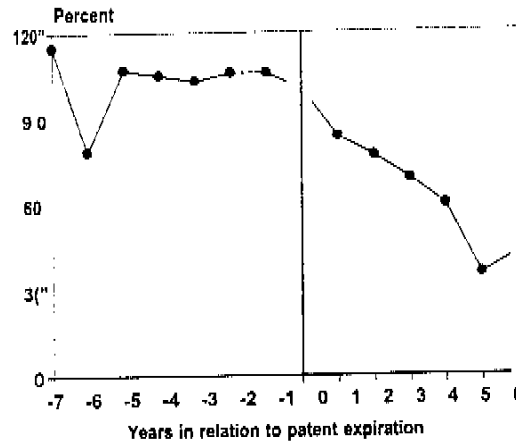
Figure 1-7—Originator Revenue* as a Percent of Originator Revenue in Year of Patent Expiration



*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.

Figure 1-8—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.

patent expiration, while the mean sales volume in physical units was 68 percent of its level in the year of patent expiration.

OTA extended the sales curve beyond the 9th year after U.S. market introduction based on these trends and also made adjustments for sales to other countries and to purchasers other than hospitals and drugstores (see chapter 4 for details). Figure 1-9 shows the projected worldwide sales for NCEs introduced in the United States from 1981 through 1983. OTA assumed that the originator compound would stay on the market only 20 years and that the products are not sold in other countries before they are approved in the United States. Overall, then, the assumptions used to build this projected sales curve were conservative.

■ Costs of Production

Sales revenues from new products must be reduced to reflect the cash outlays required to manufacture and sell them, and the ongoing R&D costs required to produce follow-on products or to justify new uses for the NCE. The net cash flows induce additional tax liabilities as well. OTA estimated these costs using data as available and

subtracted them from the net sales revenues over the life of the compound. (See chapter 4 for details of OTA's method.)

■ Net Cash Flows

The 1981-83 NCEs deliver net cash flows of \$341 million per compound (discounted to their present value in the year of FDA market approval at 9.8 percent per year). The net after-tax value of the cash flows projected for the 1981-83 cohort of new drugs is \$230 million.

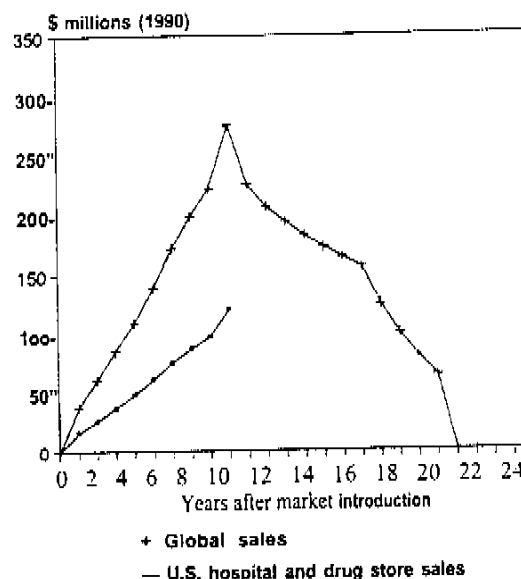
■ Net Return on Investment

These net postapproval cash flows 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 of drugs introduced in the early 1980s is about \$359 million before tax savings, or \$194 million after tax savings are considered (table 1-2). Thus, OTA concluded that the average NCE introduced to the U.S. market in the period 1981-83 can be expected to produce dollar returns whose present value is about \$36 million more (after taxes) than would be required to bring forth the investment in the R&D.

Some of the revenue and cost assumptions underlying this analysis were very uncertain, so OTA analyzed the sensitivity of the estimated returns to changes in critical assumptions. The results are somewhat sensitive to the ratio of global sales (about which we know relatively little) to U.S. sales (about which we know much more). If the ratio of global sales to U.S. sales is much greater than 2, as we have reason to believe it may be, the present value of the cash flows would be even more (after taxes) than is necessary to repay the R&D investment.

The results were not very sensitive to changes in the speed with which originator brand sales decline after patent expiration. If the average sales per compound were to decline by 20 percent per year after patent expiration, the present value of the cash flows would be \$311 million before taxes and \$209 million after taxes, still above the full after-tax cost of R&D. Fully 6 years after the

Figure 1-9—Estimated Average Global Sales Profile Per New Chemical Entity Introduced in the United States, 1981-83



SOURCE: Office of Technology Assessment, 1993; based on data from P. Coppinger, "Overview of the Competitiveness of the U.S. Pharmaceutical Industry," presentation to the Council on Competitiveness Working Group on the Drug Approval Process, Washington, DC, December 12, 1990.

passage of the Drug Price Competition and Patent Term Restoration Act there is no evidence that the rate of sales decline for originator compounds after patent expiration is approaching this rate.

What does it mean to have the average revenue per compound deliver \$36 million more in present value than was needed to bring forth the research on the drugs in the cohort? OTA estimated that excess returns over R&D costs would be eliminated if the annual revenue per compound was reduced by 4.3 percent over the product's life.

These estimates are rough predictions of the actual returns that the 1981-83 cohort of NCE's will earn over their full product lives. OTA attempted to be conservative in measuring returns, but the estimate is subject to measurement error whose magnitude is not easily assessed.

More importantly, the analysis illustrates how volatile net returns can be for drugs introduced in different time periods. This report documents how rapidly both worldwide revenues and the average cost of R&D for each new NCE can change. The wide variation in R&D costs and sales revenues across individual drugs means that estimates of both average R&D costs and returns could vary over short periods of time.

TOTAL PHARMACEUTICAL INDUSTRY RETURNS

Another more indirect way to measure returns on R&D is to estimate the profitability of research-intensive pharmaceutical companies. 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 (IRR), the interest rate at which the net present value of all cash flows 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, one would expect to see increased investment in the industry, including R&D, as investors enter to reap the high rewards. In a dynamically competitive industry, IRRs much greater than the cost of capital can not persist indefinitely. If abnormally high profits persist for a long time, 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 compared with the cost of capital would lead to disinvestment in the industry, including R&D.

The annual financial reports of public companies contain estimates of company profit rates based on accounting records. For example, net income as a percent of total "book value" of assets is a commonly used benchmark of firm profitability (301). Companies themselves report

this ratio in their annual financial statements and compare their return on assets in one year with that in previous years. Other commonly used profit ratios, such as net operating 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 industry with those of firms in other industries (301,457). The ready availability of publicly reported and independently audited data and the widespread use of these measures by companies themselves invites such comparisons. By these conventional accounting measures, the pharmaceutical industry looks very profitable compared with other industries (301,457). But these comparisons are limited in two important ways.

First, accounting profits are poor measures of true IRRs. Revenues and costs recognized in accounting statements don't correspond very well to actual cash flows. And, because profits are computed over a limited period, they don't adjust properly for the time profile of cash flows from various investments made in previous times or for payoffs that won't occur until after the profit measurement period.

Second, even if accounting profits are corrected to correspond more closely to IRRs, differences in rates of return among industries might reflect differences in their riskiness (and hence in the cost of capital). Simple comparisons that do not address differences in risk among industries can be misleading.

OTA commissioned a study comparing the IRR of 54 U.S.-based research-intensive pharmaceutical companies with the IRRs of two control groups, each with 54 firms, selected to be most similar to the pharmaceuticals on certain financial characteristics (27) (see chapter 4 for details). The accounting profit rate for the pharmaceutical companies was 4 to 6 percentage points per year higher in the study period (1976-87) than for the control firms.

The contractors used a new technique that adjusts accounting profits to obtain a closer approximation of IRRs. IRRs cannot be measured

with precision, because assumptions are required about the time profile of returns on investments, but across a wide range of assumptions about timing of cash flows, the estimated internal rate of return in the pharmaceutical firms over the 12-year study period (1976-87) was on average 2 to 3 percentage points higher per year than the internal rate of return in either control group.

The contractors did not address the question of whether a 2 to 3 percentage point difference in internal rates of return can be explained by differences in the cost of capital between pharmaceuticals and control firms. If investment in the pharmaceutical industry is riskier than in the control firms, then the cost of capital will be higher. OTA calculated the difference in the cost of capital between the pharmaceutical industry and each of the two control samples. OTA found that the cost of capital for the pharmaceutical industry was higher by 0.7 percentage points per year than one of the control samples, but lower by 1.6 percentage points than the other.

The cost of capital can vary widely over time with underlying interest rates and expected inflation, so precise measurement of each group's cost of capital over the study period is impossible. In addition, OTA's method may be subject to biases in measurement. We used the same method 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. Therefore, OTA concluded that returns to the pharmaceutical industry as a whole over the 12-year period from 1976 to 1987 were higher by 2 to 3 percentage points per year than returns to nonpharmaceutical firms, after adjusting for differences in risk.

INDUSTRY RESPONSE: INCREASING R&D

In an industry with a large number of active competitors, high returns (compared with the cost of capital) should attract new investment capital. Data on aggregate domestic and worldwide pharmaceutical R&D reveal a rapid increase in real R&D spending beginning in 1980 and continuing today. Total R&D conducted by U.S.-based pharmaceutical companies in 1975 was about \$1.1 billion; by 1990, this spending had grown to between \$7.9 billion and \$8.1 billion (table 1-3). After adjusting for inflation, U.S.-based companies' foreign and domestic R&D spending increased at about 9 percent per year between 1975 and 1990. The rate of increase accelerated over the period. Before 1980, U.S. companies' real worldwide R&D spending increased by only 5 to 6 percent per year. Between 1985 and

Table 1-3--Aggregate Pharmaceutical Foreign and Domestic R&D, Selected Years (\$ billions)

	1975	1980	1985	1987	1990	Annual percent rate of change		
						1975-80	1980-85	1985-90
<i>Compustat</i> ^a								
Current dollars.....	\$1.10	\$2.08	\$4.20	\$5.53	\$7.90	13.60/o	15,1740	13.51/0
Constant 1990 dollars ^b	2.44	3.19	4.98	6.19	7.90	5.5	9.3	9.7
<i>Pharmaceutical Manufacturers Association</i> ^c								
Current dollars.....	1.06	1.98	4.08	5.51	8.13	13.2	15.6	14.8
Constant 1990 dollars.....	2.36	3.03	4.83	6.17	8.13	5.2	9.8	10.9

^aFigures are based on a total of 133 firms listed in the Compustat file under Standard Industrial Code (SIC) code 2834 in at least 1 year between 1971 and 1990. The number of firms vary from year to year due to firms' entry and exit from SIC 2834.

^bAdjusted by GNP implicit price deflator.

^cR&D expenditures reported by Pharmaceutical Manufacturers Association member firms.

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

Table 1-4—HMG-CoA Reductase Inhibitors Currently or Formerly Under Development

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.
crilvastatin	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.
00-476	British Bio-technology	Series of compounds under development; preclinical.
BMV-22566	Bristol-Myers Squibb	Preclinical studies.
SQ-33600	Bristol-Myers Squibb	Preclinical studies, discontinued.
BMV-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.

SOURCE: Office of Technology Assessment, 1993.

1990, they increased at about 10 percent per year.¹⁵ These data do not even fully reflect the rapid increase in spending by small research-intensive biotechnology companies, a phenomenon that began in the early 1980s.

OTA's findings on returns to pharmaceutical R&D and to the industry as a whole explain why R&D expenditures have risen so fast throughout the 1980s. Investors 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 R&D.

What will this increased investment mean for pharmaceutical returns in the future? Some of the research dollars are pursuing the development of me-too NCEs that will compete with similar

products already on the market. For example, the first HMG-CoA reductase inhibitor—a new class of drugs that lowers cholesterol—was approved for marketing by the FDA in 1987. Today, three compounds are approved for marketing, one is awaiting approval, and 12 others are under active development (table 1-4). Over time, the entry of new products should dampen the potential returns on research into new NCEs in this class, as companies spend more and more money developing competing products and fighting for a share of the market.

Some research dollars are pursuing new classes of drugs, which may supplant older therapies or create new markets in areas where there was before no effective therapy. Several companies have current research programs on drugs for Alzheimer's disease, a major cause of dementia in older people, but so far no drug can offer substantial improvements in patient functioning. (See chapter 5, box 5-E for more information on

¹⁵ Because spending in various countries must be converted into a common currency, exchange rate changes can affect reported spending. The devaluation of the dollar after 1985 maybe responsible for some of the unusually high increase in total spending reported in recent years.

the status of research into drug therapies for Alzheimer's disease.) Successes in these areas could mean a new cycle of high returns to the pioneer and early me-too compounds but lower returns to the later entrants who must compete for market share in the class.

PAYMENT POLICY AND RETURNS ON R&D

Future returns to the research-intensive pharmaceutical industry depend not only on the opportunities created by scientific research, but also on the regulatory and market conditions that will govern the sale of pioneer and me-too products. OTA examined recent trends in payment policies that affect the market for new pharmaceuticals.

Sales of new ethical drugs depend on physicians' decisions to prescribe them and on patients' decisions to buy them. Physicians and patients base these decisions on judgments about a drug's quality and price compared with the quality and price of existing alternatives. The tradeoff between perceived quality and price depends on many factors, including the severity of the disease or condition for which a drug is intended, evidence of its effectiveness compared with alternative courses of action, the availability of close substitutes, and the effectiveness of advertising and promotion in convincing doctors the drug is the right choice for the patient (86).

■ Importance of Health Insurance in Determining Demand

When a patient's health insurance plan covers prescription drugs, the balance between perceived quality and price tips in favor of quality. While it protects consumers from uncontrollable and catastrophic expenses, health insurance also reduces the effective price of health care services and products. By reducing patients' out-of-pocket cost, health insurance makes them less sensitive to price than they would otherwise be (516).

Insurance coverage for prescription drugs in the United States changed during the 1980s in two ways that made the demand for prescription drugs

Table 1-5--Percent of U.S. Population With Outpatient Prescription Drug Coverage, 1979 and 1987^a

	1979	1987
People under 65.....	71-73	73-77
People 65 and over.....	36	43-46
Total.....	67-69%	70-74%

^a A detailed memorandum describing OTA's methods in preparing this table is available upon request.

SOURCE: Office of Technology Assessment, 1993; based on sources listed in table 10-2.

even less sensitive to price than it was before. First, the percent of Americans with outpatient prescription drug benefits increased, albeit modestly, over the 1980s, from 67-69 percent in 1979 to 70-74 percent in 1987, the latest year for which good data are available (see table 1-5). Although few Americans had insurance plans that covered outpatient drugs in full, the mere existence of insurance coverage makes patients less sensitive to price than they would be without such coverage (294).

Second, the structure of outpatient prescription drug benefits changed markedly over the period. In the past, almost all nonelderly people with outpatient drug benefits had "major medical" plans with an overall annual deductible that had to be met before insurance would help pay for any services or drugs. By 1989, 30 percent of these people had policies that required freed copayments for prescription drugs instead of including them in the overall deductible (table 1-6). The vast majority of people with freed copayments per prescription in 1989 paid \$5 or less per prescription (35). The insurance company picked up the rest of the bill regardless of its amount.

The switch from overall deductibles to freed copayments for prescription drugs means a richer insurance benefit structure for prescription drugs. For people whose annual medical expenses lie below their plan's annual deductible (commonly \$200 or \$250 per year), a flat copayment for prescription drugs means lower out-of-pocket prescription drug costs than do major medical restrictions. Even when patients do meet the deductible in a year, many would have higher

Table 1-6-Limitations of Prescription Drug Benefits Among Nonelderly People With Private Health Insurance Covering Prescription Drugs

	1977 ^a	1989/1990 ^b
Full coverage	3%	3%
Separate limits (copayments) ^c	9	30
Overall limits (major medical) ^d	88	61
Other limits ^e		7

^a Results based on 1977 National Medical Care Expenditure Study Survey of employers and insurers of individuals under 65 years of age.

^b Results based on U.S. Bureau of Labor Statistics 1989 and 1990 surveys of employers.

^c "Separate limits" refers to restrictions applicable only to prescription drugs, such as a copayment for each prescription.

^d "Overall limits" refers to restrictions applicable to a broader set of medical services. For example, a major medical policy may carry a \$100 deductible and 20-percent coinsurance rate that applies to all covered services, not just prescription drugs.

^e Other limits include policies that combine fixed copayments with overall limits.

SOURCE: Office of Technology Assessment, 1993, based on data from P.J. Farley, *Private Health Insurance in the U.S. Data Preview #23*, DHHS Publication No. (PHS) 88-3406, 1986, U.S. Department of Health and Human Services, National Center for Health Services Research and Health Care Technology Assessment, September 1986; U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Medium and Large Firms, 1989*, Bulletin 2363 (Washington, DC: U.S. Government Printing Office, June 1990); U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Small Private Establishments, 1990*, Bulletin 2388 (Washington, DC: U.S. Government Printing Office, September 1991); U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in State and Local Governments, 1990* (Washington, DC: U.S. Government Printing Office, February 1992).

out-of-pocket prescription drug costs under a major medical plan than under a fixed copayment.¹⁶

The impact of these improvements in prescription drug insurance benefits shows up in insurance reimbursements. The percent of total outpatient prescription drug spending in the United States paid for by insurance increased substantially, from 28 to 44 percent, between 1977 and 1987 (figure 1-10). The same trend holds among

elderly Americans, for whom private insurance paid for about 36 percent of outpatient prescription drug expenses in 1987 compared with only 23 percent in 1977.

Most private and public health insurers have little power to restrict physicians' prescribing decisions. Private insurers generally cover all prescription drugs the FDA has licensed for sale in the United States (35). Thus, FDA approval is a *de facto* insurance coverage guideline. If the physician orders a specific compound, the insurer routinely pays its share of the costs.

Despite the fact that many compounds, though protected from generic competition by patents or other market exclusivity provisions, compete for market share with similar compounds, that competition tends to focus on product characteristics, such as ease of use, favorable side-effect profiles, or therapeutic effects, and not on price.¹⁷ Companies spend a great deal on this product competition. One major U.S. pharmaceutical company reported recently that about 28 percent of its sales went for marketing (advertising and promotion) expenses (119a).

Emphasizing product competition over price competition is a rational strategy for companies operating in a market that is not very sensitive to price differentials among similar compounds. If prescribing physicians will not be swayed by lower prices, it would be foolhardy for firms to set prices for their products much lower than those of competitors. Unless or until the demand for prescription drugs becomes more price sensitive, the benefits of the competitive R&D on prices will not be felt.

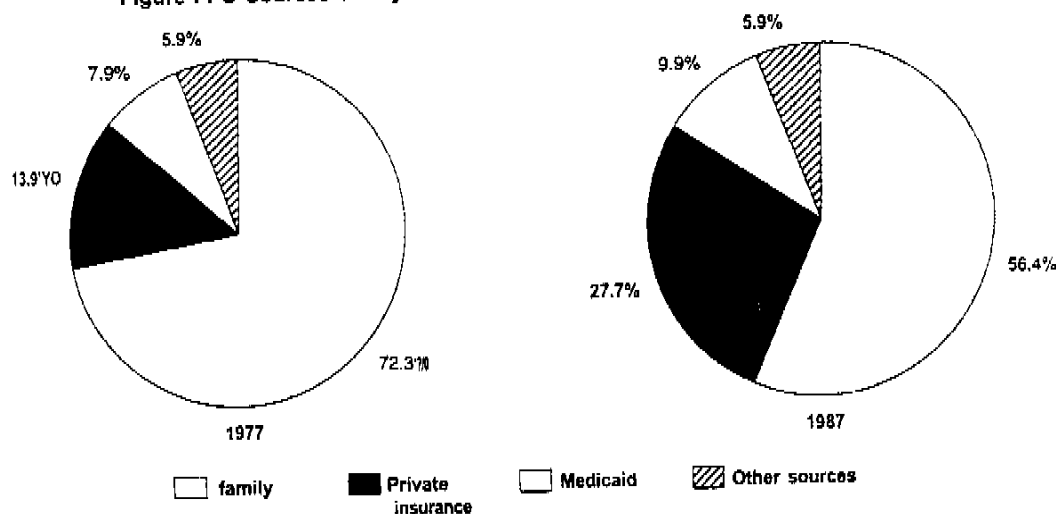
■ Different Buyers Pay Different Prices

Ethical drugs are sold through multiple distribution channels, and companies can set different

¹⁶ In most major medical plans, the insured person is responsible for sharing 20 percent or more of the cost of services above the deductible. Under a 20 percent major-medical cost-sharing requirement, any prescription with a price greater than \$25 would cost the insured person more than it would a patient with the most frequent separate copayment rate. For example, a \$30 prescription would cost someone with a major medical policy and a 20-percent cost-sharing requirement \$6, whereas the typical cost under a flat copayment would be only \$5.

¹⁷ This is not to say that price competition among competing brand-name compounds is entirely absent, or that prices of pioneer drugs are established without any concern for their effect on patient demand. Anecdotal reports suggest that new NCEs are often launched at lower prices compared with competing drugs, but the discounts are typically not high and they rarely lead the manufacturers of other compounds to meet price reductions.

Figure I-1 Sources of Payment for Prescribed Medicines in the United States



a Other sources include workmen's Compensation, Medicare, other State and local programs, and any other source of payment.

SOURCE: Data from J.F. Moeller, Senior Project Director, U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, Rockville, MD, personal communication, Mar. 12, 1991; J.A. Kasper, Prescribed Medicines: Use, Expenditures, and Sources of Payment, Data Preview (Washington, DC: U.S. Department of Health and Human Services, National Center for Health Services Research, April 1982).

prices to different kinds of buyers. For example, companies can sell direct to HMOs¹⁸ or large hospital chains and offer lower prices than they charge for drugs sold to community pharmacies. The ability to charge different prices to different kinds of buyers is referred to as price discrimination. Price discrimination increases profits by separating buyers who are price sensitive from those who are not.

Price discrimination in pharmaceutical markets takes its most extreme form when companies offer expensive drugs free or at reduced charge to people who cannot easily afford them because they lack insurance and have low incomes. Many pharmaceutical firms have developed such programs in recent years (327,458). In a separate background study under this project, OTA examined CeredaseTM, a new drug for a rare inherited disease, whose high annual cost (at least \$58,000

per year for the drug alone for the remainder of the patient's life) threatens to exhaust many patients' lifetime insurance benefits (141).¹⁹ The company that makes CeredaseTM provides the drug free to patients who have exhausted their benefits or do not have health insurance. Although these programs respond in a compassionate way to a real need, they also separate the market into two components—one with very high price sensitivity (uninsured people) and one with very low price sensitivity (insured people). The CeredaseTM program is similar in its consequences to offering a patient a lifetime supply of the drug in exchange for the remaining value of his or her insurance coverage plus associated premiums.

PRICE-SENSITIVE BUYERS PAY LOWER PRICES

HMOs, particularly those with tight organizational structures, have both the incentive and the

¹⁸ Unlike traditional fee-for-service insurance plans, HMOs (sometimes referred to as "prepaid health plans") collect a set premium for each member, but charge either nothing or a relatively small amount for each individual service. People enrolled in the HMO must receive their health care from providers designated by the HMO.

¹⁹ Approximately 71 percent of private insurance policy beneficiaries face a lifetime maximum benefit of \$1 million or less (491).

ability to influence physicians' prescribing practices to take account of cost as well as quality.²⁰ They can do this by establishing restrictive "formularies," lists of drugs that can be prescribed by participating physicians without special appeals or approvals. The power to impose limitations on prescribing has given HMOs purchasing clout with manufacturers and, over the past few years, has led manufacturers to offer substantial price discounts to some of these organizations. When there are several close substitutes in a therapeutic class, the HMO can use the formulary as a bargaining chip to exact price concessions from producers.²¹

Hospitals also have an incentive to establish formularies for drugs administered to inpatients. In 1983, Medicare adopted a new "prospective payment system" that pays hospitals on the basis of the admission, not the specific services each patient uses.²² This system created incentives for hospitals to reduce both length of stay and the cost of services offered per stay, including drugs. The incentive to develop restrictive formularies is limited, however, because most insured nonelderly hospitalized people pay for hospital care on the basis of charges for individual products and services. Pharmacy charges are passed on to the private insurance company. Nevertheless, the number of hospital pharmacies adopting formularies increased steadily in the mid-1980s. The percent of hospitals with a well-controlled formu-

lary increased from 54 percent in 1985 to 58 percent in 1989 (101.412).

PRICE-SENSITIVE BUYERS GAIN FROM PRICE COMPETITION

The success of some HMOs and hospitals in getting price concessions from manufacturers of single-source drugs (i.e., those with patent protection) attests to the potential for price competition to lower the cost of drugs to patients or their insurers. For price competition among close therapeutic alternatives to be effective in a market with price-sensitive buyers, enough similar competing products must exist to allow providers to choose among alternatives on the basis of price as well as quality. Me-too products, often derided as not contributing to health care, are therefore necessary to obtain the benefits of price competition in segments of the market that are price sensitive.

Most of the new drugs entering the world market in recent years have offered little therapeutic advantage over pre-existing competitors. A 1990 European study of the therapeutic value of new drugs first introduced in at least one of seven industrialized countries²³ between 1975 and 1989 found that only 30 percent of all NCEs were classified by a group of experts as "adding something to therapy" compared with compounds already on the market (37).²⁴ The rest fell into categories that could be called me-toos. About 42 percent of those NCEs originated in the

²⁰ Enrollment in HMOs grew from 4 percent of the population in 1980 to 14 percent in 1990 (209). But, many HMOs do not give their doctors incentives to economize in drug prescribing. A recent review of seven HMOs found the plan were structured so that the prescribing physician never bore financial risk for prescription drug costs (5-15). These HMOs were all individual practice associations or networks. These kinds of HMOs tend to have looser fiscal controls than staff-model HMOs, where physicians are either employees or partners in the organization. In 1990, pharmaceutical sales to staff-model HMOs made up 2.4 percent of the pharmaceutical market.

²¹ The power of certain classes of purchasers to exact discounts was recognized by the framers of the 1990 Medicaid Rebate law (Public Law 101-508) which requires manufacturers to offer Medicaid the "best price" (i.e., lowest price) they offer to private purchasers if the manufacturer wants to sell its products to the Medicaid patient. The strategy may have backfired, however, because manufacturers eliminated many such discounts to HMOs and hospitals when they found that they would lose the amount of the discount on a large part of their total market (431). (Medicaid makes up 10 to 15 percent of the market for outpatient drugs.)

²² Medicare beneficiaries accounted for 45.2 percent of inpatient hospital @s in 1989 and for 33 percent of the discharges (164).

²³ The seven countries were the France, Germany, Great Britain, Italy, Japan, Switzerland, and the United States.

²⁴ Each product was evaluated by [several] experts, including doctors, pharmacists, chemists, and pharmacologists, each working within the therapeutic area of the new product. The study report contains little detail on the methods used to rate drugs, so the validity of the ratings has not been verified. Over 65 percent of all compounds introduced in 1980-84 and rated as offering added therapeutic benefit were marketed in at least four of the seven industrialized countries, compared with only 31 percent of the drugs judged to offer no additional benefits.

Table 1-7—New Chemical and Biological Entities Entering the World Market by Therapeutic Category, 1975-89

	1975-79		1980-84		1985-89	
	Total therapeutic gain	% with	Total therapeutic gain	% with	Total therapeutic gain	% with
Antibiotics	25	36%	27	44%	33	27%
Anticancer	14	64	16	50	14	36
Antivirus	3	33	2	50	8	75
Cardiovascular	35	43	36	33	68	27
Nervous System	29	35	32	25	24	17
Anti-ulcer	3	67	7	29	15	20
Hormones	12	17	13	39	10	50
Anti-inflammatory	26	23	30	13	19	5

SOURCE: P.E. Barral, "Fifteen Years of Pharmaceutical Research Results Throughout the World 1975-1989," (Antony, France: Foundation Rhone-Poulenc Sante, August 1990).

United States were judged to offer therapeutic benefits, so well over one-half of all drugs introduced in the United States were judged to offer no therapeutic benefit. Over the entire study period, the majority of drugs in almost every therapeutic category did not "add something to therapy" (see table 1-7). These results suggest the supply of therapeutic competitors is large and the potential for price competition in those segments of the market with price-sensitive buyers is potentially vast.

The problem with me-too drugs is not that they are sometimes imitative or of modest therapeutic benefit. Imitation is an important dimension of competition, and the more choices consumers have, the more intense will be the competition. The personal computer industry provides a clear illustration of how rapid improvements in quality can coincide with steep price reductions (46). The problem with me-too drugs is that a large part of the market in the United States is very insensitive to price and does not get the full benefits of price competition that would be expected from the availability of an array of similar products.

GENERIC COMPETITION GIVES INSURERS MORE CONTROL OVER DRUG PRICES

Once a drug loses patent protection, it is vulnerable to competition from copies whose therapeutic equivalence is verified by the FDA. These generic competitors compete largely on the

basis of price, since they can claim no quality advantage over the brand-name drug.

Private and public health insurers have initiated programs to encourage dispensing of cheaper versions of multisource compounds (those with generic equivalents on the market). These strategies include using mail-order pharmacies, waiving beneficiaries cost-sharing requirements when prescriptions are filled with generic versions, or refusing to pay more than a certain amount for a drug with a generic competitor. Medicaid, the health insurance program for the poor, mandates substitution with cheaper generic drugs unless the prescribing physician specifically prohibits it in writing on the prescription form.

These programs have substantially reduced brand-name compounds' unit sales and revenues, but it takes several years after the compound's patent expires for the full brunt of generic competition to be felt (see figures 1-7 and 1-8). Indeed, OTA found that 6 years after patent expiration, brand-name drugs still held over 50 percent of the market in physical units (table 1-8).

PRICING SYSTEMS DIFFER ACROSS COUNTRIES

Not only is the market for prescription drugs segmented among different classes of buyers in the United States, but it is also segmented internationally. Pharmaceutical companies

Table 1-8-Originator's Market Share for 35 Compounds Losing Patent Protection 1984-87

Year	Dollar Sales	Unit Sales ^a
-7	100%	100%
-6	99	100
-5	99	100
-4	99	100
-3	99	100
-2	99	100
-1	99	100
0	95	94
+1	86	73
+2	84	65
+3	84	57
+4	85	51
+5	83	44
+6	85	62

^a Year 0 is the year of patent expiration.

^b Unit sales are measured in defined daily dose.

SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, "Economic Impact of Multiple Source Competition on Originator Products," contract paper prepared for office of Technology Assessment, U.S. Congress, December 1991.

charge different prices for the same drug in different countries (439a,457).

