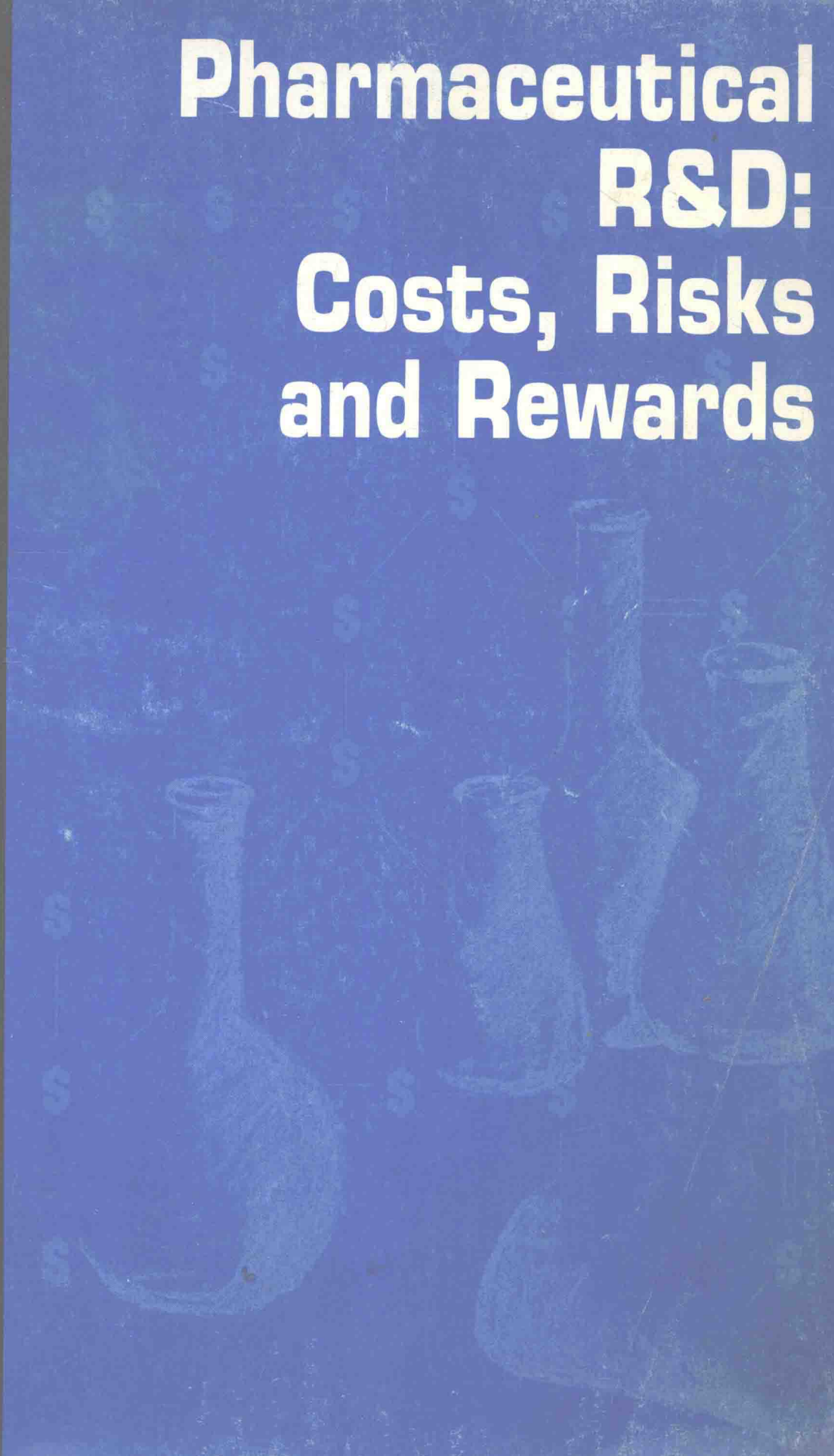
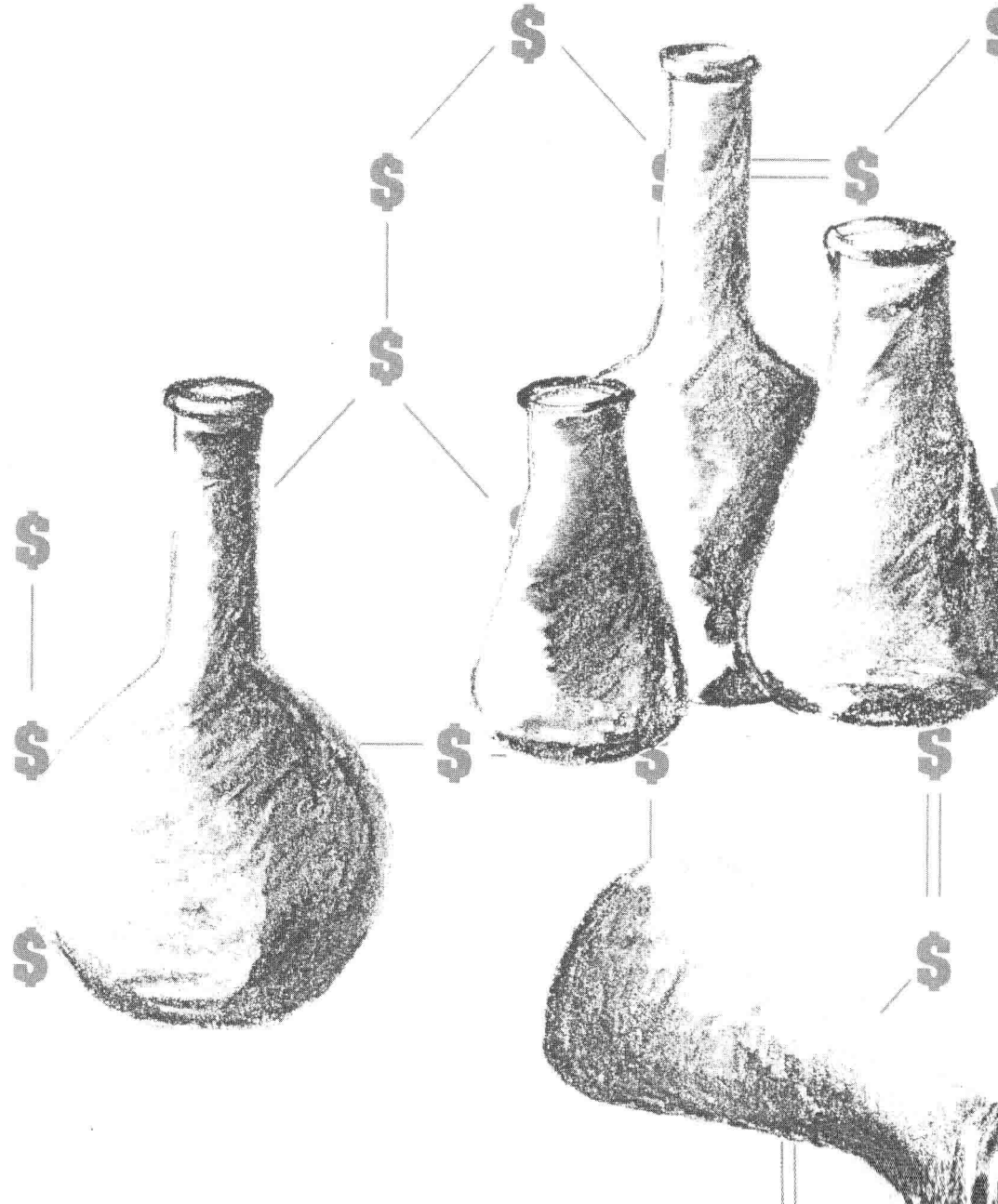
Pharmaceutical R&D: Costs, Risks and Rewards



