Chapter 3

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Innovation in the pharmaceutical industry is dependent on many factors including scientific knowledge, profit levels, research and development (R&D) expenditures, and expected returns to research investment. Clearly these factors are interactive and dependent on decisions made in the private sector. Government action can, however, affect these factors and thereby increase or decrease the likelihood that innovation will occur.

in this chapter, trends in both pharmaceutical innovation and the determinants of innovation are examined so that the effects of patent-term extension on innovation may be assessed in chapter 4.

DECISIONMAKING IN THE INDUSTRY

Before examining any of these trends, some characteristics of decisionmaking in the industry will be noted briefIy, for, no matter what the actual trends, it is how the trends are perceived in the decisionmaking process that determines R&D activities. If decisionmakers foresee declines in the returns to research investment, they will invest less and innovation levels may decline. The decline, however, would not be noticeable for several years because of the time that elapses between research discoveries and product marketing. Decisions made today, therefore, will affect the supply of drugs over the next 10 to **15** years.

The current decisionmaking environment for pharmaceutical innovation has been compared to the "gamblers ruin" problem, in which investment is made with an uncertain distribution of returns, and the objective of the investor is to win often enough to avoid experiencing severe cash-flow difficulties in the interim. No matter how high the return to investment, a firm that experiences a sufficient number of research failures in a row will not have adequate capital to hold out for the eventual "big win. " In an environment of increasingly uncertain returns to pharmaceutical research, only firms with R&D budgets that are large enough to fund several projects at a time can survive the periods of little return and achieve eventual success.[1]

Because of the nature of pharmaceutical research, the characteristics of the decisionmaking process can be very important. One study notes that scientists have less control over research activities than they did in the 1960's and that the decisionmaking process has become more financially oriented. [2]

As a result, research projects undertaken today may receive closer scrutiny than in the past, and assessments of the likelihood of financial and therapeutic success may become more important in corporate decisionmaking. However, the decisionmaker's expectations for different projects may vary, and different *firms will* perceive the market in different ways.

'Thomas R. Stauffer, "Discovery Risk, Profitability Performance, and Survival Risk in a Pharmaceutical Firm, " in *Regulation, Economies, and Pharmaceutical Innovation,* Joseph Cooper (cd.) (Washington, DC.: The American University, 1976), pp. 93-122.

'Steven N. Wiggens, "The Pharmaceutical Research and Development Decision Process, " *Drugs and Health (Washington,* D. C.: American Enterprise Institute for Public Policy Research, *1980).*

TRENDS IN PHARMACEUTICAL INNOVATION

Pharmaceutical innovation is usually measured by the number of new chemical entities (NCEs) introduced, Although this information can be obtained easily, it fails to reflect innovations resulting from new formulations, new combinations of active ingredients, or new uses for existing drugs. Of the 1,916 notices of claimed investigational exemption for a new drug (INDs) pending at the Food and Drug Administration (FDA) on October 1, 1980, only 43.4 percent were for NCEs. Of the 209 candidates judged by FDA to offer important therapeutic gains, 86 were not NCEs. Thus, NCE introductions provide an incomplete measure of innovation and one that gives no weight to differences in therapeutic value.

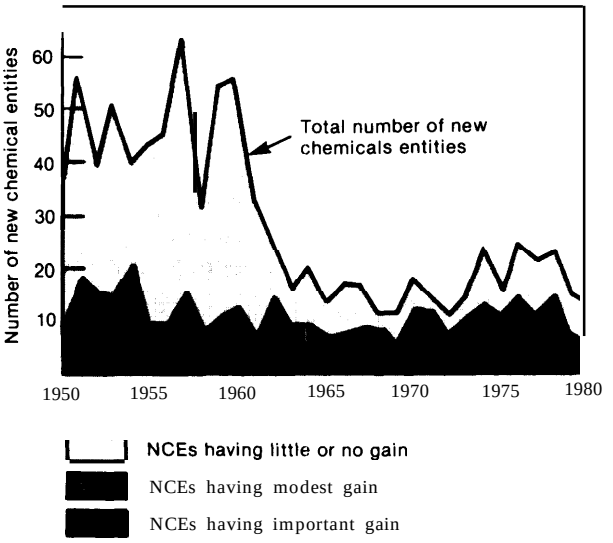
Figure 2 depicts the number of NCEs approved by FDA over the last 30 years, along with FDA's judgments on their therapeutic value. Although the criteria used for assessing the value of the innovations have been subjective and have varied over time, FDA's judgments can provide some perspective on the trends in NCE introductions.