Most other industrialized countries have universal health insurance that includes prescription drugs, so patients' demand for drugs is not very sensitive to the price charged. Nevertheless, the prices paid tend to be more strictly controlled by the third-party payers in these countries than in the United States. Drug payment policy in each of these other countries is governed by two potentially conflicting objectives: minimization of health insurance prescription drug costs and encouragement of the domestic pharmaceutical industry. National prescription drug payment policies represent a blend between these objectives. In other industrialized countries, drug payment policy is generally developed with explicit recognition of the two policy objectives.

Virtually all of the five countries whose pharmaceutical reimbursement systems OTA reviewed—Australia, Canada, **France**, Japan, and the United Kingdom—use some mechanism for controlling the price of single-source as well as multiple-source drugs. Four of the

five countries do so directly by setting payment rates for new drugs based on the cost of existing therapeutic alternatives. The pricing policies in these countries reward pioneer, or "breakthrough," drugs with higher prices than me-too drugs, although they accomplish this objective through different mechanisms, and the prices of breakthrough drugs may still be low in comparison with those obtained in the United States.

These countries obtain reduced prices for new drugs through pricing systems that do not use market mechanisms or price competition to determine the demand for prescription drugs. They use price regulation or price control as a substitute for price competition. The importance of politics in determining prices in countries with price controls is illustrated by the favorable prices explicitly granted to locally developed or manufactured products in some of the countries whose pharmaceutical payment systems OTA examined. In contrast, prices in the United States are determined in the market, but, because of the structure of health insurance, a large part of the market gives inadequate consideration to price in making prescribing and purchasing decisions.

■ Implications of Increasing Price Competition for R&D

If the price-sensitive segment of the market for health care services in the United States continues to grow, either through natural evolution or through a national health reform initiative, revenues from many existing and new drugs would fall as price competition expands. The United States accounts for 27 percent of total spending on ethical pharmaceuticals among countries in the Organization for Economic Cooperation and Development and is the largest single national market. Changes in the U.S. market therefore can have a major impact on worldwide pharmaceutical revenues.

A decline in expected revenues would reduce a drug's expected returns and would certainly cause R&D on some new drug products to be discontinued or reduced. The market may not support as many close competitors in a therapeutic

tic class. R&D on me-too drugs could decline as firms come to realize that the makers of pioneer drugs will respond to competition with price reductions of their own.

Research on pioneer drugs could also decline as firms realize that the returns to the winner are likely to be reduced by early price competition from me-too drugs. Fewer competitors might follow each specific line of research, and companies might choose to specialize in certain scientific or medical areas. How much dynamic changes in the R&D environment might affect aggregate R&D investment is impossible to predict with any certainty. Much would depend on the supply of technological opportunities, regulatory barriers to new drugs, and the present availability of acceptable therapies for specific diseases. It is likely, however, that industrywide investment in R&D would grow more slowly or even decline.

Systems that control prices, especially those that control the launch prices of new drugs, also affect R&D, and it is even more difficult to predict the directions or overall magnitude of their effect on R&D. The effects would depend on how prices were set and how high they are. For example, a system that controlled only the prices of me-too drugs could have effects on R&D that are very different from a system that controlled all new drug prices. Price regulation adds an additional level of uncertainty to the process of R&D which, as a new risk, lowers expected returns from R&D investments.

Would a decline in R&D or a slowdown in its rate of growth be a bad thing? A widely accepted principle is that, left to its own devices, private industry invests too little in R&D. The patent system, which offers temporary monopolies over new products, processes, and uses, is built on this principle (366). The monopoly granted by patents allows firms to charge more for inventions than they could without such protection from competition. Other public policies, such as subsidies and tax policies that favor R&D, are predicated on the assumption that patents alone are insufficient to bring forth the level of R&D that maximizes the general welfare of society. The high direct

Federal subsidies of basic research and training of scientific personnel are a result of the principle that private industry has inadequate incentives to engage in basic research.

Despite this general principle, there is no theoretical basis for predicting that R&D is always lower than the socially optimal level. When R&D takes place under conditions of rivalry, as it certainly does in pharmaceuticals, that rivalry can lead to wasteful and duplicative R&D efforts and lower returns to the public as a whole than to private industry (102,170,222, 338,365,418). That is, the public can end up paying too much for the benefits it receives from the competitive R&D. The relationship between private and social returns depends on many factors, such as the cost of innovation, the profitability of existing products the innovation will replace, how easy it is for rivals to copy innovations, how easy it is for a new company to enter a particular field, and how rival companies react to each others' moves (222,365).

Statistical studies of the private and social rates of return on R&D in other industries generally find rates of return on R&D to the public as a whole substantially greater than private rates of return on R&D (166). Yet, in the pharmaceutical industry health insurance weakens the role of price competition, so findings from other industries are not germane to pharmaceuticals. Because the "appropriate" level of demand for prescription drugs in the United States cannot be inferred from the existing level of demand, it is impossible to know whether on the whole there is too much R&D or too little R&D on new drugs.

THE REGULATION OF PHARMACEUTICAL R&D

Numerous regulations at both the State and Federal level in the United States control the products of the pharmaceutical industry. But, the Federal Food, Drug, and Cosmetic (FD&C) Act has the greatest influence over the drug R&D process. As the agency charged with implementing this body of law and regulation, the FDA has

slowly grown in importance since its inception in 1938.

Regulatory requirements unquestionably increase the cost and time necessary to bring a new drug to market. Because it is difficult to sort out the effects of regulation from other factors that could alter drug R&D time and costs, however, the effect cannot be quantified. Most studies of the impact of FDA regulation on the cost of bringing new drugs to market examined the effect of the 1962 Kefauver-Harris Amendments, which added the requirement that drugs must be shown to be effective as well as safe before they can be approved for marketing. Little attention has been paid to how more recent management and regulatory changes at the FDA altered the resources required for the drug R&D process.

Since 1977, the FDA has undertaken a number of initiatives to simplify and clarify the new drug review process and to expedite the review of new drugs identified by the agency as therapeutically important. Most of the initiatives were implemented in the late 1980s, so their effects, if any, on the cost or speed of the R&D process may not yet be discernible.

One initiative designed to make important but not-yet-approved drugs for life-threatening conditions available quickly to the public is the Treatment Investigational New Drug (IND) program. Established in 1987, the Treatment IND program codifies a long-standing agency practice of releasing investigational drugs to practicing physicians on a case-by-case basis for use in the treatment of immediately life-threatening diseases where no immediate alternative treatment exists. To date, 23 drugs have been made available under this program.

A unique feature of the Treatment IND program is that the sponsoring firm may sell the drug to patients under the program at a price that covers not only manufacturing and handling costs, but R&D as well. Five Treatment INDs have so far



Photo credit: NATIONAL INSTITUTES OF HEALTH

Aerial view of the National Institutes of Health campus in Bethesda, Maryland. Over \$2 billion is spent each year on intramural research in Federal biomedical laboratories.

been supplied by the sponsor at a price. In the case of alglucerase, the drug's manufacturer generated \$5 million in revenue through the Treatment IND while the drug was still in the R&D process (141).

Selling investigational new drugs under the Treatment IND program allows companies to generate returns on their R&D investment before the FDA has certified that the drug is safe and effective. The FDA, the agency responsible for reviewing companies' requests to charge under a Treatment IND, lacks the expertise and the authority to determine whether cost data provided by companies are accurate and justify the price they wish to charge. In the case of Ceredase™, the price charged under the Treatment IND (\$3.00 per unit) was only slightly lower than the drug's price after the drug was approved for marketing (\$3.06 per unit in 1991 net of free goods, uncollected revenues and rebates to the Medicaid program) (141).

FEDERAL TAX POLICIES AFFECTING PHARMACEUTICAL R&D

In 1987, drug companies claimed \$1.4 billion in credits against their Federal income taxes.²³ Of

²³ This does not include over \$900 million foreign tax credits. Unlike other tax credits which are designed to simulate certain types of behavior among taxpayers, foreign tax credits are simply a mechanism to prevent U.S. firms from being taxed twice on income earned in another country.

this amount, only about \$90 million was for credits whose specific purpose was to stimulate R&D. The tax credit for conducting business operations in U.S. possessions such as Puerto Rico accounted for over \$1.3 billion in foregone taxes from the pharmaceutical industry in 1987. Pharmaceutical companies are the main beneficiary of this tax provision, claiming just over 50 percent of all dollars claimed under this credit in 1987. Overall, the tax credits reduced the amount of taxes drug companies would have otherwise owed the U.S. Government by 36 percent and equaled 15 percent of the industry's taxable U.S. income.

Although the aggregate value of R&D-oriented tax credits *earned* by the industry is relatively small (\$105 million), the pharmaceutical industry is a major user of such credits (table 1-9). The pharmaceutical industry earned almost 10 percent of all R&D oriented tax credits in 1987. The industry's differential ability to use such credits attests to its greater research orientation than other industries and the rapid growth of its

research expenditures. These credits represent an indirect subsidy to the industry for undertaking activities deemed to be in the public interest.

FEDERAL SUPPORT FOR PHARMACEUTICAL R&D

The Federal Government is the mainstay of the country's health sciences enterprise. Health-related R&D reached almost \$10 billion in 1990. Some of this money is spent in government laboratories on intramural research (\$2.6 billion in 1990), but the vast majority of this federally sponsored health-related R&D is awarded to universities and private nonprofit laboratories through extramural grants and contracts. The money not only supports scientists but also has paid for much of the infrastructure of health research facilities in use today at American universities. The Federal Government also provides the bulk of support for training scientific personnel. Some of that training is paid for under research grants and contracts, but in 1989 alone

Table 1-9—Research Tax Credits Earned by the Pharmaceutical Industry in 1987^a

	Aggregate credit claimed (\$ thousands)	Number of firms claiming credit	Aggregate credit earned as a percent of aggregate earned by all industries
Research and experimentation tax credit^b			
Firms with assets <\$50 million.....	\$6,455	147	3.10/0
Firms with assets > \$50 million and < \$250 million. .	2,042	9	2.0
Firms with assets of \$250 million or more.	88,878	28	12.6
All firms.....	97,375	184	9.6
University-based basic research tax credits			
Firms with assets < \$50 million.....	3	90	17.3
Firms with assets > \$50 million and < \$250 million. .	0	39	0.0
Firms with assets of \$250 million or more.	2,257	43	10.7
All firms.....	2,260	990	6.4
Orphan drug tax credits			
Firms with assets <\$50 million.....	0	0	—
Firms with assets > \$50 million and < \$250 million. .	0	0	—
Firms with assets of \$250 million or more.	5,358	8	84.3
All firms.....	5,358	8	84.3

^a Estimates for tax year 1987 are from the LLS. Treasury's Statistics of Income (SOI) sample weighted to reflect relevant populations. Pharmaceutical industry is defined as SOI industry group 2830 minus firms with assets of \$250 million or more and known not to be involved in pharmaceuticals. Tax Credits *earned* are not equivalent to tax credits *claimed* because the former does not reflect insufficient tax liability in current year, or carry-forwards from previous years.

^b Research and experimentation credit estimates are net of university-based basic research credit.

SOURCE: Office of Technology Assessment, 1993. Estimates provided by U.S. Congress, Joint Committee on Taxation.

the NIH spent \$256 million on 11,585 training awards in the life sciences.

Although most of the research supported by the NIH and other Federal health research organizations is aimed at understanding the basic mechanisms of health and disease, the Federal Government supports a substantial amount of research directly targeted to the development of new pharmaceuticals. OTA estimates that NIH and other Public Health Service (PHS) research organizations spent approximately \$400 million in 1988 for preclinical pharmaceutical research and \$250 million for clinical pharmaceutical R&D. This spending includes 13 targeted drug development programs whose specific mission is to develop new medications for particular diseases or conditions.

The pharmaceutical industry is particularly adept at mining the motherlode of knowledge created by government-sponsored biomedical research and training. The pharmaceutical industry benefits from the Federal investment in extramural and intramural research through its collaborations with universities and academic researchers and through its contacts with intramural researchers at NIH and other Federal health research laboratories. In the past decade, Federal technology transfer policies have provided new incentives for both federally supported academic researchers and government researchers to collaborate with private industry in bringing to the market patentable inventions arising from federally supported research.

■ Federal Technology Transfer Policy

Today, any inventions arising out of the substantial Federal support to academic research are essentially the property of those institutions. The Bach-Dole Patent and Trademark Act of 1980 (Public Law 96-517) gave universities, nonprofit organizations and small businesses the rights to inventions resulting from research supported with Federal grants. This law was in part the impetus for the creation in the 1980s of university-sponsored enterprises whose purpose is to commercialize biomedical research findings.

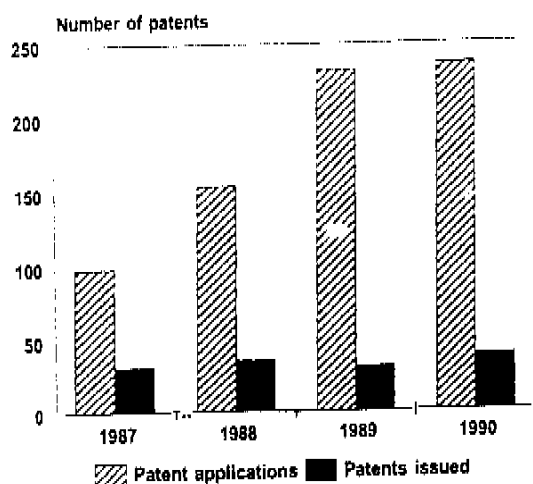
Universities and nonprofit organizations can license their valuable inventions to commercial enterprises and share in the revenues the inventions generate.

Inventions arising from the \$2.6 billion annual investment in intramural Federal research have also been encouraged by legislation whose purpose is to foster commercial innovation. The Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480) made the transfer of Federal technology to the private sector a national policy and a duty of Federal laboratories. Among its provisions, the act required that Federal laboratories spend at least 0.5 percent of their research budgets on efforts to transfer technology from the laboratory to the marketplace. Additional legislation in 1984 directed the Department of Commerce to issue regulations governing licensing of technologies developed in Federal laboratories (Public Law 98-620).

These initiatives proved insufficient to bring about the desired amount of formal interaction between government and industrial scientists. The Federal Technology Transfer (FIT) Act of 1986 (Public Law 99-502) followed with financial and professional incentives to Federal scientists to actively pursue the commercialization of their inventions. The act also requires Federal agencies to share at least 15 percent of royalties from any licensed invention with the inventing scientists, and it directs agencies to establish cash awards with other personnel involved in productive Federal technology transfer activities.

The legislation also permitted Federal laboratories to enter into formal cooperative research and development agreements (CRADAs) in which a Federal agency provides personnel, services, facilities, equipment or resources (but not money) and a private company provides money, personnel, services, facilities, equipment or other resources for R&D. The law leaves implementation of CRADA policy up to the research agency, but as part of a CRADA the Federal laboratory can agree in advance to grant licenses to the collaborating partner on any inventions resulting from research under the agreement.

Figure I-11—Public Health Service Patent Applications and Patents Issued, 1987-90



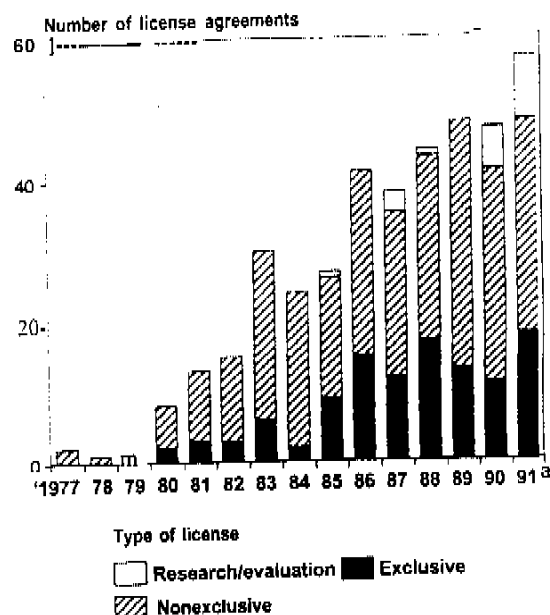
SOURCE: The Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1991.

Early data suggest that the FTT Act may be successful in increasing the patenting of inventions created in Federal biomedical research laboratories. The number of patents filed annually by the Public Health Service (which includes NIH) has grown dramatically since 1987, the first year for which data on PHS patents are available. The number of applications more than doubled between 1987 and 1989 alone (figure I-11).

■ Licensing Inventions from Federal Laboratories

The Federal government has steadily increased the number of licenses issued on its biomedical patents throughout the 1980s (figure I-12). Royalties paid to the inventing agency typically do not exceed 5 to 8 percent of the resulting product sales. The PHS policy is to grant **exclusive** licenses only in cases where substantial additional risks, time and costs must be undertaken by a licensee prior to commercialization (484,486). Otherwise, PHS tries to negotiate nonexclusive

Figure I-12—Licenses Issued by the U.S. Department of Health and Human Services, Fiscal Years 1977-91



^a Number in fiscal year 1991 annualized from the number of agreements reached during first 4 months of the year.

SOURCE: Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1991.

licenses. Firms collaborating with Federal health laboratories under CRADAs, however, may have built into the CRADA at its inception the right to negotiate an exclusive license to any invention arising out of the collaboration. The advent of CRADAs in recent years²⁶ may portend even more exclusive licenses in the future.

Royalty income to PHS agencies from licenses is a small fraction of the total PHS intramural budget. In 1988, the total NIH royalty income was just 0.03 percent of total NIH intramural spending. NIH takes the position that the purpose of royalties is to stimulate technology transfer by "offering an attractive incentive to encourage [PHS] scientists to participate in collaborations

²⁶ 109 separate agreements were signed by the end of fiscal year 1990.

with industry, . . . rather than to augment or replace funds appropriated by Congress for research (75).

The net returns to both the NIH scientists and the commercial firm rise and fall directly with the ultimate price of the product to consumers (individual patients and their private and public health insurers). The PHS policy governing exclusive licenses, including those granted under CRADAs, requires that prices of commercial products be commensurate with 'the extent of 'public investment in the product, and the health and safety needs of the public' (486). The policy further states that licensees may be required to provide 'reasonable evidence' to support their pricing decisions. To date, this policy has been implemented only in one case--the antiviral ddI, manufactured under an exclusive license by Bristol-Myers Squibb.

At present, the PHS has no established mechanism or standards for reviewing the reasonableness of prices for products marketed under exclusive licenses and lacks the legal authority to enforce its policy in cases where prices would be deemed unreasonable.

The need for review of prices of drugs licensed from public agencies results from the failure of the market for prescription drugs to assign appropriate values to new technologies. Because most patients have health insurance policies that pay for a large fraction of the charges for covered drugs and other health care products and services, they may be willing to "purchase" such care even when it is worth less to them than what the seller charges. Insurers have little flexibility in

choosing what pharmaceuticals to cover and what prices to pay.

Although the question of what is a "reasonable" price is subject to differing interpretations, the term is commonly used to mean the price charged does not greatly exceed the full cost of researching, developing, manufacturing, marketing and distributing the drug, where cost includes a return on the investment sufficient to cover investors' risks or failure and opportunity costs of capital.

OTA's contractor study of the costs of developing and manufacturing the drug CeredaseTM demonstrated that determining such costs is a difficult task. Expertise in cost analysis is critical to such a review. Even the best and most sophisticated efforts to assess costs will fall short if they are not based on an audit of detailed cost accounting data. Access to such data is possible only with full cooperation of the company producing the drug.

Implementing PHS's fair pricing clause for exclusive licenses in more than a cursory way could conflict with the Federal goals of technology transfer and the collaborative development of new medicines with industry. When faced with potential government scrutiny of their books and manufacturing processes, some firms may opt not to license drug technology developed at NIH. Whether such reactions would be frequent enough or universal enough to delay the availability of new therapies can only be judged through experience. So far, NIH has been reluctant to take on the task of demanding detailed cost information as part of its technology transfer function.

The Costs of Pharmaceutical R&D 3

This chapter brings together existing evidence on the cost of bringing new pharmaceuticals to market. It begins with background on how to measure such costs and then moves to an assessment of existing studies of research and development (R&D) costs. These studies are retrospective: they estimate the costs of R&D for pharmaceutical products developed and brought to market in the past. R&D costs can change quickly as underlying scientific, technical, or regulatory conditions change, so it is dangerous to predict much about the future, or even about today's R&D costs, from studies of past costs. In the last part of the chapter, the Office of Technology Assessment (OTA) examines recent trends in some critical components of the cost of bringing new drugs to market.

A FRAMEWORK FOR ESTIMATING R&D COSTS

R&D is an investment in a potential future stream of revenues from the sale of successful new drugs. Unlike other kinds of investments, such as a new manufacturing plant, the success of a pharmaceutical R&D investment is highly uncertain and may take many years to be realized. The investors in pharmaceutical R&D must be able to "expect" not only to recoup their actual cash outlays for R&D but also to be compensated for the risk they took of losing their investment altogether and for the time they spent waiting for the investment to pay off. Without such an expectation, no investor would put his or her money on the line.

The full cost of the R&D investment can be thought of as the minimal 'expected' payoff required to induce the investor to lay out the money at each step of the research project. The 'expected' payoff does not mean an assured payoff; rather, it means the minimal payoff required from the drugs that successfully reach the market after taking into account the chances of success and failure and the expected development time involved.



The full cost of bringing a new drug to market, as defined above, is clearly higher than the cash outlays spent to discover and develop successful new drugs. It also includes the cash outlays spent on projects that fail.¹ And, it must include the *opportunity cost of capital*, the rate of interest that dollars invested at a given level of risk must earn in exchange for being tied up in the investment (\$9,285).

The opportunity cost of capital for pharmaceutical R&D is higher than the interest rate on safe investments, such as insured bank deposits or government bonds, but just how high the cost of capital for pharmaceutical R&D projects is depends on how investors evaluate the risks of these investments. (See appendix C for a detailed discussion of the cost of capital.) The risk and, therefore, the cost of capital varies across different projects and even within the same R&D project at different stages of development. The cost of capital for any investment also varies from year to year with underlying changes in the risk-free rate of interest (e.g., on bank deposits). Thus, the full cost of R&D varies widely over time and across projects.

To measure the full cost of bringing a new drug to market, all outlays required to achieve the successes (including spending on projects that fail) must be compounded (or capitalized) at an interest rate equal to the cost of capital, to their present value (or capitalized value) at the date of market approval. For example, \$1 million invested 1 year ago should be worth \$1.1 million today if the cost of capital for that investment was 10 percent per year.

Note again that the full cost of bringing a new drug to market is much higher than the amount of money companies must actually raise to fund R&D projects. To pursue R&D, companies must raise only enough cash to cover the actual outlays associated with the successful and unsuccessful

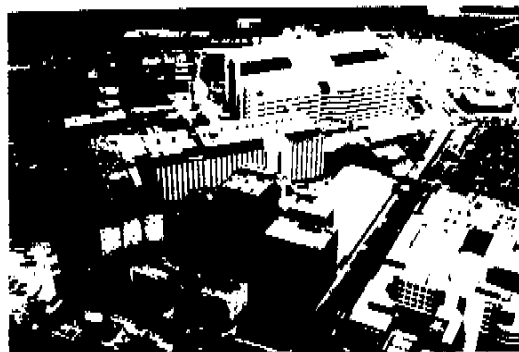


Photo credit: THE UPJOHN COMPANY

R&D expenditures include substantial investment in research facilities and equipment. The Upjohn Company recently built this new addition to its research facilities, the 'white' building located at the top of the photograph. It encompasses more than 700,000 square feet, was constructed at a cost of \$120,000 million, and will house more than 500 scientists.

projects. Estimating the full cost of bringing a new drug to market, by contrast, provides a way of gauging how much money must be earned from the successful drugs, once they reach the market, to justify the research outlays.

EXISTING STUDIES OF R&D COSTS

Two major approaches have been used to estimate the cost of bringing new drugs to market. One approach examines project-level data acquired from pharmaceutical firms. The second approach analyzes R&D expenditures and new products at the industry level. Table 3-1 contains a summary of selected pharmaceutical R&D cost studies of both kinds—project-level and industry-level—listed in the order of the R&D period studied.

Project-level studies try to measure costs incurred at each stage of development and the percent of drugs that will successfully pass each stage, and then use these calculations to arrive at a final cost estimate. The key advantage of the project-level approach is that, if sufficiently

¹ When the full cost of R&D is estimated with historical data, averaging of outlays across winners and losers must take place across the entire industry, or at least a good part of it, because individual companies may have unusual experiences. For example, a company could have mismanaged its research, leading to relatively few successes and high outlays per success. Though investors in that company might have lost money, they need not be rewarded for their bad judgment. The experience of the industry as a whole is a good basis for estimating the true (and uncontrollable) probability of success and failure of R&D projects.

Table 3-1—Summary of Selected Pharmaceutical R&D Cost Studies

Study	Sample years	Estimation method	Data source	Estimated R&D costs	Constant dollar year	Opportunity cost of capital	Preclinical costs	Treatment of unsuccessful projects
<i>Project-level studies</i>								
Schnee, 1972	1950-67 (market introductions)	Average development cost and time for 75 projects marketed in one large firm.	R&D project cost data reported by one firm.	NCEs: \$534,000.	Current dollars	0%	Not included	Not included
Hansen, 1979	1963-75 (projects entering human testing)	181U expenditure profile built for sample of approximately 67 self-originated NCEs, not all successful.	NCE sample and \$54 million R&D project expenditures from 14-firm survey.		1976	8%	Assumed to be \$30 ^a allocated over 3 years prior to IND filing).	Estimated 12.5% NCE success rate.
DiMasi et al. 1991	1970-82 (projects entering human testing)	R&D expenditure profile built for sample of 93 self-originated NCEs, not all successful.	NCE sample and \$231 million R&D project expenditures from 12-firm survey.		1987	9%	Estimates from reported preclinical and clinical period expenditures.	Estimated success rate by phase for sample NCEs.
<i>Industry-level studies</i>								
Bally, 1972	1949-69 (market introductions)	Regression of total U.S. drug introductions in U.S. firms 1949-69 on total research expenditures (lagged 5 years), FDA regulation stringency, and a measure of depletion of research opportunities.	Total R&D data: PMA survey. New drug introductions: Paul de Haan, Inc.	Pre-1982: \$2.5 million. Post-1982: \$6 million.	1958	0%	Implicit	Implicit
Schwartzman, 1976	1966-72 (NCE approvals)	Allocation of total R&D expenditures (lagged 5 years) to NCEs introduced in 1966-72.	R&D expenditures: \$24.4 million PMA survey.		1973	0%	Assumed to be 50%	Implicit
Wiggins, 1987	1970-85 (NCE approvals)	Regression of NCE introductions on total R&D expenditures (lagged 4 years); FDA approval times, by therapeutic class. Adjusted for Hansen's time profile.	NCEs: FDA. R&D expenditures: PMA surveys.		1985	8%	Implicit	Implicit
Grabowski & Vernon, 1989	1970-79 (NCE approvals)	Analysis of industry R&D expenditures and NCE production. R&D time profiles modified from regression estimates.	NCEs: FDA. Total R&D expenditures: PMA surveys.		1986	9%	Implicit	Implicit

a. Wiggins originally reported \$125 million; adjustment for technical error changes the number to \$108 million (DiMasi et al., 1991).

KEY: NCE = new chemical entity; IND = investigational new drug; FDA = U.S. Food and Drug Administration; PMA = Pharmaceutical Manufacturers Association.

SOURCES: J.E. Schnee, "Development Cost: Determinants and Overruns," *Journal of Business* 45(3):347-374, 1972; M.N. Bally, "Research and Development Costs and Returns: The U.S. Pharmaceutical Industry," *Journal of Political Economy* 80(7):70-85, 1972; D. Schwartzman, *The Expected Return From Pharmaceutical Research* (Washington, DC: American Enterprise Institute, 1975); R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics*, R.A. Chien (ed.) (Lexington, MA: D.C. Heath and Co., 1979); S.M. Wiggins, *The Cost of Developing a New Drug* (Washington, DC: Pharmaceutical Manufacturers Association, 1987); H.G. Grabowski and J.M. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science* 38(7):804-821, July 1990; J.J. DiMasi, A.N. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:103-142, 1991.

reliable data can be obtained, it provides the most detailed view of the costs of particular projects and overall development costs. These studies look at a sample of new product introductions (virtually always new chemical entities (NCEs))² and use project cost data obtained from companies to estimate the average cost of bringing a product to market. Although Clymer (79) and Schnee (367) took this project-level approach in early studies, they calculated only the cash R&D outlays of a single firm, and Schnee did not consider the cost of failure. These studies are therefore not considered further.

The prototype of project-level R&D cost estimation is a pair of studies published by Hansen in 1979 and DiMasi and colleagues in 1991 (109,175). They used very similar methods and data sources to estimate the present value in the year of U.S. market approval of the costs of discovering and developing NCEs. The results of these studies have been used to estimate net returns to R&D and to estimate recent changes in the cost of developing new drugs.

Industry-level studies examine the relationship between new product introductions and industry research expenditures. An estimated regression equation that predicts NCE introductions as a function of R&D expenditures in previous years as well as other external factors (such as regulatory controls) is then solved for the R&D expenditures required to bring one additional NCE to market.³

The advantage of these industry-level studies is that data on product introductions and research expenditures are verifiable and readily available at the industry level. The disadvantage is that the introduction of NCEs in any year must be related

to a pattern of past R&D expenditures that is complex and often beyond estimation with the limited number of years of data available. This approach was pioneered by Baily (32), but the cost estimate from that study is based on very old data that are not converted to present values.

A recent estimate based on a study by Wiggins (520) is the most comprehensive analysis using this approach. Wiggins followed the general method first used by Baily, but Wiggins had more data at hand and used less restrictive assumptions about the nature of the relationship between expenditures and new drug production. Therefore, this chapter focuses on the Wiggins study.

Grabowski and Vernon (159) also used published aggregate R&D expenditure data to estimate the cost of successful drug development. Though Grabowski and Vernon did not estimate development time profiles with statistical analysis, their estimate provides another point of reference for comparison among methods, and it is also summarized here.

