Government and Technical Progress
I. INTRODUCTION

Although the pharmaceutical industry dates back to the last century, its development into a major industry with its current characteristics began about forty years ago. Prior to the 1930s, the industry was largely a commodity-based industry producing a relatively small number of chemical compounds and engaging in little research or development of new pharmaceuticals.

The present era of the research-oriented pharmaceutical industry had its origins in the mid-1930s when the first important group of antinfensive drugs were introduced. In particular, sulfanilamide was introduced in 1936 after it was discovered to be effective against streptococi bacteria without having toxic effects on human cells. This development stimulated considerable interest in research on other potential drug therapies. Several important drugs, most notably penicillin, and the other "magic bullet" antibiotics were introduced over the next decade and a half. After World War II, pharmaceutical research broadened to cover several different therapeutic areas. A number of new drugs were introduced to deal with cardiovascular, respiratory, neurological, and other disease categories.

The development of an R&D-oriented pharmaceutical industry has been closely intertwined with the rise of scientific understanding of conditions of health and sickness, and of the nature and causes of various diseases more generally. The post-World War II era has seen an enormous increase in research in the biomedical science, undertaken largely by scientists and physicians at medical schools, and funded largely by government.
This development of the pharmaceutical industry into a research-based industry competing in terms of new drug innovation also has been accompanied by the evolution of extensive government regulations of new drug innovations. Government regulation in this industry in fact dates back to the Pure Food and Drug Act of 1906.\(^{(1)}\) Early drug regulation, however, was directed primarily at patent medicine abuses. In 1938, following a drug disaster that killed over 100 children, the Food, Drug and Cosmetic Act was passed by Congress. This law required new drugs to be approved as safe by the Food and Drug Administration (FDA) before they could be introduced into interstate commerce. It also provided the basis for the separation of pharmaceuticals into ethical drugs, that may be purchased only with a doctor's prescription, and proprietary drugs, that may be generally sold over the counter. In 1962 Congress further passed the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act. These amendments required that a new drug's efficacy, as well as its safety, be demonstrated on the basis of well-controlled scientific tests prior to marketing approval by the FDA. Furthermore, they extended FDA regulatory controls to the clinical development process in order to protect human subjects involved in new drug testing.

In addition to these FDA regulatory controls, numerous other public policies impact the innovational process in the pharmaceutical industry. The opportunities for new drug discoveries are enhanced by government support of basic research in the biomedical sciences. The economic incentives for undertaking drug research and development are affected by federal patent and tax policies. In addition, there are a number of federal and state programs that are directed at the marketing and distribution of drugs that also can have potentially significant effects on the economic returns to new drug innovation (e.g., state substitution laws, product formularies, the Maximum Allowable Cost program of Medicare and Medicaid reimbursements, and so on).

While the pharmaceutical industry has been one of our most innovative industries, the level of new drug introductions appears to have declined significantly from the earlier post-World War II period. The reasons for and social significance of this decline have been the subject of considerable attention by both policy makers and academicians. At the same time, there is cautious optimism in some circles at present about the future prospects for the industry in the next few decades, given the possibility of several important drugs now in the pipeline (especially in the emerging biomolecular research area).

Several important changes in government policies toward the industry, especially in the regulatory and patent areas, have been recently proposed and are now under active debate. This is therefore a particularly apt time to examine the effects of government policies on innovation in the ethical drug industry. The first sections of this chapter provide an overview of industry structure and the character of technical progress in ethical drugs. The last half of the chapter then turns to an analysis of public policy impacts on drug innovation and also discusses the policy changes currently under active discussion by Congress and other related parties.

II. INDUSTRIAL ORGANIZATION

Industry Demand and Growth

Table 6.1 presents some historical data on the value of shipments for the Bureau of Census pharmaceutical preparations industry Standard Industrial Classification—a system of Census Bureau for defining industries—(SIC) 2834. These data are further disaggregated into domestic ethical drug and proprietary drug sales and overall exports to other countries. The rapid rate of growth in ethical drug industry sales since 1939 is clearly evident from the data in Table 6.1. In the period between 1939 and the early 1960s, growth occurred at a truly explosive pace with the value of shipments increasing more than an order of magnitude in nominal terms. Over the last two decades, the rate of growth in value of shipments has slowed significantly, but still remains above the average for all manufacturing.

Table 6.2 presents a breakdown of ethical drug sales for 1978 into broadly defined therapeutic categories. The two leading categories are central-nervous-system drugs (i.e., antiarthritics, tranquilizers, antidepressants, analgesics, drugs for epilepsy and stroke, etc.) and antibiotics. These two categories collectively account for almost 40 percent of total sales. The remaining sales are divided rather evenly among the other therapeutic categories.

Table 6.3 presents information on the buyer side of the market for ethical drugs. This table shows that approximately 75 percent of ethical drug sales are made through retail pharmacies. Retail prescription sales currently account for about 5 percent of total national expenditures for health services and supplies.

