Summary 1

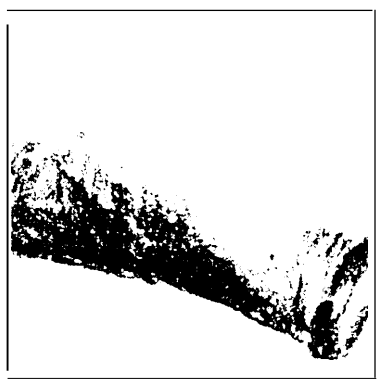
In this assessment, the Office of Technology Assessment examined the costs of pharmaceutical research and development (R&D), the economic rewards from that investment, and the impact of public policies on both costs and returns. Below is a brief synopsis of the study's major conclusions:

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.

. 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.[1] 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.

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.

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 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 l-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 inhibitor 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 l-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 product 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.

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 monoclinal 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]

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[3] Another 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 biological 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.

[4] How 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 subcategories: 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 l-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.[6] 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-

[6] 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. Scherer 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 fired 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.

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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 fins, 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) (520).

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).

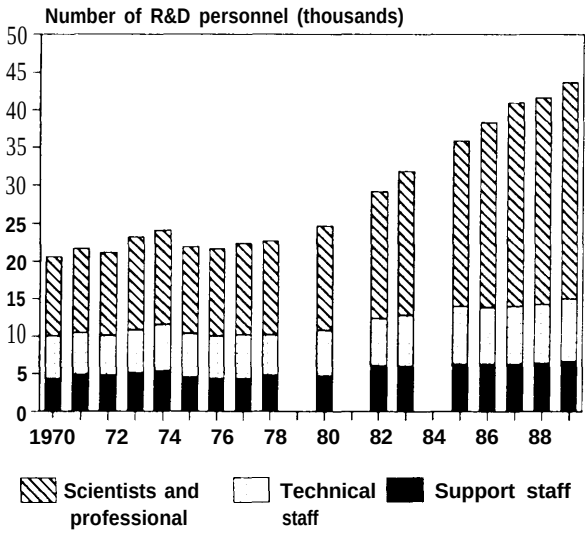
OTA also examined whether trends in three R&D cost drivers-the costs of research personnel, the size of clinical trials, and the cost of animal research-were consistent with the estimated increases in cash R&D outlays per successful NCE between the periods that Hansen and DiMasi studied.

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 l-l). 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 I-l—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 I-l—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	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, I IT, 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

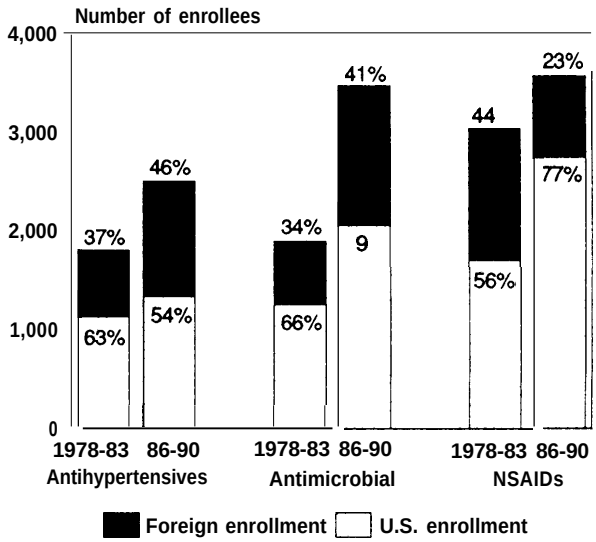
Pharmaceutical executives claim that the number of people enrolled in clinical trials has increased dramatically over time. A rapid increase in trial sizes would be consistent with an increase in the estimated cost of phase III clinical trials from $5.7 million for each NCE entering the phase in Hansen's 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: antihy - pertensives, 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 compress total R&D expenditures into the pre-NDA period.

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.

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 ver-@ 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 per 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 fro'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 fins, 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 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.