■ The Hansen and DiMasi Studies

METHODS

The two studies by Hansen (175) and DiMasi (109) are based on samples of NCEs first entering human testing in specified time periods. The sample of NCEs for each study was selected from a set of data on NCEs constructed and maintained by the Tufts University Center for the Study of Drug Development (CSDD) from an ongoing triennial survey of over 40 pharmaceutical firms. The early study examined approximately 67 NCEs, discovered and developed by 14 U.S. pharmaceutical firms that first entered human trials between 1963 and 1975. The second study

² DiMasi defines "NCE" as "a new molecular compound not previously tested in humans" (107). In keeping with DiMasi's definition this report uses the term NCE to refer to both therapeutic drugs and biologicals.

³ Industry-level analyses are therefore estimates of marginal costs of NCE production. As DiMasi observed, marginal costs and average costs are not likely to be equal unless R&D is subject to constant returns to scale (109). In an R&D-intensive pharmaceutical firm, there may be substantial economies of scale, particularly at low levels of expenditure. However, from the standpoint of the industry as a whole, marginal costs may more closely approximate average costs. A more important criticism of the marginal cost measure is that the marginal NCE (i.e., the next one that would be brought forth by an infusion of new R&D expenditures) is not determined by costs alone but by the present value of net returns. The marginal NCE might be a low-cost project with low revenue prospects. Therefore, marginal research cost does not have much meaning from the standpoint of R&D decisions.

examined 93 NCEs, discovered and developed by 12 U.S. firms, that were first tested in humans between 1970 and 1982 (109).

Both studies looked only at NCEs that were actually discovered by the firms themselves (i.e., self-originated), not licensed from other companies, and the samples in both studies included unsuccessful as well as successful NCEs. Products acquired through joint ventures or licenses were excluded because part of the costs of these R&D projects would have been borne by other firms and could not be measured easily.

The study authors surveyed the firms sponsoring the sampled NCEs for information about the costs incurred from year to year as each NCE traveled through the drug development process. Many of the sampled products were abandoned during the clinical testing phase, and the costs were adjusted for these abandonments. With year-by-year estimates of spending for each project, the authors could build a time profile of expenditures throughout the development period. These time profiles were then combined with information about the survival experience of the NCEs under study to estimate the average cash outlays¹ for clinical research.

A portion of R&D cost is devoted to the discovery of NCEs. These basic and preclinical research activities cannot be allocated to specific NCEs, so the authors of each study asked firms to report information that would allow estimation of preclinical research expenditures. In the early study, firms were asked to report total NCE R&D expenditures in the United States between 1962 and 1975 as well as "basic research" expenditures.² Overall, firms reported that 51 percent of all NCE R&D expenditures were for basic re-

search, so Hansen assumed an amount equal to the total average development period cost went to basic research in the preclinical period, spread equally over 3 years prior to the initiation of clinical testing.

DiMasi used a more involved methodology to estimate both the amount of preclinical cost and the timing of those costs. Firms reported total self-originated NCE R&D expenditures and preclinical research expenditures between 1970 and 1986. Preclinical expenses averaged 60 percent of total self-originated NCE research.³ This estimate was revised to 58 percent to account for trends in the data over the time period on which the estimate was based.⁴ These estimated preclinical costs were spread evenly over 42.6 months prior to the initiation of the clinical period.⁵

The estimated cash outflows, spread over the discovery and development periods according to the time profile reported by companies, were converted to their present value in the year of market approval. The early study used a real (inflation-adjusted) cost of capital of 8 percent; the later study used 9 percent.

RESULTS

Table 3-2 shows how the actual estimated cash expenditures (in 1990 constant dollars) changed between the two studies. Total cash outlays per successful new NCE were estimated at \$65.5 million (1990 dollars) by Hansen and at \$127.2 million by DiMasi, a 94 percent increase in estimated real (inflation-adjusted) outlays per successful new drug over the period of the two studies. If the midpoint of the study years is used to calculate the rate of increase in cash outlays,

¹ The reported expenditures don't correspond exactly to cash outlays because charges for indirect costs, overhead, or capital equipment and facilities may be made using allocation or depreciation methods that don't correspond in time to actual cash outlays. The term "cash costs" is used here to differentiate the reported expenditures from their present values in the year of market approval.

² Development costs included clinical costs and short-term preclinical animal studies.

³ Since clinical period expenditures occur later than preclinical expenditures, the ratio of preclinical period real R&D to total real R&D expenditures overestimates the true preclinical period contribution when total expenditures are rising (109).

⁴ The length of the preclinical period was estimated from data in the CSDD database on NCEs approved for marketing by the U.S. Food and Drug Administration (FDA) in the years of the study. The preclinical period is defined in that database as the length of time from synthesis of a drug to the beginning of human clinical studies.

Table 3-2-Cash Outlays per Successful New Chemical Entity:
Hansen and DiMasi (\$ 1990 millions)^a

Study	Study years (midpoint)	Clinical cost	Preclinical/discovery		Total cash outlays per success
			cost	As percent of total cost	
Hansen, 1979,	1963-75 (1969)	\$29.9	\$35.6	54%	\$65.5
DiMasi et al., 1991	1970-82 (1976)	53.8	73.4	58	127.2
Rate of increase (%).		79	106		94

^a All estimates were adjusted for inflation using the GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, adapted from R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics*, R.A. Chien (ed.) (Lexington, MA: D.C. Heath and Co., 1979); J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

this pair of studies suggests that real R&D cash outlays per successful NCE increased at an annual rate of about 9.5 percent in the study years.⁸

The increase in cash outlays per success is moderated by an improvement in the success rate of the drugs in the two study cohorts. Whereas Hansen projected an ultimate success rate from human testing to approval by the U.S. Food and Drug Administration (FDA) of 12.5 percent, DiMasi and colleagues estimated about 23 percent of the projects would be successful. Without this improvement, the increase in cash outlays per success would be even higher.

Because the estimated ratio of preclinical costs to clinical costs was higher in the later study than in the early study, the increase in real cash outlays is somewhat greater for preclinical costs than for clinical period costs, but the annual rates of increase were not very different—10.3 percent per year for preclinical costs compared with 8.3 percent per year for clinical period costs.

Total R&D costs capitalized to the date of approval for marketing increased from \$108 million to \$259 million (in 1990 dollars) over the

course of the two study periods, an inflation-adjusted increase of 139 percent, or 12.4 percent per year from the midpoint of the early study (1969) to the midpoint of the later study (1976). The even more rapid increase in fully capitalized costs was due to cost-increasing changes in two components of the estimates:

- An increase in the estimated cost of capital from 8 percent in the early study to 9 percent in the later study.
- An increase in the total development time from 9.6 to 11.8 years, led by a longer preclinical period in the later study (42.6 months, compared with 36 months) and a longer period of regulatory review once a new drug application (NDA) is filed with the FDA (30.3 months compared with 24 months).

The change in the assumed cost of capital alone would account for little of the increase in total capitalized costs. OTA reconstructed Hansen's cost analysis using a 9 percent cost of capital. This change, in the absence of any others, increased Hansen's total cost estimate by only 5 percent to

⁸ Comparison of the midpoints of the study years may understate the true difference in time between the studies and may therefore overstate the rate of change over the time period. Although the database from which the sample of NCEs in each study was drawn shows the median years for self-originated NCEs receiving investigational new drugs in the two studies were 7 years apart (107), the cost estimates in the early study were based more heavily on the older NCEs in the sample than were the cost estimates in the second study (176). If a steady upward trend in the real cost of R&D was occurring throughout the decades of the two studies, the cost estimates of the early study would be biased downward.

approximately \$114.8 million (in 1990 dollars). Increasing the discovery/development period to match that of the DiMasi study without any other changes would increase Hansen's total cost estimate to \$122.7 million (13 percent higher than the baseline estimate). Together, a higher cost of capital and a longer R&D time profile (in the absence of any other changes) increased Hansen's estimated cost to \$132.9 million (in 1990 dollars), only 23 percent higher than the baseline estimate. Thus, without the very large changes in estimated cash outlays over the two periods, the inflation-adjusted rise between the two periods in R&D costs per success would have been relatively modest.

■ The Wiggins Study

Wiggins regressed the total number of NCEs that the FDA approved between 1970 and 1985 on the estimated total NCE-oriented research spending in previous years⁹ and on the average delay in NDA approval times for drugs approved 5 years earlier. The regression equation was then transformed into an estimate of the extra cash research outlay required to bring forth one additional NCE. This estimate of marginal R&D cash outlay per additional NCE was \$75 million in 1990 dollars.

Wiggins' analysis is based on NCE approvals for marketing, not NCEs entering human testing. If the average time from the filing of an investigational new drug (IND) application to approval of the drug by the FDA was 6.5 years (as Hansen's early survey indicated), then Wiggins' sample corresponds to NCEs first entering clinical testing between roughly 1963 and 1979, a period that overlaps substantially with the Hansen study (1963 to 1975). Thus, Wiggins' estimate of \$75

million in cash costs is roughly in line with Hansen's estimate of \$65.5 million, especially when one considers Wiggins' analysis probably covers a somewhat more recent population of NCEs than does Hansen's.

Wiggins' NCE sample is different from Hansen's, however, because it includes licensed-in products as well as self-originated NCEs. It is unknown how the full costs of discovery and development for licensed-in products compare with those of self-originated drugs. Though the cost of developing licensed-in products is likely to be lower for the licensee, if the licensor is a Pharmaceutical Manufacturers Association (PMA)-member company, then Wiggins' method would have captured the early costs.

Although Wiggins converted cash R&D costs to their present value at the time of market approval, he did so by assuming the cash costs followed Hansen's estimated time profile.¹⁰ Like Hansen, Wiggins used an 8 percent cost of capital. Starting with higher out-of-pocket expenses, Wiggins necessarily concluded the full cost of bringing an NCE to market is higher than Hansen predicted. In 1990 dollars, Wiggins' estimated cost of discovery and development of a new NCE is \$123.4 million¹¹ compared with \$108 million estimated by Hansen (175).

■ The Grabowski and Vernon Study

Grabowski and Vernon (160) also used annual aggregate R&D data reported by PMA to estimate the average cost of developing new NCEs approved by the FDA for marketing during the 1970s. Like Wiggins, Grabowski and Vernon estimated the cost per NCE for both self-originated and licensed-in drugs. They assigned

⁹ The average research expenditures for NCEs in the third, fourth, and fifth year prior to FDA market approval as reported to the Pharmaceutical Manufacturers Association was used as the measure of research expenditure.

¹⁰ Since Wiggins' analysis included licensed-in as well as self-originated drugs, he should have used a different, and probably shorter, time profile for the licensed-in drugs. Data on development times for approved licensed-in drugs suggest they are substantially shorter than the development times for approved self-originated products (107), which suggests lower costs to the licensee. Had Wiggins applied a different profile to the licensed-in drugs, his estimate of total capitalized cost would have been lower.

¹¹ This value disagrees with Wiggins' estimate, \$144 million in 1990 dollars. As discussed by Woltman (524) and DiMasi et al. (109), Wiggins made an error in calculating the total capitalized cost. OTA's re-estimate, \$123.4 million, is slightly lower than DiMasi's recalculation, \$124.7 million in 1990 dollars, because of differences in price indexes used.

R&D expenditures in each year between 1962 and 1978 to product introductions in the years 1970-79 using assumptions about the application of each year's expenditures to the future years' introductions. For example, Grabowski and Vernon assumed that in 1965, 10 percent of R&D expenditures for NCEs was spent on drugs introduced in 1970, 10 percent on drugs introduced in 1971, etc.¹²

This weighting scheme was then used to estimate the cost of introductions in each year. Compounding these values to the date of market introduction at 9 percent, Grabowski and Vernon estimated the mean cost per successful NCE approved by the FDA between 1970 and 1979 was \$142 million in 1990 dollars. Because the weighting scheme assumes a total discovery/development period of 8 to 12 years (lengthening over the period of study), this estimate corresponds to NCEs first entering human testing in the period roughly bounded by 1965 and 1972. This period falls within the bounds of Hansen's study years.

Whereas Hansen's total estimated cost in 1990 dollars with a 9-percent discount rate is \$114.8 million for drugs entering testing in the period, Grabowski and Vernon estimated an average cost of \$142 million. For NCEs approved in 1975, Grabowski and Vernon estimated cash R&D outlays of \$86.7 million in 1990 dollars compared with \$65.5 million estimated by Hansen.

■ Comparison of Estimates

The studies discussed above are best compared by standardizing for constant dollar year and cost of capital, chosen here to be 1990 and 9 percent. Table 3-3 shows the estimates from each reviewed study.

The three studies of research conducted on NCEs first entering clinical testing in the 1960s and early 1970s use different methods and arrive

Table 3-3-Estimates of the Full Cost of Bringing a New Chemical Entity to Market' (\$ 1990 millions)

Study	First year of clinical testing (midpoint)	
	1963-75 (1969)	1970-82 (1976)
Hansen, 1979.....	\$114.8	—
DiMasi et al., 1991.....	—	\$259
Wiggins, 1987.....	131.5	—
Grabowski and Vernon, 1990....	142	—

^a All estimates were adjusted for inflation using the GNP implicit price deflator and were calculated at 9 percent cost of capital.

SOURCE: Office of Technology Assessment, 1993.

at estimates differing by up to 25 percent. Since the methods used in each study are not completely independent,¹³ more congruence might have been expected.

Because neither Wiggins nor Grabowski and Vernon differentiated between licensed-in and self-originated drugs, their estimates should be lower, or at least no higher, than those of Hansen. Yet the cash outlays estimated in both industry-level studies are higher than those of Hansen. Hansen estimated cash outlays per successful NCE of \$65 million; Wiggins estimated \$75 million; and Grabowski and Vernon estimated \$86.7 million.

VALIDITY OF R&D COST ESTIMATES

All of the R&D cost studies described above begin with estimates of R&D cash outlays in each phase of development, the time required to complete each phase, and the success rate for projects in each phase of the process. These estimated cash flows are then capitalized with a cost of capital that differs among studies. The validity of the studies rests ultimately on the accuracy of the estimates of cash outlays and the timing of those outlays. In this section, OTA analyzes the validity of the estimates of cash

¹² These assumptions were based in part on a regression estimate Thomas made in 1986 (421).

¹³ Hansen used the sample firms' self-reported data on R&D expenditures to estimate basic research costs to their present value; Wiggins used Hansen's time profile generated from a survey of companies' NCE introductions to capitalize costs, and Grabowski and Vernon's time profiles were based largely on data supplied by the CSDD NCE database, the same database from which Hansen's sample was drawn and from which estimates of Hansen's R&D time profile were partially drawn.

outlays, their timing, and the success rates from stage to stage in the development process.

Are the estimates of cash outlays accurate? OTA addressed this question in two ways. First, we critically assessed the validity of the methods and data sources used to arrive at the estimates and the potential importance of departures from full validity. Second, we attempted to corroborate the findings with data from independent or semi-independent sources.

The assessment of validity of the methods concentrates on the project-level studies of Hansen (175) and DiMasi (109) for two reasons. First, the DiMasi study offers the most recent estimate which industry representatives and others have quoted widely as the definitive estimate of research costs (325). Second, the other studies based on aggregate R&D expenditures draw from the project-level analyses of Hansen and DiMasi for estimates of the time profile of development and are therefore partially dependent on them.

■ Validity of Study Methods

The validity of the project-level studies depends on three aspects of the study methods:

- Sample of firms;
- Sample of NCEs; and
- Accuracy of survey responses regarding:
 1. clinical period cash outlays,
 2. preclinical period cash outlays,
 3. phase-specific development times, and
 4. phase-specific success rates.

THE SAMPLE OF FIRMS

Both Hansen and DiMasi examined NCEs originated at U.S.-owned, research-intensive pharmaceutical firms. Hansen's early study included 14 firms willing to respond to the survey; DiMasi's later study included 12. Because the samples were predominantly large well-

established companies in both surveys, the reported R&D costs may not reflect the cost experience of small and relatively young firms,¹⁴ although the direction of potential biases between large and small firms is unknown.¹⁵ Even if systematic differences in R&D costs by firm size or total R&D commitment do exist, they should not survive for long, for the industry would gradually reorganize to operate at the most efficient level. The responding firms in the DiMasi study represented 40 percent of domestic R&D, as measured by PMA, and the distribution of R&D by therapeutic class in these firms was virtually identical to the distribution of R&D in the U.S. pharmaceutical industry as a whole.¹⁶ Thus, the sample of firms appears to pose no serious threat to the validity of the study.

THE SAMPLE OF NCEs

Both studies selected a sample of NCEs that originated within the company's U.S. research organizations. NCEs were selected from a database maintained by CSDD of new products under development. Probability samples were drawn from the universe of NCEs in the CSDD database, but some nonresponding companies could have biased the sample. Furthermore, neither study reported the within-firm response rate. If firms failed to provide data on some NCEs for which data were poor, or if they selectively reported on NCEs for some other reason, the sample of NCEs could be biased. Again, the effect of such potential biases on cost estimates cannot be judged.

The adequacy of the sample size to reliably predict costs is determined by the underlying variation in the costs to be measured. The sample size in the Hansen study was 65 to 70 NCEs. The precise NCE sample size was not reported. DiMasi examined 93 NCEs. The higher the

¹⁴ The emergence of dozens of small biotechnology firms performing pharmaceutical research in the 1980s would make this point more salient for periods later than those studied by Hansen and DiMasi.

¹⁵ Pharmaceutical firms may experience decreasing returns to scale of R&D at low levels of R&D (213). Comanor found the marginal productivity of research personnel is inversely related to the size of the firm (85), but after controlling for R&D levels, Jensen did not find such a relationship (213).

¹⁶ Hansen did not provide estimates of the proportion of domestic R&D accounted for by the 14 firms in his sample.

Table 3-4-Confidence Intervals for Clinical Period Cash Outlays in DiMasi Study
(\$ 1987 millions)

Phase	Mean cost ^a	Standard deviation	95% confidence interval for mean percent of estimated mean	Probability that true mean is within 10 percent of estimated mean
i.....	\$2,134	\$4,519	\$1,184- 3,084	0.34
ii.....	3,954	5,230	1,729- 4,179	0.36
iii.....	12,801	13,974	8,236-17,366	0.41
Long-term animal.....	2,155	2,411	1,480- 2,830	0.46
Other animal.....	648	1,183	49 - 1246	0.17

^a Calculated for all new chemical entities entering the phase.

SOURCE: Office of Technology Assessment, 1993, based on data provided in J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

underlying variation in costs, the larger the sample size must be to meet any required level of precision. Hansen did not report on the observed variation in costs among NCEs, so there is no way to evaluate the precision of his estimate.

DiMasi did report the sample standard deviation of cash outlays in each phase of the clinical period. Table 3-4 shows the standard deviations, the 95-percent confidence intervals¹⁷ for the true mean cash outlay in each clinical phase, and the estimated probability that the true mean cash outlay in each phase lies within 10 percent of the estimated mean. The chance that the true mean cost is no more than 10 percent greater or less than the estimated cost of each phase ranges from 17 to 46 percent over the different clinical phases. To have a higher chance of estimating the mean costs with no more than a 10-percent error in either direction, the sample size must be bigger.

Because the cost of one phase may be correlated with the cost of another, the precision of the estimate of total cash costs cannot be computed with the existing data (106). Thus, the precision of the total cost estimate is unknown.

ACCURACY OF SURVEY RESPONSES

The project-level studies depend on data supplied by responding companies that are unavailable from other sources. The accuracy of such data depends on two factors: the ability of firms to provide accurate data (i.e., does the company

have access to accurate information?), and the motivation of firms to provide accurate data.

Clinical Period Cash Outlays--OTA's interviews with pharmaceutical company managers indicated that, once projects reach the clinical stage, virtually all companies have project-level cost accounting systems that keep track of funds spent on speckle projects, generally identified by the chemical or biological compound. Therefore, most firms have the ability to report data on overall clinical period outlays.

OTA was unable to obtain much information about the structure of such accounting systems; hence, the ability of firms to identify expenditures by clinical phase is unclear. All companies would have an accurate picture of monthly charges to individual project accounts, however, and the dates at which phase I, phase II, and phase III trials began are available to companies, so allocation of costs by date is a reasonable approach to estimating the distribution of costs by phase. If companies responded to survey questions with this approach, the phase-specific estimates would be reasonably accurate.

Companies responding to either survey may have handled indirect, overhead, and capital costs in inconsistent or biased ways.¹⁸ For example, in some companies the costs of a central computer may be billed to specific projects based on actual use; in others, these costs are charged to projects based on a predetermined allocation formula.

¹⁷ A 95-percent confidence interval means there is a 5 percent chance the true mean will lie outside the interval.

Such differences in cost allocation conventions may explain part of the high variation in reported phase-specific costs among NCEs.

The money spent to acquire capital equipment and facilities used in research (referred to as capital expenditures) sometimes is not allocated to project-level management cost accounts. How companies allocated these expenses to specific NCEs for the purpose of the survey is unknown. If a responding company estimated only direct expenditures in its clinical period R&D, but included R&D capital expenditures in its total R&D expenditures, the costs in the clinical period would be underestimated, but the ratio of preclinical period costs to total R&D costs would be overestimated. Because clinical period costs occur later, the total capitalized cost would appear higher using this method. On the other hand, plant and equipment costs are always accounted for with depreciation formulas, which spread costs out for a number of years subsequent to the actual capital expenditure.¹⁹ Because a proper cost estimate should be based on actual cash outlays, the delay in accounting for capital costs will skew expenditures toward the end of the period and will cause the total costs of R&D capitalized to the point of market introduction to be underestimated.

One hypothetical scenario that a pharmaceutical firm presented to OTA estimated that total costs capitalized to the point of market introduction could be underestimated by as much as 12 percent because of depreciation methods, but the size of the underestimate depends critically on assumptions about the initial cost of facilities and equipment, their useful life, the length of time such assets are used for the project, their remain-



Photo credit: THE UPJOHN COMPANY

The cost of testing NCEs in humans has risen rapidly in recent years. New diagnostic tests make for more expensive and larger clinical trials.

ing value at the end of the project, and the extent of shared use among different research projects.

Preclinical Cash Outlay--Both of the project-level studies estimated the preclinical cash outlays for each sampled NCE from company survey responses to similar (but not identical) questions about annual expenditures for total NCE-oriented R&D and preclinical NCE-oriented R&D.²⁰ In DiMasi's study the reported ratio of preclinical to total expenditures was 66 percent, but DiMasi adjusted this estimate to 58 percent to account for trends in total spending over time. In Hansen's study the reported ratio of basic to total NCE

¹⁸ Although the survey questionnaires did contain questions about the methods of estimating overhead, indirect, and capital costs associated with research projects, the questions were structured broadly and the study authors have provided no details about how such costing methods may have varied (109, 175).

¹⁹ If a piece of equipment, bought new, has a 10-year life, for example, the company might charge this expenditure off at 10 Percent of its initial cost each year over the next 10 years. This annual depreciation charge would then be allocated across the projects that shared in use of the capital equipment.

²⁰ DiMasi asked companies to report total expenditures for self-originated NCE R&D and preclinical expenditures for self-originated NCE R&D in the period 1970-86. Hansen asked companies to provide estimates of total and "basic" NCE-oriented R&D conducted in the United States in the years 1962-75.

research was 51 percent. When basic research is combined with short-term preclinical animal research (estimated separately in Hansen's study) to obtain an estimate of the percent of preclinical expenditures (i.e., comparable to DiMasi), the resulting ratio is 54 percent.

The accuracy of these estimates depends both on the capability of firms to separate preclinical expenditures for NCEs from those of other products (such as combination drugs, new formulations, new drug delivery systems, etc.) and on their motivation to report such expenditures accurately.

The capability of firms to identify such preclinical expenditures would depend on the structure of their cost accounting systems. Although OTA did not have access to information on the structure of these systems in any firm, virtually all companies of reasonable size have in place project-level cost accounting systems. Projects to extend product lines of existing NCEs are probably separately identified. Any project to develop a licensed-in drug is also likely to have its own account. Separating projects among the categories required to estimate the preclinical ratio would require categorizing these projects, which can be done with a reasonable level of effort by knowledgeable personnel. Thus, it is reasonable to assume companies can slot R&D expenditures into the detailed categories needed for the estimate.

Motivation is another matter. Because the estimated ratio of preclinical cost to total R&D cost cannot be verified without an independent audit of cost accounting information, a company that understood the use to which the data would be put and with a strategic incentive to overestimate the preclinical ratio could do so without potential for discovery.

Although the firms responding to the early study may not have been aware of the potential policy uses of the study's conclusions, those responding to the later study would surely have been aware of the use to which the data would be

put and its potential use in political debates. A brief review of the methods and findings of the early study could alert respondents to the importance of preclinical costs to the final full cost estimate. Thus, the motivation to overestimate this percentage cannot be discounted, especially in DiMasi's later study.

If companies responding to the DiMasi survey overestimated the percent of self-originated U.S. R&D expenditures devoted to preclinical research by 5 percentage points, so that the true percent was 53, as in Hansen's study, the estimated total cost of developing a new NCE would be \$228 million in 1990 dollars, 12 percent less than the \$259 million estimated by DiMasi et al.

Phase-Specific Development Times—The studies used identical methods to estimate a typical development time profile for NCEs in their sample. Responding companies reported the start date and ending date for each NCE entering a phase. The study researchers then calculated the mean phase length for all NCEs entering the phase.²¹ Not only do companies have **accurate archival** records to provide these dates, but companies also must report on the start and progress of clinical testing to the FDA. Although data reported to the FDA are not in the public domain unless an NCE is ultimately approved for marketing, it is unlikely companies would deliberately misreport such data in survey responses.

The length of the period from submission of a new drug application to FDA approval was not estimated from the company survey; rather, the authors estimated average new drug application review times from the CSDD NCE database. In the early study, Hansen used the reported mean time from NDA submission to approval of all approved NCEs in the database, 24 months. DiMasi used the reported mean NDA review time for approved self-originated NCEs first tested in humans between 1970 and 1982, 30.2 months.

OTA re-estimated the NDA review period for all self-originated U.S. NCEs in the CSDD

²¹ The mean phase lengths were weighted to take account of sampling probabilities.

database approved between 1967 and 1979, the time corresponding to Hansen's sample of NCEs (107).²² The estimated approval time was 26 months. Thus, Hansen may have slightly underestimated the review time in the early study. The effect on total costs is negligible, however. Hansen's estimate would increase from \$108 million to \$110 million.

Companies also did not report the length of the preclinical period, but the studies' authors estimated it through other means. DiMasi used the CSDD database on approved NCEs which contains company reports on the date of first synthesis of a compound and the date of first human clinical testing. Because NCEs can be identified as self-originated or licensed-in, DiMasi was able to estimate the preclinical period for the large sample in the CSDD database of approved self-originated NCEs that U.S. firms developed during the study period. The mean estimated length of the preclinical period was 42.7 months.²³

Hansen had no information at hand with which to estimate the length of the preclinical period. He simply assumed that the period was 36 months in length. OTA analyzed published CSDD data on NCEs approved between 1969 and 1982 and found the mean reported preclinical period was about 30 months. (107). A shorter preclinical period would reduce Hansen's estimated costs slightly (see table 3-5).

The preclinical period as defined by DiMasi (107) begins at the point of synthesis of a compound. Since firms must screen multiple products to obtain a lead compound (399) and engage in basic research to understand disease pathways before synthesizing a new product, this period could understate the length of the true preclinical period. If the true mean preclinical

Table 3-5--Effects of R&D Time Profile on Costs of R&D in Project-Level Studies' (\$ 1990 millions)

Study	Capitalized cost	Percent increase (decrease) from baseline
<i>Hansen (1979)^a</i>		
• Baseline estimate	\$108	—
• NDA review time		
26 months	109	0.9%
• Preclinical time		
30 months	106	(1.8)
43 months	109	0.9
60 months	114	5.5
• NDA review time/preclinical time		
26 months/30 months	108	0
26 months/43 months	110	1.8
26 months/60 months	115	6.4
<i>DiMasi et al. (1991)^b</i>		
• Baseline estimate	259	—
• Preclinical time		
60 months	270	4.2

a Estimates were adjusted for inflation using the GNP implicit price deflator.

b Cost of capital is 8 percent.

c Cost of capital is 9 percent.

KEY: NDA = new drug application.

SOURCE: Office of Technology Assessment, 1993, based on data provided in J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991; R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics*, R.A. Chien (ed.) (Lexington, MA: D.C. Heath and Co., 1979).

period was 5 years, the cost estimates would increase modestly (see table 3-5).

The combined impact on total capitalized costs of potential changes in the NDA review times in the Hansen study and a longer preclinical period is shown in table 3-5. The estimated capitalized costs increase modestly—by about 4 to 6 percent in both studies—as a result of these potential errors in timing.

²² Hansen estimated a mean 4.5-year lag between IND and NDA submission and a 2-year period from NDA submission to approval. Therefore, the Hansen study period for NCEs first entering human trials in 1963-75 would correspond roughly to NCEs reaching approval between 1969 and 1982.

²³ Although the preclinical period for drugs that were ultimately not approved may have been different from the period for drugs that were, OTA is unaware of any potential systematic differences that would suggest a bias in the estimate.

Success Rates—The estimated probability of reaching each clinical phase was based on survey responses. These data are both available and likely to have been reported accurately by survey respondents. Both studies predicted final approval rates not from the study sample, but from a large sample of NCEs in the CSDD database. DiMasi estimated the ultimate approval rate—23 percent—for the population of survey firm NCEs in the CSDD database that met the survey inclusion criteria. Hansen's estimated approval rate—12.5 percent—was based on all NCEs in the CSDD database covering the years of his study.²⁴

Recently published data from the CSDD database suggest that Hansen's predicted success rate for his cohort of NCEs may have been slightly low. After 17 years of experience, approximately 14 percent of self-originated U.S. NCEs first investigated in humans between 1964 and 1975 had been approved, and further approvals were obtained later (107). A 14 percent success rate (rather than a 12.5 percent rate) would reduce Hansen's estimated capitalized cost per successful NCE by 11 percent, from \$108 million to \$96.2 million in 1990 dollars.

It is too early to tell whether DiMasi's predicted overall success rate will be borne out by history. The effect of the 1.5 percentage point difference in success rate on the estimated cost of Hansen's NCE sample reflects the importance of small errors either way in success rates on the ultimate cost of R&D.

■ Corroborating Evidence

The estimates of R&D cash outlays and capitalized costs in the project-level studies are imprecise and potentially biased, but the magnitude and net direction of these errors cannot be predicted. Therefore, OTA looked for estimates of R&D costs from independent data sources to provide

additional confidence about the accuracy of the estimates from the project-level studies.