The concentration of buyers in the retail market is very low. There are approximately 60,000 retail pharmacy outlets in the United States and perhaps 200,000 to 300,000 physicians who prescribe drugs on a regular basis. The individual doctor is an important decision maker, although he does not pay the price for the product. It is the doctor, and not the patient, who decides which product and which brand will be
GOVERNMENT AND TECHNICAL PROGRESS

Table 6.1. Pharmaceutical Preparations, except Biologicals, for Human Use
(Value of Product Shipments in Millions of Dollars)

<table>
<thead>
<tr>
<th>Year</th>
<th>Ethical</th>
<th>Proprietary</th>
<th>Exports</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1939</td>
<td>148.5</td>
<td>152.4</td>
<td>*</td>
<td>301.0</td>
</tr>
<tr>
<td>1947</td>
<td>520.7</td>
<td>317.6</td>
<td>*</td>
<td>838.3</td>
</tr>
<tr>
<td>1954</td>
<td>1088.9</td>
<td>368.3</td>
<td>*</td>
<td>1457.2</td>
</tr>
<tr>
<td>1963</td>
<td>2001.6</td>
<td>787.1</td>
<td>99.3</td>
<td>2888.1</td>
</tr>
<tr>
<td>1967</td>
<td>2885.8</td>
<td>999.5</td>
<td>112.7</td>
<td>3998.0</td>
</tr>
<tr>
<td>1972</td>
<td>4286.8</td>
<td>1427.8</td>
<td>125.0</td>
<td>5839.6</td>
</tr>
<tr>
<td>1977</td>
<td>6607.9(b,c)</td>
<td>2221.2(c)</td>
<td>260.3(d)</td>
<td>8829.1</td>
</tr>
</tbody>
</table>

(*) not reported separately

Definition of Terms

Ethical: products primarily advertised or otherwise promoted to or prescribed by the health professionals

Prescription legend: a drug product which by federal law is available only by prescription by a licensed physician

Over-the-counter Professional: a drug product sold over-the-counter and primarily promoted to the professions

Proprietary: a drug product primarily advertised or otherwise promoted to the general public.

(a) Includes pharmaceutical preparations of industries not classified as SIC 2834.

(b) In 1977, the ethical category was split up into prescription legend and over-the-counter professional.

(c) Includes exports.

(d) Figure obtained from Current Industrial Report 1977; MA 28G (77)-1 Table 5.

Source: Bureau of Census, Census of Manufacture Industry Statistics, Group 28C

THE PHARMACEUTICAL INDUSTRY


<table>
<thead>
<tr>
<th>Class</th>
<th>Relative Share of Sales (in percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>23.6</td>
</tr>
<tr>
<td>Antifunginfectives</td>
<td>15.0</td>
</tr>
<tr>
<td>Gastrointestinal and</td>
<td>11.8</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Neoplasms and Endocrine</td>
<td>9.7</td>
</tr>
<tr>
<td>Vitamins and Nutrients</td>
<td>9.6</td>
</tr>
<tr>
<td>Cardiovasculars</td>
<td>9.4</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>7.8</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>10.2</td>
</tr>
<tr>
<td>Totals</td>
<td>100.0</td>
</tr>
</tbody>
</table>


prescribed. It is generally maintained that doctors decisions in this regard are primarily influenced by considerations of product quality and reputation of the manufacturer and only secondarily by a product's price. Consequently, demand for ethical drugs is often taken to be relatively inelastic over broad ranges in price - in large part because of the quality orientation of doctors' prescribing decisions. In recent years, however, state substitution laws have given pharmacists more scope for discretion in product selection for multisource products. The exact effects of these laws on retail dispensing patterns still remains to be seen.

The institutional sector - hospitals and various government purchasing agencies - accounts for about 25 percent of total sales and is considerably more concentrated than the retail drug area. Drugs purchased by these institutions tend to be bought in large quantity lots, often using competitive bidding procedures. Consequently, demand in this market is generally assumed to be more price elastic than it is in the re-
Table 6.3. Percentage Distribution of Manufacturers' Domestic Sales among Retail Pharmacies, Hospitals, Government Agencies, 1970.

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
<th>($ millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retail</td>
<td>74.5</td>
<td>4296.9</td>
</tr>
<tr>
<td>Hospital</td>
<td>14.4</td>
<td>831.8</td>
</tr>
<tr>
<td>Government</td>
<td>11.1</td>
<td>639.4(*)</td>
</tr>
<tr>
<td>Total</td>
<td>100.</td>
<td>5768.1</td>
</tr>
</tbody>
</table>

*Prescription drugs only.


tail sector and generic product sales are more concentrated in this section.