Although the total number of NCEs approved by FDA has dropped significantly since 1950, the number of NCEs approved since 1963 has remained relatively constant. The bulk of the decline in FDA approvals occurred in the early 1960's and involved NCEs considered to offer little or no therapeutic gain. This decline may have been the result of the more stringent FDA drug approval process adopted in 1962. The FDA data indicate that approvals of NCEs offering important or modest therapeutic gain have remained relatively stable.

Trends in innovation have also been measured by NCE sales as a percentage of total ethical drug sales. By this measure, innovation is declining. NCE sales accounted for *20* percent of total sales in 1957 to 1961, 8.6 percent in 1962 to 1966, and 6.2 percent in *1972* to *1976*.[3] Actual sales of NCEs have, however, grown since 1962 because total sales have grown,

Thus, interpretations of trends in innovation depend on the measures used and the time period being measured, but, by most measures, innovation does not appear to be increasing.

Figure 2.—Annual Approvals of New Chemical Entities Reflecting FDA's Judgment of Therapeutic Potential



SOURCE: Testimony of J. Richard Crout before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce. April 1, 1981.

[3] Henry Grabowski and John Vernon, "Government Policy and Innovation in the Pharmaceutical Industry," draft report (Durham, N. C.: Duke University, 1980).

THE KNOWLEDGE BASE

New drugs will not be developed unless scientific progress is made. Advances in the understanding of drug therapy and the physiological interactions in the body, along with advances in molecular biology, have opened up important frontiers in pharmaceutical innovation. Technological advances have improved pharmaceutical research techniques for identifying the

types of chemicals that should be synthesized for biological testing, and screening tests have been developed to determine whether a chemical has a good probability of being safe and efficacious.

As the therapy provided by drugs continues to improve, new pharmaceuticals will, however, have to meet tougher standards. Furthermore, as testing procedures become more sophisticated, more drug candidates will be rejected earlier because problems will be detected sooner.

FACTORS AFFECTING RETURNS TO RESEARCH INVESTMENT

The anticipated rate of return is believed to play a major role in the pharmaceutical industry's decisions to invest in innovative activities.

Several studies have indicated that the rates of return to research investment have declined significantly over the last two decades.[4] The assumptions made in these studies about costs, product lives, and profit margins have, however, been questioned.[5] Because of the unavoidable uncertainties involved with assumptions which must be made to project rates of return, this report focuses on the underlying factors affecting returns to research investment.

The major determinants of returns to research investment are the costs involved in R&D activities, the levels of R&D expenditures, and the revenues and profits of the industry. These factors are not only interrelated but are also dependent on other influences. The costs of R&D are controlled by inflation, regulatory actions, and technological advance. R&D expenditures are influenced by current revenues of the firm, by rates of returns, and by the decisionmaker's expectations for the future. Revenues are determined by prices and the quantities sold which, in turn, are determined by market demand, patent protection, and the number and types of competitors.

In the following discussion, the conclusions drawn pertain to the industry as a whole; but the reader is reminded that R&D costs, prices, sales volume, and profits vary among pharmaceutical products. Most companies are dependent on a few high-income drugs for substantial portions of their revenues. Table 3 provides the sales of the three leading products of selected manufacturers as a percentage of the manufacturers total sales. The effect of the determinants on these high-income drugs may be of particular concern to the pharmaceutical industry.

Table 3.—Percentage of Corporate Pharmaceutical Sales Accounted for by Three Leading Products[a]

	1970	1975	1979
Abbot	36	33	28
American Home Products:			
Ayerst	64	74	84
Wyeth	37	44	43
Bristol-Meyers:			
Bristol	69	46	28
Mead-Johnson	40	38	37
Burroughs-Wellcome	NA	56	51
Ciba	47	NA	55
Lederle	48	31	32
Lilly	46	60	43
Merck	35	44	44
Pfizer	52	65	65
Robins	43	45	46
Roche	80	80	70
Searle	45	49	44
Shering	42	48	40
SmithKline	44	42	66
Squibb	28	31	23
Upjohn	47	50	56
Warner- Lambert:			
Warner	53	NA	NA
Parke-Davis	25	27	22

NA = not available
[a]U S sales

SOURCE: Charles River Associates, Inc, "The Effects of Patent-Term Restoration on the Pharmaceutical Industry, " a report to OTA, May 4, 1981.

[4]Charles River Associates, Inc., "The Effects of Patent Term Restoration on the Pharmaceutical Industry, " prepared for OTA, May 4, 1981, pp. 4-1 to 4-3.

[5]Ibid.

TRENDS IN REVENUES AND PROFITS

The revenues and profits of the industry have direct bearing on the amount of funds available for R&D activities. As seen in chapter 2, profits in the pharmaceutical industry have been relatively stable. As shown in table 4, the revenues of U.S.-based firms from the sales of ethical pharmaceuticals have grown significantly since *1965*, even on a constant-dollar basis. Real growth has occurred in both foreign and domestic sales.