Occasionally anecdotal data come to light on the cash outlays required for the development of specific NCEs. For example, in depositions filed for a patent infringement lawsuit, Genentech claimed it had spent \$45 million to develop Protropin™, its human growth hormone product. (494) and Eli Lilly certified that it had spent \$16 million between 1980 and 1987 on its effort to develop its version of the drug (495). In another example, a 1980 report of the development cost of an oral systemic drug for chronic use estimated \$21 million in outlays in the clinical period (226). Unfortunately, anecdotal estimates of this kind do not help verify industrywide costs, because they are self-selected and do not reflect the cost of failures or basic research.

OTA attempted to corroborate the estimates of R&D costs with two approaches. First, the industry-level studies reviewed in the previous section produced independent estimates of R&D cash outlays per success. The consistency of these studies' findings on cash outlays with those of the project-level studies is examined below. Second, data on trends in important components of R&D costs are examined to determine whether they are consistent with the rapid rise in real cash outlays implied by the two project-level studies of R&D costs.

INDUSTRY-LEVEL STUDIES

The industry-level studies help to verify the reasonableness of total cash outlays required to produce an NCE. These studies begin with aggregate R&D spending reported to PMA by its member companies (320). Because Wiggins' estimate of cash outlays per successful NCE is completely independent of data obtained in the project-level study, Wiggins is a good corroborative source.²⁵

²⁴ Both studies used Kaplan-Meier survival curve analysis (219,225) to estimate the ultimate success rate in the NCE cohort under study.

²⁵ Grabowski and Vernon's estimate of R&D cash costs is less useful for corroborative purposes than Wiggins' estimate because the estimated cash outlays are built from an assumed relationship between NCE approvals in 1 year and R&D expenditures in previous years.

Wiggins estimated cash outlays per successful NCE at \$75 million (in 1990 dollars) compared with Hansen's estimate of \$65.5 million (in 1990 dollars). Because Wiggins was estimating the cost of developing all NCEs, not just self-originated NCEs, his cost estimate should be conservative. The population of NCEs entering testing was somewhat more recent than Hansen's, however, and Hansen's cost estimates are based more heavily on drugs entering human testing in the earlier years of his sample. Overall, then, Wiggins' study suggests Hansen's estimated cash outlays are not out of line with the true costs and may even be slightly underestimated.

However, before one can conclude that Hansen's estimate of cash outlays is too low, it is necessary to assess the validity of the aggregate R&D data reported to and compiled by PMA and used by Wiggins in his analysis. Are these company-generated estimates accurate? PMA does not audit its member companies' reported R&D expenditures, but comparison of PMA data with publicly available financial statements suggests that R&D spending reported to PMA has increased at rates very similar to those recorded in companies' financial statements. (See chapter 2.) Although OTA cannot rule out the possibility that PMA-member firms systematically overestimate human pharmaceutical research by the same percent each year, this congruence in rates of change with audited financial records suggests the PMA aggregate R&D data are reasonably sound estimates of total R&D spending.

The total R&D spending reported to PMA includes spending not only on new drug products but also on modifications and extensions of existing products. PMA publishes the firms' reported percent of R&D devoted to new products in most years. Between 1973 and 1987 this reported percentage varied in the range of 79 to 82. Wiggins used 80 percent as an estimate of the

proportion of total PMA spending devoted to NCE R&D. The accuracy of the reported expenditures cannot be verified. How companies define "new products" is unclear; if they include follow-on products such as new formulations, the estimate could be inflated for the purpose of estimating NCE expenditures. If it is too high, then the cash outlays estimated by Wiggins would be slightly high.²⁶

Although there are no industry-level studies available to corroborate DiMasi's project-level analysis, DiMasi conducted his own check on his estimates using aggregate PMA data. He allocated a portion of U.S. firms' aggregate NCE R&D costs in each year of the period 1967 to 1987 to the production of NCEs in subsequent years. Using this approach he estimated the cash outlays per successful new drug at \$155 million (in 1990 dollars) compared with the survey-based method of \$127.2 million. This allocation technique assumed that the production of self-originated successful NCEs would continue into future years at an average rate of 7.9 per year, despite the fact that real R&D spending rose rapidly over the period. The validity of this assumption is tenuous.

OTA did a quasi-independent check of the results of the DiMasi study using data on aggregate R&D spending by the U.S. pharmaceutical industry and the total number of self-originated NCEs introduced by pharmaceutical companies. OTA used DiMasi's estimates (109) of aggregate R&D spending on self-originated NCEs by the U.S.-based industry between 1967 and 1987, which were obtained from PMA. The total cash R&D outlays estimated in the DiMasi study (\$127 million in 1990 dollars) were attributed to each self-originated NCE approved between 1979 and 1989, spread out over the time profile estimated in DiMasi's study. Total self-originated R&D expenditures for the U.S. pharmaceutical industry in 1977²⁷ calculated in this way were just

²⁶ Followup R&D conducted on existing products that have already been approved for marketing represents a real R&D cost that is not included in any of the empirical studies but which affect the company's net returns. This issue will be discussed in the next chapter on measuring returns.

²⁷ The year 1977 was the only one in which all self-originated NCE research would be for NCEs approved in the 1979-89 period.

5 percent less than PMA's aggregate spending estimates for that year. This result would suggest the costs, time profiles, and ratios of self-originated to total R&D found in the DiMasi project-level study are at least internally consistent with one another.

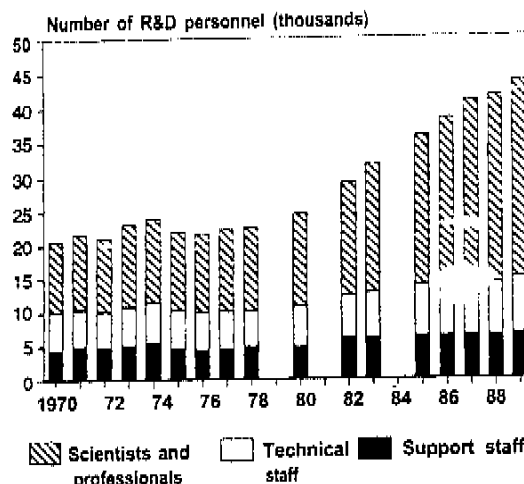
UNDERLYING COMPONENTS OF OUT-OF-POCKET COSTS

The Hansen/DiMasi studies imply that real cash outlays per successful NCE almost doubled in the 7-year period separating the midpoints of their study years, from \$65.5 million to \$127.2 million (in 1990 dollars). The increase would have been even greater had the ultimate success rate not improved markedly. The two surveys cover NCEs first entering human testing in 1963-75 and 1970-82. Is there any evidence to support such a rapid increase in the real costs of conducting research between the two periods? OTA examined data on three inputs to pharmaceutical R&D—research personnel, animal research subjects, and human research subjects—to learn more about the factors driving the increase in costs per successful NCE.

Research Personnel—The number of R&D personnel that PMA member firms employ remained fairly stable throughout the 1970s but began to grow rapidly in 1980 (figure 3-1). Most of this growth was in scientific and professional personnel, which numbered about 12,000 in 1977, but increased to almost 29,000 by 1989. Greater detail is unavailable on the kinds of jobs these new employees performed.

As the R&D workforce grew, so grew the salaries of biomedical research personnel employed by industry (figure 3-2); however, after adjusting for general inflation,²⁸ salaries actually decreased a bit. From 1973 to 1979, the median annual salary of biological scientists employed by business and industry decreased from \$59,961 to \$52,545 (in 1990 dollars), and from 1981 to 1989 it rebounded from a low of \$49,176 to \$56,600.

Figure 3-1—Research and Development Personnel in Pharmaceutical Companies, 1970-89



SOURCE: Office of Technology Assessment, 1993, based on Pharmaceutical Manufacturers Association Annual Survey Reports.

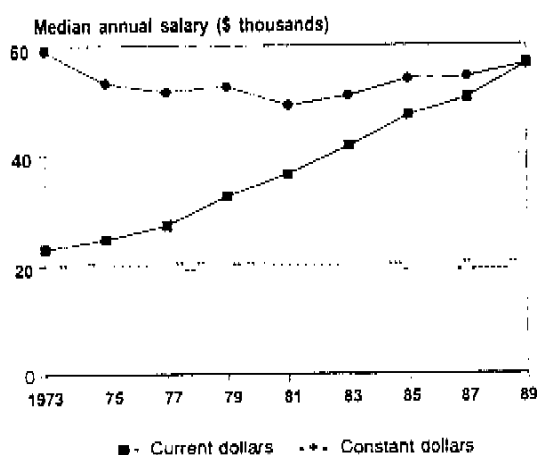
If labor costs boosted the cost of bringing new drugs to market, it was largely due to the increased labor input per NCE, not wages.²⁹ How much of the increase in employment in the 1980s reflects increased labor inputs per successful NCE, versus adjustments for a larger field of NCEs entering each phase of clinical testing, or a greater commitment to basic research, is unknown. The most that can be said is that the trends in research personnel are not inconsistent with a substantial increase in R&D cash outlays per NCE for those NCEs first entering clinical research in the late 1970s and early 1980s.

Animal Research—Although data indicate the number of some types of animals used in pharmaceutical R&D may have decreased over the last decade, other evidence is consistent with increases in the per unit costs of animal testing.

One drug company, Hoffman-La Roche, reported that the number of animals it used fell from 1 million in 1979 to just under 250,000 in 1988 (204). Data collected by the U.S. Department of Agriculture (USDA) also shows a significant

²⁸ Inflation adjustments were made using the GNP implicit price deflator.

²⁹ The salary data do not reflect the costs of employee benefits, however, which may have increased in real terms over the period.

Figure 3-2—Median Annual Salary of Doctoral Biological Scientists^a

^a Employed in business and industry.

SOURCE: National Science Foundation, Surveys of Science Resource Series, *Research and Development in Industry*, 1987, Detailed Statistical Tables, NSF 89-323 (Washington, DC: U.S. Government Printing Office, 1989); National Science Foundation, Surveys of Science Resource Series, *Research and Development in Industry*, 1988, Detailed Statistical Tables, NSF 90-319 (Washington, DC: U.S. Government Printing Office, 1990).

decline in absolute and relative use of animals for experimentation between 1975 and 1988 in States with a disproportionate number of industrial pharmaceutical R&D laboratories (459,460). However, these data are not definitive, since many pharmaceutical firms contract with other facilities to conduct their animal tests in other States. In addition, the USDA numbers do not include rodents, which make up the bulk of all animals employed in drug R&D, especially in the early efficacy and safety testing of potential drug candidates that companies ultimately abandon (133).

Beyond these few facts, several forces have been at work over the last 10 years to both increase and decrease the use of animals in pharmaceutical research. Because early testing involves the greatest number of animals, it also has the greatest potential for reduction. Hoffman-

La Roche said most of its reduction in the use of animals came from these early phases of the R&D process. Also, improvements in *in-vitro* testing and other innovations like computer modeling (described in chapter 5) may decrease some of the demand for rodents (133).

On the other hand, an earlier OTA report concluded that alternatives to many types of animal testing are limited (447). Also, pharmaceutical executives interviewed by OTA suggested any efficiencies brought about by such innovations in the R&D process are counterbalanced by the increased number of compounds to be tested for pharmaceutical activity. In addition, the number of animals used in later safety testing is largely governed by regulatory standards.³⁰

Any possible decline in the number of animals used in drug R&D in the past decade was met by significant increases in the cost of acquiring animals and conducting tests in animals. An OTA contractor surveyed 3 major commercial breeders of animals used in drug R&D and 11 laboratories that perform such research for pharmaceutical firms. Table 3-6 shows trends in the costs of

Table 3-6—Trends in the Cost of Acquiring Research Animals (\$ 1990)

Species	Cost per animal				Fold increase
	1977	1980	1987	1990	
Rats	—	5.29	—	8.45	1.6
Mice	—	0.92	—	1.35	1.5
Guinea pigs	—	—	—	25.30	—
Rabbits	8	—	33.6	—	4.2
Dogs	195	—	—	300-500	1.5-2.6
Monkeys	391	—	—	1,000	2.6

NOTE: All costs were adjusted using the GNP implicit price deflator. Facilities surveyed were Charles River, Taconic Farms, and Hazleton. These facilities focus on breeding only. Although Hazleton conducts testing, it is carried out in a separate division.

SOURCE: Office of Technology Assessment, 1993, based on W.G. Flammand M. Farrow, "Recent Trends in the Use and Cost of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, April 1991.

³⁰ See table 6-1 in chapter 6 for estimates of the number of animals typically used in each category of pharmaceutical safety testing.

Table 3-7—Price of Animal Studies^a (\$ 1990 thousands)^b

Study	Estimated price in 1980	Price range in 1990	Fold increase	Number of Labs providing information
Acute rats.	\$0.8	\$4-5	5-6.25	8
28-day toxicity in rats.	15	30-65	2-4.3	6
Subchronic rats.	38	55-143	1.4-3.8	8
2-year rat bioassay.	384	250-575	.7-1.5	5
Teratology rats.	23	52-70	2.3-3.0	5
Acute monkey.	14	39-62	2.8-4.4	6
Subchronic monkey.	74	108-184	1.5-2.5	6
Acute dog.	23	22-51	9.6-22.1	7
Subchronic dog.	4E	72-147	1.6-3.2	7

a Each laboratory surveyed was given an identical protocol on which the price is based. The "cost" includes profit as well as all direct and indirect costs. Laboratories surveyed were Hazleton, Bioresearch, IIT, TSI Mason, Bio/dynamics, Pharmakon, PAI, and IRDC.

b All prices were adjusted to 1990 dollars using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, based on W.G. Flamm and M. Farrow, "Recent Trends in the Use and Cost of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, DC, April 1991.

commonly used species.³¹ The data indicate a significant upward trend in the real cost of acquiring all species of animals examined, with especially large increases in the costs of non-rodents.

OTA's contractor also surveyed eight facilities that conduct toxicological animals studies about the increases in their fees for tests involving various species. The results (shown in table 3-7) suggest the total costs of testing, which implicitly includes the cost of the animals' breeding, has also risen significantly over the last 10 years.

Another indicator of the potential increase in animal costs is PMA member firms' spending for safety and toxicological tests, R&D functions that use animals heavily. Between 1980 and 1989, spending for these functions went from \$102 million to \$565 million in 1989 dollars. Spending for safety testing increased from 7 to 10 percent of all R&D spending on human pharmaceuticals over the same 1980-89 period (321,324). However, these measures are imperfect, since not all animal testing is for safety and toxicology and not all safety and toxicology testing involves animals. The increase could reflect the increase in the

number of NMEs tested for safety and toxicological effects during the 1980s.

Among the suggested reasons for animal cost increases in the OTA survey of animal research facilities are: 1) increased demands that animals be healthy and virus-free, largely eliminating the use of pound animals and explaining the particularly large increase in costs of some studies involving dogs; 2) stricter regulation of animals' living conditions under the Animal Welfare Act (most recently amended by Public Law 99-198), other government guidelines, and professional standards set by the American Association for Accreditation of Laboratory Animal Care; and 3) increased security for facilities housing animal research (133).

Research on Human Subjects—Pharmaceutical executives claim that the size of human clinical trials has increased dramatically over time. A rapid increase in trial sizes is consistent with an increase in the estimated cost of phase III clinical trials from \$5.7 million (in 1990 dollars) for each new chemical entity (NCE) entering the phase in Hansen's study to \$14.3 million (in 1990 dollars) in DiMasi's study. Part of the explanation

³¹ Because each surveyed laboratory specializes in particular species, cost data for each type of animal are drawn from only one laboratory (except for dogs, which are represented by data from two breeders).

for such a large increase may be a change in the mix of drugs being tested from those for acute illness to those for chronic illness. Drugs for chronic use often require larger trial sizes.

Even within specific categories of drugs, however, the size of trials appears to have increased. OTA surveyed pharmaceutical companies for the size of clinical trials conducted prior to FDA approval for NCEs in three classes: antihypertensives, antimicrobials, and nonsteroidal anti-inflammatory drugs (NSAIDs). (See chapter 6 for a more detailed discussion of the survey and its findings.) Drugs in each class approved for marketing between 1978 and 1983 were compared with those approved between 1986 and 1990.³² Table 3-8 shows the total number of subjects entered in trials up to the point of NDA submission. The average number of subjects increased between the two periods, with the largest increase occurring in research conducted outside the United States.

Although the drugs examined in the clinical trial survey do not correspond very well to the Hansen/DiMasi research periods (only the later years of the Hansen study correspond to the approved drugs in the 1978-83 period), they do

show convincingly that the number of subjects in clinical trials increased in the period between the later years of the Hansen study and the later years of the DiMasi study.

The rapid increase in the number of foreign subjects suggests that the rising cost of preapproval research may be explained in part by the globalization of research strategies over time. If U.S. firms began to prepare self-originated NCEs for entry into foreign markets earlier, and if foreign governments increased their requirements for premarket approval over time, as they did during the 1970s, the estimated cost of developing NCEs in the IND-NDA period would increase even though part of the cost increase was for approval in other markets.

■ Conclusions About Validity of Existing Estimates

Although the cost estimates of bringing an NCE to market are imprecise and potentially biased, corroborative evidence from the aggregate studies suggests they are not grossly overestimated. The Hansen/DiMasi studies suggest: 1) the cost of developing NCEs rose rapidly in the 1970s and 1980s, and 2) increases in the numbers of employed research personnel, the size of clinical trials and the cost of animals are potentially important causes of this rise.

Some of the observed cost increase may be due to the restructuring of R&D into an integrated global process in the 1970s and early 1980s. U.S.-based firms became more aggressive in conducting the development required for approval of NCEs in other countries, thus compressing R&D expenditures into the pre-NDA approval phase. Nevertheless, these R&D costs, which may have been undercounted in the earlier studies because they occurred after the FDA approval date, are justifiable R&D outlays. Although the actual cash outlays required to bring a new drug to all of its potential markets may not have increased as rapidly as the studies suggest,

Table 3-8-Mean Enrollment in Clinical Trials Prior to New Drug Application, 1978-83 and 1986-90 (number of drugs in parentheses)

	1978-83	1986-90	Ratio of period 2 to period 1
Antihypertension drugs, . . .	1,791 (9)	2,485 (9)	1.39
U.S. studies,	1,126 (8)	1,355 (9)	1.19
Foreign studies,	665 (8)	1,150 (9)	1.73
Antimicrobial,	1,885 (15)	3,461 (12)	1.84
U.S. studies,	1,248 (15)	2,049 (11)	1.64
Foreign studies,	637 (15)	1,412 (11)	2.22
Nonsteroidal antiinflammatory drugs,	3,036 (4)	3,575 (4)	1.18
U.S. studies,	1,698 (4)	2,745 (4)	1.62
Foreign studies,	1,338 (4)	830 (4)	0.62

SOURCE: Office of Technology Assessment, 1993.

³² Hansen's study years @ 6 * first entering testing between 1963 and 1975) corresponds roughly with introductions between 1970 and 1981. DiMasi and colleagues' study years (1970-82) corresponds roughly with introductions between 1978 and 1990.

the recent estimates of DiMasi and colleagues of the pre-FDA approval cash outlays are reasonably accurate.

Can more or different kinds of studies improve on the existing estimates? More careful analysis of project cost accounts and adjustment of estimates for different cost allocation rules would give a more consistent estimate across firms, but it is unlikely the resulting estimates of cash outlays would be very different, and probably not lower.

Gaining access to proprietary company management cost accounts in a large enough number of companies would be very costly and would take many years. Although Congress has the power to subpoena financial data, pharmaceutical companies have demonstrated a willingness to actively resist providing access to this proprietary data. Past efforts of the U.S. General Accounting Office to obtain data on pharmaceutical costs were ultimately unsuccessful after many years of effort that ultimately involved decisions in the U.S. Supreme Court. (See appendix D for a history of the court cases and a legal analysis of congressional access to pharmaceutical companies' financial data.)

To summarize, the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NCEs first tested in humans between 1970 and 1982. The rapid increase in inflation-adjusted R&D cash outlays over the relatively short observed time span separating Hansen's and DiMasi's studies illustrates how quickly such costs can change and how sensitive such costs are to changes in R&D success rates over time.

OTHER FACTORS AFFECTING VALIDITY

■ The Cost of Capital

Capitalizing costs to their present value in the year of market approval more than doubles the cost of R&D as estimated by DiMasi and colleagues, from \$127 million (in 1990 dollars) for

cash R&D outlays per successful drug to \$259 million (at a 9 percent interest rate). While the practice of capitalizing costs to their present value in the year of market approval is a valid approach to measuring R&D costs, little is known about the appropriate cost of capital for R&D projects.

A completely accurate measurement of capitalized cost would require the analyst to know, for each dollar spent on the particular sample of NCEs studied by DiMasi, the cost of capital that pertained to that investment at the time it was made. Even though these are retrospective studies, the cost of capital that should be assigned is the cost the investors actually faced at the time they made their investments.

The cost of capital varies widely across types of research projects and with successive investments as the project progresses toward the market. (See appendix C for an explanation.) It also changes from day to day as the risk-free interest rate changes. But detailed data on the actual riskiness of particular projects invested at specific times simply do not exist. Consequently, the fully capitalized cost of R&D associated with the NCEs entering testing in DiMasi's study can be only crudely approximated.

All of the R&D cost studies reviewed in this chapter assumed the cost of capital for R&D investments was constant across all projects and over the entire period during which the R&D spending on the sampled NCEs was taking place. Myers and Shyam-Sunder estimated for OTA the inflation-adjusted weighted average cost of capital for a sample of pharmaceutical firms at three points in time, January 1, 1980, January 1, 1985, and January 1, 1990, at 9.9, 10.7 and 10.2 percent respectively (285). For pharmaceutical companies as a whole, then, a reasonably rough approximation for the cost of capital over the period of DiMasi's study would be 9 to 10 percent. (The higher the cost of capital, the higher would be the estimated R&D cost, so DiMasi's choice of 9 percent is conservative in that regard.)

Pharmaceutical firms can be thought of as collections of investments, some with high risk and some with low risk. R&D investments are

riskier than other investments pharmaceutical companies make, but for reasons that are different from conventional ideas about risk (see appendix C for explanation). The earlier in the R&D process the investment is (e.g., at the preclinical phase of research), the higher its cost of capital is likely to be. How much riskier R&D investments are than the other investments of the firm cannot be precisely estimated with existing data, however. The best that can be done to get a quantitative estimate of the cost of capital for pharmaceutical R&D projects is to examine the cost of capital for firms investing largely in R&D and having relatively little investment in ongoing operations.

Myers and Shyam-Sunder estimated the real cost of capital for seven small pharmaceutical firms, three of which were biotechnology firms, at 14 percent, 4 percentage points higher than the cost of capital for 15 large pharmaceutical companies. In an unrelated study, Stewart (409) estimated the cost of capital for business risk for 1,000 publicly traded companies in the United States and Canada. Companies whose main business was providing R&D services (R&D laboratories) had a cost of capital for business risk approximately 4.5 percentage points higher than the cost of capital for business risk for the drug companies in Myers and Shyam-Sunder's sample. Shyam-Sunder's recent update of the Myers and Shyam-Sunder paper found a 2.6 percent difference in the net cost of capital between 30 biotechnology firms and 19 large pharmaceutical firms (390).³³ The results of these studies suggest that a 4 percent differential in the cost of capital from the beginning to the end of the research process is a reasonable upper bound for the capitalized costs of early R&D.

The weighted average cost of capital for pharmaceutical firms with ongoing operations (after adjusting for inflation expectations) was roughly 9 to 10 percent over the past 15 years. Investments in manufacturing capacity should therefore be below that value, while R&D investments should be above it. A reasonable upper bound on the true cost of capital for early pharmaceutical R&D can be constructed by assuming investments in a manufacturing plant have a 10 percent cost of capital (a high estimate). Applying the 4 percent spread (a relatively high estimate) to the 10 percent cost of capital, the real cost of capital for early R&D would be no greater than 14 percent.

OTA recalculated DiMasi's study with a cost of capital that decreases linearly over the life of R&D projects from 14 to 10 percent. The resulting capitalized cost in DiMasi's study increases from \$259 million to \$359 million (in 1990 dollars). Thus, an upper bound on the full cost of bringing NCEs to market in the 1970s is roughly \$359 million. These calculations highlight the sensitivity of the estimate of fully capitalized R&D costs to assumptions about the cost of capital for R&D.

TAX SAVINGS FROM R&D

A company's effective cost of bringing a new drug to market is substantially reduced by tax savings the company (or its investors) receives when it invests in R&D. The net cost of every dollar spent on research must be reduced by the amount of tax avoided by that expenditure. These tax savings from R&D come about both from deductions and from tax credits that reduce a company's tax liability when it spends money on R&D.³⁴

³³ A 1989 survey of approximately 145 biotechnology firms engaged in therapeutic health markets reported R&D expenses accounted for 67 percent of product sales (64).

³⁴ Companies get tax breaks from a number of provisions in the Federal tax code that effectively reduce the amount of taxes they owe on earned income. (See chapter 8 for details.) Some of these tax savings are not influenced by the amount of money the company invests in R&D. For example, companies that manufacture products in Puerto Rico and other U.S. possessions can take advantage of a tax credit on income from those operations (see chapter 8). The amount of the possessions tax credit that can be claimed is unaffected by how much R&D the company performs. Thus, the effect of taxes on the cost of R&D must be computed as if the possessions tax credit did not exist. Only those tax savings that come about from conduct of R&D should be included in the analysis.

Table 3-9--U.S. Corporate Marginal Tax Rates, 1971-91

Taxable Income (\$)	1971-74	1975-78	1979-81	1982	1983	1984-86	1987*	1988-91
0-25,000	22	20	17	16	15	15	15.0	16
25,000 -50,000	48	22	20	19	18	18	16.5	16
50,000 -75,000	48	48	30	30	30	30	27.5	25
75,000-100,000	48	48	40	40	40	40	37.0	34
100,00-335,000	48	48	48	46	46	46	42.5	39
335,000-1,000,000	48	48	48	46	46	46	40.0	34
1,000,000-1,405,000	48	48	48	46	46	51	42.5	34
1,405,000+	48	48	48	46	46	47	40.0	34

* 1987 tax rates were based on average rates paid in 1986 and 1988. Figures shown are the average or rates paid by all firms in 1987.

SOURCE: U.S. House of Representatives, U.S. Congress, "The Overview of the Federal Tax System," 102d Congress (Washington, DC: U.S. Government Printing Office, April 10, 1991).

Under section 174 of the Federal tax code, qualifying R&D expenses are deductible from taxable income. This tax deduction reduces the cost of qualifying R&D by the amount of the company marginal tax rate.³⁵ Table 3-9 presents the U.S. corporate marginal tax rates for the years 1971 to 1991. Because of the size and sales of most major pharmaceutical firms, the bulk of their taxable income would fall into the highest tax bracket.³⁶ Hence, in the simplest analysis, the cost of R&D spending should be reduced by the top tax rate.³⁷ Between 1971 and 1991, this marginal tax rate fell from 48 to 34 percent, thus effectively raising the cost of R&D. (It also raised the after-tax revenues from products resulting from the R&D, so the importance of taxes is not nearly

as great when measuring net R&D returns, rather than R&D costs in isolation.)

In the R&D period covered by DiMasi (1970-87), the rate declined from 48 to 46 percent. With a 46-percent tax rate, the after-tax cost of \$1.00 of R&D undertaken at the time of DiMasi's study would be: $\$1.00 - \$0.46 = \$0.54$.³⁸ Today, the net cost of a dollar of R&D undertaken by an established company with positive net income would be \$0.66.³⁹

During the 1980s two tax credits were put into effect that reduce the cost of pharmaceutical R&D. In 1981, Federal tax law was amended to include a tax credit for any firm when it increases "qualifying" R&D expenses. This credit carried a statutory credit rate of 25 percent of qualifying

³⁵ If a firm conducts R&D in other countries that allow R&D to be deducted from taxable income but have tax rates that differ from those in the United States, the company may realize a different net rate of reduction in the cost of its R&D.

³⁶ Since the firms studied by Hansen and DiMasi made up 40 percent of domestic R&D, they were probably composed largely of well established pharmaceutical firms.

³⁷ Unlike other R&D expenses that are deducted in the year they are made, capital expenditures for R&D, such as new R&D equipment or facilities, are depreciated from taxable income over several years. The shorter the period of depreciation the greater will be the effect of tax savings on the cost of R&D. Prior to 1981, Federal law required firms to deduct R&D capital expenditures in equal amounts over the useful life of the equipment or building, which could be 10 years or more. Beginning in 1981, firms could fully depreciate R&D capital expenditures within 3 years, although in 1986 Congress raised the period to 5 years. Not much is known about the depreciation schedules used to estimate R&D costs in the Hansen and DiMasi studies. Depreciation schedules on tax returns may be different from those for financial statements, and without more detailed information it is impossible to know whether the net tax savings for R&D capital expenditures are higher or lower than the statutory marginal rate. OTA assumed for the analyses here that R&D capital expenditures are taxed at the marginal tax rate.

³⁸ As explained in chapter 8, not all R&D expenses meet the definition of "qualifying" laid out in section 174 of the tax code. This definition becomes important for calculating the orphan and R&D tax credits discussed below. However, it is not important here for calculating the deduction, because R&D expenses not deductible under section 174 are nonetheless deductible as other business expenses.

³⁹ Small startup biotechnology firms may have little or no taxable income, but tax losses can be carried forward into future years. Still some firms may never become profitable, and the value of future tax benefits is less than those that can be used immediately. Therefore, the net cost of research to such small firms may be higher than for established pharmaceutical firms.

expenses until 1986, when the rate was reduced to 20 percent. The credit pertains only to increases in R&D, not to actual expenditure levels, so the extent to which it actually reduces the cost of R&D would depend on research spending trends in firms themselves. Because pharmaceutical R&D grew rapidly in the 1980s, the pharmaceutical industry may have benefited more than other industries from the R&D tax credit.

The Orphan Drug Act of 1983 (Public Law 97-414) provided a 50-percent tax credit for qualifying clinical R&D on investigational drugs that have been granted orphan status by the FDA. The credit is available only for "qualifying" clinical research, not for animal or laboratory research and not for supervisory or other kinds of R&D expenditures typically disallowed by the Internal Revenue Service. Also, when the credit is applied, the expenses cannot be deducted, so the net cost of a dollar of qualifying research under this credit is effectively \$0.50. Companies without current taxable income cannot save the credit for use in future years, however, so startup research-based firms may not have access to this credit.