Supply-Side Structure

Three distinct segments or subgroups of competitors can be identified in the ethical drug industry. The first and by far the most important groups from the standpoint of industrial innovation consists of the large, research-intensive multinational firms. These firms account for the major share of both new product introductions and total ethical drug sales. At the other end of the competitive spectrum is a large number of generic manufacturers that specialize in producing unbranded products at low prices after the originating firm's patent has expired. In-between these extremes is a third group of primarily domestic firms that have research programs to develop new drug products under their own brand names, but on a much smaller scale than the multinationals.

THE PHARMACEUTICAL INDUSTRY

There are perhaps 12 to 15 U.S. firms that can be placed in the research-intensive multinational group. These firms together with their foreign multinational counterparts compete in a worldwide market. Competition among the multinationals centers in the discovery and promotion of new drugs that are capable of winning significant market shares in the international market. These drug products are typically protected by product patents (and perhaps also process patents) and marketed under copyrighted brand names. Although many of the U.S. multinationals produce an extensive line of both brand-name and generic products for the domestic market, their profits and sales tend to be disproportionately tied to a handful of single-source products developed by the company and promoted under brand names.

Table 6.4 presents the ethical drug sales ranking for 24 pharmaceutical firms with U.S. hospital and pharmacy sales in excess of 100 million dollars in 1978. The U.S. pharmaceutical market is not dominated by a few firms. Instead, sales are distributed rather evenly across many major firms. This is reflected by the fact that the top four and eight leading firms account for only 24 and 42 percent, respectively, of ethical drug sales. Nevertheless, the 24 leading firms listed in Table 6.4 collectively account for nearly 80 percent of total sales and the multinational firms predominate among this group. In addition to several U.S. multinational firms, there are six foreign multinational firms among those leading firms (three headquartered in Switzerland, and one each from Germany, the United Kingdom, and Mexico).

Table 6.5 presents worldwide sales data for the U.S. human ethical pharmaceutical industry for the period 1965 to 1978. These data show the importance of foreign sales in the growth of the industry over recent periods. In 1978, foreign sales represented 41 percent of total sales compared with only 25 percent in 1965. Foreign sales have been growing at twice the rate of domestic sales for U.S. firms in recent years. In addition, a list of estimated sales for the top-ranked multinational firms in 1977 compiled by the United Nations Center on Transnational Corporations indicates 10 of the largest 20 pharmaceutical firms are U.S. firms, although the number—one-ranked firm is German ( Hoechst).

In contrast to the competitive orientation of the multinationals around new product development and introduction in worldwide markets, the generic firms specialize in producing low-cost multisource products after patent rights have expired. There are at present several hundred manufacturers specializing in generic products but their collective market share is less than 10 percent of the ethical drug market. Their sales are concentrated in certain products with above-average tendencies for generic prescribing and for certain institutional buyers that are particularly price sensitive.
As discussed above, there are at present some important policy developments and structural trends that may influence the competitive position of generic products in the market. In particular, several states have enacted laws that encourage pharmacists to substitute generic products for the brands that have become available recently. These developments suggest that the substitution trend will accelerate, and that the amount of substitution may exceed that of the past years. This trend is likely to result in an increase in the sales of generic products, and in a decline in the sales of branded drugs, which will have a significant impact on the profitability of the industry.

The data in Table 6.4 show that the pharmaceutical industry is not dominated by a few firms, but rather by a large number of smaller firms. This is in line with the findings of the survey conducted by the Pharmaceutical Manufacturers Association. The survey indicates that the industry is becoming more competitive, with a larger number of firms entering the market. This is likely to result in increased competition and lower prices for consumers.

In this chapter, we will discuss the future of the pharmaceutical industry, with a focus on the competitive opportunities for generic firms. This issue will be discussed further in the next chapter.
because drugs oriented to one therapeutic use (e.g., vitamins) are generally not substitutes for those in other categories (e.g., antibiotics or antidepressants). Although no classification scheme of "therapeutic markets" is likely to satisfy everyone, a prior attempt to define such markets by one of the authors yielded four-firm concentration ratios that averaged 68 (Vernon, 1971). These data are presented in Table 6.6 and cover a selected group of 19 therapeutic markets. In another study, Cocks and Virts (1974) constructed therapeutic markets by systematically evaluating physicians' prescribing habits. Their scheme yields markets that are generally more broadly defined than those in Table 6.6, and as a consequence, had somewhat lower concentration ratios. Nevertheless, however one defines therapeutic categories, one tends to observe much higher levels of concentration for these markets than for the industry as a whole.

Some analysis has been undertaken in recent years of the dynamic "instability" of the market shares of ethical drug sales as well as within particular therapeutic markets. Although drug markets are subject to considerable concentration at any given point in time, one might also expect to observe a high rate of turnover in firm market shares over time as a consequence of the rapid flow of new product introductions in this industry.

Douglas Cocks (1975) has undertaken an analysis of this issue. Specifically, he first computed an instability index for the ethical drug industry and compared it with similar indices computed for 20 industries by Hymer and Pashigian (1962) in a prior analysis. Only one industry was found to have a higher "instability index" than pharmaceuticals. In addition, he found a higher degree of volatility of firm market shares within particular therapeutic classes associated with rival new product introductions displacing established market leaders over the ten-year period examined in his analysis.