Table 1-2—After-Tax R&D Costs Estimated by DiMasi Under Different Assumptions About the Cost of Capital[a] ($ 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.

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.

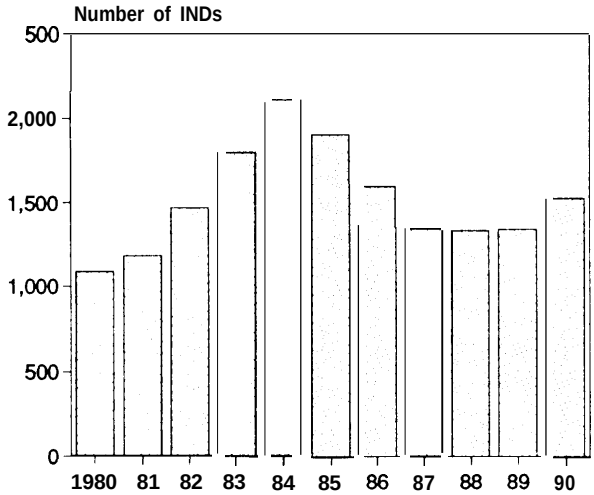
One outgrowth of the expanding base of knowledge about disease mechanisms is the endless supply of possible research directions that this knowledge creates. For example, drug receptors that reside on the surface of cells mediate many of the most important functions in the body and are extremely promising 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.

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.

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

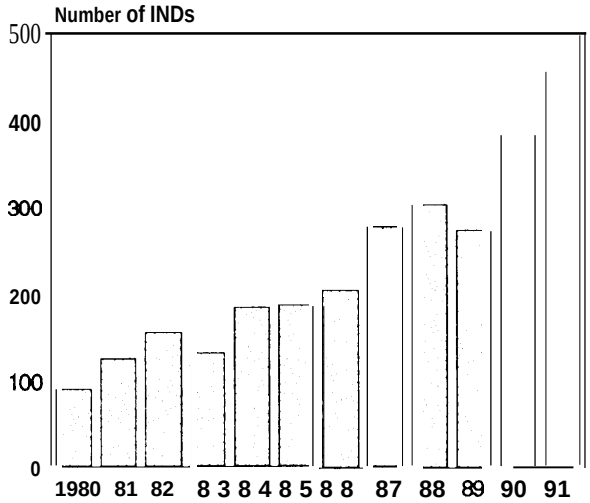
Figure 1-3—IND Applications Received by the Center for Drug Evaluation and Research



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* Evacuation *Statistic/ Report: 1991,* U.S. Department of Health and Human Service, Rockville, MD, 1992.

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 Biologies Evaluation and Research, U.S. Food and Drug Administration.

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 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.

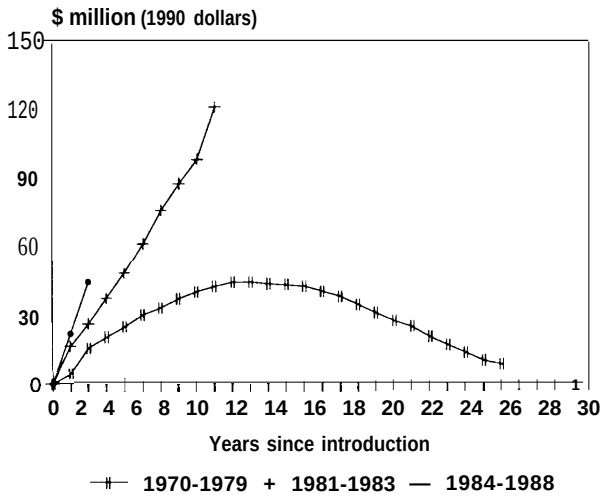
To predict the sales curve for the 1981-83 NCEs beyond the 9th year, OTA examined trends in effective patent lives and in the loss of revenue after patent expiration.

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 (339).

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.