Because these credits are of recent vintage and would not apply to the vast part of the research undertaken in the time periods studied by Hansen and DiMasi, they would not affect the net costs of that research. Chapter 8 contains estimates of the extent to which these credits have been claimed in recent years.

To illustrate how important tax savings are to net R&D costs, OTA recalculated the R&D cost per new chemical entity from DiMasi's estimates (table 3-10). The sample of NCEs that DiMasi studied underwent the great bulk of discovery and development at a time when the marginal tax rate was 46 to 48 percent. Adjusting for tax savings (using a 46-percent rate) without any other changes reduces the net cash outlays per NCE from \$127.2 million to \$65.5 million, and it reduces the total costs capitalized to the point of market introduction from \$259 million to \$140 million. When the cost of capital was permitted to decrease linearly from 14 to 10 percent over the

Table 3-10-After-Tax R&D Costs Estimated by DiMasi Under Different Assumptions About the Cost of Capital" (\$ 1990 millions)

Cost of capital (%)	Before-tax savings	After-tax savings (46%)
9	\$258,650	\$139,671
10	279,112	151,045
Variable (10 - 14)	359,313	194,029

a All assumptions, given in 1990 dollars, were adjusted for inflation using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, estimates adapted from J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

life of the R&D projects, the net after-tax cost was \$194 million. This estimate is an upper bound on the cost of bringing new drugs to market for products that first entered human testing in the 1970s.

Lower tax rates in the 1980s would raise the net costs of research, all other things being equal, to as much as \$237 million in after-tax dollars, but because R&D outlays per successful drug are extremely sensitive to changes in technical and regulatory conditions, it is impossible to predict the cost of R&D for projects beginning today. The rising number of biotechnology-based drugs under investigation in recent years (see below) may radically alter the time and expenditure profile in ways that can not be predicted from the DiMasi study.

RECENT TRENDS IN THE COST OF R&D

The studies of R&D costs reviewed in this chapter examined NCEs that entered testing in the 1960s and 1970s. There are few data sources, outside of aggregate R&D expenditures, to establish trends for drugs that entered clinical research in the 1980s. As the previous chapter described, R&D spending climbed dramatically in real terms throughout the 1980s, but the ultimate impact of these spending increases on the cost of developing NCEs will depend on the productivity of the research in bringing promising NCEs into clinical testing and ultimately to market.

OTA compared recent data (from the 1980s) on the outputs of pharmaceutical research, the length

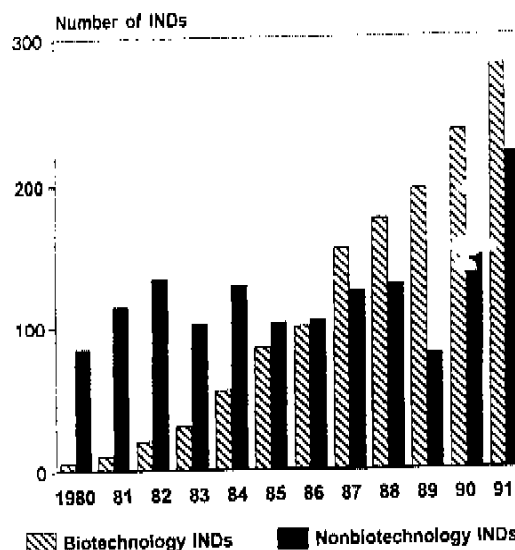
of the development period and success rates for NCEs with data from the 1970s, overall, the data suggest the output of preclinical research—the submission of investigational new drug applications for new molecular entities—has increased in the 1980s. Moreover, the rate of success in reaching the NDA stage or market approval has improved for NCEs introduced in the 1980s. However, the higher success rates for NCEs may be partly driven by an increase in the proportion of INDs for licensed-in drugs.

■ Trends in Commercial INDs for NCEs

Data published by the FDA Center for Drug Evaluation and Research show the total number of commercial INDs handled by the Center increased from an average of 253 per year between 1975 and 1980 to 334 per year between 1981 and 1990.⁴⁰ (See chapter 6 for more detail.) Because the same NCE, may have multiple INDs, and new uses or formulations of existing drugs also require INDs, the total number of INDs is not a perfect indicator of increases in the number of NCEs entering clinical development. Data from CSDD'S NCE survey of over 40 companies indicate the number of INDs for NCEs increased from 210 per year in 1975-78 to 299 per year in 1983-86 (107).⁴¹ Although INDs for U.S. self-originated NCEs grew by 25 percent between the periods, the percent of all NCE INDs that was for self-originated drugs declined from 60 to 53 percent between the two periods. Licensed-in drugs and INDs submitted by foreign firms grew as a proportion of total NCE INDs submitted to the FDA.

Not only did the number of INDs increase rapidly throughout the 1980s, but the makeup of the drugs shifted from chemically synthesized compounds to biotechnology drugs (see figure 3-3) (66). This substantial shift means that the technologic and regulatory conditions that influence drug R&D costs have changed in the decade

Figure 3-3-Biologic Applications for Investigational New Drugs, Fiscal Years 1980-91



SOURCE: Federal Coordinating Council for Science, Engineering, and Technology, Office of Science and Technology Policy, Executive Office of the President, *Biotechnology for the 21st Century: A Report by the FCCSET Committee on Life Sciences and Health* (Washington, DC: U.S. Government Printing Office, February 1992).

of the 1980s. Success rates, regulatory delays, the length of the preclinical and clinical period, and costs of clinical research may be vastly different for these new drugs. Prediction of today's cost of bringing a new drug to market on the basis of the kinds of drugs that were being tested in the 1970s—the period of DiMasi's study—is bound to be inaccurate.

■ Trends in Success Rates

Data CSDD supplied on NCEs developed by companies responding to its ongoing survey indicate the probability of reaching the NDA stage was higher for NCEs first entering clinical testing between 1980 and 1982 than it was for NCEs first entering clinical testing in the 1970s.

⁴⁰ The published IND numbers do not include biologicals, because the Center for Biologics does not compile such data. Biological products under development were few in the 1970s, but grew rapidly in the 1980s.

⁴¹ DiMasi and colleagues also give information on the 1979-82 period. See chapter 6 for more detail.

Table 3-11 shows the proportion of NCEs in the CSDD sample for which an NDA was filed within 48 or 60 months of IND filing for four cohorts of NCEs first entering clinical testing.⁴² In addition, the FDA supplied OTA with more recent data on a sample of NCEs whose first commercial INDs were filed in the 1984-86 period that were compared with an earlier published FDA analysis of a similar group of INDs first filed 1976-78. INDs reaching the NDA filing stage within 54 months increased from 6.8 to 11 percent. (Though few NMEs were approved from the 1984-86 cohort, the overall approval rate was also higher. See chapter 6 for more detail.)

Although overall success rates have improved in the recent past, the improvement may be due in part to a shift in NCEs from self-originated to licensed-in. Licensed-in drugs have higher success rates than do self-originated drugs, probably because they are self-selected for success. For example, of NCEs entering testing between 1970 and 1982, an NDA was submitted within 48 months for 7 percent of self-originated drugs, compared with 21 percent of licensed-in drugs (427). At 60 months, 28 percent of licensed-in NCEs had reached NDA submission compared with 9 percent of self-originated drugs. Of NCEs entering human testing among U.S. companies, those licensed-in grew from about 21 percent in 1975-78 to 27 percent in 1983-86 (107). Thus, the improvement in success rates for drugs first entering testing in the 1980s is at least partly due to the changing source of NCEs.

■ Recent Development of Orphan Drugs

Since 1983, Federal law has stimulated the development of orphan products through a series of incentives and subsidies, including the tax credit for clinical research on designated orphan drugs. (See chapters 8 and 9 for more detail.) These products may have a very different cost

Table 3-11-Percent of NCEs Reaching NDA/PLA Submission in Given Time Intervals

Year in which NCE entered clinical trials	Percent filing NDA/PLA within:	
	48 months	60 months
1965-69.....	4.6%	7.0%
1970-74.....	8.0	12.0
1975-79.....	10.0	13.0
1980-82.....	12.0	17.0

KEY: NCE = new chemical entity; NDA = new drug application; PLA = product license application.

SOURCE: Office of Technology Assessment, 1993, based on data supplied by Tufts University Center for the Study of Drug Development from its database of NCEs reported by 41 pharmaceutical firms.

structure from other NCEs, not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs. Although FDA approval standards are no different for this class of drugs than for others, orphan drugs are likely to have smaller and quicker clinical research studies than other studies because of the relative rarity of the diseases studied.

The FDA provided OTA with confidential data on new molecular entities (NMEs) whose first commercial IND was filed in the years 1984-86. (See chapter 6 for more detail on this sample of drugs.) Within 54 months of the IND filing, an NDA had been filed for 11 percent of all INDs, and 3.8 percent had been approved (see chapter 6), whereas for NMEs that had orphan designations, an NDA had been filed within 54 months for 33 percent, and 11 percent had been approved.⁴³

Regulatory approval times also appear to be shorter for orphan drugs. For example, during the period 1985-90, the average approval time for approved drugs without orphan designation was 29.3 months, while for approved orphan drugs it was 27.4 months (168). For products classified as "A" by the FDA, the approval time for non-orphans was 25.7 months, while for orphans it

⁴² A regression of NDA filing rates on time indicated the increase shown in the table was statistically significant at the 10 percent level. Of significance for both the 48-month and 60-month success rates.

⁴³ OTA identified nine NMEs for which the first commercial IND had been filed in 1984-86, and which had been granted an orphan designation. An additional four NMEs in the IND cohort had orphan designations, but data on the sponsoring company were inconsistent and they were not used. (Exclusion of the four NMEs did not change the results materially.)

was 18.1 months (168). Although it is impossible to know whether the ultimate success rate for orphan products will be higher or lower than for nonorphans, the sensitivity of development costs to success rates suggests orphan drugs may have a substantial cost advantage.

CONCLUSIONS

The increase in the inflation-adjusted cost of developing a new drug from the early 1970s to the late 1970s is dramatic. Real cash outlays per successful NCE increased by almost 100 percent in the period. The evidence suggests that, in 1990 dollars, the mean cash outlay required to bring a new drug to market (including the costs of failures along the way) **was in the neighborhood of \$127 million** for drugs first entering human testing in the 1970s. The size of this required cash investment depends on the rate of success at each stage

of development and the **ultimate** productivity of the research enterprise. Small differences in the ultimate success rate can make a big difference in the cost per approved NCE. Other factors, such as changes in R&D technology and regulatory conditions, can also have dramatic and rapid impacts on costs. Thus, the estimates of the R&D cost per successful product are inherently unstable over time.

The fully capitalized cost of bringing a new drug to market cannot be measured with great accuracy because the cost of capital for R&D investments is unknown. The best evidence suggests, however, that for drugs first entering human testing in 1970-82, the after-tax cost per successful drug, capitalized to the point of FDA approval for market, was somewhere between \$140 million and \$194 million (in 1990 dollars).

Appendix B

Methodology for Section II ("PhRMA's Own Data Contradicts the \$500 Million Claim")

The aggregate analysis in Section II is roughly modeled after a study by S.N. Wiggins ("The Cost of Developing A New Drug," Washington, D.C., Pharmaceutical Manufacturers Association, 1987).

This aggregate analysis is not perfect, for several reasons explained below, but it has been reviewed by three economists with acknowledged expertise in the pharmaceutical industry and they have found it sound.

The first imperfection in Public Citizen's analysis is that it relies on PhRMA data, which has not been verified for accuracy.

The second imperfection is that PhRMA reports R&D spending in two categories – 1) "domestic" (which includes all spending by American and foreign-based companies in the U.S.) and 2) "abroad" (which only includes overseas spending by U.S.-based companies). Neither of these categories is ideal for this particular analysis, as explained below.

Public Citizen's aim was to show simply the amount PhRMA reported that the industry spent on R&D, and then divide that spending by new drugs approved for market (over a time frame that corresponded to R&D spending). That simple division ought to produce a spending-per-new drug figure derived from the industry's own data. This figure would not include the opportunity cost of capital, so it would reveal how much drug companies actually spent on R&D for each new drug – on average – including failures.

Here's how Public Citizen arrived at the figures:

To get an accurate apples-to-apples analysis, one would need to know all R&D (both here in the U.S. and abroad) that led to the discovery and development of drugs approved for market in the U.S. over an appropriate time frame.

The problem is, these numbers don't exist in public records and PhRMA doesn't report its data in such fashion. The FDA records how many new drugs are approved for market each year, but it does not identify the location of spending that connects directly to each new drug approved.

For example, consider PhRMA's reported spending in two categories – "domestic" and "abroad." These two categories do not necessarily capture all relevant spending pertaining to drugs approved for market in the U.S. In some cases, these two categories might underestimate spending; in other cases, they could overestimate.

It could be that foreign-based companies conducted R&D overseas for a drug that was approved in the U.S. and such spending would not be evident in PhRMA's data. Conversely, PhRMA's reported spending might include R&D costs here and abroad that had nothing to do with new drugs approved in the U.S.

Public Citizen considered identifying those new drugs approved by the FDA that were developed only by U.S.-based companies, and then comparing those drugs to spending (both here and abroad) by U.S. companies. But such an analysis might be left counting U.S. company spending that did not pertain to these drugs; or it might not capture overseas spending by foreign-based companies on these drugs; or it might not account for the licensing deals by which foreign-based companies perform contract work on specific drugs for U.S.-based companies and vice versa.

Given those limitations, it did not make sense to winnow the list of FDA-approved drugs down to those that were mainly developed by U.S.-based companies. So Public Citizen was left with PhRMA's reported annual R&D spending and the FDA's annual tally of new drugs approved for market. Economists advised that a comparison of these numbers would provide a rough estimate of R&D spending per new drug (including failures).

Public Citizen then wanted to account for the roughly seven-year lag between R&D spending and new drug approval. Thus, this measure compares R&D spending for 1994 to new drug approvals for the year 2000.

To be even more accurate, this measure accounts for years in which spending on new drugs was extraordinarily high or low. It compares spending over seven-year periods with new drug approvals over seven-year periods. An annual average was calculated for each period, which has the effect of smoothing out peaks and valleys.

The results? From 1988 through 1994, PhRMA reported total R&D (domestic and abroad) spending of \$69.7 billion. Adjusted for inflation, it is \$88.0 billion in year 2000 dollars, for an average of \$12.56 billion per year (See Table B-1). During the period 1994-2000, the FDA reported that 667 new drugs were approved for market, or 95.3 new drugs approved each year, on average.

Dividing the average annual spending by average annual new drug approvals, we see that average R&D spending per new drug in this period was \$87.0 million (after accounting for R&D tax deductions).

Table B-1
Average R&D Cost per New Drug Approval During the 1990s
(Rolling 7-Year Average with 7-Year Lag, \$ in millions)

Domestic + Foreign R&D Spending

7-Year R&D Period	Average Annual R&D Spending	7-Year NDA Period	Average Annual New Drugs Approved	Pre-Tax R&D Spending per New Drug	After-Tax R&D Spending per New Drug
1988-1994	\$12,564.3	1994-2000	95.3	\$131.9	\$87.0
1987-1993	\$11,523.2	1993-1999	91.3	\$126.2	\$83.3
1986-1992	\$10,417.6	1992-1998	92.4	\$112.7	\$74.4
1985-1991	\$9,339.1	1991-1997	88.6	\$105.4	\$69.6
1984-1990	\$8,433.5	1990-1996	80.4	\$104.9	\$69.2

Source: Spending data comes from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2000; NDA data comes from U.S. Food and Drug Administration, Center for Drug Evaluation and Research, December 31, 2000. (All spending figures have been inflated to year 2000 dollars.)

Note: Domestic R&D includes expenditures within the United States by research-based pharmaceutical companies. Foreign R&D includes expenditures outside the United States by U.S.-owned research-based pharmaceutical companies.

Some critics might find fault with the seven-year lag, arguing that in accounting terms, today's R&D expenses are paid by today's revenue. Thus, R&D spending in any year ought to be compared with drugs brought to market that same year. As mentioned earlier, this study rejects that argument because it doesn't reflect the reality that R&D spending invariably precedes the marketing of a drug, and, as noted earlier, DiMasi agrees that spending should be lagged two to 12 years. Nevertheless, Public Citizen calculated R&D spending for current drug approvals and current research expenditures and found that spending remained close to \$100 million per drug, with costs in the 1990s ranging from \$99 million to \$118 million per drug. (See Table B-2)

Table B-2
Average R&D Cost per New Drug Approval During the 1990s
(Rolling 7-Year Average with No Lag, \$ in millions)

Domestic R&D Spending Only

7-Year Period	Average Annual R&D Spending	Average Annual New Drugs Approved	Pre-Tax R&D Spending per New Drug	After-Tax R&D Spending per New Drug
1994-2000	\$17,054.1	95.3	\$178.98	\$118.1
1993-1999	\$15,627.1	91.3	\$171.19	\$113.0
1992-1998	\$14,289.9	92.4	\$154.60	\$102.0
1991-1997	\$13,123.4	88.6	\$148.17	\$97.8
1990-1996	\$12,025.2	80.4	\$149.51	\$98.7

Source: See above.

Appendix C

“NIH Contributions to Pharmaceutical Development: Case Study Analysis of the Top-Selling Drugs,” an administrative document dated February 2000. Prepared by NIH Office of Science Policy.

See attached



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

May 7, 2001

Bob Young
Research Director, Public Citizen's Congress Watch
Public Citizen
215 Pennsylvania Avenue S.E.
Washington, D.C. 20003

RE: FOI Case No. 26177

Dear Mr. Young:

This is a final response to your Freedom of Information Act (FOIA) request dated January 9, 2001. You requested a copy of "NIH Contributions to Pharmaceutical Development," an administrative document dated February 2000, which was described in the "References" section of a May 2000, report by the Joint Economic Committee of the United States Congress.

A search of the Office of Science Policy, NIH, produced 38 pages of records responsive to your request. That document is enclosed.

Provisions of the Act allow us to recover part of the cost of responding to your request. Because the cost fell below the \$25 minimum fee, there is no charge for the enclosed material.

Sincerely,

Susan R. Cornell, Esquire
Freedom of Information Officer
National Institutes of Health
Building 31, Room 2B39
9000 Rockville Pike
Bethesda, MD 20854

Enclosure:

38 pages

NIH CONTRIBUTIONS TO PHARMACEUTICAL DEVELOPMENT

CASE STUDY ANALYSIS OF THE TOP-SELLING DRUGS

INTRODUCTION

The United States is the acknowledged world leader in innovative biomedical science and technology. U.S. pharmaceutical and biotechnology companies are among the nation's most internationally competitive industries. This economically advantageous position owes chiefly to the continuing stream of advances in the basic biomedical sciences over the last five decades. Efforts to harness the potential of the revolutionary advances of the last several decades in genetics, molecular biology, and related disciplines are now extensive — advanced pharmaceuticals, genetic and other new human health therapies, and a host of commercial applications outside of medicine. The unique U.S. system of public support for science, mainly through the National Institutes of Health, is the foundation of that success.

An ongoing series of studies in the Office of Science Policy at NIH has been designed to analyze the effectiveness of public funding of biomedical research. Because product development is a good measure of the practical usefulness of research advances, case studies of products now on the market have been used to illustrate the health and economic benefits of NIH-funded research. The intellectual history underlying development of eight commercially successful products has been documented, and the results are presented here. These products include the five top-selling pharmaceuticals and three non-medical biotechnology-based products.

Background

The health and economic benefits created by the U.S. pharmaceutical industry result from an informal public-private partnership. Federal support for basic research has been acknowledged by the pharmaceutical industry to be the foundation for its success. According to the largest pharmaceutical industry trade association¹, "the National Institutes of Health plays a vital role in drug discovery by funding basic research into the fundamental mechanisms of disease. This allows industry to focus on finding ways to intercept disease mechanisms."

Some less obvious ways that public funding creates an infrastructure on which privately-funded research builds have been documented. For example, a 1993 report to the U.S. Congress² details the role of NIH in training biomedical scientists, many of whom subsequently work in industry, and in supporting the construction of buildings and laboratories at universities across the country in the 1950s and 1960s. A 1994 survey of life science firms also showed that industry funding of academic biomedical research is growing, and that scientists are increasingly combining public and private funds in the same research projects.³ The authors of the 1994 survey point out that life

sciences companies draw on the scientific knowledge generated by a publicly-funded research infrastructure in academia.

Perhaps most striking are recent studies that suggest that continued Federal support for biomedical research over the past half-century has encouraged pharmaceutical companies to act in ways that enhance their productivity. Based on their detailed analyses of the organization of pharmaceutical research and development, including interviews with senior industry scientists and managers, Cockburn and Henderson suggest that those pharmaceutical companies that organize in ways that most effectively tap the results of publicly-funded science are those that are most successful.⁴ For example, they found that those firms whose scientists publish a higher fraction of papers coauthored with university-based biomedical researchers obtained more patents per research dollar, on average, than firms whose scientists work less closely with the public sector.

Two earlier case study analyses have assessed the input of various sectors of the biomedical science community. Maxwell & Eckhardt looked at 32 drugs introduced prior to 1990 and concluded that non-industrial contributions (universities, government labs, non-profit research institutes, hospitals) play an important role in drug discovery. Without these nonindustrial contributions, approximately 60 percent of the drugs would not have been discovered or would have had their discoveries markedly delayed.⁵ More recently, Cockburn and Henderson⁶ constructed case histories of medications identified by industry experts as having had the most impact upon therapeutic practice between 1965 and 1992. Among these 21 drugs, publicly-funded research was instrumental to the development of 16, or 76%. Comparing their results from a more recent group of drugs to Maxwell and Eckhardt's earlier study, Cockburn and Henderson suggested that "public sector research appears to have become more important over time, as one might expect given the increasing role of modern molecular biology in drug discovery."

Although the intent of these studies is to demonstrate the utility of public funding to industry productivity, they still may under represent the effects of basic research. Other reports have appeared which question or underplay the role of basic research in medical and technological advances. For example, in response to a survey conducted in the late 1980s research and development managers at major U.S. pharmaceutical firms reported that only one-quarter of the products and processes they had commercialized in the previous decade would not have been developed without delay in the absence of recent academic research.⁷ A recent survey reported that private industry was the first to synthesize over 92 percent of drugs approved between 1981 and 1990.⁸

Maxwell & Eckhardt state that "the availability of a new and independently discovered drug [often] provided an essential tool that permitted a much needed verification of some at-risk concept." The book concludes that 38 percent of the drugs resulted entirely from industry input and that industry was the largest contributor to drug and medicine production. A similar stance is taken further in an editorial and follow-up letter in recent issues of *Science*,⁹ which state that all research that is "unconnected to useful products" should be privatized, although in another paragraph it is noted that companies are phasing out their non-targeted research because it is not cost effective. The letter comments that the flow of usefulness is usually from technology to

science rather than vice versa.

Private industry does play a large and growing role in medical research. By 1994, industry accounted for over half of the total national investment in medical research. However, most of this private investment was for applied research and product development. In 1992 (the most recent year for which figures are available), 38% of the pharmaceutical industry's total R&D investment of \$8.8 billion was used for applied research, 48% was spent on product development, and only 14% was applied to basic research.¹⁰ To the extent that basic research into the underlying mechanisms of disease drive new medical advances, the R&D in industry is not performing the role played by public research funding.

Whether the conclusions are reached by survey or case study, what these analyses have in common is that by carefully defining what constitutes a necessary contribution, much of the enabling intellectual background that led to the new product is removed from consideration. Maxwell & Eckhardt define a contribution as separate from its framework of science; work that is "permissive" as distinct from that which is "contributory"; and a "necessary forerunner" as not directly involved in the innovation. The present study was undertaken to determine whether and to what extent public funding of research enabled the development of certain medically or commercially successful products. Additionally, this study begins to lay a basis for discussing the specific ways by which those who expand fundamental understanding of the workings of the natural world are as important to technological advance as those who implement that knowledge.

METHODOLOGY

Case studies were used to illustrate the public/private partnership in drug development. An intellectual history was drawn of the top five drugs from a list of the 13 drugs which sold \$1 billion or more in 1994 and 1995. These five top-sellers are the antidepressant Prozac, the two antihypertensives Vasotec and Capoten, the antiherpes drug Zovirax, and the ulcer and gastritis drug Zantac. We choose not to highlight known NIH success stories. Instead, these drugs were selected based on their market success as the objective indication of their benefits to health. The analysis began with a simple Medline search using the chemical name of the drug to find several review articles. These reviews and the original research articles they cited provided a view of the understanding of the disease and the technical capabilities at the time the product was developed. As discussed below, patent citations were not useful in developing these cases.

The scientific discoveries that led to the necessary concepts and techniques were identified, along with the names and affiliations of the scientists performing the work. Rather than attempt to identify a small number of "key papers," which does not accurately represent the way scientific ideas develop in the research community, the approach taken was to identify major areas of research which led to drug discovery and the individuals or laboratories who were significantly involved. Each case is presented in two parts: a story describing how the ideas and events came together, and a table which identifies scientists and their affiliations, contributions, references, and support acknowledgments when available.

Example products for case studies were selected based on their commercial success, where the role of NIH in their development initially was unknown. Example medical products were selected from the broad category of therapeutic drugs. This category of medical products was selected because drugs provide important health benefits, and because they are often more cost-effective than other medical interventions.¹¹ We obtained a list of the 13 pharmaceuticals with sales over \$1 billion in 1994, provided by the Pharmaceutical Research and Manufacturers Association of America (PHRMA)¹², and selected the five drugs with the highest worldwide sales. These are: Vasotec and Capoten (antihypertensives), Zovirax (an antiviral agent), Prozac (an antidepressant), and Zantac (an antiulcer agent).

CASE STUDIES OF TOP SELLING DRUGS

Pharmaceutical discovery and development is an excellent illustration of the benefits to health of publicly funded research. Drugs and medicines are a major tool of health care and the most cost-effective medical intervention. Additionally, the pharmaceutical industry is one of the United States' most competitive international enterprises. A close look at the process of drug discovery reveals the interactive partnership between academic and industry scientists and shows how NIH funded research underlies the development of treatments for disease. The intellectual histories discussed here emphasize the need to keep both industry and medicine supplied with this resource of new ideas and techniques.

Case studies were used to trace the development of the five top-selling pharmaceuticals. The case studies (Appendix A) are presented in two parts, first a story of the ideas and technical advances which led up to the discovery, followed by a table which lists the scientists who were involved in each area of science, and documents their affiliations (NIH-supported academic, foreign academic, or industrial) and their contributions with references to the scientific literature. The science and areas of research underlying the case study drugs are described briefly below, followed by an interpretation of the findings.

Research Summary

Prozac (Fluoxetine) is used for the treatment of depression and several other psychological disorders. It acts by increasing the concentration of the signaling substance serotonin in the connections (synapses) between nerves. Three areas of research underlie its development: 1) research on blood pressure and antihistamine drugs, 2) the neurochemical basis of depression, and 3) the molecular basis of neuronal signal transmission.

Antihistamines, like many other drugs, act on the substances which nerve cells (neurons) use to transmit signals. The first antidepressant was developed following the observation of mood changes after taking certain antihistamines. Basic research on the transmission between neurons had found several of the message molecules, and an early antidepressant drug became an important tool in discovering how the signal is sent and then terminated. Psychiatric conditions could now be studied at the molecular level by showing how these signal molecules and neuron communication mechanisms underlie mental states. Through the interaction of these two fields of study and the use of the first generation drugs as research tools, the correct neurotransmitter, serotonin, was targeted. Industry scientists chose another antihistamine drug as the chemical basis for this search.

Capoten (Captopril) and Vasotec (Enalapril) are used to treat hypertension, and they act by inhibiting a crucial enzyme, ACE, in a cascade of molecular signals which regulate blood pressure. Two areas of research underlie these drugs: 1) research on the renin/angiotensin/aldosterone (R/A/A) system of blood pressure regulation, and 2) enzyme kinetics studies of the bovine enzyme carboxypeptidase, which is very closely related to ACE.

Research on the involvement of the kidney in initiating hypertension found the substance renin,

which causes vessel walls to constrict, thereby increasing blood pressure. Renin was subsequently shown to act by activating another molecule, angiotensin. Later, angiotensin was found to occur in two forms; AI is converted by angiotensin converting enzyme (ACE) to the active form AII. AII has two hypertensive effects, first by directly causing blood vessels to constrict, and second by inducing aldosterone production by the kidney. Aldosterone causes salt retention, which increases blood volume and thereby raises blood pressure as well. An early ACE-inhibiting drug derived from snake venom became a tool for continued study of the R/A/A system. Using chemical information about ACE, captopril was discovered through the adaptation of a molecular model of bovine carboxypeptidase plus its inhibitor. Captopril had serious side effects, however, and another company was able to alter the chemical structure to produce a drug with longer activity while lacking the side effects, enalapril.

Zovirax (Acyclovir) treats herpes simplex virus (HSV) infection by inhibiting the ability of the virus to replicate its DNA, thereby blocking its growth. Three research areas contributed to its development: 1) the virology of HSV, 2) studies of the enzymes of DNA replication, and 3) research on nucleotide analogs and their potential as antimetabolite cancer drugs.

The study of the replication of DNA in cells lead to the characterization of the enzymes which are involved. When HSV was isolated from sores on the skin, it was shown to have a large DNA genome which replicates and expresses genes in the same manner as the cells. Closely following the discovery of the cellular enzymes, the DNA replication enzymes of HSV were also found and characterized. During this time, the idea was developing that, since DNA consists of a chain of nucleotides, chemically altered forms, or analogs, of nucleotides could be incorporated into the growing DNA chain or could bind to the replication enzymes, thereby halting cell growth. This would mainly affect rapidly growing cells, such as cancer. Although nucleotide analogs had proven somewhat useful against HSV previously, they acted equally on the body's growing cells and so were very toxic. Once HSV was found to make its own enzymes with slightly different properties from those of the cell, analog drugs for cancer were also screened for one which would preferentially inhibit HSV rather than cellular replication. Acyclovir had this property, and was found to inhibit two of the viral DNA replication enzymes, while not killing the cells.