Conditions of Entry

Three major factors have been cited in the literature as important sources of entry barriers in the ethical drug industry: patents, brand differentiation, and scale advantages in research and development.

Patents play a significant role in the innovative process for the ethical drug industry. This is in apparent contrast with many other technologically progressive industries (Taylor and Silberston, 1973, chap. 10).

In the case of pharmaceuticals, the main output from the R&D process is the knowledge and evidence that a particular chemical entity is a safe and effective therapy in the treatment of a particular disease, plus the FDA certification of this evi-
dence in terms of marketing approval. Once this knowledge becomes publicly available, however, the costs of imitation by rival producers are usually low. Hence, there is little to stop rival firms from producing this compound on similar terms as the innovator in the absence of legal barriers such as those afforded by the patent system.

An important ruling by the Patent Office in 1948 concerning the antibiotic streptomycin opened the door to the patenting of new drugs. That is, new drugs would not be patentable if they were simply natural substances. In the case of streptomycin, the Patent Office ruled that the natural materials found by Waksman, streptomycin's discoverer, were not in suitable form for medical use. By making chemical modifications to streptomycin so that it could be purified, however, the Patent Office ruled that Merck had created a "new composition of matter," and therefore should be awarded a patent on this new product. Without this ruling, R&D on antibiotics would not have been an attractive, or necessary, competitive instrument for the pharmaceutical companies.

Firm R&D strategies are oriented around developing products that are patentable. Over 90 percent of the new chemical entities coming to the U.S. market in recent years have involved drugs protected by product patents. Furthermore, approximately half of all prescription drug sales at the present time involve single-source products protected by patents.

A patent barrier, of course, can be overcome by the development of chemically distinct substitutes for the established market leader's product. As discussed above, there is in fact considerable market share turnover in this industry associated with the introduction of new chemical entities. One strategy for inventing around an existing firm's patent that has received considerable attention in the literature is "molecular modification." This refers to the development of a similar compound so as to retain a rival product's main therapeutic effects (or hopefully to improve them), but at the same time possesses a chemically distinct structure that can be patented. Our discussion in Section III on the character of technical progress indicates that many such "families" of drugs with similar chemical structures and therapeutic properties have been developed in just this manner.

Nevertheless, the strategy of developing "me too" products through molecular modification is neither costless nor always guaranteed to produce an effective substitute for an established product. In contrast to imitative products involving already approved substances by the FDA (i.e., generic equivalents) chemically differentiated products must undergo full-scale reviews of safety and efficacy by the FDA. Hence, these drugs must be tested on the same scale as all previously approved products. Therefore, under current regulatory conditions, the imitating firm is faced with several million dollars in development costs and several years in lag time before chemically distinct follow-on drugs can be marketed as approved new drugs.

Data from trade sources indicate that firms in the drug industry as a whole spend a little over 10 percent of their sales on research and development expenditures and at least a comparable percentage on promotional outlays. Promotional outlays per dollar of sales tend to be greatest in the early stages of product life cycle when information on a new drug is being initially diffused. As noted above, products are promoted under brand names with the objective of building up a stock of good will or specific preference in the minds of physicians for the innovating firm's product. This has historically provided an important source of product differentiation advantages vis-à-vis new entrants after patents expire (i.e., competitively advertised brands and generic products).

There is also evidence that the firm that introduces the first product of a new "family" of drug therapies can obtain important product differentiation advantages relative to follow-on imitative products. Bond and Lean (1977) have examined this issue in a recent FTC study. In the case of the oral diuretic market, for example, they found that the first drug on the market, Merck's Diuril, introduced in 1958, enjoyed substantial competitive advantages over a number of therapeutically similar (but chemically distinct) drugs that followed it on the market. These data indicate that Merck spent less than half as much per sales dollar on promotion for Diuril than follow-on products and also charged a significantly higher price than competitors. Despite these policies, in 1971, 13 years after the original introduction of Diuril, it was still the market leader with a 33 percent share of the oral diuretic market. Bond and Lean further found that those follow-on products that were most successful in capturing market shares were those that offered significant therapeutic gain over established diuretics, rather than merely relying on high promotion levels or price discounts.

At the present time there is evidence to suggest that the major drug firms are concentrating more of their R&D efforts on developing drugs that embody new approaches to disease treatment and less on development of "me too" products. This reflects, at least in part, the strong upward trends in the costs and times for developing and obtaining FDA approval of a new drug entity compared with a few decades ago. Data discussed in the next section indicate that R&D costs have escalated sharply relative to overall returns for new drugs and hence there is less economic incentive to develop "me too" products. Of course, firms are still motivated to explore compounds with chemically related structures to those of existing products in hopes of developing products with improved therapeutic properties. There does appear, however,
to be an increased emphasis on drug candidates with significant market share potential to compensate for increased development costs.