Office of Technology Assessment

Pharmaceutical R&D: Costs, Risks and Rewards



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Foreword

Pharmaceutical costs are among the fastest growing components of health care costs today. Although increases in the inflation-adjusted prices of ethical drugs and perceived high prices of new drugs have been a concern of congressional committees for over 30 years, the growing Federal role in paying for prescription drugs has increased the concern over the appropriateness of prices relative to the costs of bringing new drugs to market. Specific policies of U.S. and other governments can alter the delicate balance between costs and returns to pharmaceutical R&D, with ramifications for the future health of Americans, for health care costs, and for the future of the U.S. pharmaceutical industry.

OTA's report focuses mainly on the economic side of the R&D process. Pharmaceutical R&D is an investment, and the principal characteristic of an investment is that money is spent today in the hopes of generating even more money in the future. Pharmaceutical R&D is a risky investment; therefore, high financial returns are necessary to induce companies to invest in researching new chemical entities. Changes in Federal policy that affect the cost, uncertainty and returns of pharmaceutical R&D may have dramatic effects on the investment patterns of the industry. Given this sensitivity to policy changes, careful consideration of the effects on R&D is needed.

The specific request for this study came from the House Committee on Energy and Commerce and its Subcommittee on Health and the Environment. The Senate Committee on the Judiciary's Subcommittee on Antitrust, Monopolies, and Business Rights endorsed the study.