Zantac (Ranitidine) treats ulcer and gastritis by blocking the signaling molecule histamine from causing cells in the stomach and duodenum to produce acid. An earlier drug from which ranitidine was derived, cimetidine (Tagamet), was the first drug which could distinguish between the two types of molecules on cells, called receptors, which bind to histamine and determine what the cell's response will be. These two drugs specifically block the H2 but not the H1 type receptors, permitting acid secretion to be blocked without inhibiting other necessary functions of histamine. Three lines of research underlie these developments: 1) the discovery and characterization of histamine, 2) the concept of receptors on cells for various signaling molecules, and 3) the discovery of two types of receptors for adrenaline and a drug specific for the second type.

The signaling molecule histamine was discovered early in this century, and its chemical structure and many affects on different tissues became well known. Meanwhile, the mechanisms by which

cells receive and respond to such signals were under intense study, and the idea that cells had specific receptor molecules for these signals was slowly developing. After it was proposed that two different types of receptors for adrenaline would explain its different effects, a chemical was found which blocked only the second type of receptor. Based on this, a drug was developed to protect a weakened heart from overstimulation by adrenaline, by blocking this second receptor type. After this, histamine was also proposed to have two types of receptors, H1 and H2, the second of which stimulated acid secretion. By patterning a search after the discovery of the adrenaline blocker, and by making use of the well-known chemistry of histamine, the H2 receptor and a drug which would specifically block it were found. The resulting drug, Tagamet, was effective, but due to serious side effects it was soon replaced by Zantac, which was the product of research starting with a different chemical backbone.

Analysis of Drug Case Studies

Scientific progress over several decades underlies the development of each of the five top-selling drugs. They were conceived through research conducted in the 1950s, '60s and early '70s, developed and patented in the 1970s, and FDA approval was based on clinical results from the 1970s and '80s. NIH-funded research played a critical role in drug discovery in each of these cases. Researchers at U.S. universities and at NIH contributed by discovering basic phenomena and concepts, developing new techniques and assays, and participated in clinical applications of the drugs. However, these cases also demonstrated that public and private sector biomedical research are interwoven, complementary parts of the highly successful U.S. biomedical sciences endeavor.

Basic research lays the groundwork for drug discovery. The field of research that underlies most pharmaceutical drug development is organic chemistry and synthesis. The first techniques for isolating the active chemical in a natural substance, and then modifying its molecular structure at will, were developed during the previous century. The contemporary organic chemistry that is cited in industry research papers is frequently supported by NIH grants; however, the large majority of chemical methods are unattributed because they are old or widespread enough to be considered part of the "general knowledge." Laboratory models—the cells, tissues, or animals in which the drugs are to be tested—are of equally critical importance. The basic methods of cell culture and animal surgery were developed in the early part of this century. These older methods are unattributed, although they originate in academic science, but most specific models, or assays for specific enzymes, usually have come from the individual academic labs as part of their research results, and are cited by industry researchers in the scientific literature. Most lines of research have strong roots in European universities, but with each decade since World War II, the US contribution rose sharply as a result of NIH funding.

For a pharmaceutical company to target a disease for drug development, there must be an acceptable market potential. If the condition is widespread, causes serious disease and currently no adequate therapy exists, there is likely to be a sufficient demand for the drug to support the cost of development. Also, some insight into the cause of the disease, or a means to approach it, is usually needed. Industry scientists draw upon an existing body of scientific knowledge

when they consider these factors and begin a research and development effort. In some cases, that scientific knowledge is well-developed, but in other cases, less is known when drug development begins.

The research which ultimately led to Prozac began when the mood-altering effect produced by an antihistamine was noticed by a surgeon, at which point industry scientists began supplying him with experimental drugs. At the time, little was known about the physical basis of depression. In the cases of the other drugs, industry entered the field only after academic scientists had clarified the disease to the point of finding the enzyme or hormone that the drug acted upon. Before any work began on the development of Zovirax, publicly-funded basic researchers had discovered the cell's mechanism of DNA replication, followed by discovery of the replication enzymes made by herpes simplex virus (HSV) which were similar but not identical to the cellular enzymes. The use of nucleotide analogues (altered versions of the nucleotide building blocks of DNA) as inhibitors of tumor cell growth was pioneered in academic laboratories also. Based on these advances, industry scientists applied their work on nucleotide analog inhibitors to finding an antiviral drug. An industry scientist developed the precursors to both Zantac and Capoten after publicly-funded scientists identified the signaling substances involved in gastritis and high blood pressure, respectively, and developed the concept of how these substances acted.

Public and private research play complementary roles. The biology of a disease was usually worked out by academic scientists, while the search and testing of drugs was performed by industry, although there is often overlap in these roles. Using existing scientific knowledge, industrial scientists search for a substance with the desired activity. Once a potential drug is discovered, industry scientists conduct extensive in vitro and animal tests until they are ready to patent the invention and publish the results. Then, further studies by the company and by academic researchers on the drug's mechanism of action and its effects on animals and, eventually, on human patients, fit into a framework of continuing basic and applied advances. In many instances, a new drug becomes an experimental tool of academic researchers to understand the physiological system and the disease pathology. These continued studies often further clarify the disease mechanism and provide leads for drug improvement, as well as aid the company in getting FDA approval. Technological innovation did not follow a one-directional "pipeline," in which basic research leads applied research, and applied research leads to product development. The process involved feedback in both directions between publicly funded labs and industrial researchers.

None of the top sellers in these case studies are "first generation" drugs; they are the result of a great deal of basic research on the disease mechanism which allowed more specific targeting of the underlying problem. Sometimes this extension of knowledge included the use of the first generation drug itself. In the development of Prozac, the discovery of an earlier drug by industrial researchers preceded and enabled the discovery by academic scientists of the particular signal transmitter in the brain which the drug was acting upon to alleviate depression. This knowledge permitted the company to hunt for a more active and specific next generation drug. The result was Prozac, which itself then became an important tool in greater understanding of the neurological basis of depression. In the other cases, the particular enzyme or hormone

central to the disease mechanism was already discovered before the first drug was produced. Capoten and its antecedent drug were tools for increasing level of sophistication at which renal hypertension was understood, thereby permitting better management of the disease and pointing the way to the next step in drug design. Zantac and Zovirax were not as important in elucidating the disease process, but nonetheless were very important in ongoing progress in treatment.

The route to drug discovery is unpredictable. When scientists select chemicals to be tested for drug action, they may use either an empirical or rational design approach. In the empirical approach, collections of compounds are screened to find an active drug, where the initial lead is the activity of a natural substance or a chance observation. Knowledge of the biological system or the mechanism of drug action is not needed, although the screening process makes use of models and assays developed through basic research. Rational design of compounds for a particular activity requires knowledge of the biological system. When the target is defined—e.g., the enzyme or gene responsible for a crucial cellular activity—then an inhibitor or modifier of its function can be sought. This rational design step provides a chemical series of potential drugs, and therefore is followed by another round of screening to find the most active form. In practice, most pharmaceutical development has been a combination of these two approaches.

The five cases differ in the degree to which purely empirical discovery versus a rational targeting step were important. The development of Zovirax and the drug that preceded it was based on rational design of specific molecules to inhibit known enzymatic activities, with no purely empirical discovery phases. Capoten, Vasotec, and Zantac were also produced by the use of rational design steps based on the prior discovery of the molecular targets, although the initial drug with the activity of Capoten was derived from the activity of a natural substance. Among the five cases, Prozac was the least dependent on a rational approach, as the first drug with antidepressive properties was an entirely empirical discovery. However, the development of Prozac itself resulted from rational design aimed at one neurotransmitter out of several.

Research may be targeted to the cure of a particular disease, or aimed at understanding basic mechanisms and gaining knowledge for which no immediate application is apparent. Disease-targeted research can be effective in fueling progress in a given area. However, just as often, results from other fields of research led to breakthroughs in disease concepts or in drug discovery. These five drugs all arose from both disease-specific and unrelated fields of research. The discovery of Zantac depended on advances in three fields which were unrelated to gastritis and ulcer disease: the chemical structure and biological activity of histamine, the broad concept of cellular receptors, and the work which culminated in the development of a cardiac drug. Two out of three areas supporting the discovery both of Zovirax and of Prozac were unrelated to the disease that these drugs treat. The discovery of Capoten and Vasotec arose mainly from a broad research effort targeted to the study of hypertension, heart and kidney disease, but knowledge from research in protein chemistry and enzyme kinetics provided the critical lead needed to produce Capoten. It is not always possible to predict the source of new inspiration. Basic research aimed at understanding biological mechanisms and gaining knowledge for which no immediate application is apparent has been a vital supply of new ideas, and can only be sustained

through public support.

In the last few years, the process of drug discovery has been revolutionized by combinatorial chemistry, which is the general name for a collection of new methods to produce enormous numbers of related molecules in an orderly, tagged series. These technologies speed up empirical drug search by generating a diversity of compounds to screen for a lead. Although these methods were to a great extent designed by the industry scientists who need them, they have their roots in publicly-funded basic research. Molecular structure modeling is currently used for rational drug design and lead production. Once again, the initial concepts and techniques needed for structural modeling come from NIH funded labs, while it is now industry scientists who continue to develop the techniques. Because even the most perfect model can only produce a set of potential drugs, structure modeling and combinatorial chemistry are used in concert to maximize the efficiency of drug design, once a target is selected. Knowledge of the underlying disease mechanism which reveals the enzyme, cell, or symptom that should be targeted continues to be generated by NIH-funded research.

Advances in molecular and cellular biology have created the new biotechnology industry, which is based on an entirely new concept of drugs and medicines. Biotech drug and medicine development is, if anything, even more based in and interrelated with public sector research than drug development in the big pharmaceutical firms.

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7. Edwin Mansfield, "Academic research and industrial innovation," Research Policy 20 (1991): 1-12.

8. Tufts University, 1991 (need complete cite on this).

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Ranitidine (Zantac)

Ranitidine is used to treat gastric ulcers by blocking acid secretion in the stomach, allowing them to heal. It is more active than the first acid inhibitor, and it is better tolerated and lacks the serious side effects of the previous drug. It was the number one selling drug in 1994 and 1995, which indicates the demand for a treatment of gastritis and ulcers. The development of the first "histamine H₂-receptor antagonist" drug, which preceded ranitidine, represented a new concept in ulcer treatment. This class of drug acts by controlling acid secretion by blocking the substance that signals the stomach to produce acid. A very large body of research on histamine, its physiological effects, and its mechanism of action are behind the targeted research which resulted in these drugs. Two other areas that figured significantly were the developing concept of receptors on cells for biological signaling molecules, and the research leading to the cardiac drugs known as the β -blockers which grew from it.

The substance histamine was discovered near the turn of the century by European scientists, although at the time it was thought to be the result of bacterial growth. Another European academic scientist conducted an extensive set of experiments demonstrating histamine's complex physiological actions, which included the ability to alter blood pressure through effects on blood vessels, and to cause constriction of the bronchiolar and other smooth muscle (ie, the muscle of organs and vessels.) Ten years later, a U.S. researcher demonstrated that histamine was a normal component of the tissues, and by 1926 the European group had confirmed this. It was also shown, in two European academic labs, that histamine induces secretion of acid in the stomach. During this time, the chemical properties and methods of purification of histamine were also being defined. In 1937, an academic scientist in France developed the first inhibitor of histamine, but it was not until 1942 that industry scientists developed an antihistamine which could be used as a drug. Over the next 8 years, a large number of antihistamines were developed by foreign and US companies, although notably one US academic researcher developed the highly successful drug diphenhydramine (Benadryl) which also became the chemical basis of Prozac. These drugs blocked some but not all of the actions of histamine.

The ideas leading to the production of ranitidine had their beginning in the study of neurotransmission in the sympathetic nervous system and the development of the cardiac drugs known as β -blockers. The sympathetic nerves are part of the autonomic nervous system which regulates the functions of organs. The neurotransmitter adrenaline was first characterized and purified at the turn of the century by the U.S. scientist who later identified histamine as a normal substance in tissues. Understanding of the function of adrenaline and noradrenaline had progressed to the point in the 1930s where it was known that they could cause either excitatory or inhibitory responses in tissues, but there was a great deal of confusion as to how this happened. Several groups developed drugs which blocked the excitatory response to adrenaline in all tissues except the heart. The most successful of these adrenaline antagonist drugs was one produced by a US academic scientist, which became a widely used research tool, as well as a chemical lead for industry pharmaceutical development.

During this time, the notion of specific "receptors" on cells, which mediate the cell's uptake and response to a variety of substances both natural and medical, was slowly emerging. The receptor concept was highly controversial, mainly due to the variety of phenomena it had to account for. In 1948, a U.S. academic scientist performed experiments with several of the known adrenaline blockers and showed that two separate types of receptors, α and β , must exist, which could not be classified simply as excitatory and inhibitory. All the drugs available at the time blocked the α type of receptor. However, this work ran counter to the prevalent theory of the day, and was not accepted. Ten years later, an industry team began

testing analogs of adrenaline to find one with improved bronchodilator activity. An analog is a molecule similar enough to adrenaline, for example, that it will bind to the adrenaline receptor, but has a modification that prevents the physiological activity from occurring while also preventing the binding of adrenaline itself. These scientists reported the first compound, DCI, which blocked the inhibitory actions of adrenaline. A U.S. academic scientist realized the potential of DCI to act on the heart, and performed the experiments which put the new inhibitor together with the α and β receptor concept. He pointed out that the receptors which DCI blocks in the heart had to be the β type, which stimulate the heart but cause inhibition in most other tissues. Upon hearing these results, a scientist at ICI in Europe, who was seeking drugs to protect the heart from excitation by adrenaline, realized that DCI had the activity he was looking for. His team eventually produced the first of the β -blocker drugs, propranolol, in 1962, which was a breakthrough in treatment of heart disease. This scientist, James Black, emphasized in his papers that his work was initiated based on the concept of α and β adrenergic receptors published in 1948. He is also the connection between the cardiac drugs and the antihistaminic drugs for treatment of ulcers.

As the various effects of histamine were studied through the use of antihistamines, it became clear that several effects were not inhibited by these drugs, including the secretion of gastric acid. In keeping with the developing concept of specific receptors, a European lab defined the receptors which were blocked by these antihistamines as H1 receptors, and postulated that one or more additional types must exist. Based on this and his previous experience with β -blockers for the heart, it was obvious to Black to look for the other form of histamine receptor which mediated the effects on acid secretion by the stomach, and a chemical to specifically block them. Now at Smith-Kline French (SKF), Black and his team made analogs of histamine to test for inhibition, using the knowledge of the isolation and chemistry of histamine. But even with this auspicious start, it was 8 years later, after testing 700 compounds, before one having the required activity without the negative effects was found. The article describing the discovery of H2 receptors and the production of a chemical which inhibited them was published by the SKF research team in 1972. In it, they remark that the work was based on analogy with the β -receptors in the heart and on the structure of histamine. This first inhibitor was not useful as a drug, but after several years of additional research, the SKF scientists published the description of cimetidine (Tagamet) in 1975, the first H2-receptor antagonist drug. Cimetidine was widely tested in clinical trials, and proved useful, but had a number of serious side effects stemming from the fact that it also inhibited another physiological system.

Over the next 3 or 4 years, scientists at several companies tested different types of organic molecules for H2 antagonist activity. Certain molecular features of cimetidine, which probably were responsible for its side effects, were also thought to be a necessary part of its activity. The Glaxo team began experiments with a different molecular basis, and in 1979 they published the discovery and initial testing of ranitidine. This drug is 5 to 10 times as potent per chemical weight as cimetidine and is longer lasting. Also, since ranitidine is more specific for the H2 histamine receptors, it lacks the side effects that were problematic with cimetidine. Over the next 10 years a very large number of trials of ranitidine were conducted in US and foreign academic clinical centers, testing its usefulness for a variety of conditions and its effects on many functions of the body such as the immune system, the liver, blood pressure, respiration, and many aspects of the gastrointestinal system.

The story of ranitidine also offers an example of how continuing research and more understanding of the underlying disease process leads to improvements in treatment. It had long been thought that the excess production of stomach acid seen in ulcer and gastritis patients was itself the cause of the conditions. This idea was bolstered by the observation that when acid secretion was suppressed with H2-antagonist drugs the ulcers would heal, although recurrence was the rule. In 1983, just as ranitidine was brought to market,

the bacterium *Helicobacter pylori* was isolated from the stomachs of gastritis and ulcer patients by a scientist at an Australian university medical center. He proposed that the bacteria were the cause of the patients' conditions, and described methods for culturing the organism. Within the year, 4 additional reports of the same finding were published from other European medical centers, and many more followed once researchers knew to look for it. Over the next 5 years, many medical centers in the U.S. and Europe began clinical trials to test the association of *H. pylori* with disease, and to try various antimicrobial treatments to eliminate it.

Bacteria had been found in ulcer patients before the 1983 discovery, but the difficulty of culturing the organism was not realized, and most researchers found no bacteria. One laboratory which had isolated bacteria in the 1970s concluded they were not causative, since healing with antacid did not affect the infection. After the reports linking *H. pylori* to ulcer and gastritis appeared in 1983 and 1984, academic researchers continued to improve culture methods. As they discovered features of the organism's biology, new detection assays rapidly appeared. One significant feature is its production of the enzyme urease. Urease had been discovered well before *H. pylori*, but it was thought to be produced by the stomach. Forty years later, in 1968, it was proven to be bacterial in origin, although its importance still was not recognized. Following the discovery of *H. pylori*, a European group showed that these bacteria produce the urease, and soon thereafter another foreign research team developed a diagnostic assay based on urease. Subsequently, easier and more accurate assays were developed in two U.S. laboratories. One of these was the scientist who discovered *H. pylori*, who returned to the U.S. and established a laboratory at the University of Virginia.

The idea that *H. pylori* was the cause of most chronic gastritis and ulcers was not readily accepted by the medical community. Increased understanding of the organism not only improved treatment, it explained features of the pathology so that physicians would accept the new concept and adopt the treatment regimen for their patients. The association of chronic hyperacidity with ulcer was an argument against the significance of *H. pylori*, especially when it turned out that in culture the bacteria are susceptible to acid. Soon, academic researchers in Europe and the U.S. demonstrated that the bacteria alter the secretion of acid from the stomach while having a mechanism of creating a "microenvironment" that is protected from acid. Clinical trials have shown that acid secretion returns to normal after the bacteria is eliminated. Also, *H. pylori* is killed by a wide spectrum of antibiotics in culture, yet treatment with many of these antibiotics resulted in only temporary relief of the condition, followed by recurrence. The discoverer of *H. pylori*, now in the U.S. and using NIH funding, found that in the stomach the bacteria are much more resistant, and treatment with multiple antibiotics is required. Another objection was based on consistent recovery of *H. pylori* from stomachs of people without gastritis or ulcer. A U.S. research team with NIH funding studied the means by which the bacteria colonize the epithelium of the stomach and upper small intestine. He saw that inherited differences in proteins on the surface of the cells determined the ability of *H. pylori* to grow and therefore determined the individual's susceptibility. By the late 1980s, several US and foreign academic groups had realized that *H. pylori* is linked to gastric cancer. The ability of the organism to increase acid production by the stomach is thought to be linked to its defenses, its resistance to antibiotic treatment, and to its involvement in cancer, although the mechanism is not yet known.

A one time antibiotic treatment regimen to eliminate *H. pylori*, as opposed to long term maintenance with H₂-antagonist drugs, recurrence, and sometimes surgery as a last resort, is an obvious benefit both to the patient and to the health care insurer. However, this story highlights the risky nature of pharmaceutical development, given the possible decline in sales of ranitidine, which itself was the product of some relatively low investment chemical manipulation by Glaxo once Smith-Kline French had invested in the

effort and expense of proving the concept and developing the prototype. Clinical studies have shown that ranitidine is effective in relieving pain and speeding the healing during treatment regimen to eliminate *H. pylori*. Also, several conditions that are not caused by *H. pylori*, such as ulcer caused by aspirin, gastric-esophageal reflux and a hereditary hyperacidic condition, respond well to ranitidine.

Research Leading to the Development and Use of Ranitidine

USA = affiliated with academic institution or NIH in the U.S.
 Frn = foreign academic institution
 Ind = industry labs (other than Glx)
 Glx = Glaxo researchers

△ = referenced in SQ or MK papers
 ★ = key contribution
 ⊕ = review article

Adrenergic receptors and cardiac β-blocker drugs

Scientist	Affiliation	Contribution [references] support acknowledgements
Goodman	USA	Made the adreneline antagonist most widely used in studies of its action and as the basis for further drug design [Nickerson & Goodman 1947 J. Pharmacol. Exp. Ther. 99:167]
Ahlquist	USA	★Early studies of substances with adrenergic effects; proposed separate α and β type receptors for adrenaline, which may be either excitatory or inhibitory in different tissues [Ahlquist 1948 Am.J.Physiol. 153:586]
Slater, Powell	Ind	Synthesized the first antagonist of adrenaline's inhibitory effects, DCI, based on an adrenaline analog asthma drug [Powell & Slater 1958 J.Pharmac.Exp.Ther. 122:480]
Moran	USA	First showed that DCI would relax the response of the heart to adrenaline; identified it as a blocker of Ahlquist's β type adrenergic receptors [Moran & Perkins 1958 J.Pharmac.Exp.Ther. 124:223] NIH H-2953; PHS Sr. Research Fellowship
Black	Ind	Developed first β-blocker drug for use in cardiac patients [Black & Stevenson 1962 Lancet ii:311; Black et al. 1964 Lancet i:1080] ICI

Histamine and its two types of receptors

Scientist	Affiliation	Contribution
Windaus, Vogt	Frn	First synthesized histamine [Windaus & Vogt 1907 Ber. 40:3691]
Dale	Frn	★Demonstrated the physiological effects of histamine, and that its effect is on smooth muscle; proved that it is a natural constituent of tissues [Barger & Dale 1910 J.Physiol. London 40:38; <i>ibid.</i> 41:318; Best et al. 1927 <i>ibid.</i> 62:397; Dale 1929 Lancet i:1233]
Ackermann	Frn	Early work on the isolation and chemical properties of histamine [Ackermann 1910 Ztschr.f.physiol. Chem. 65:504; Ackermann & Fuchs 1938 <i>ibid.</i> 257:153; Ackermann & Moir 1938 <i>ibid.</i> 255:75]
Abel	USA	First purified and characterized adrenaline. Isolated histamine from tissues, and showed it was had physiological activity [Abel 1898 Proc.Am.Physiol.Soc. P.3-5; Abel & Kubota 1919 J.Pharmac.Exp.Ther. 13:243; Abel & Nagayama 1920 <i>ibid.</i> 15:347]
Popielski	Frn	First showed that histamine induces gastric acid secretion [Popielski 1920 Pfluger's Arch. 178:214]
Bovet	Frn	Developed the first antagonist of excitatory adrenaline response, and based on that, later synthesized the first antagonist of histamine [Fournau & Bovet 1933 Arch.Int.

Pharmacodyn. 46:178; Bovet & Staub 1937 C.R. Seances Soc.Biol.Paris 124:547]

Code	Frm	Important method of recovering histamine from tissues and blood; relationship of histamine to gastric ulcer and anaphylactic shock [Code 1937 J.Physiol. 89:257; Code & Ing 1937 J.Physiol. 90:501; Code 1939 Am.J.Physiol. 127:78; Code & Varco 1942 ibid. 137:225]
Loew, Chickering	Frm	Histamine stimulates acid secretion from the stomach [Loew & Chickering 1941 Proc.Soc.Exp.BiolMed. 48:65]
Schild	Frm	Developed a widely used assay for determining the potency of a chemical relative to histamine. Showed that certain histamine actions were inhibitory rather than excitatory, proposed multiple receptors, naming the excitatory ones H1-receptors. [Schild 1942 J.Physiol.101:115; Ash & Schild 1966 Br.J.Pharmac.Chemother. 27:427]
Black	Ind	Described the H2 histamine receptors responsible for acid secretion, and made the first inhibitor of them [Black et al. 1972 Nature 236:385] Smith-Kline French

Drug development and testing

Scientist	Affiliation	Contribution
Ganellin, Parsons Brimblecomb	Ind	Testing and chemical analysis of cimetidine and its precursor H2 antagonists [Black et al. 1973 Agents & Actions 3:133; Brimblecomb et al. 1975 J.Int.Med.Res. 3:86; Durant et al. 1975 J.Med.Chem. 18:905; Ganellin et al. 1976 Fed.Proc. 35:1924; Brimblecomb et al. 1978 Gastroent. 74:339] Smith-Kline French
Brittain	Glx	Designed, synthesized, and tested ranitidine. [Bradshaw et al. 1979 Br.J.Pharmacol. 66:464P; Brittain & Daly 1981 Scand.J.Gastroent. Suppl. 69:1]
Richards	Glx	Testing of many effects of ranitidine in animals and humans, comparison to cimetidine [Richards 1983 J.Clin.Gastroent. 5 Suppl. 1:81]

Clinical trials

Scientist	Affiliation	Contribution
Hirschowitz	USA	Compared efficacy and dose of cimetidine with the earlier drugs in animals; reviewed a large body of clinical trials of cimetidine [Gibson et al. 1974 Gastroent. 67: 93; Hirschowitz 1979 Ann.Rev.Pharm.Tox. 19:203; Danilewitz et al. 1982 NEJM 306:20] NIH AM-09260; VA support
Walt	Frm	Efficacy and side effects of ranitidine studied, in comparison to cimetidine [Walt et al. 1981 Scand.J.Gastroent. 16(Supp 69):81; Walt et al. 1981 Gut 22:49 & 319; Walt et al. 1981 Gastroent. 80:1311]
Boyd, Peden	Frm	Efficacy and side effects in comparison to cimetidine [Peden et al. 1979 Lancet i:690; Boyd et al. 1980 Gut 21:A922; Boyd et al. 1981 Scand.J.Gastroent. 16(Supp 69):81; Peden et al. 1981 Scand.J.Gastroent. 16:325]
Langman	Frm	Comparison of ranitidine and cimetidine for several activities [Langman et al. 1980 Br.Med.J. 281:473; Henry et al. 1980 ibid 281:775; Langman et al. 1981 Scand.J. Gastroent. 16(Supp 69):115]

Gibinski	Fm	Large scale trial for efficacy of ranitidine for ulcer, reviewed multicenter trials [Gibinski et al. 1981 Hepatogastroent. 28:216; Gibinski 1981 Curr.Med.Res.Opin. 7:516]
Conner,Sawyer	USA	Thorough review of early clinical trials for ranitidine [Berner et al. 1982 Clin. Pharm. 1:499]
ADIS	Fm	ADIS Drug Information Services, Auckland, New Zealand - Thorough review of large scale ranitidine trials up to 1989 [Grant et al. 1989 Drugs 37:801]

Helicobacter pylori

Scientist	Affiliation	Contribution
Davies		Urease is of bacterial origin [Delluva et al. 1968 Biochim. Biophys. Acta 17:646]
Colin-Jones, Steer	Fm	Isolated bacteria from ulcer patients, but did not conclude they were causative [Steer & Colin-Jones 1975 Gut 16:590]
Marshall	Fm/USA	★Isolated and cultured H. pylori from stomach of ulcer patients; continued experiments proving it is the cause of ulcer and gastritis. At UVA: diagnostic assay; virulence determinants and growth requirements discovered; clinical trials of several antibiotic treatments [Marshall & Warren 1983 Lancet i:1273; Marshall et al. 1985 Med.J.Austr. 142:439; at UVA: Marshall 1989 Gastroent.Clin.Biol. 13:50B; Marshall et al. 1990 Gastroent. 99:697; Marshall 1991 J.Gastroent. Hepat. 6:121; Marshall et al. 1993 Dig.Dis.Sci. 38:1674; Peura et al. 1996 Am.J. Gastroent. 91:233] NIH S07RR-05431
Tytgat	Fm	H. pylori makes the urease; early clinical trials of antibiotic therapy [Langenberg et al. 1986 Lancet i:1348; Tytgat & Rauws 1987 Aliment. Pharmacol. Ther. 1:527S]
Wise, McNulty	Fm	Devised a simple assay of urease to diagnose H. pylori [McNulty & Wise 1985 Lancet i:1443]
Graham	USA	Many clinical studies on epidemiology and antibiotic efficacy; devised simplified assay for H. pylori infection; studied its genetics, and identified cellular receptors and bacterial proteins involved in infection [Graham et al. 1987 Lancet i:1174; Evans et al. 1988 Infect. Immun. 56:2896; Graham et al. 1989 Gastroent. Clin.Biol. 13:84B; Evans et al. 1993 J.Bacteriol. 175:674; al-Assi et al. 1995 Am.J.Gastroent. 90:1411; Yousfi et al. 1995 Alim.Pharmacol. Ther. 9:209] NIH M01RR-00350; R01DK-39919; Veterans Administration

Acyclovir (Zovirax)

Acyclovir is used for the treatment of herpes simplex virus (HSV) infection. Acyclovir is not only a much more effective inhibitor of HSV replication than previous antiviral drugs, it was the first to specifically inhibit replication of the virus without interfering in the cell's replication. Because of this specificity, and unlike the earlier nonspecific antivirals, its toxicity to the patient is very low. The main areas of research used by Burroughs Wellcome (BW) scientists to produce acyclovir were the virology of HSV, the characterization of the enzymes of DNA replication, and the synthesis and use of nucleoside analogs as antimetabolite drugs. The development of several specific cell culture techniques for growing and testing the virus were necessary as well. The discovery of acyclovir was based on acquired scientific knowledge rather than on the observation of an unexpected action by another drug or the action of a naturally occurring substance. Only when the understanding of HSV and of DNA replication and cell division had reached the point where a degree of rational design could be used was the first generation drug, and later acyclovir itself, produced.

HSV was isolated from oral and genital lesions in the 1920s. Once identified, it was shown to be widespread and responsible for several different diseases. HSV causes cold sores and a common venereal disease in a large percent of the normally healthy population. If it infects the cornea and conjunctiva of the eye, there will be recurrent outbreaks which eventually can cause loss of vision. Various neurological syndromes can occur, chiefly encephalitis. All of these symptoms are especially severe and persistent in newborns and in immunosuppressed patients, where HSV can cause massive outbreaks of sores at the local point of infection or disseminated infection throughout the body. Additionally, it may cause abortions and birth defects, and was thought at the time acyclovir was developed to be oncogenic. The clinical and basic research describing these diseases demonstrated that HSV was an appropriate target for industry antiviral drug development.