It also appears that, as a result of the sharp increase in the costs and riskiness of developing new drugs, economies-of-scale considerations in drug R&D are a much more important factor than was the case a few decades ago. This is consistent with the findings of recent studies that drug innovation is now much more concentrated in the large drug firms than was the case in the early 1960s (Grabowski and Vernon, 1976).

**Industry Profitability and Pricing Trends**

The pharmaceutical industry has ranked near the top of the manufacturing sector in terms of overall profit rates for most of the post-World War II period. This aspect of industry performance, together with the high-price cost margins on particular products, has received considerable attention from congressional committees beginning with the highly publicized Kefauver Hearings (2) in the late 1950s and 1960s.

In recent years, however, there has been a noticeable tendency for industry profit rates to begin converging toward the average obtained by the entire manufacturing sector. In Table 6.7, earnings data based on FTC's Quarterly Financial Reports are presented for the pharmaceutical industry and the overall manufacturing sector for the period 1956-1979. These data indicate that pharmaceutical earnings as a percentage of net stockholder equity have consistently been above the average for all manufacturing over this period. At the same time there is a clear trend evident in these data for the difference in the profit rates to narrow over time. This is especially true in the pre-tax profit series. Among other things, this apparently reflects, with some response lags, the lower rates of industry growth and slower rates of new product introductions in recent years compared with the early postwar period. These trends (together with recent technological developments that have produced more optimistic assessments of industry's prospects over the immediate future) will be discussed in detail in the next part of the chapter.

Another issue that has received considerable attention, primarily in academic studies, is the potentially significant bias present in reported profit rates for the drug industry (and other industries with similar characteristics) that results from the expensing rather than capitalizing of so-called intangible capital outlays - i.e., R&D and advertising investment expenditures. It is standard accounting practice to expense these intangible capital outlays even though conceptually they are in fact investment expenditures with expected returns distributed over future periods. Recent academic analyses by Clarkson (1977) and Grabowski and Mueller (1978) have adjusted report-

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**Table 6.7. Rates of Return on Average Stockholders Equity, 1956-1979.**

<table>
<thead>
<tr>
<th>Year</th>
<th>Pharmaceutical Industry</th>
<th>All Manufacturing</th>
<th>Pharmaceutical Industry</th>
<th>All Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956</td>
<td>34.6%</td>
<td>22.6%</td>
<td>17.8%</td>
<td>12.3%</td>
</tr>
<tr>
<td>1957</td>
<td>37.4%</td>
<td>20.0%</td>
<td>18.6%</td>
<td>11.0%</td>
</tr>
<tr>
<td>1958</td>
<td>34.5%</td>
<td>15.4%</td>
<td>17.7%</td>
<td>8.0%</td>
</tr>
<tr>
<td>1959</td>
<td>34.1%</td>
<td>18.9%</td>
<td>17.8%</td>
<td>10.4%</td>
</tr>
<tr>
<td>1960</td>
<td>32.5%</td>
<td>16.6%</td>
<td>16.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>1961</td>
<td>32.4%</td>
<td>15.9%</td>
<td>16.7%</td>
<td>8.8%</td>
</tr>
<tr>
<td>1962</td>
<td>32.4%</td>
<td>17.6%</td>
<td>16.8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>1963</td>
<td>32.8%</td>
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<tr>
<td>1964</td>
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<td>18.2%</td>
<td>11.6%</td>
</tr>
<tr>
<td>1965</td>
<td>37.1%</td>
<td>20.0%</td>
<td>20.3%</td>
<td>13.0%</td>
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<tr>
<td>1966</td>
<td>37.0%</td>
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<td>19.3%</td>
<td>18.7%</td>
<td>11.7%</td>
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<tr>
<td>1968</td>
<td>35.1%</td>
<td>20.8%</td>
<td>18.3%</td>
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<td>1969</td>
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<td>20.1%</td>
<td>18.4%</td>
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<tr>
<td>1970</td>
<td>32.3%</td>
<td>15.7%</td>
<td>17.6%</td>
<td>9.3%</td>
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<tr>
<td>1971</td>
<td>31.9%</td>
<td>16.5%</td>
<td>17.8%</td>
<td>9.7%</td>
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<tr>
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<td>32.7%</td>
<td>18.4%</td>
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<td>10.6%</td>
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<tr>
<td>1973</td>
<td>33.1%</td>
<td>21.8%</td>
<td>18.9%</td>
<td>12.6%</td>
</tr>
<tr>
<td>1974</td>
<td>29.7%</td>
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<td>18.7%</td>
<td>14.0%</td>
</tr>
<tr>
<td>1975</td>
<td>27.7%</td>
<td>18.9%</td>
<td>17.7%</td>
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<tr>
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<td>28.1%</td>
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<tr>
<td>1977</td>
<td>29.9%</td>
<td>23.2%</td>
<td>18.2%</td>
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<tr>
<td>1978</td>
<td>28.5%</td>
<td>24.5%</td>
<td>18.8%</td>
<td>15.0%</td>
</tr>
<tr>
<td>1979</td>
<td>28.8%*</td>
<td>25.7%</td>
<td>19.3%*</td>
<td>16.4%</td>
</tr>
</tbody>
</table>

*A considerable number of companies were reclassified by industry. The percentage of companies reclassified in the drug industry is unknown.*

**Note:** for purpose of this table the pharmaceutical industry is defined as corporations primarily engaged in manufacturing biologicals, inorganic and organic medicinal chemicals, and pharmaceutical preparations; and grading and grinding botanicals.