OTA was assisted in this study by an advisory panel of business, consumer, and academic leaders chaired by Frederick M. Scherer, Ph.D., Professor of Economics, John F. Kennedy School of Government at Harvard University.

OTA gratefully acknowledges the contribution of each of these individuals. As with all OTA reports, the final responsibility for the content of the assessment rests with OTA.

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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory panel members. The panel does not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

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[1] From September 1989 to September 1991.

[2] From February 1991 to February 1992.

[3] From August 1989 to July 1991.

Contents

- 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's 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.

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.

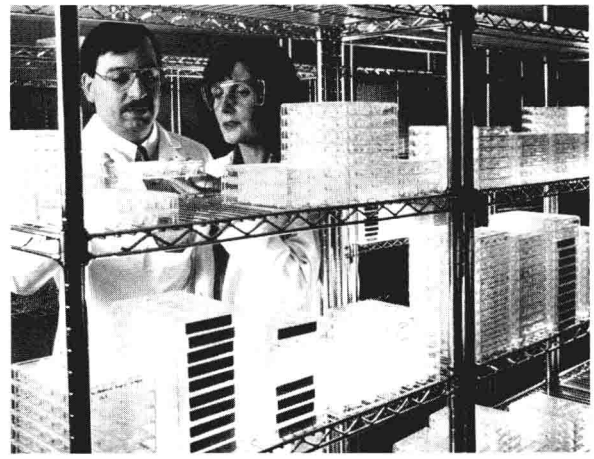

Photo credit: ELI LILLY AND COMPANY

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.

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 1-A—The Content of Pharmaceutical R&D

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

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

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

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

ISSUES BEYOND THE SCOPE OF THIS STUDY

OTA did not examine the implications for the competitiveness of the U.S.-based pharmaceutical industry of Federal policies affecting pharmaceutical R&D. The U.S.-based industry is a leader in the discovery and development of new drugs, particularly important new drugs with global markets. The U.S.-based industry has introduced roughly one out of every four new compounds introduced to the world market since 1961 (68,342) and is so far unchallenged as the leader in biotechnology-based drugs and vaccines. All of the 15 biotechnology-based drugs and vaccines approved in the United States as of August 1991 were developed by U.S.-based firms (453).

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

THE NATURE OF PHARMACEUTICAL R&D INVESTMENTS

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

Pharmaceutical R&D includes many different scientific and clinical activities (see box 1-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 monoclonal antibodies or implantable drug infusion pumps. Follow-on products also must undergo preclinical and clinical testing before they can be marketed, but the amount of R&D required to prove safety and effectiveness is usually less than for the original compound.

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

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

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

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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 biologicals in data they present on NMEs, whereas in this report the term NCE is used to refer to therapeutic drugs and biologicals but not to diagnostic products. OTA uses the term NME only when discussing work that specifically employs FDA's definition of that term.

[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.

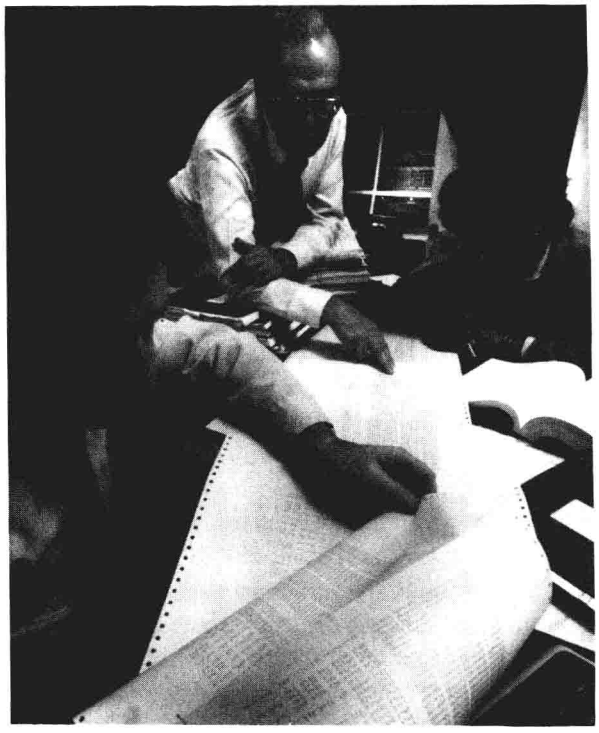
5 percent), is referred to as the **present value** of money.

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.



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

For example, suppose the average NCE entering clinical testing has a 1-in-5 chance of ultimately reaching the market. If it does, it will make on average $100 million for the company. The expected dollar return, then, is $20 million.[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.