Around 1930, a European scientist showed that cold sores were the result of a virus, and people with recurrent outbreaks had antibodies against this virus in their blood. In the 1960s, the structure of the HSV particle and its mechanism of budding from cells was described. Researchers in NIH-supported laboratories found that HSV enters neurons through their endings in the skin, remains permanently latent in the central nervous system, and reactivates from these neurons to produce the skin lesions and other complications. European scientists first reported that HSV's genome is a large double strand of DNA. Subsequently the viral DNA was sequenced and mapped, and the mechanism of its replication was described. A large number of genes were discovered, and their expression was studied and related to phases of the viral life cycle. HSV was found to encode its own enzymes for DNA replication, rather than using cellular enzymes as some viruses do. The two viral enzymes which are specifically inhibited by acyclovir were among those that were detected, purified and characterized. This understanding of HSV's life cycle was gained through research in publicly funded academic laboratories mainly but not entirely in the US. The knowledge and methods developed in these labs permitted testing of acyclovir for efficacy and mechanism of action, diagnosis in patients, and appropriate application of the drug to the particular manifestations of HSV infection.

During this time, the details of the synthesis of DNA by dividing cells were being discovered. In the early 1960s, the enzyme activities involved DNA replication were detected. Over the following ten years, the details of DNA replication were worked out, and the cellular enzymes DNA polymerase (pol) and thymidine kinase (TK) were extensively characterized. DNA pol adds one nucleotide at a time to the growing DNA chain during replication, while TK is one of a number of enzymes which prepare the nucleotides in the form which DNA pol can use. Assays for measuring the activity of these enzymes were developed as this research proceeded. Closely following the progress with the cellular enzymes, HSV researchers detected and purified the TK and DNA pol made by the virus, which are the enzymes that are inhibited by acyclovir. This work

was mainly performed in NIH-funded academic research labs, several of which were referenced in BW literature for techniques of enzyme assay and purification.

Monolayers of cells that were shown to be susceptible to HSV, as well as embryonated chicken eggs, were used to detect HSV growth and isolate its enzymes. These methods were also used by the industry scientists to test the inhibition by antivirals, and cell culture and plaque assay were used to test numerous compounds at different concentrations and conditions. Then, appropriate animal disease models that mimic the natural disease were used in the next phase of testing. All these assays and models were developed in academic research labs. The BW scientists conducted extensive tests of the activity, efficacy, and concentration of acyclovir in established cell lines, using their own modifications of previously developed assays.

A great deal of research during the 1940s and 1950s was being directed towards developing antimetabolite drugs - chemicals that poison growing cells - because of their potential usefulness against cancer. The nucleotide bases were known by this time to be the constituents of DNA, and in 1954 a team of scientists at a university in the U.S. showed that tumor cells incorporate nucleotides more rapidly than do normal cells. Interest began to grow in nucleotide analogs - nucleotides with a chemical modification - as antimetabolite drugs which could inhibit DNA synthesis. The idea was that an analog which could be incorporated into the growing chain of DNA but would then block any further elongation of the chain would mainly kill rapidly growing tumor cells. Two different U.S. academic scientists developed the first two nucleotide analog drugs for treating cancer. Soon after, in 1959, another publicly funded U.S. researcher synthesized the nucleotide analog idoxuridine, which eventually was found to have antiviral activity when applied to skin infected with HSV. This was the first clinically effective antiviral drug. However, its usefulness was limited by its high toxicity, since it acted by inhibiting DNA synthesis and therefore affected the cells of the body as well as the virus.

Development of these drugs by the academic scientists interested BW in nucleotide analogs as replication enzyme inhibitors. Along with the growing understanding of enzymology and the enzymes of DNA synthesis, scientists at BW were extensively researching the enzyme adenosine deaminase, and designing and testing inhibitors of it. They found that a part of the chemical structure of nucleotides which is required for normal DNA synthesis is not required for a nucleotide analog to enter the first step of the reaction, binding to the enzymes. Therefore, these analogs offered a means of inhibiting the enzymes. One of the potential inhibitors designed and tested by this team, the nucleotide analog acycloguanosine (acyclovir), was found in the UK labs of BW to have excellent and highly specific activity against HSV. In 1977, BW scientists published the article detailing their tests of the selective action of acyclovir on HSV growing in cell cultures. To define and test the mechanism of action of acyclovir, understanding of the existence and mechanism of DNA pol and TK, and the discovery that HSV makes its own enzymes with distinct properties, was needed. The BW team demonstrated that acyclovir acts preferentially to inhibit viral but not cellular enzymes in two ways: first, only the viral TK activates the drug to a usable form; second, the viral DNA pol is inhibited approximately 3000-fold over the cellular DNA pol. This paper referenced 33 articles, 20 articles by researchers at United States universities receiving NIH and NSF support; 5 articles by researchers at European academic institutions; and 8 articles by industry scientists. In 1978, a second article reported the actual synthesis of acyclovir, and it cited 13 articles, 3 from NIH supported labs, 7 from industry, and 3 by foreign researchers. In this article, 5 papers from publicly funded research were cited for nucleotide organic chemistry, techniques for which companies usually cite only their own chemical methods, not academic research.

After the production and in vitro and animal testing of acyclovir by BW scientists, clinical trials were

conducted by academic clinical institutions. Most of these were supported by a combination of NIH grants and funds from BW. The drug's efficacy was tested for different manifestations of HSV infection, in different modes of application, and for other herpes viruses. Improvements in acyclovir's effectiveness through combination with other drugs were reported. The mechanisms of acyclovir resistance in HSV strains, which arise frequently in immunosuppressed patients, were studied. BW has continued to synthesize new forms of the drug and to test them for efficacy and pharmacokinetic properties, and these also were incorporated into the research of academic virologists and clinicians. The delivery vehicle of the topical form of acyclovir changed from DMSO to polyethylene glycol to propylene glycol; the use of PEG was described by US academic scientists and the use of propylene glycol was described by European academics.

Research Areas Leading to Production and Testing of Acyclovir

USA = affiliated with academic institution or NIH in the US

Ind = industry or private foundation

Frn = foreign academic institution

BW = Burroughs Wellcome

△ = referenced in BW's papers

★ = key article

1. Culture techniques for growing virus in cells

Scientist	Affiliation	Contribution [references] support acknowledgements
Dulbecco	USA	Invented the technique of producing viral plaques in monolayers of cells, widely used to test the antiviral activity of large numbers of compounds. [1952 PNAS 38:747-52]
Niven	Frn	Cell differentiation state and susceptibility to viral infection; first cultivation of HSV in human cells [Bang & Niven 1958 Br.J.Exp.Path. 39:317]
Scherer	USA	Detailed the use of a pure strain of mouse cells for the cultivation of virus. [1953 Amer. J. Pathol. 29:113] National Foundation for Infantile Paralysis, Inc.
Tyrell	Frn	Different cell types or stages of cell development affect susceptibility to virus; defined cellular conditions required for viral growth. [Tyrell et al., 1958, Brit.J.Exp.Path.39:178; Hoorn&Tyrell, 1965, ibid 46:109]

2. Isolation and description of herpes simplex virus

Scientist	Affiliation	Contribution
Andrews	Frn	★First showed presence of antibodies in serum to herpes, and showed relationship between these and recurrent cold sores. Also, one of the first reports of growth of virus in cell cultures. [Andrews, 1929 Brit.J.Exp.Path. 10:188; Andrews & Carmichael 1930 Lancet 1:857.]
Kucera	USA	Described growth of HSV in cell monolayers. [1966, Proc. Soc. Exp. Biol. Med 122:258.] NIH grants # CA-12197 and CA-12382.
Sarov	Frn	Showed that HSV has a large, double-stranded DNA genome. [1968, Becker et al. Virology 36:184.]
Keir, Gold	Frn	First demonstrated induction of a DNA pol by HSV. Showed that the pol was immunologically distinct from the host cell pol. [Keir & Gold, 1963 Biochem Biophys Acta 72:263-76; Keir et al., 1966 Virology 30:154-7.]
Roizman	USA	Defined the features of the HSV genome, and details of its gene expression. Purified HSV specific proteins, permitting immunological studies of HSV. [Kieff et al. 1971, J. Virol. 8:125; Frenkel & Roizman 1971, J. Virol. 8:591; Spear & Roizman 1972, J. Virol. 9:143] NIH grants # CA-08494 and CA-19264; NSF grants # BMS73-06940 and GB38799; U. Chicago Cancer Research Ctr. CA-14599; Amer. Cancer Soc. VC1031
Nahmias	USA	Antibodies to HSV-1 and -2 permit identification of the virus in clinical specimens. [Nahmias et al., 1970 Am. J. Epidem. 91:539.] NIH CA-11433, CC-00555, NS-22301.

Kit, Dubbs	USA	★Cited for describing the HSV thymidine kinase activity and an assay for it. [Kit & Dubbs '63 Biochem. Biophys. Res. Comm. 11:55; Dubbs & Kit '64 Virology 22:493.] NIH grant CA-06829-02 and 06656-01; NSF GB620; Amer. Medical Assoc. ERF 71; grant from the Leukemia Society
Bastian, Tralka	USA	Demonstrated that HSV is latent in ganglia. [Bastian et al., 1972 Science 178:306.] NCI intramural
Barringer	USA	Demonstrated that HSV is latent in neurons of the sacral ganglions. [Barringer, 1974 NEJM 291:828.] VA hospital; National Multiple Sclerosis Society.
Overall	USA	In an animal model, recurrent skin lesions result from reactivation of latent virus in the nervous system. [Stanbury et al., 1982 J. Infec. Dis. 146:397.] NIH AI-42524, AI-10217.
Honess, Watson	Fm	Isolated HSV TK. [1974; J.Gen. Virol. 22:171; 1977, J.Virol. 21:584.]
Purifoy	USA	★First purification of HSV-encoded DNA pol [Purifoy & Schaffer, 1975 J.Virol.16:498; Powell & Purifoy, 1977 J.Virol24:618] NIH PO1CA-10893
Huang	USA	Cited for method of purifying DNA pol. [1975. J. Virol. 16:298.] NIH grants NHLI-72-2911, AI-12717, and fellowship F22 CA-04032

3. Enzymes involved in DNA replication

<u>Scientist</u>	<u>Affiliation</u>	<u>Contribution</u>
Monod, Jacob	Fm	Early description of mechanisms and principles of enzyme action. [Monod & Jacob 1961 Cold Spr. Harbor Symp Quant. Bio 26:389.]
Maley	USA	Described cellular thymidine kinase (TK) activity [Maley & Maley 1962 Biochemistry 1:347] NIH # CA-5119; Am. Heart Assn.
Kornberg	USA	★Described several distinct DNA polymerase (pol) activities in bacterial cells, distinguished the main pol of replication, its physical properties and mechanisms, and the mechanism of its use of dNTPs [Bruttig et al. '71 PNAS 68:2826; Englund et al. '69 J. Biol. Chem. 244:3045 & 3048; Deutscher & Kornberg '69 J. Biol. Chem. 244:3019; Geffer et al. '71 PNAS 68:3150.] NIH R01GM-07581
Kessel	USA	Cited for assay of levels of nucleoside phosphorylating activity. [Kessel, 1968 J.Biol.Chem. 243:4739] NIH grants # PH 43-66-541, C6516 (NCI)
Lerman	USA	Cited for assay of pol activity. [Altman & Lerman '70 J. Mol. biol. 50:235] NIH GM-13767; NSF GB-4119; Altman was supported as a University Fellow at U. Colorado.
Livingston	USA	★Purified the main polymerase of cellular replication and described features of its mechanisms. [Livingston et al. 1975 J.Biol.Chem.250:] NIH grant # AI-06045.

Cheng, Ostrander USA

Cited for method of preparation of cytosol fractions to assay phosphorylation by TK, and for technique to purify HSV TK from cells. [Lee & Cheng, 1976 J.Biol.Chem. 251:2600; Cheng & Ostrander, 1976 ibid 251:2605] NIH grant # CA-05298, CA-13038; Amer.Cancer Soc. # CH-29

4. Nucleoside analog antimetabolite drugs and organic chemical synthesis

Scientist	Affiliation	Contribution
Cantarow, Paschkis	USA	Tumor cells incorporate nucleosides more rapidly than normal cells [Cantarow & Paschkis, 1954]
Heidelberger	USA	Designed and tested one of the first nucleoside analog antimetabolites, fluorouracil, in collaboration with Hoffman-La Roche chemists [Heidelberger et al. 1957 Nature 179:663]
Dekker	USA	Designed and tested the nucleoside analog cytarabine [Walwick et al. 1959]
Prusoff	USA	Designed and synthesized the first nucleoside analog antiviral agent, idoxuridine. [Prusoff, 1959, Biochem.Biophys.Acta 32:295.] CY-3076
Preiss, Handler	USA	Cited in early BW articles for organic synthetic methods. [Preiss & Handler 1957 JBC 225:759.] NIH grant # RG-91; contract with Atomic Energy Commission and Duke U. # AT-(40-1)-289.
Flaks	USA	Cited for synthetic methods. [Flaks et al. '57 JBC 228:201.] NIH, NCI, PHS and NSF support acknowledged but no grant #s given.
Seegmiller	USA	Cited for organic synthesis methods. [Seegmiller et al., 1967 Science 155:1682.]
Rozenberg	Frn	Cited for organic synthesis methods. [Holmsen & Rozenberg, 1968, Biochem.Biophys.Acta 157:266.]

5. Drug development and testing

Scientist	Affiliation	Contribution
Schaeffer	BW	Described the organic synthesis of acyclovir, and reported toxicity testing in animals. [Schaeffer et al., 1978, Nature 272:583-5]
Elion	BW	Described the mechanisms of action of acyclovir on viral polymerase and thymidine kinase, and demonstrated preferential inhibition of viral rather than cellular replication through specific interaction with both enzymes. [Elion et al., 1977, PNAS 74:5716-20.]
DeClercq	Frn	Extensive testing of acyclovir sensitivity of different strains of HSV. [DeClercq et al., 1980, J.Inf.Dis.141:563.]

6. Clinical trials

<u>Scientist</u>	<u>Affiliation</u>	<u>Contribution</u>
Benjamin	USA	Cited in clinical trials for viral assay and typing in clinical specimens. [1977 J. Clinical Micro. 6:571]
Crumpacker	USA	Clinical trial of effectiveness on primary lesions. [Crumpacker et al., 1979 Antimicrob.Ag. and Chemo.15:642.] NIH grant # CA13431; grant from BW.
Corey, Nahmias	USA	Clinical trials of acyclovir. [Corey et al., 1982 NEJM 306:1313; Corey et al., 1983, Ann.Int. Med. 98:914.] NIH grants # AI-14495 and AI-20381; grant from BW.
Meyers, Wade	USA	Efficacy trials of oral and intravenous acyclovir for HSV and CMV infections, especially in immune suppressed patient; frequency of resistant HSV strains with multiple treatment cycles. [Wade et al., 1982 Am. Intern.Med. 96:265; Meyers et al., 1982 Am.J.Med.73:229; Wade et al., 1983 J.Inf.Dis.148:1077; Wade et al., 1984 Ann.Intern.Med.100:823.] NIH CA-18029 and CA-26966.
Whitley	USA	Efficacy trial for severe and neonatal HSV infection. [Whitley et al., 1982 Amer. J. Med 73:165.] NIH grant # AI-12667, CA-13148 and RR-032; grant from BW.
Fiddian, Mindel	Fm	Efficacy in primary herpes infection. [Mindel et al. 1982 Lancet 1:697; Fiddian et al., 1983 J.Antimicrob.Chemo.12:67; Mindel et al., 1984 Lancet 2:57.].
Bryson	USA	Efficacy of oral acyclovir in genital infection. [Bryson et al., 1983 NEJM 308:916; Reichman et al., 1984 JAMA 251:2103.]
Pagano	USA	Efficacy trial for EBV [Pagano et al., 1983 J.Antimicrob.Chemo.12, SupplB:113; Pagano & Datta 1982 Am.J.Med.73:18 . NIH grant # AI-17205; grant from BW. J. S. Pagano referenced as the source of HSV for testing in Elion et al 1977.
Mertz	USA	Efficacy trial of oral acyclovir in genital herpes [Mertz et al. '84 JAMA 252:1147]

Captopril (Capoten) and Enalapril (Vasotec)

Captopril and enalapril are drugs that control hypertension by inhibiting an enzyme (ACE) that is critical in blood pressure regulation. Hypertension is a complex disorder which can be based on the malfunction of several normal mechanisms, and the primary initiating causes of it are still not entirely understood. Left untreated, hypertension causes progressive damage to kidneys, heart, and systemic blood vessels. Captopril and enalapril are highly effective in breaking the chain in the system that is involved in up to 70% of hypertension. Captopril, developed by Squibb, is a novel drug resulting from an extended research effort. Enalapril, made by Merck, is an improved ACE inhibitor based on an alteration of the chemical structure of captopril, so the development of these two drugs is combined in a single story. The discovery of ACE inhibitors began with a natural substance, but the production of captopril was one of the earliest successful examples of rational drug design using molecular modeling to provide the lead.

In addition to organic chemistry, there is one broad field of research which underlies captopril and enalapril discovery: the study of the hormones renin, angiotensin and aldosterone (the R/A/A system) and their involvement in hypertension and congestive heart failure. Also, at one small but crucial point, very basic research into enzyme biochemistry and kinetics provided the necessary insight that directly lead to the development of captopril. As early as 1898, the kidney was suspected of involvement in hypertension, and a substance extracted from kidneys which raised blood pressure in rabbits was termed renin. In the 1930s, the idea of a renal source of hypertension was revived by a US research group, who isolated renin and showed that it strongly elevated blood pressure. About 5 years later, a foreign and a US group both found that renin is an enzyme that activates another protein, which eventually was named angiotensin. Angiotensin increases blood pressure by its very powerful constricting effect on arteries and capillaries. In the mid-1950s, NIH-funded researchers were surprised to observe that angiotensin is actually two separate proteins, and an enzyme converts angiotensin I (AI) to the active form, angiotensin II (AII). They had discovered angiotensin-converting enzyme (ACE), the enzyme which is inhibited by captopril and enalapril. A number of laboratory models were developed along the way by this group, which later were used by Squibb and Merck in their drug tests. These included the use of strips of guinea pig ileum for initial test of inhibitory effect, and several rat and dog models of hypertension, for which US and foreign academic researchers are referenced in the companies' publications.

In 1962, researchers in Europe found that a snake venom had the effect of relaxing blood vessels, thereby rapidly lowering blood pressure. These scientists subsequently localized ACE to the lungs, and showed that the substance in snake venom blocked the conversion of AI to AII by inhibiting ACE. Scientists at Squibb isolated the active molecule in the snake venom and called it teprotide. Although it did not prove feasible as a human drug, it was used in many studies of the involvement of renin and AI/AII in hypertension, many of which were conducted in US academic labs. During this time, an NIH-funded scientist in the US showed that another hormone made in the kidney, aldosterone, is involved in blood pressure regulation by causing the kidney to retain sodium and increase the blood volume. In addition to its vasoconstrictive effect, this researcher and his group found that angiotensin also induces aldosterone secretion by the kidney, thereby increasing blood pressure by a second mechanism. When Squibb developed teprotide, the company scientists provided it to this academic group in the clinical trials which were the first to show that ACE inhibitors could decrease blood pressure in humans. This academic researcher and the many scientists who worked in his laboratory played a central role in working out the R/A/A mechanism of hypertension and convincing other medical researchers of its importance. They performed many animal and human studies both before and after the discovery of teprotide which were critical to the understanding of blood pressure regulation, and performed many clinical studies of captopril as well.

Another system of heart and blood pressure regulation had been discovered a few years earlier, the adrenergic system, and drugs known as " β -blockers" had been developed to control it. The concept that the R/A/A system could be the cause of hypertension at first was discounted by most researchers because the adrenergic system alone was thought to explain the condition. A large number of animal and clinical studies ensued using the β -blockers, teprotide, and several drugs which act at other steps in the R/A/A system, and the importance of renin, angiotensin, and aldosterone in maintaining normal and hypertensive blood pressure was slowly accepted by the medical community. These studies, in the large laboratory mentioned above and in several others, also revealed that the two systems are linked through the involvement of renin, and began to show the significance of hypertension in congestive heart failure. Several important assays, for renin, aldosterone, and the relative concentration of AI and AII, were developed along the way. The majority of these studies came from US academic labs receiving public funding, with several foreign academic and Squibb group contributions as well. Since market potential is needed for a company to begin an R&D effort, the increasing evidence of the importance of the R/A/A system in hypertension, kidney and heart disease was a factor in the decisions of Squibb and later of Merck to push their efforts to develop ACE inhibitor drugs.

The Squibb group worked for the next six years to improve on teprotide. Their breakthrough idea came when a US academic lab with NIH funding discovered an inhibitor of a bovine enzyme that is related to ACE. They published structural data and a model proposing that the inhibitor fit into the enzyme's active site. The scientists at Squibb made a chemical series based on the inhibitor, and found one that weakly inhibited ACE. Finally, they designed a model of ACE and inhibitor interaction based on the structural model of the bovine enzyme. The necessary data for the Squibb group to make this model came from the studies of another NIH-funded US academic lab on the structural and catalytic properties of ACE. The Squibb group, with data from their own inhibitor studies, used computer graphics to predict inhibitor structures that would bind better to the ACE active site. From this model, they synthesized a series of potential inhibitor molecules to test, and the result was captopril.

In 1977, Squibb scientists published the description of the modeling, synthesis and initial in vitro and animal testing of captopril. They demonstrated that captopril inhibits the action of AII and lowers blood pressure in hypertensive rats. This article references 15 papers, 7 from US universities receiving NIH funding, 7 from their own or other industrial labs, and one article by researchers at a European university. The US articles were cited for background knowledge, clinical trials with teprotide, and mechanisms of ACE action and testing. In 1978, they published two detailed reviews which describe extensive enzyme activity studies and animal testing, in which they acknowledge the many academic research groups whose work they drew upon. The majority of these were publicly funded US researchers.

The first clinical trial of captopril was performed by a Swiss research group in collaboration with Squibb researchers. Subsequently, captopril was used in a large number of studies revealing the fundamental relationship of AII to several aspects of hypertension and congestive heart failure. Clinical studies also showed the importance of determining whether the mechanism driving the hypertension is the R/A/A system or the adrenergic system. NIH funded researchers developed a very effective diagnostic test, using a single dose of captopril to measure the degree to which the R/A/A system is at fault, which was widely used in choosing between the ACE inhibitors, the beta-blockers, and several other types of drugs that are available. Several groups proved the importance of ACE inhibition in treating congestive heart failure. It is important to the company to know when and how the drug should be given so that its effectiveness and therefore the demand for it is maximized. The clinical trials revealed several side effects of captopril as well.

Scientists at Merck sought to modify captopril to remove some of the side effects. They made the

observation that the captopril molecule had a certain side chain shared by another drug that caused the same side effects. They synthesized a series of substitutions of this side chain, and tested them in vitro for enzyme inhibition, then in animals for effect on blood pressure. This series produced enalapril, which has slightly higher activity than captopril, with much longer duration of action. The article describing the design, synthesis and initial testing of enalapril appeared in 1980. It contained 20 references, 9 to NIH funded labs, 9 to their own and Squibb's publications, and two to foreign researchers. US research papers were cited for background knowledge of R/A/A, clinical results, and chemical and enzymatic methods.

The effectiveness of ACE blockade for lowering blood pressure was already proved as a concept with teprotide and captopril. Clinical trials of enalapril were performed in both US publicly funded labs and in foreign medical institutions. It was shown to be effective in lowering blood pressure, while lacking the side effects of captopril. A US team saw that with long term use of enalapril, a persistent blockade of the R/A/A system and therefore improvement in the hypertensive cycle occurs. The US researchers performing clinical trials were supported by a combination of NIH grants and money from Merck of obesity, alcoholism, premenstrual syndrome, and various phobias and mental disorders.

Research Leading to the Development and Use of Captopril and Enalapril

USA = affiliated with academic institution or NIH in the U.S.
 Frn = foreign academic institution
 SQ = Squibb researchers
 MK = Merck researchers

↔ = referenced in SQ or MK papers
 ★ = key contribution
 ⇨ = review article

Renin, Angiotensin, Aldosterone, and Hypertension

Scientist	Affiliation	Contribution [references], support acknowledgements
Tigerstedt, Bergmann	Frn	Described a substance from the kidney, renin, which elevates blood pressure. [Tigerstedt & Bergman 1898 Skand.Arch.Physiol. 8:223]
Goldblatt	USA	Isolated renin and proposed a renal origin of hypertension. [Goldblatt et al., 1934 J.Exp.Med. 59:347] American Medical Assn. grant
Page	USA	Renin acts as an enzyme to increase blood pressure by converting a substance in blood, later seen to be angiotensin; AII stimulates the heart and effects other tissues [Kohlstaedt et al. 1938 Proc.Soc.Exp.Biol.Med. 39:214; Page & Olmstead 1961 Am.J.Physiol. 201:92] Cleveland Clinic Foundation
Munoz	Frn	Discovered angiotensin and showed that renin is an enzyme that activates it in the blood. [Munoz et al. 1939 Nature 144:980; Braun-Menendez et al. 1940 J.Physiol. 98:283]
Skeggs	USA	★Discovered and characterized ACE, as cited in SQ and MK papers; cited by MK for method of purifying ACE [↔Skeggs et al. 1954 J.Exp.Med. 99:275; Skeggs et al. 1958 J.Exp.Med. 108:283; ↔Dorer et al. 1974 Circ.Res. 34:824; Skeggs et al. 1976 Am.J.Med. 60:737] NIH R01HL-17243
Ferreira, Vane	Frn	★Substance in snake venom relaxes blood vessels, from which teprotide was derived. Localized ACE and showed that the snake venom substance inhibited it. [Ferreira 1965 Br.J.Pharma.Chemother. 24:163; Ng & Vane 1967 Nature 216:762; Bakhle 1968 Nature 220:919; Collier et al. 1973 Lancet 1:72]
Laragh	USA	★Role of renin, angiotensin and aldosterone in hypertension, and many details of the system. Importance of aldosterone induction by angiotensin. Rat model of renal hypertension. Use of captopril to test the underlying cause of hypertension. [Laragh et al. 1960 J.Clin.Invest. 39:1091; ↔Gavras et al. 1975 Science 188:1316; Laragh 1978 Prog. Cardiovasc.Dis. 21:159; Niarchos et al. 1979 Circ.Res. 45:829; Cody & Laragh 1982 Am. Heart J. 104:1184] NIH # HL-18323; P17HL-14148; M01RR-00645
Case	USA	Role of renin and aldosterone in hypertension; comparison of different types of drug treatment for hypertension; worked closely with Laragh [Case et al. 1976 Am.J.Med. 61:790; Case 1977 NYState J.Med. 77:2100; Atlas & Case 1981 Clin.Endocrin.Metab. 10:537; Atlas et al. 1983 Am.J.Nephrol. 3:118] NIH P50HL-18323
Tree, Robertson	Frn	Relationship of renin, angiotensin, and aldosterone in hypertension; significance of salt regulation; developed several widely used assays for renin and angiotensin in blood serum [Brown et al. 1964 Biochem.J. 93:594; Davies et al. 1973 Lancet 1:683; Waite et al. 1973 J.Endocrin. 57:329; Lebel et al. 1974 Lancet 2:308]

Davis	USA	Aldosterone is involved in hypertension and congestive heart failure; it is induced by renin and angiotensin. Angiotensin and aldosterone maintain blood pressure. [Yankipoulos et al. 1959 J.Clin.Invest. 38:1278; Carpenter et al. 1961 <i>ibid.</i> 40:2026; Davis et al. 1962 <i>ibid.</i> 41:378; Johnson & Davis 1973 Science 179:906] NIH # R01HL-10612
Erdos	USA	Exact enzymatic action and substrate specificity of ACE determined [Igie et al. 1972 Circ.Res. SupplII II-51; Oshima et al. 1974 Biochim.Biophys.Acta 350:26] NIH HE-08764; 5T01-HE-05859; Office of Naval Research contracts N00014-68-A-0496 and N00014-69-A-0385.
Soffer	USA	★Structural, catalytic and physiologic properties of ACE described; data used in Squibb's model of ACE. [Das & Soffer 1975 J.Biol.Chem. 250:6762; Soffer 1976 Ann.Rev.Biochem. 45:73; Soffer & Sonnenblick 1978 Prog.Cardiovasc.Dis. 21:167] NIH # R01AM-12395; P01GM-11301; P. HL-15088; HL-21394; HL-07071
Johnson, Needleman	USA	Cited for rat model of renal hypertension. Role of autonomic nerves versus renin & angiotensin in hypertension [Douglas et al. 1976 J.Pharm.Exp.Ther. 196:35] HE-14397; He-14509; RR-5418-12; HL-19586; training grant GM-02016

Drug concept, synthesis and testing

Scientist	Affiliation	Contribution [references] support acknowledgements
Wolfenden	USA	★Cited by SQ for the model of an enzyme and its inhibitor which was used to model and design captopril [Byers & Wolfenden 1973 Biochemistry 12:2070] NIH #R01-GM-18325
Rubin	SQ	ACE inhibitors can lower blood pressure in rats. Efficacy and dose range of captopril in animals [Engel et al. 1973 Proc. Soc.Exp.Biol.Med. 143:483; Rubin et al. 1978 Prog.Cardiovasc.Dis. 21:183]
Ondetti, Cushman	SQ	Modelling, synthesis, and testing of captopril [Ondetti et al. 1977 Science 196:441; Prog. Cardiovasc. Dis. 21:176,183]
Patchett	Mk	Synthesized and described the action of enalapril. [Patchett et al., 1980 Nature 288:280]

Clinical trials

A large number of clinical trials appeared rapidly after the introduction of captopril and of enalapril. Far from all groups involved can be cited; instead, trials by groups which were heavily involved and ones by the Squibb or Merck groups are cited, as well as review articles summarizing the outcomes of many trials.