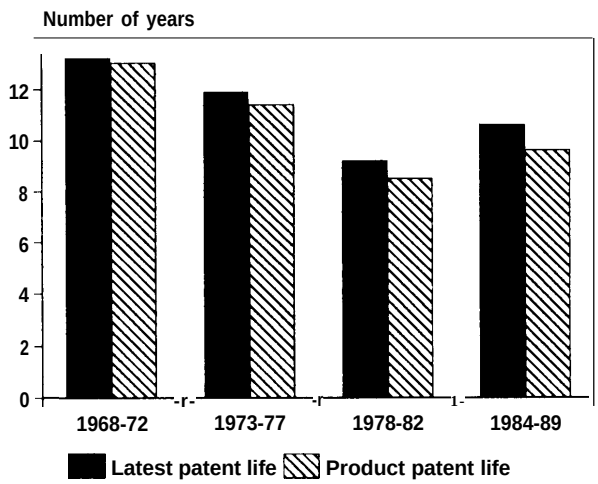
Figure 1-6 shows recent trends in the average effective patent life for NCEs. As expected, after declining steadily throughout the 1970s and early 1980s, effective patent life rebounded somewhat in the years since 1984.

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.

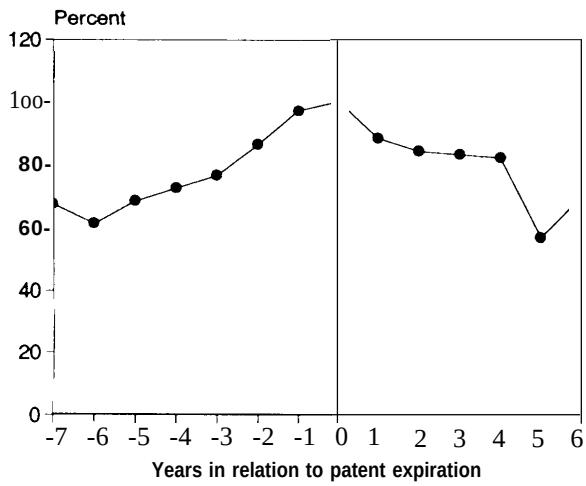
the Drug Price Competition Act. Nevertheless, the introduction of these new products can keep the compound's revenues high for years after the effective patent life ends.

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

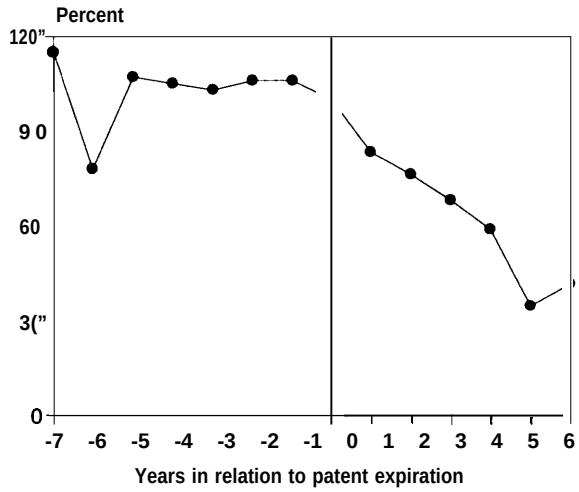
Figure 1-7-Originator Revenue[a] as a Percent of Originator Revenue in Year of Patent Expiration



[a]Based on 1990 dollars.

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

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.

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.

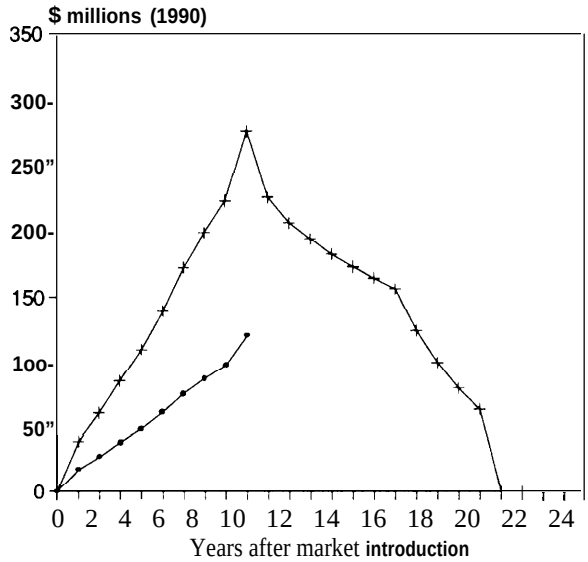
Net Return on Investment

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 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.