**Source:** Quarterly Financial Reports (for manufacturing, mining and trade corporations) 1957-1979, Federal Trade Commission.
ed profit rates in several industries including drugs and have found that profit rates in ethical drugs do have a significant upward bias on this account. In the Grabowski and Mueller study, for example, more than half the reported differences in profit rates between the drug industry and the overall sample mean were eliminated when R&D and advertising outlays were capitalized rather than expensed. While there is room for disagreement on the appropriate assumptions for making such profit rate adjustments, it is clear that these adjustments do tend to reduce further the difference between drug industry and overall manufacturing accounting profit rates observed in Table 6.7.

Another issue that has received considerable public policy attention is the high rate of price inflation in health services sector. The price performance of prescription drugs, however, has been in marked contrast with other sectors of the health services industry. In Figure 6.1, we present trends in the consumer price index for prescription drugs, for medical care (excluding drugs), and for all items over the period 1965 through 1979. While overall health-sector prices have increased at a much more rapid rate than the CPI index over this period, relative prices for prescription drugs have declined over time. The decline is especially pervasive during the 1960s. It has continued at a diminished rate over more recent periods. It should also be noted that current government price indices tend to adjust for product-quality improvements inadequately so that they tend to overestimate the degree of inflation in technologically progressive sectors vis-a-vis nonprogressive ones.

In summary, the ethical drug industry, in common with many other technologically progressive industries, has experienced above-average profit rates and declining relative prices over time. Accounting measures further tend to overstate both profitability and price inflation in research-intensive industries with high rates of product innovation. Nevertheless, given these measurement error problems, there is also a definite tendency in recent periods for some convergence toward the average for all manufacturing evident in the time trends on both these variables. The possible reasons for this are discussed further in our analysis in the following sections on technical progress in this industry.

Fig. 6.1. Comparison of selected price indices, 1960-1979 (1967=100).

Source: Pharmaceutical Industry Fact Book as constructed from the following original sources - CPI indices; Consumer Price Index Detailed Reports, various issues; Firestone index - Firestone, various issues.

III. BASIC CHARACTERISTICS AND SOURCES OF TECHNICAL PROGRESS

Social and Economic Effects of New Drug Discoveries

As we noted earlier, the modern drug industry began in the mid-1930s with the introduction of the first sulfonamide drug. Since that time hundreds of new drugs have been introduced in the United States. Some of the major discoveries that have been introduced over the post-World War II period includes:

- Synthetic penicillins
- Tetracyclines
important drugs have been discovered. The complex system of
drug development and FDA involvement is the next topic. A
well-known study of the cost of developing a marketable NCE
is also reviewed.

Drug Discovery

The process of drug discovery involves a multidisciplinary
research-team approach that is generally characterized by
considerable trial-and-error search effort. Serendipity has also
played an important role in many major discoveries.
Some examples of how drugs have been discovered will provide
further insight (3).

The original sulfa drug, sulfanilamide, was a life-saving
drug in many severe human infections. It was discovered in
1935 by Domagk who observed that the red dye sulfamidochry-
soldine was effective against streptococcal infections in mice.
It had, however, several serious side effects, including kidney
damage. Medicinal chemists therefore synthesized almost 5000
derivatives of sulfanilamide in search of compounds that were

free of the serious side effects. Two of the most successful
drugs from this group have been sulfathiazole and sulfadia-
zine.

A chance clinical observation that patients taking sul-
fanilamide often excreted a larger than usual volume of urine
led to the development of a whole new class of diuretic drugs.
Again, testing of many closely related chemical compounds was
necessary to discover the most effective diuretics. Similarly,
serendipitous clinical observation of patients on sulfanilamide
therapy led to antithyroid and oral hypoglycemic drugs.

There are many additional examples of drugs that were
discovered by chance observation. The most famous is, of
 course, Fleming's discovery of penicillin. The important major
tr tranquilizer, chlorpromazine, was the result of the unexpected
discovery that certain of the antihistamines are potent de-
pressants of the central nervous system. Others include the
antihypertensive actions of the Beta-blockers, the antiinflam-
matory effects of the steroids, and the antigout action of
allopurinol.