As shown in table 5, the relationship between revenues and R&D expenditures in the U.S. pharmaceutical industry has also been stable. For the years 1965 through 1978, research expenditures ranged between 8.2 and 8.8 percent of total sales. The stability of this relationship suggests that trends in revenues may be a good indicator of trends in R&D expenditures.

Table 4.–Sales of Pharmaceutical Products of U.S. Based Firms 1965-78

Year	Total domestic and foreign sales (millions)	Deflator	Deflated sales (millions)	Real growth in sales (percent)
1965	$ 3,939	103.2	$ 3,817	Base year
1966	4,340	102.6	4,230	10.8%
1967	4,744	100.0	4,744	12.2
1968	5,302	99.0	5,356	12.9
1969	5,837	99.5	5,866	9.5
1970	6,425	99.3	6,470	10.3
1971	7,009	99.0	7,080	9.4
1972	7,739	99.1	7,809	10.3
1973	8,722	99.9	8,731	11.8
1974	9,956	104.2	9,555	9.4
1975	11,554	113.2	10,207	6.8
1976	12,775	120.3	10,619	4.0
1977	13,838	125.4	11,035	3.9
1978	15,978	131.9	12,114	9.8

SOURCE: Derived from Pharmaceutical Manufacturers Association-OPA, April 1981, using BLS, producer price deflator for pharmaceuticals

Table 5.—Research and Development Expenditures and Sales Revenues of U.S. Ethical Drug Industry (1965-78)'

Year	Domestic sales total	Foreign sales (including exports) total	Domestic R&D current dollars (millions)	Foreign R&D current dollars (millions)	Ratio of R&D to sales in current dollars[b] (percent)
1965	$2,940	$ 999	$ 304.1	$ 24.5	8.30/o
1966	3,178	1,162	344.2	30.2	8.6
1967	3,393	1,351	377.9	34.5	8.7
1968	3,808	1,494	410.4	39.1	8.5
1969	4,135	1,702	464.1	41.7	8.7
1970	4,444	1,981	518.6	47.2	8.8
1971 , ...	4,796	2,213	576.5	52.3	8.6
1972	5,136	2,603	600.7	66.1	8.6
1973	5,644	3,078	643.8	108.7	8.6
1974	6,273	3,683	726.0	132.5	8.6
1975	7,086	4,468	828.6	144.9	8.4
1976	7,867	4,908	902.9	164.9	8.4
1977	8,434	5,404	984.1	197.7	8.5
1978	9,411	6,567	1,089.2	222.0	8.2

[a] Veterinary-use pharmaceutical research and development is excluded for the years 1965 through 1974.
[b] Globalpharmaceutical R&D and sates of U.S firms.

SOURCES Henry Grabowski and John Vernon, "Government Policy and Innovation in the Pharmaceutical Industry, " draft report, November 1980, and Pharmaceutical Manufacturers Association, "Annual Survey Report– 1979-80" (Washington, D C : PMA, 1980),

Prices of Drugs Sold

Revenues are determined by the prices and quantities of drugs sold. Pharmaceutical prices have risen very slowly since **1967,** but, because the quantity of drugs sold has increased there has been real growth in revenues (see table 4). The Firestone Report of August 1980 indicates that pharmaceutical producers' prices (wholesale) have risen **46.1** percent since **1967.** Prices of all industrial producers have risen, on average, **136.5** percent since **1967.** Table *6* indicates that producer price indexes for all industries have typically been considerably higher than producer price indexes for pharmaceuticals.

Producer prices vary among therapeutic classes. Table 7 shows the average change in producer prices by therapeutic category. From tables *6* and 7, it can be seen that the average growth in price across all therapeutic classes was **46.1** percent and that the average price change ranged from – **17.8** to + **187.0** percent.

According to a study of price statistics of all NCEs introduced into the United States between 1958 and 1975, prices also vary with the therapeutic value of the drug. Of the NCEs classified as important therapeutic gains, 44 percent had prices that were more than double the prices of the closest competitive products; of the NCEs providing modest, little, or no therapeutic gain, about **10** percent had prices more than double the prices of the closest competitors. Similarly, *30* percent of the former had prices that were less than *120* percent of the closest competitors' prices and about *72* percent of the latter had prices that were less than *120* percent of the closest competitors' prices. [b]This study also indicates that prices for NCEs vary widely: introductory prices ranged from about one-quarter of the price of the closest competitive product to 15 times the price of the closest competitive product.[7]

Table 6.—Producer Price Indexes for Selected Years
(1967 = 100)