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.

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 fins, 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 fins.

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)

						Annual percent rate of change		
	1975	1980	1985	1987	1990	1975-80	1980-85	1985-90
Compustat [TMa]								
Current dollars	$1.10	$2,08	$4.20	$5.53	$7.90	13.60/o	15,1?40	13.5!/0
Constant 1990 dollars[b]	2.44	3.19	4.98	6.19	7.90	5.5	9.3	9.7
Pharmaceutical Manufacturers Association[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

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

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

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.
crilvastain	Pan Medica	Phase II clinical trials.
dalvastatin	Rhone-Poulenc Rorer	Phase III clinical trials.
BAYW6228	Bayer	Phase II clinical trials.
HR780	Hoeschst	Phase II clinical trials.
CI 981	Warner-Lambert	Phase I clinical trials.
00-476	British Bio-technology	Series of compounds under development; preclinical.
BMY-22566	Bristol-Myers Squibb	Preclinical studies.
SQ-33600	Bristol-Myers Squibb	Preclinical studies, discontinued.
BMY-21950	Bristol-Myers Squibb	Phase I clinical trials.
GR-95030	Glaxo	Preclinical studies, discontinued.
SC-45355	Searle	Preclinical studies, discontinued.
L-659699	Merck	Preclinical studies.
L-669262	Merck	Preclinical studies.
CP-83101	Pfizer	Preclinical studies.

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 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).

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.

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

	1 977'	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) 86-3406, 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 andLoca/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 freed 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 (1 19a).

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.

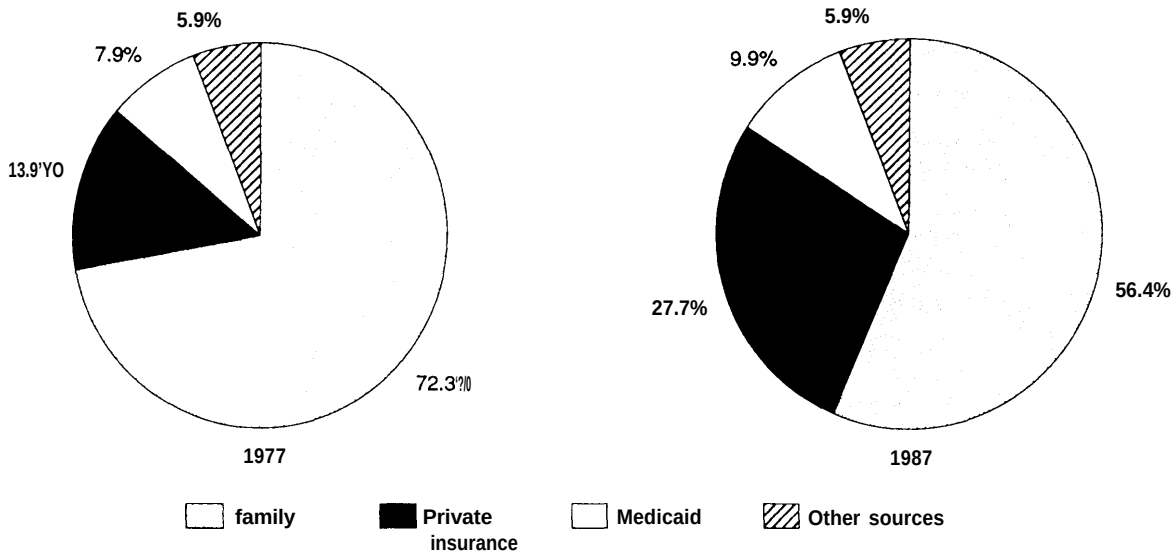
Different Buyers Pay Different Prices

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-l O-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 HMOs[18] 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 Ceredase™, 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 Ceredase™ 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 Ceredase™ 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 formulary 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 countries[23] 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