Random screening is another technique of drug discovery.
Schwartzman (1976) has described one especially interesting
e xample. In search of a drug to combat tuberculosis, Lederie
Laboratories systematically tested a file of 103,000 chemical
compounds that had been developed by its parent company for
a variety of purposes. Eventually, after many years, a com-
pound originally developed for use as an antioxidant additive
for rubber was found to be effective against tuberculosis. Six
hundred similar compounds were synthesized and the important
antitubercular drug ethambutol was discovered.

These examples suggest that drug discovery is largely an
empirical, trial-and-error process. However, this situation is
changing dramatically. For example, a 1979 article in Business
Week observes that:

More and more, the development job is done today
by setting forth in advance very specifically the
characteristics desired in a new drug. The mole-
cules of the chemical compound are designed, atom
by atom, to affect a pretargeted physiological pro-
cess in the body - inhibiting or stimulating, for
instance, the flow of a specific enzyme. Examples of
drugs developed in this fashion are Smith-Kline's
Tagamet; Squibb's Capoten; and Lilly's Dobutrex.

We will return to "discovery-by-design" in the discussion
below of sources of pharmaceutical innovation.

Of course the actual discovery of a new drug is only the
first step in the lengthy process of drug innovation. In the
following section we turn to the development of a drug once it
has been synthesized and thought to possess potential thera-
peutic benefits.
Drug Development

Figure 6.2, reproduced from an article by William M. Wardell (1979) p. 10, provides a good overview of the present system of drug development and FDA regulation. As explained earlier, once a new chemical compound has been tested in animals and found to be worthy of human testing, the developer must file an IND (Investigational New Drug application) with the FDA.

![Diagram of drug development phases](image)

**IND (1962)**
- **Preclinical**
- **Clinical**
- **NDA: 1938**

**IND Filing**
- **NDA Submission**
- **NDA Approval**

**Chemical Lab.**
- Preclinical (Animal or Pharmacology)

**Tolerance**
- Preclinical

**Time Required (minimum)**
- 3 yrs (?)
- 4-6 yrs
- 2-3 yrs

**Attrition**
- 10,000 (?)
- 1,000 (?)
- 10
- 5
- 1
- 1

**Cost ($1976)**
- $30 million
- $24 million

**Average Effective Patent Life (from NDA approval date)**
- 1966
- 1977
- 13.8 yrs
- 9 yrs

**Fig. 6.2. Drug development (U.S.A.)**


If approved by the FDA, the drug proceeds through three phases of clinical testing. The first phase is directed toward examining a drug's possible toxic effects and is performed on healthy individuals under highly controlled situations. If a drug successfully completes this stage, it is then tested on a relatively small number of patients to examine its effectiveness. It is then carefully evaluated from a therapeutic and marketing standpoint before the decision to begin phase three is made. Phase three involves expanded studies in large patient populations with a substantial escalation in development expenditures. If a drug passes these three phases of testing and is considered to have sufficient market value to warrant commercial introduction, an NDA (New Drug Application) is submitted to the FDA. Marketing can commence upon receiving an approved NDA.

Several further points should be made with reference to Figure 6.2. The time required to pass through the three testing phases is shown to be four to six years with an additional two to three years for NDA approval. The attrition rates show that for every ten drugs entering the IND stage, only one will have an NDA submission. Notice that Figure 6.2 shows no further attrition. According to Wardell, "the one survivor that reaches an NDA submission has a ninety percent chance of being approved by the FDA, given five years' for review at FDA."

The cost figures shown in Figure 6.2 are based on a study by Ronald W. Hansen. Hansen (1979) obtained survey data from 14 pharmaceutical firms on the R&D costs for a sample of NCEs first tested in man from 1963 to 1975. As shown, the discovery cost per NCE was estimated at $30 million and the development cost at $24 million, or a total cost of $54 million. This $54 million figure represents the capitalized value (at 8 percent interest and in 1976 dollars) at the date of marketing approval.

It should be pointed out that the $54 million includes the cost of NCEs that enter clinical testing but are not carried to the point of NDA approval. For example, Hansen found that by the end of 15 months of clinical testing, testing had ended on over 50 percent of the NCEs that had entered human trials. Hence, the $54 million figure should be interpreted as the average expected cost of discovering and developing a marketable NCE.

The Sources of Pharmaceutical Innovation

We begin by considering some data concerning the expenditures for health R&D in the United States. Table 6.10 shows total health R&D expenditures (not just drug-related), the portion of that total accounted for by the federal government, and the privately financed drug R&D outlays by the pharmaceutical industry.

Of the federal health R&D figure of $3.8 billion, $2.6 billion was health R&D support accounted for by the National Institutes of Health. While we do not know the total amount of federal support for drug R&D, there are several formal programs concerned with drug development. The largest is the National Cancer Institute Drug Development Program with an annual budget of over $200 million. This program is discussed further in the next section.
Table 6.10. Expenditures on Health R&D (Billions of Dollars).