Year	All industries	Pharmaceutical industry
1949	75.3	117.3
1969	106.0	100.1
1974	153.8	109.3
1975	171.5	116.2
1976	182.4	123.8
1977	195.1	131.7
1978	209.4	138.8
1979	236.5	146.1

SOURCE *The Firestone Report,* August 1980, p 4

Table 7.—Average Percentage Change in Producer's Prices by Therapeutic Category, 1969-79

Group	Percent
Contraceptives, oral	+187.0
Sedatives	108.6
Antiobesity	81.3
Cough and cold	72.6
Bronchial therapy	66.7
Hormones	63.2
Diabetic therapy	63.0
Antiarthritics	62.3
Antispasmodic	60.7
Cardiovascular	53.9
Vitamins	46.5
Dermatologicals	41.1
Analgesics	38.0
Diuretics	34.7
Psychotherapeutics	17.5
Anti-infectives	– 1.4
Broad and medium specialists	0.0
Penicillin	– 17.8
Sulfa and antibacterial	+ 24.6
All others	57.1
Total	46.0

SOURCE. *The Firestone Report,* August 1980, p 2

The prices and quantities of drugs sold are determined by several factors: market demand, patent protection, and the number and type of competitors. In chapter 2 demand was examined, in this chapter other determinants of revenues are examined.

Product Lives.—Product lives do not necessarily parallel patent lives. Irrespective of the patent, a drug will be prescribed and consumed as long as no other drug or therapy comes along that is better and as long as the disease or condition for which the drug is prescribed continues to be prevalent in the society.

Table 8 lists the 15 top selling drugs in the United States in 1980 and their new drug application (NDA) approval date. The table in-

[7]Duncan W. Reekie, "Price and Quality Competition in Drug Markets: Evidence From the United States and the Netherlands," *Drugs and Health* (Washington, D. C.: American Enterprise Institute for Public Policy Research, 1980), p. 132.
[b]Ibid., p. 134.

Table 8.—Top Selling Drugs by Volume in 1980 and Year of N DA Approval

Drug (trade name)	Year
Valium	1963
Inderal	1967
Dyazide (dyrenium)	1964
Lanoxin	(a)
Tylenol with codeine	(a)
Lasix	1966
Dimetapp	(a)
Motrin	1974
Tagamet	1977
Darvocet-N	1972
Dalmane	(a)
Aldomet	(a)
Ortho Novum	(a)
Actifed	(a)
Keflex	1971

[a]Approval priorto 1963

SOURCE. *American Druggist*, February 1981, for ranking; FDA, private communication, for NDA approval data forNCE(June 1981)

dicates that 9 of the 15 drugs have product lives of 17 years or more.

Product lives are shortened by competition from other drugs and nondrug therapies, but a widely accepted drug may be able to retain a significant market share when competition emerges.

Since the 1950's, the average product life of drugs has increased. Product lives, however, vary widely depending on the competition within the therapeutic class.

Patent Protection. —Patents protect against competition from other generically equivalent products. (For a discussion of patents, see ch. 5.) Patents do not protect against competition from nonequivalent drugs or nondrug therapies.

Effective patent terms for pharmaceuticals have been declining. The average effective patent life for patented NCEs receiving FDA approval has reportedly declined from 13.6 years for drugs approved in **1966** to *9.5* years for drugs approved in 1979.[8] Three factors have contributed to this decline: an increase in the duration of the clinical and regulatory period required for drug approval; a slight increase in the time between the filing of a patent application and clinical testing; and a decrease in the time between patent application filing and patent issuance. Sixty percent of the decrease in effective patent life has been attributed to the increased testing and regulatory period and 40 percent to the other two factors.

Effective patent lives vary widely among products. Table 9 indicates that the effective patent lives of the drugs with the highest revenues ranged from 11 to 17 years.

Some of the factors influencing effective patent terms are undergoing change. The duration of the FDA regulatory procedure may be stabilizing. The average time between the filing and issuance of a patent application is increasing slightly as a result of a backlog of patent applications in the Patent Office. Thus, there is reason to believe that the decline may not continue in the future. Furthermore FDA is now giving highest priority to the drugs that it believes will provide significant therapeutic advances, hence, these drugs may fare better than the average drug in the future.

Competition and Concentration.—Competition, whether it comes from generically equivalent drugs or nonequivalent drugs, affects both the prices of drugs and the quantities sold. One indication of the degree of competition in an industry is the extent to which sales are concentrated among the leading firms in the industry. The relationship between innovation and concentration is disputed. According to some, high levels of concentration favor innovation since the more highly concentrated the market structure, the greater the ability to obtain higher profits. The higher profits can serve as incentives for innovation and make additional revenues available for R&D.