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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 plain 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 seven] 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-I-7—New Chemical and Biological Entities Entering the World Market by Therapeutic Category, 1975-89

	1975-79		1980-84		1985-89	
	Total	% with therapeutic gain	Total	% with therapeutic gain	Total	% with therapeutic gain
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[b]
-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 g 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 therapeu-

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 such 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 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).

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.

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.[25] Of

[25] This docs not include over $900 million foreign tax credits. Unlike other tax credits which are designed to stimulate 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 mill ion..	$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

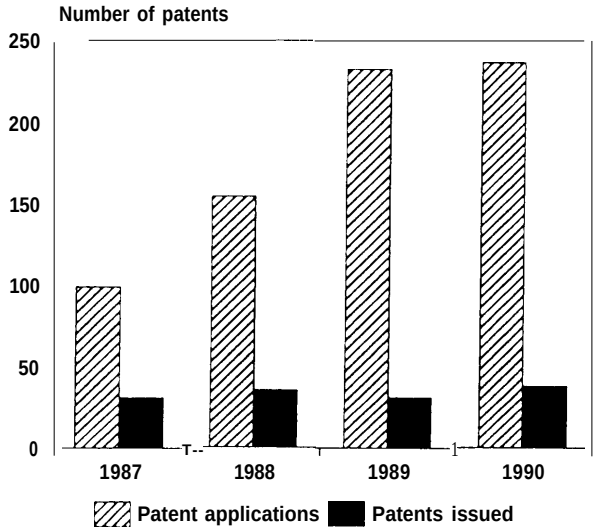
Today, any inventions arising out of the substantial Federal support to academic research are essentially the property of those institutions. The Bach-Dole Patent and Trademark Act of 1980 (Public Law 96-517) gave universities, nonprofit organizations and small businesses the rights to inventions resulting 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.

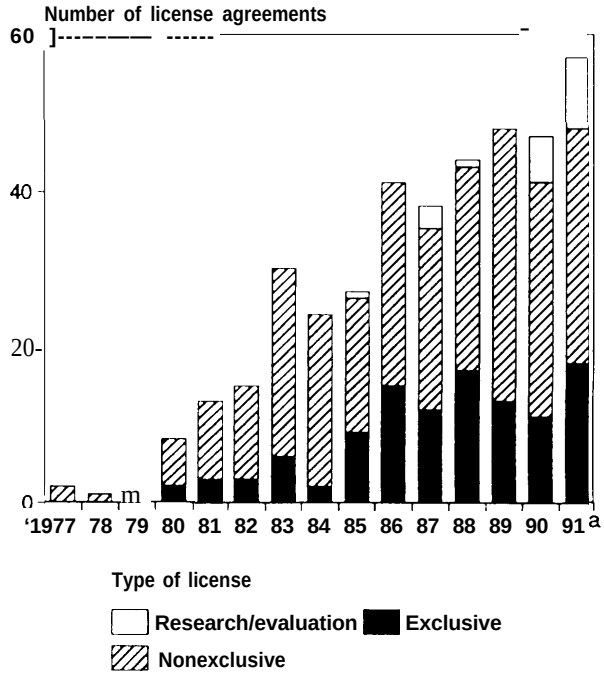
The legislation also permitted Federal laboratories to enter into formal cooperative research and development agreements (CRADAs) in which a Federal agency provides personnel, services, facilities, equipment or resources (but not money) and a private company provides money, personnel, services, facilities, 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-n-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.

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.

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 1-11).

Licensing Inventions from Federal Laboratories

The Federal government has steadily increased the number of licenses issued on its biomedical patents throughout the 1980s (figure 1-12). 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 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 years[26] 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 that 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 Ceredase™ 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.