Scientist	Affiliation	Contribution [references] support acknowledgements
Laragh	USA	First test of ACE inhibitor, teprotide, in humans. Efficacy trial comparing captopril with another type of drug for hypertension [Gavras et al. 1974 NEJM 291:817; Case et al. 1977 NEJM 296:641; Gavras et al. 1978 NEJM 298:991; Case et al. 1978 Prog.Cardiovas.Dis. 21:195; Niarchos & Laragh 1984 Am.J.Med. 77:407] NIH # HL-18318; grant from Squibb

Cohn, Levine	USA	Clinical application of assay for renin in blood; use and efficacy of teprotide, captopril, and enalapril for congestive heart failure [Cohn & Notargiacomo 1969 Am.J.Med.Sci. 257:344; Levine et al. 1979 Trans.Assoc.Am.Physicians 92:203; Levine & Cohn 1982 Am.Heart J. 104:1159; Levine et al. 1980 Circulation 62:35] NIH R01HL-09785; R01HL-11533
Atkinson Robertson	Frn	Efficacy of captopril and its effect on levels of renin, angiotensin, and aldosterone; reviewed clinical studies in 1979 [Atkinson et al. 1979 Clin. Sci. 57: 283-291; Atkinson & Robertson 1979 Lancet 2:836]
Tarazi	USA	Clarified relationship of R/A/A and adrenergic systems; role of R/A/A in heart failure; early clinical testing of enalapril [Wollam et al. 1977 Drugs 14:420; Tarazi 1980 J.Lab.Clin.Med. 95:155; Fouad et al. 1983 J.Hyperten. 1(Supp):135; Fouad et al. 1984 Hyperten. 6:167; Bravo & Tarazi 1979 Hypertension 1:39] NIH R01HL-15837
Cody	USA	Efficacy and long term effects of enalapril tested; reviewed clinical trials comparing captopril to enalapril, and their usefulness in heart disease; longtime associate of Laragh [Cody et al. 1984 Am.Heart J. 108:81; Kubo et al. 1984 Clin.Res. 32:182A; Cody 1984 Am.J.Med. 77:71] NIH M01RR-47033, 47034, and 47035

Fluoxetine (Prozac)

Fluoxetine is the most widely used drug for the treatment of depression, and is also effective for several other psychological disorders. Fluoxetine was the first "selective serotonin reuptake inhibitor" (SSRI), meaning that, unlike the previous drugs, it does not affect other signaling molecules. For this reason, it lacks the serious side effects which caused a majority of patients to stop taking the earlier antidepressant drugs. The discovery of fluoxetine by Eli Lilly is an example in which an element of rational design was made possible by research into the underlying pathology of mental illness, combined with some very astute observation which twice prompted the selection of a chemical for screening. Fluoxetine is also a good example of academics and industry working closely as partners, because drugs provided by industry scientists permitted advances in understanding of neurotransmission and depression by academic researchers, which in turn suggested the next step in drug design. As for most drugs, the methods of organic synthesis were a necessary background for the development of fluoxetine, and numerous cell culture and animal models were required for its testing. Three other research areas were involved also: the molecular basis of neuronal signal transmission, the neurochemical basis of depression, and surprisingly, research on blood pressure and antihistamine drugs.

The initial observations of mood altering activity came as side effects in the search for drugs with antihistamine effects. These antihistamines provided the chemical basis for both the earliest antidepressive drugs and for fluoxetine itself. Early in this century, a French surgeon, along with scientists at Rhone-Poulenc, observed that antihistamine drugs which stabilized blood pressure also elevated the mood of surgical patients. Based on these results, a Swiss doctor tested a series of antihistamine drugs provided by the Geigy Company for a number of psychiatric conditions, and in 1958 found one which had pronounced antidepressive activity. This was imipramine, the first of a series of antidepressive drugs which were widely used in key studies that determined some of the physiological basis of depression. Those studies were closely tied to the developing knowledge of neuronal signaling mechanisms, and together they permitted a focused search by Eli Lilly scientists. When the Eli Lilly team began their search for a drug with a more specific action against depression, they selected another antihistamine drug as the chemical basis, diphenhydramine (Benadryl), which was developed in an NIH-funded university in the U.S. Eli Lilly synthesized a series of molecules from this basic structure and tested them with assays developed by researchers studying neurochemistry and psychiatry.

The discovery of many cardiovascular, antihistamine, tranquillizing and antidepressive drugs is interrelated because they all act on the substances which nerve cells (neurons) use to transmit stimulatory or relaxing signals. The neurons in the autonomic nerves, which regulate organ function, use some of the same signal molecules used by neurons in the brain. These substances were first discovered around the turn of the century, and later came to be known as neurotransmitters. In the mid 1950s, serotonin was simultaneously found by U.S. and foreign academic researchers. In the early 1960s, norepinephrine (NE), dopamine, and later serotonin, were identified as neurotransmitters in the brain. It was discovered that when a neuron sends a signal, it releases a neurotransmitter into the synapse, where the neuron receiving the signal picks it up. Then, the signal is terminated by "reuptake" of the excess neurotransmitter at specific sites on the first neuron. If this reuptake is blocked, the availability of the neurotransmitter is increased. It is at the step of blocking the reuptake site that fluoxetine has its effect. When it was discovered that different neurotransmitters are localized to different specific neuronal systems in the brain, scientists realized that these molecules played distinct roles in mental function. These are the basic features of brain physiology and the basis of depression that were understood at the time and were required to determine the mechanism of imipramine action. All of this research was performed in academic institutions in the US and in Europe. The majority of important findings on neuronal signaling were performed in US laboratories funded by NIH grants. The key process of reuptake upon which fluoxetine is based was discovered by a Nobel-winning scientist at the NIH.

As the neurotransmitters were discovered, scientists also began to recognize their relationship to various psychiatric conditions. In early studies, before their function was understood, NE and dopamine were found in the urine in different amounts in normal, depressed or manic patients, which first suggested their involvement in mental states. Later, clinical improvement in depressed patients treated with imipramine correlated with an increase in NE excretion. During the 1960s, U.S. and foreign researchers who were studying the mechanism of imipramine action saw that this drug increased the concentration of NE and serotonin in the neuronal synapses of the brain by inhibiting their reuptake. Eli Lilly scientists began to look for an antidepressive drug without imipramine's side effects on the heart and other functions. Two sets of observations led them to seek a drug that would preferentially inhibit serotonin but not NE reuptake. First, serotonin was being increasingly recognized as an important brain neurotransmitter, and its levels were low in the cerebrospinal fluid of depressed patients. Second, in testing the mechanism of action of a series of drugs based on imipramine, increasing inhibition of serotonin reuptake, not NE reuptake, correlated with antidepressive effect. Both sets of observations were made by US publicly funded and foreign academic scientists in about equal proportion.

A review article [Schildkraut, 1973 *Ann.Rev.Pharmacol.* 13:427] written one year before the appearance of fluoxetine by a US academic scientist who was a major contributor to the field gave a thorough view of biochemical psychiatry at the time Eli Lilly scientists began their work. By 1970, it was known that drugs that had an effect on mania or depression increase the concentration of one or another of the neurotransmitters at certain sites in the brain. The article documents the large amount of interest in the various neurotransmitters and their involvement in these mental conditions, and the large number of studies involved in revealing the details. Also shown is the great number of studies and clinical trials attempting to alter these states by adding the deficient neurotransmitters, and to understand how the body processes the added neurotransmitters and the drugs. Once again, US and foreign labs were cited in approximately equal numbers. Eli Lilly researchers also were cited for experiments with several antidepressant drugs.

In addition to the foundational scientific knowledge that underlies fluoxetine development, many critical laboratory systems and assays were developed in the academic research labs. Several behavioral tests for depression or stimulation in rats and mice permitted the assay of potential drug series. The method of preparing "synaptosomes," a specific fraction of nerve tissue, permitted all of the work on reuptake inhibition, as well as all of Eli Lilly's drug testing. This method was initially developed in a US lab receiving NIH grants. Several assays and imaging methods were developed by both US and foreign academic scientists to measure the amount of neurotransmitter at specific sites in the brain. Many of these assays were used in testing fluoxetine prior to its FDA approval.

Experiments on the physiological responses to the antihistamine diphenhydramine were conducted by Eli Lilly and foreign researchers. These studies suggested that this drug might have the desired effects on NE and serotonin, and led the Eli Lilly team to use it as the chemical basis for synthesis and screening. Eli Lilly had also been studying serotonin action in rat brain and the effects of several earlier drugs on this system, drawing upon the methods and findings of US and European researchers. They established very detailed quantitative comparisons of the effects, which became standards for future comparisons of fluoxetine activity. Eli Lilly's documentation of the synthesis and preliminary testing of fluoxetine was first published in 1974. This paper cited 17 references, 7 from publicly funded US labs, 8 from foreign academic labs, and 2 of their own papers. One of the latter two references was for the major testing method using synaptosomes, mentioned above, and cited their own work for modifications to the procedure. The US labs were referenced for background knowledge in both neuronal transmission and biochemical psychiatry, for methods, and for means of analyzing and comparing drug activity.

Clinical trials were published by US and European academics and by Eli Lilly scientists. The drug's efficacy was tested and compared with other antidepressants. A standard scale to score symptoms of depression for severity and improvement was referred to in many of these trials, which was developed by NIH scientists. Trials included determination of dose range, tissue distribution, effects in different patient populations, side effects, effects of long term treatment, and other features which relate to the clinical use of the drug. Fluoxetine received FDA approval for use to treat depression in 1988. Many clinical studies were conducted after that for treatment

Research Leading to the Development and Use of Fluoxetine

USA = affiliated with academic institution or NIH in the U.S.
 Frn = foreign academic institution
 EL = Eli Lilly researchers
 Ind = other industry researchers

△ = referenced in EL papers
 ★ = key contribution
 ⊕ = review article

Antihistimine Drugs as Antidepressants

Scientist	Affiliation	Contribution [references] support acknowledgements
Laborit, Charpentier, Courvoisier	Frn/ Ind	First observed mood-altering effect of an antihistimine, and developed the first psychoactive drug [Charpentier, 1947 Comptes Rendus 225:306]
Kuhn	Frn	★ Tested drug series based on antihistimine, and developed imipramine. [Kuhn, 1958, Am.J.Psychiat. 115:459]
Rieveschl	USA	Developed the antihistimine diphenhydramine, used as the starting point for fluoxetine. [

Neurotransmission

Scientist	Affiliation	Contribution
Axelrod, Kopin	USA	★ Mechanism of neurotransmitter signal termination by reuptake; action of imipramine and other early antidepressants in blocking reuptake. Cited for assay of drug effect on reuptake of NE [Axelrod & Tomchick 1959 Nature 184:2027; △ Hertting et al., 1961 J.Pharmacol.Exp.Ther. 134:146; Herttig et al., 1961 Nature 189:66 Glowinsky et al., 1965 J.Neurochem. 12:25; Axelrod, 1965 Rec.Progr. Hormone Res. 21:597] NIH intramural Z01MH-00401-4; Z01MH-00421-3
Page	USA	Discovered serotonin, simultaneously with Gaddum [Twarog & Page 1954 Am.J.Physiol. 175:157] Cleveland Clinic Foundation
Gaddum	Frn	Discovered serotonin, simultaneously with Page [Amin et al. 1954 J.Physiol. 126:596]
Vogt	Frn	Neurotransmitters function in brain activity, and are differently distributed in the regions of the brain. [Vogt 1954 J.Physiol. 123:451]
Iverson	USA	Function of neurotransmitters in synapses of the brain. Developed widely used method of brain dissection, brain injection, and extraction and measurement of substances. [Glowinsky & Iverson, 1966 J.Neurochem. 13:655; Iverson & Dravitz 1966 Mol.Pharmacol. 2:360] NIMH intramural
Schanberg	USA	Measurement of serotonin accumulation and uptake in synaptosomes. [Schanberg 1963 J.Pharmacol.Exp.Ther. 139:191] NIH B-940; USPHS predoctoral fellowship
Green	USA	Serotonin accumulates in brain slices and subcellular fractions, methods of measuring it. [Robinson et al. 1965 J.Pharmacol.Exp.Ther. 147:236] GM-10313; 2K3-GM-2459; ST1-GM-5903

Snyder	USA	Serotonin reuptake in different regions of rat brain, kinetic measurement, and the effects of imipramine on the system. [Snyder & Coyle 1968 J.Pharm.Expr.Ther 165:78; Shaskan & Snyder, 1970, J.Pharm.Expr.Ther. 175:404] NIH RO1-NS-07275, PO1-GM-16492, K3-MH-33128, postdoctoral support on GM-01183.
Merrills	Ind	Imipramine blocks reuptake of serotonin, as well as NE; reuptake occurs in synaptosomes [Blackburn et al., 1967 Life Sci. 6:1653] Pfizer
Renyi,Ross	Frn	Relative effects of imipramine and other drugs on serotonin reuptake [Ross & Renyi 1967 Life Sci. 6:1407]

Biochemical psychiatry

Scientist	Affiliation	Contribution
Schildkraut	USA	Role of serotonin in depression, and the effects of imipramine on neurotransmitter metabolism. [Schildkraut et al., 1966 Am.J.Psy. 123:690; Schildkraut & Kety, 1967 Science 156:21; Schildkraut 1973 Ann.Rev.Pharmac. 13:427] MH-15413
Carlsson, Fuxe	Frn	★Block of serotonin reuptake is basis of antidepressive action of imipramine. Distribution of neurotransmitters in brain, the idea that they are the molecular signals of neurons, and effects of drugs on the reuptake of the neurotransmitters. [Carlsson et al., 1958 Science 127:471; Dahlstrom & Fuxe, 1964 Acta Physiol.Scand. 62:232; Fuxe 1965 ibid 64:247; Carlsson et al., 1968 J.Pharm.Pharmacol. 20:150; Carlsson & Lindqvist, 1969 ibid 21:460; Carlsson 1970 ibid 22:729; Carlsson et al., 1969 Eur.J.Pharmacol. 5:357]
Brodie	USA	A drug causing depression decreases serotonin in brain, the first link of drug action and mood to brain biochemistry. Developed widely used animal model of depression. Compared actions and effects of imipramine and its metabolites [Shore et al. 1955 Science 122:284; Plotscher et al. 1955 Science 122:374; Sulser et al. 1962 Ann.NYAcad.Sci. 96:279; Sulser et al. 1964 J.Pharmac.Exp. Ther. 144:321] NIH NIMH intramural
Goth	USA	Diphenhydramine effects on reuptake of serotonin and NE detailed, which caused the EL scientists to select it as the basis of drug series testing for SSRI action. [Isaac & Goth, 1965 Life Sci. 4:1899; Isaac & Goth, 1967 J.Pharmacol.Exp.Ther. 156:463] ST1-GM-74203
Roth	Ind	Developed a mouse standard antidepressant assay [Barnett et al. 1969 Int.J.Neuro Pharmac. 8:73] Shering
Weil-Malherbe	Frn/USA	First observed that NE and dopamine are excreted in urine in different amounts in manic or depressed patients. Importance of serotonin in depression. Several collaborative papers with Axelrod in US. [Strom-Olsen & Weil-Malherbe, 1958 J.Mental Sci. 104:696; Weil-Malherbe et al. 1959 Science 129:1226; Whitby et al., 1961 J.Pharmacol. Exp.Ther. 132:193]
Sharman	Frn	Neurotransmitter concentrations are decreased in the cerebrospinal fluid of depressed patients. [Ashcroft & Sharman, 1960 Nature 186:1050]

Design and testing of Fluoxetine

Scientist	Affiliation	Contribution
Lineweaver, Burke	USA	Cited for method of measuring affinity constants, to test drug effects on serotonin reuptake. [Lineweaver & Burke, 1934 J.Amer.Chem.Soc. 56:685] USDA
Dixon	Fra	Cited for a method to determine enzyme inhibitor constants. [Dixon 1953 Biochem.J. 55:170]
Wong, Molloy	EL	★Selected diphenhydramine for synthesis of drug series; made and tested fluoxetine. Extensive assay of its actions and selectivity [Wong et al. 1974 Life Sci. 15:471; Wong et al. 1975 J.Pharmac.Exp.Ther. 193:804; Wong et al. 1983 Biochem.Pharmacol. 32:1287; 33:69; Wong et al. 1991 Neuropsychopharm. 5:43]
Fuller	EL	Extensive testing of fluoxetine in animals for efficacy, toxicity, and metabolism [Fuller et al. 1974 Life Sci. 15:1161; Fuller et al. 1975 J.Pharmacol. Exp.Ther. 193:796; Fuller & Wong 1977 Fed.Proc. 36:2154]
Mandell	USA	Developed assay to measure serotonin in brain, and showed increase caused by fluoxetine [Geyer et al. 1978 J.Pharmacol.Exp.Ther. 207:650] DA-00265

Clinical Trials

A large number of clinical trials appeared after the introduction of fluoxetine, as well as additional SSRI drugs and trials comparing them with fluoxetine. It would not be possible to cite all groups involved; instead, trials by groups which were heavily involved and ones from the EL team are cited, as well as review articles summarizing the outcomes of many trials.

Scientist	Affiliation	Contribution
Lemberger	EL	Specific reuptake inhibition in patients shown, and method of measuring fluoxetine potency on serotonin uptake in patients. Tissue distribution, absorption, and excretion in normal, elderly, and kidney patients; tested drug interactions [Lemberger et al. 1978 Clin.Pharmacol.Ther. 23:241; Lemberger et al. 1978 Science 199:436; Lemberger et al. 1985 J.Clin.Psych. 46:14]
Bremner	USA	Initial dose range trial for fluoxetine [Bremner 1984 J.Clin.Psych. 45:414]
Stark, Hardison	EL	Multicenter trials showed fluoxetine as effective as imipramine without side effects [Stark & Hardison 1985 J.Clin.Psych. 46:53]
Guy	USA	Manual for scoring symptoms on a depression scale measuring severity and improvement, cited in several clinical trials [ECDEU Assessment Manual for Psychopharmacology, US HEW, Bethesda, MD]
Cohn, Wilcox	USA	Fluoxetine more effective in major depression than imipramine, w/o side effects. [Cohn & Wilcox 1985 J.Clin.Psych. 46:26]
Masco, Sheetz		Fluoxetine compared with other drugs is as effective w/o side effects [Masco & Sheetz 1985 Adv. In Ther. 2:275]

Appendix D

Tax Methodology

Drug companies are allowed a tax deduction for all qualified research and development expenses. That means all money spent on R&D can be deducted from a company's taxable income. This generates enormous savings for drug companies and substantially lowers the cost of bringing a new drug to market.

In Example 1 (see next page), Company A has spent \$10 million on R&D and collected \$100 million in revenues. At a statutory tax rate of 34 percent, Company A would pay \$34 million in federal taxes without the R&D deduction. After the deduction, Company A's taxable income is only \$90 million, lowering its tax bill to \$30.6 million. Company A has saved \$3.4 million in taxes due to the R&D tax deduction.

In Example 1, Company A saved \$3.4 million in taxes after deducting R&D expenses, which is 34 percent of the \$10 million the company spent on R&D. Every dollar Company A spends on R&D lowers its taxable income by \$1. Put another way, every dollar Company A spends on R&D lowers its tax bill by \$0.34. In effect, every dollar Company A spends on R&D only costs the company \$0.66 because of the money it saves in taxes.

Since every dollar spent on R&D can be deducted, the net cost of R&D to drug companies will always be reduced by the statutory tax rate. This is true regardless of the tax rate or the amount spent on R&D. If Company A had spent \$20 million on R&D then it would have saved \$6.8 million, which is 34 percent (Example 2). If the statutory tax rate changed to 46 percent then Company A would have saved \$4.6 million in taxes after deducting \$10 million spent on R&D (Example 3).

This R&D tax deduction should not be confused with other tax credits the drug industry receives. The deduction of R&D expenses is different from other tax credits because it is a deduction that reduces the taxable income of a company. The drug industry enjoys several tax credits that are applied after the amount a company owes in taxes has been calculated. In other words, a tax credit reduces the amount of tax owed (or tax liability), while a deduction affects the amount of income that is subject to the statutory rate.

Example 1

Statutory Tax Rate	34%		
Gross Income	\$100,000,000	Taxes Before Deduction	\$34,000,000
R&D Deduction	\$10,000,000		
Taxable Income	\$90,000,000	Taxes After Deduction	\$30,600,000
		Difference	\$3,400,000
		Percentage of R&D Expenditure	34%

Example 2

Statutory Tax Rate	34%		
Gross Income	\$100,000,000	Taxes Before Deduction	\$34,000,000
R&D Deduction	\$20,000,000		
Taxable Income	\$80,000,000	Taxes After Deduction	\$27,200,000
		Difference	\$6,800,000
		Percentage of R&D Expenditure	34%

Example 3

Statutory Tax Rate	46%		
Gross Income	\$100,000,000	Taxes Before Deduction	\$46,000,000
R&D Deduction	\$10,000,000		
Taxable Income	\$90,000,000	Taxes After Deduction	\$41,400,000
		Difference	\$4,600,000
		Percentage of R&D Expenditure	46%

Endnotes

¹ National Public Radio, “Talk of the Nation,” hosted by Juan Williams, Jan. 2, 2001

² U.S. Food and Drug Administration statistics cited by Donald Drake and Marian Uhlman, “Making Medicine, Making Money” (1993), published by Andrews and McMeel, p. 72.

³ National Institutes of Health, “NIH Contribution to Pharmaceutical Development,” Administrative Document, February 2000.

⁴ Office of Technology Assessment, U.S. Congress, “Pharmaceutical R&D: Costs, Risks and Rewards,” 1993.

⁵ Alice Dembner, “Public Handouts Enrich Drug Makers, Scientists,” *The Boston Globe*, April 5, 1998.

⁶ Joseph DiMasi et al., “The Cost of Innovation in the Pharmaceutical Industry,” *Journal of Health Economics* 10:107-142, 1991.

⁷ PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2000, “Recent Estimates of the Cost of Developing New Drugs,” pg. 65, cites estimate by Boston Consulting Group that the fully capitalized pretax costs of pharmaceutical R&D had risen “to perhaps over \$500 million.”

⁸ Center for the Study of Drug Development, Tufts University web site
<http://www.tufts.edu/med/csdd/images/spspeak.pdf>

⁹ *Ibid.*

¹⁰ See n. 6.

¹¹ Office of Technology Assessment, U.S. Congress, “Pharmaceutical R&D: Costs, Risks and Rewards,” 1993.

¹² See n. 6.

¹³ See n. 6, footnote 29. DiMasi writes: “One difference is that the FDA includes diagnostic agents and we do not. Another difference is that we include a few therapeutically significant biologics, where the FDA does not include any.”

¹⁴ According to the U.S. Food and Drug Administration, only 311 of the 857 New Drug Applications (NDAs) approved for market in the 1990s were new molecular entities (NMEs), which are similar to DiMasi’s NCEs.

¹⁵ Office of Technology Assessment, U.S. Congress, “Pharmaceutical R&D: Costs, Risks and Rewards,” 1993.

¹⁶ See n. 6.

¹⁷ Kenneth I. Kaitin and Elaine M. Healy, “The New Drug Approvals of 1998, 1997 and 1996: Emerging Drug Development Trends in the User Fee Era,” Tufts Center for the Study of Drug Development, January 2000, published in PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2000, pg. 117.

¹⁸ CenterWatch, “The Speed Demons of Clinical Drug Development: The Fastest Major Pharmaceutical Companies,” 1999. Published in PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2000, pg. 123.

¹⁹ Lehman Brothers, “Drug R&D Costs, Success Rates, and Emerging Technologies: A Look at Three Future Scenarios,” 1997, published in PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2000, pg. 80.

²⁰ S.N. Wiggins, “The Cost of Developing a New Drug,” Pharmaceutical Manufacturers Association, June 1987.

²¹ See n. 6.

²² Pharmaceutical Research and Manufacturers of America, “Annual Survey 2000,” List of Tables, 2001, <http://www.phrma.org/publications/publications/profile00/>.

²³ U.S. Food and Drug Administration, “NDAs Approved in Calendar Years 1990-1999 by Therapeutic Potentials and Chemical Types,” December 31, 1999, <http://www.fda.gov/cder/rdmt/pstable.htm>.

²⁴ PhRMA’s full definition of research expenditures is: “Every year, PhRMA surveys its member companies – the country’s leading pharmaceutical and biotechnology companies – on their individual R&D expenditures. These expenditures are defined as the total costs incurred for all pharmaceutical research and development activity, including salaries of employees who conduct, support or supervise R&D; supplies and equipment used in R&D; a fair share of overhead; contract research expenditures; the costs of synthesis and extraction of compounds; the costs of laboratory testing (pre-clinical); expenditures involved in formulating the dosage and testing the stability of compounds; the expenditures incurred in three-stage, FDA-supervised clinical trials; the costs of post-marketing studies, and bioavailability studies.” Accessed at <http://www.phrma.org/publications/backgrounders/development/invest.phtml>

²⁵ Marcia Angell (editor-in-chief), “The Pharmaceutical Industry – To Whom Is It Accountable?,” *New England Journal of Medicine*, June 22, 2000.

²⁶ See n. 6.

²⁷ Pharmaceutical Research and Manufacturers Association, “Annual Survey 2000,” List of tables, 2000

²⁸ Dembner, see n. 5; also Public Citizen interviews with Wendy Schact, Congressional Research Service and John Hansen, deputy director, General Accounting Office, Health Team.

²⁹ Public Citizen update of Drake and Uhlman, “Making Money, Making Medicine,” 1993.

³⁰ Iain Cockburn (University of British Columbia) and Rebecca Henderson (MIT), “Public-Private Interaction and the Productivity of Pharmaceutical Research,” National Bureau of Economic Research, April 1997.

³¹ Dembner, see n. 5.

³² National Institutes of Health, “NIH Contributions to Pharmaceutical Development,” Administrative Document, February 2000, p. 2.

³³ *Ibid.*

³⁴ *Ibid.*

³⁵ *Ibid.*

³⁶ See n. 4, Appendix D: Congressional Access to Proprietary Pharmaceutical Industry Data.

³⁷ *Ibid.*

³⁸ *Ibid.*

³⁹ Public Citizen analysis of lobby disclosure reports filed with the Secretary of the Senate and Clerk of the House pursuant to the Lobby Disclosure Act of 1995; Public Citizen analysis of campaign contributions reported to the Federal Election Commission and compiled by the Center for Responsive Politics; and Jamieson, et al., “Issue Advertising in 1999-2000 Election Cycle,” Annenberg Public Policy Center of the University of Pennsylvania, February 1, 2001 <http://www.appcpenn.org/issueads/1999-2000issueadvocacy.pdf>.

⁴⁰ Special Committee on Aging, U.S. Senate, “The Drug Manufacturing Industry: A Prescription for Profits,” September 1991.

⁴¹ See n. 25.

⁴² *Fortune* magazine, April 2001, Fortune 500 (www.fortune.com).

⁴³ Public Citizen update of Stephen W. Schondelmeyer calculation, “Competition and Pricing Issues in the Pharmaceutical Market,” PRIME Institute, University of Minnesota based on data found in *Fortune* magazine, 1958 to 1999; *Fortune* magazine, April 2000, Fortune 500 (www.fortune.com).

⁴⁴ *Ibid.*

⁴⁵ Lee Clifford, "The Story of American Business," *Fortune*, April 16, 2001.

⁴⁶ Public Citizen analysis of stock prices for calendar year 2000 obtained from Commodity Systems Inc., accessed at <http://www.finance.yahoo.com>.

⁴⁷ Donald Drake and Marian Uhlman, "Making Medicine, Making Money," Andrews and McMeel, (1993), p. 72.

⁴⁸ *Ibid.*

⁴⁹ U.S. Food and Drug Administration, "NDAs Approved in Calendar Years 1990-1999 by Therapeutic Potentials and Chemical Types," December 31, 1999, <http://www.fda.gov/cder/rdmt/pstable.htm>.

⁵⁰ Congressional Research Service Memorandum, "Federal Taxation of the Drug Industry," December 1999.

⁵¹ Internal Revenue Service, "Corporation Sources Book," cited in Congressional Research Service Memorandum, December 1999.

⁵² U. S. General Accounting Office, "Pharmaceutical Industry: Tax Benefits of Operating in Puerto Rico," May 1992.

⁵³ See n. 50.

⁵⁴ National Institute for Health Care Management, "Prescription Drugs and Intellectual Property Protection," August 2000.

⁵⁵ Rachel Zimmerman, "Drug Makers Find a Windfall Testing Adult Drugs on Kids," *The Wall Street Journal*, Feb. 5, 2001, p. A1.

⁵⁶ U.S. Food and Drug Administration, "The Pediatric Exclusivity Provision," Status Report to Congress, January 2001.

⁵⁷ PricewaterhouseCoopers, "Pharma 2005 Silicon Rally: The Race to e-R&D," published in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2000.

⁵⁸ *Ibid.*

⁵⁹ Brian O'Reilly, "There's Still Gold in Them Thar Pills," *Fortune* magazine, July 23, 2001.

⁶⁰ Jeremy Kahn, "The World's Largest Corporations: Global 500 by the Numbers," *Fortune* magazine, July 23, 2001.

⁶¹ Kenneth I. Kaitin and Elaine M. Healy, “The New Drug Approvals of 1998, 1997 and 1996: Emerging Drug Development Trends in the User Fee Era,” Tufts Center for the Study of Drug Development, January 2000, published in PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2000, pg. 117.

⁶² U.S. General Accounting Office, “Prescription Drugs: Spending Controls in Four European Countries,” May 1994, p. 8.

⁶³ Office of Technology Assessment, U.S. Congress, “Pharmaceutical R&D: Costs, Risks and Rewards,” 1993.

⁶⁴ *Ibid.*

⁶⁵ *Ibid.*

⁶⁶ Company yearly earnings reports analyzed by Public Citizen, April 2001.

⁶⁷ IMS Health, “IMS Health Reports...,” October 19, 2000.

⁶⁸ Harris, Gardiner, “Drug Firms, Stymied in the Lab, Become Marketing Machines,” *The Wall Street Journal*, July 6, 2000, citing research from Competitive Media.

⁶⁹ See n. 67.

⁷⁰ National Institute for Health Care Management, “Prescription Drugs and Mass Media Advertising,” September 2000.

⁷¹ Barents Group LLC, “Factors Affecting the Growth...,” National Institute for Health Care Management, 1999.

⁷² Michael Wilkes, et al., “Direct to Consumer Prescription Drug Advertising...,” *Health Affairs*, March/April 2000.

⁷³ See n. 68.

⁷⁴ Merrill Lynch, “A Medicare Drug Benefit: May not be so Bad,” June 23, 1999.

⁷⁵ U.S. Food and Drug Administration, “Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients,” Final Rule, *The Federal Register*, December 2, 1998, p. 66661.