According to others, concentration can have negative consequences for innovation. In a very competitive market, consumer demands interact with costs of production to determine what drugs firms will produce and what the prices of these drugs will be. In highly concentrated markets, some or much of that power shifts to the producers, and innovation may therefore be determined by corporate needs, rather than consumer needs. The producers may be able to maintain high levels of profitability without innovation. Innovation may also suffer because the factors leading to the more highly concen-

[8]M. Eisman and W. Warden, "The Decline in Effective Patent Life of New Drugs," *Research Management*, January 1981, p. 18-21.

Table 9.—Effective Patent Lives of 1980 Top Sellers by Revenues

Drug (trade name)	1980 U.S. sales (millions)	Patent approval	NDA approval (date)	Patent expiration	Effective patent (years)
Tagamet	$250	1976	1977	1993	16
Valium	230	1968	1963	1985	17
Inderal	200	1967	1967	1984	17
Motrin	150	1968	1974	1985	11
Aldomet	150	1964	(a)	1981	17
Dyazide (dyrenium)	145	1963	1964	1980	16
Keflex	140	1970	1971	1987	16
Clinoril	125	1972	1978	1989	11

[a]Approved prior to 1963

SOURCE For ranking and sales New *York Times*, Sunday, May 17, 1981, quoting Oppenheimer and Co For NDA approval date and patent information private communication from FDA

trated market can discourage the entry of new firms.

The measurement of concentration has been a subject of controversy. When market shares of firms are calculated as a percentage of total pharmaceutical sales, concentration is relatively low in the pharmaceutical industry. When market shares are measured as a percentage of sales in particular therapeutic categories, concentration in some categories is quite high. When one looks at market shares over time, one finds that the firms in the leadership positions change considerably.[9] Since the shift in market positions is attributed to new product introductions, some economists suggest that this measurement is the one most relevant to innovation.

Competition From Nonequivalent Drugs.—Competition from nonequivalent drugs was somewhat higher between 1972 and 1980 than between 1963 and 1971. Table 10 shows the number of firms receiving NCE approvals and the number of NCEs approved, by FDA category, for those two periods. By aggregating NCE approvals for two 8-year periods, it was found that both the number of firms and the number of NCEs have increased for all but one category of drugs. The table does not explore entries and exits, but considerable turnover has occurred in the firms producing NCE drugs. For example, of the **20** firms producing cardiorenal drugs in the **1972-80** period, 15 had not produced such drugs in the earlier period.

[9]Douglas Cocks, "Product Innovation and the Dynamic Elements of Competition in the Ethical Pharmaceutical Industry, " in *Drug Development and Marketing* (Washington, D. C.: American Enterprise Institute,]975).

Table 10.—Number of Firms Receiving FDA Approval and Number of Drugs Approved, by FDA Drug Category (1963-71 and 1972-80)

	1963-71		1972-80	
FDA division	Firms	NCEs	Firms	NCEs
Cardiorenal	10	13	20	23
Neuropharmacological	20	25	17	23
Metabolism and endocrine	11	14	13	19
Anti-infectives	34	47	36	49
Oncology and radiopharmaceutical	12	24	23	45
Surgical-dental	12	13	13	16

SOURCE Food and Drug Administration, private communication, June 1981

Competition From Generically Equivalent Drugs.—After a patent expires, competition may emerge from generically equivalent drugs. Such drugs are manufactured by production-intensive firms who market nonbranded drugs under generic names and by research-intensive firms who market branded drugs either under trade names or under generic names accompanied by firm names. The reputation of research-intensive companies may enable their products to command higher prices than products marketed under generic names alone.

The revenues of branded and nonbranded drugs which either had not been patented or had patents that expired were about $4.4 billion in 1979; some of those drugs, however, did not have competition from generically equivalent drugs. Only about 7 percent of the revenues for branded and nonbranded drugs were earned by production-intensive firms with the remainder earned by the research-intensive firms.[10]

[10]Interview with William Haddad, Generic Pharmaceutical Industry Association, Apr. 21, 1981.

Branded and nonbranded drugs compete among themselves, as well as with the originally patented products. For example, a pharmacist, to avoid a large inventory, may carry only one branded and one nonbranded product. Competitive factors including price influence his choice of products.[1]

The Federal Trade Commission estimated that between **42.1** percent and 74.3 percent of the wholesale price of branded drugs could be saved by the dispensing of nonbranded products instead of more expensive branded drugs. 1[2]

Counter-Competitive Forces.—An important influence on the level of competitive activity when patents expire is the ease of market entry for generically equivalent products. Barriers to market entry arise from the requirements for FDA approval of generically equivalent products and from nongovernmental factors.

As stated in chapter 2, FDA plans to reinstitute its paper NDA procedure. This practice should significantly lower the barriers to second entrants. However, many firms seeking approval will not be able to provide such data and the FDA requirements for them will continue to discourage entry. FDA has also announced that it plans to consider changing its regulations so that its abbreviated NDA procedure could apply to some post-1962 drugs .13

FDA bioavailability tests also can act as barriers to market entry. Bioavailability relates to the absorption of drugs into the body. Tests for bioavailability are required in cases where precise dosage is critical because of narrow margins separating ineffective, effective, and toxic doses. When such tests are required, they may be difficult and time-consuming, and therefore act as disincentives to second entrants.

Nonregulatory barriers to successful market entry also exist. A principal barrier is the third-party aspect of consumer drug selection. The physician, who prescribes a drug for his patient, frequently cannot keep informed about alternative versions of a particular drug and their relative prices, and may prefer branded products because he believes them to be safer. This preference for trademarked brand-name drugs tends to give strong marketing advantages to first-entrant drugs that are therapeutically effective. These advantages can endure over time, and latecomers may need to wage vigorous promotion campaigns or offer improved substitute products to overcome these advantages. With gradually increasing product selection by pharmacists, this timing-of-entry barrier may be weakening.

Pharmacist preference can, however, also act as an entrance barrier. Pharmacists may be reluctant to fill prescriptions for brand-name drugs with generic equivalents because they fear they may be liable if generic equivalents cause injury.

Although pharmacists and physicians play a key role in determining the market for drugs, they are frequently influenced by consumer opinion. Thus, consumer preference also acts as a barrier to entry. Many drugs, have a particular size, shape, and color which are claimed by the innovator firm to be proprietary. A generic product that looks different from the product that the consumer customarily uses may be rejected in favor of a familiar product.

Forces Favoring Competition.—As discussed in chapter 2, actions taken by the Federal and State governments over the past decade have facilitated the development of the low-cost generic market. More than 40 States have repealed laws which prevented pharmacists from substituting generic equivalents for prescribed brand-name drugs. Some of the State substitution laws, such as New York's, require pharmacists to fill prescriptions with the least expensive generic products available according to a State formulary. Other States permit substitutions only when physicians specifically note that substitutions can be made.

The Federal Government's Maximum Allowable Cost (MAC) program, which affects reimbursements to pharmacists under medicaid, also encourages competition, Under the MAC program, the lowest wholesale price of a generically equivalent, multisource drug is identified. The

[1] "Federal Trade Commission, "Drug Product Selection, " Washington, D. C., 1979 (staff report to FTC).
[2] Ibid.
[13] 46 Federal Register 24445, Apr. 30, 1981.

MAC regulations limit the reimbursement to the pharmacist to that lowest identified wholesale price plus a reasonable dispensing fee. Because a growing percentage of all prescriptions are paid by medicaid, MAC is expected to have a significant effect as more drugs fall within the MAC program. Because MAC encourages pharmacists to stock low-priced generic products, pharmacists may be more inclined to use these products when filling prescriptions of nonmedicaid patients.

Several other Federal actions also favor competition: the Government-wide Quality Assurance Program is designed to increase competition among drugs purchased by the Department of Defense, the Veterans Administration, and the Public Health Service; the Model State Prescription Drug Product Substitution Act is designed to assist States in developing laws that encourage the dispensing of generically equivalent drugs; and the FDA list of therapeutically equivalent drug products is designed to provide an authoritative statement regarding generic drug quality. The Supreme Court has also had an impact by voiding, as unconstitutional, laws which prohibited the retail advertising of drugs and drug prices.

The full impact of the repeal of the antisubstitution laws and the Federal Government actions may not yet have been felt. One study reported the market share of 12 selected patented drugs before and after patent expiration for drugstore and hospital markets through **1978.** After patent expiration, each of these drugs retained more than a 90-percent share of the drugstore market and more than an 80-percent share of the hospital market. Six of the drugs retained more than a 97-percent share of both markets in **1978.** The retail price, in constant dollars, of 4 of the 12 drugs declined; the greatest decline was about *35* percent .14 It is not clear if price declines were due to generic competition or other factors, such as competition from new patented drugs or the waning of product life.

Trends **in Generic Competition.** —The trends in generic competition activity levels after patents expire are uncertain. The full impact of recent actions by the Federal and State governments facilitating generic competition has not yet been felt. While these actions have thus far had relatively minimal effects, they could potentially have substantial effects *on* the revenues and profits of innovator firms. Barriers to subsequent entrants can provide a countervailing force to these Government actions. Over the next few years, as the patent terms end for many high-income drugs, the trends will become more obvious.

[14]Meir Statman, "The Effect of Patent Expiration on the Market Position of Drugs, " in *Drugs and Health,* Robert B. Helms (cd.) (Washington, D. C.: American Enterprise Institute for Public Policy Research, 1980), pp. 140-151.

THE COSTS OF RESEARCH AND DEVELOPMENT

Thus *far,* the factors that influence revenues have been discussed. The returns to R&D investment, however, also depend on R&D costs and expenditures.

The average absolute R&D costs for new chemical entities are difficult to ascertain. Several average R&D cost estimates have been made. One estimate projected the R&D cost for a self-originated NCE (one not licensed from another source) to be *$54* million (in **1976** dollars). This calculation included $21 million in opportunity costs of capital (the money that could have been earned by investing in an alternative venture at an 8-percent return for the number of years between the initial investment and the start of sales income) and the costs of failures (7 failures for each success at the clinical stage).[15]

[15]R. W. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes, " in *issues in Pharmaceutical Economics,* Robert 1. Chien (cd.) (Lexington, Mass.: Lexington books, 1980).

Rather than relying on estimates of R&D costs, the factors influencing R&D costs to ascertain trends in R&D costs have been reveiwed in this report. The costs of R&D have increased. Part of the increase is due to inflation; facilities, equipment. and salaries are all subject to inflationary pressures. The Biomedical Research and Development Cost Index of the National Institutes of Health (NIH) has outpaced both the Consumer Price Index and the Bureau of Labor Statistics Producer Price Index for Pharmaceuticals. Many commentators expect such pressures to continue in the future.

Some of the increase in costs has been due to regulatory actions. Testing standards have become more stringent and have required longer amounts of time to conduct. FDA is, however, trying to expedite its approval of new drugs and the duration of the drug approval process may therefore stabilize. Table 11 shows the time required for FDA approval of NCEs between *1976* and *1980.* The average time and the median number of years needed to obtain approval dropped in **1980.**

Table 1 1.—Average and Median Number of Years Between IND Filing and NDA Approval for NCEs

Year	Average years	Median years
1976	5.8	5
1977	7.8	7
1978	5.2	5
1979	8.9	9
1980	8.2	7.5

SOURCE: Private communication from FDA, June 1981

Technological advances have helped to counter the upward trend in R&D costs. By all accounts, the sophistication of pharmaceutical R&D has increased. Some of these advances may provide more efficient (and therefore less costly) ways of conducting research. Although we have no data on this trend, technological advance can be expected to stem some portion of the rising costs in the future.

In an attempt to keep R&D costs down, U.S. firms are committing increasing amounts of research expenditures abroad where regulatory procedures often permit more rapid and less costly drug development.

Expenditures in Research and Development

Real growth has occurred in expenditures of funds for R&D. In table 12, the current foreign and domestic dollars spent on R&D have been deflated for the years 1965 through 1978, using the (NIH) biomedical R&D cost deflator (1967 = 100). R&D expenditures **have** apparently kept up with and surpassed the rate of inflation for biomedical research. This upward trend may be expected to continue in the near future. Many research-intensive firms have indicated that they are increasing R&D expenditures. For example, Merck & Co. expects to spend *$280* million on R&D in *1981, 20* percent more than in *1980.* [16]

[16] William Fallwell, "U.S. Drug Companies Held Up Well in Recession," *Chemical and Engineering News,* Mar. *9, 1981,* p. 8.

Table 12.—Trends in R&D Expenditures

Year	Total domestic and foreign R&D (millions current dollars)	Deflator	Deflated R&D (millions constant dollars)
1965	329	92.5	356
1966	374	95.8	390
1967	412	100.0	412
1968	449	104.7	429
1969	506	110.4	458
1970	566	117.5	483
1971	629	124.1	507
1972	667	130.3	512
1973	753	136.5	552
1974	859	145.2	592
1975	974	160.7	606
1976	1,068	172.7	618
1977	1,182	186.4	634
1978	1,311	200.3	655

SOURCE Table 5 and information obtained from the Pharmaceutical Manufacturers Association, April 1981,

Of concern is the allocation of funds between basic research and product development. Declining expenditures on basic research could result in a reduced number of new drug introductions in the future. Industry officials have indicated that a shift from basic research to product development is taking place. Lewis Sarett **(1981)** of Merck& Co. reported in congressional testimony that a recent survey of U.S. firms by the Organization for Economic Cooperation and Development indicated that pharmaceutical firms are reducing the research share of their R&D budgets. To avoid the risks of research, firms are increasingly licensing technology from other sources and are spending more on development.[17] Nevertheless, preliminary information provided in table 13 suggests relatively little change in emphasis.

Rising costs can also be expected to shift R&D program emphasis among therapeutic classes because some types of drugs can be developed less expensively than others. In periods of rising costs, firms can be expected to emphasize the less costly research areas. Table 14 shows the percentage of R&D expenditures for different therapeutic categories for the years 1975-79. Although some shifts in expenditures are evident, the shifts tend to be more toward areas in which significant therapeutic advances are occurring (e. g., cardiovascular) than toward areas which involve lower costs (e. g., anti-infectives).

These shifts in expenditures, however, may not indicate any shift in decisions about R&D spending. Expenditures vary depending on where the innovation is in the development process, and these shifts may therefore only reflect normal research progress.

[17] For another example, see: D. Schwartzman, "Innovation in Pharmaceutical Industry;" J. R. Virts and J. Fred Weston, "Expectations and Allocation of R&D Resources;" and Grabowski and Vernon, op. cit.

Table 13.—Relative Funding of Basic and Applied Research in the Pharmaceutical Industry
(millions **of dollars)**

Year	(1) Basic research	(2) Applied R&D	Column 2 as percent of total
1968	60	375	86.2
1969	67	417	86.2
1970	93	474	83.6
1971	77	535	87.4
1972	78	501	87.2
1973	90	605	87.1
1974	107	683	86.5
1975	112	783	87.5
1976	119	883	88.1
1977	131	959	88.0

NOTE: For the purpose of this table. the pharmaceutical industry IS defined as corporations primarily engaged in manufacturing biologicals, Inorganic and organic medicinal chemicals, pharmaceutical preparations, and grading, grind. ing, and milling of botanicals.

SOURCE. Derived from National Science Foundation, *National Patterns of Science and Technology Resources 1980,* tables *42* and *45*

Table 14.—Percentage of R&D Funds Spent by Therapeutic Class (1975-79)

Therapeutic class	Percent of total R&D spending[a] 1979	1978	1977	1976	1975
Anti-infectives	18.7	18.3	19.2	19.5	20.1
Central nervous system and sense organs	16.3	16.9	17.0	16.2	18.0
Cardiovascular	18.6	17.3	15.2	13.2	14.9
Neoplasms, endocrine system, and metabolic diseases	15.3	16.1	15.7	14.7	15.5
Gastrointestinal and genitourinary system	6.3	6.7	6.0	5.8	5.1
Respiratory	4.0	4.4	4.0	4.1	5.5
Biological	2.5	3.0	3.1	3.1	3.0
Dermatologicals	2.9	2.8	3.2	2.8	2.8
Vitamins	2.5	2.2	2.5	1.5	1.1
Diagnostic	0.5	0.6	0.8	1.2	1.2
Other human preparations	6.7	5.6	6.3	10.5	6.1
Veterinary preparations	5.3	5.7	6.6	7.2	6.5
Veterinary biological	0.4	0.4	0.4	0.2	0.2

[a] In the United States only

SOURCE" Pharmaceutical Manufacturers Association

SUMMARY OF FINDINGS

Research-intensive companies are committing increasing amounts of funds toward pharmaceutical R&D, and therefore, the potential exists for major pharmaceutical discoveries. Factors have been highlighted which, based on historical trends, will affect pharmaceutical innova-

tion. Below is a summary of these major trends. Following that is a summary of factors whose effects are uncertain.

Historical Trends That May Discourage Innovation

- The costs of research and development are increasing significantly.
- The price of drugs has generally not kept pace with the increase in R&D costs.
- Effective patent lives have declined, but may be stabilizing.
- A decline in the returns to R&D investment is widely perceived.

Historical Trends That May Contribute to Innovation

- The pharmaceutical industry continues to enjoy high and stable profitability in terms of return to stockholder's equity.
- Recent technological advances have improved research techniques and enhanced the efficiency of research activities. Researchers are no longer totally dependent on the expensive hit-or-miss method for screening new drugs.
- The competitive environment for innovation appears stable for most therapeutic classes, and there is no lessening of competitive pressure for innovation.
- Markets and sales of drugs are growing.

Uncertainties Affecting Innovation in the Future

Historical trends do not reflect recent governmental actions that may affect the postpatent exclusivity of many drugs. These actions include the repeal of antisubstitution laws, adoption of FDA procedures that facilitate approval of generic equivalents of previously approved drugs, adoption of Government reimbursement programs favoring use of low-priced generic equivalents, and court rulings that allow advertising of drug prices.

Although these actions have, thus far, had only minimal effects on the rates of return to R&D investments and on the revenues and profits of research-intensive companies, they could have substantial impact in the future.

If the effects prove to be substantial, firms will probably be unable to maintain their current levels of research. The public, however, will not perceive a decline in innovation for many years. By the time such a decline is noted, the public will face a period of lagging innovation, since new research efforts will not bear fruits for at least a decade.