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Health R&amp;D</th>
<th>Federal Health R&amp;D</th>
<th>Private Drug R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>.9</td>
<td>.4</td>
<td>.2</td>
</tr>
<tr>
<td>1965</td>
<td>1.9</td>
<td>1.2</td>
<td>.3</td>
</tr>
<tr>
<td>1970</td>
<td>2.8</td>
<td>1.7</td>
<td>.5</td>
</tr>
<tr>
<td>1975</td>
<td>4.6</td>
<td>2.8</td>
<td>.8</td>
</tr>
<tr>
<td>1978</td>
<td>6.2</td>
<td>3.8</td>
<td>1.1</td>
</tr>
</tbody>
</table>


The relative importance of private versus public institutions (government, universities, and nonprofit foundations) in the discovery and development of new drugs has been a controversial issue. For example, the famous Kefauver Committee hearings on the pharmaceutical industry which began in December 1959, dealt extensively with the medical value of the R&D effort of the industry.

Comanor (1966) has referred to that controversy as the "battle of the lists." That is, the committee staff and the industry prepared competing lists of new drugs. The committee list tended to concentrate on drugs that embodied what it considered to be major therapeutic advances, and emphasized the role of public institutions. The industry list, on the other hand, "included new drugs that may not have embodied large steps forward but that are in frequent use and thereby seem to have the confidence of the country's physicians. A large majority of the drugs on this list were discovered and developed within industry laboratories."

Schwartzman (1976) p. 13 has assembled some more recent data on this question. As shown in Table 6.11, close to 90 percent of the NCEs introduced over the 1950 to 1969 period were discovered by private ethical drug firms (U.S. and foreign). Furthermore, this percentage exhibits a tendency to increase over time as evidenced by the 5 percentage-point increase in 1960 to 1969 over the earlier ten-year period. His analysis also reveals that the industry accounted over the 1960-1969 period for 86 percent of the therapeutically most important drugs, as classified by Martin Seif of the FDA. The result is consistent with similar analyses of this question by Schnee (1971) and Deutsch (1973).


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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Industry</td>
<td>86</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Notes: List of NCEs. Selected from Paul de Haen, New Product Survey and Nonproprietary Name Index, Codiscoveries are each given half credit where the source of discovery could not be determined, it was assigned to other.


Such exercises as these, though useful, tend to deemphasize a basic point. The roles of private and public institutions are largely complementary rather than competitive. Professor Ernst B. Chain, a Nobel laureate for his work in penicillin development, has made this point well. Chain p. 450 (1963) observed that large industrial laboratories are ideal for "large-scale screening for new antibiotics, large-scale pharmacological testing, and the synthesis of a vast number of analogous or related substances with the aim of improving one or the other property of a drug." The academic laboratory, on the other hand, is designed "to break fundamentally new ground towards a better understanding of the laws of Nature, and in this way to lay the basis for eventual industrial exploitation of the scientific discoveries emanating from its work."

A more recent description of the complementary nature of private and public R&D was given by Richard D. Wood, chief executive of Eli Lilly, in a 1979 interview:
The industry depends on the productivity of research, and research goes in cycles. Some of it is serendipity, but progress depends mostly on what comes out of basic medical research and the knowledge it produces. Then industry can take hold of this knowledge and develop new drugs. Sometimes this occurs in step fashion, and you reach a new plateau of medical knowledge that gives further impetus to new drugs. [Business Week p. 135, 1979].

On the other hand, David Schwartzman (1976, p. 30) has argued that, in pharmaceutical R&D "there exists no simple flow-through from basic to applied R&D. Basic research advances relevant to drug discovery, in contrast to the role of basic research in other fields, do not lead in any direct way to new drugs. New drugs cannot be designed by logical deductions from valid general principals; chemical theory alone is not enough and biological theory is woefully inadequate." Schwartzman goes on to observe that the majority of discoveries can be traced to one of three sources: naturally occurring compounds, accidental discoveries, and modifications of previously known drugs. In his view, this explains the relatively high proportion of drug discoveries made by the industry.

In this connection, we should emphasize the trend noted earlier that "discovery-by-design" appears to be replacing the more inductive trial-and-error methods emphasized by Schwartzman. One inference from this trend is the strengthening of the linkage between basic biomedical research and drug innovation.

According to Dr. William I. H. Shedden (Business Week, p. 137), vice president in charge of clinical evaluation at Eli Lilly, scientists at Lilly are now taking a "very fundamental biological approach" in some of their research. (4) Dr. Shedden observed that in the old days the chemists would make a batch of compounds and send them over to the biologists to put into animals to see what would happen. In contrast, today the biologists ask the chemists to design molecules to accomplish particular effects.

One highly successful example of drug design is the antiulcer drug, Tagamet, which was introduced by Smith Kline in 1977 and is already the second largest-selling U.S. drug. Knowing that the hormone histamine is a potent stimulant of the gastric secretions that can lead to ulcers, Smith Kline scientists sought a compound that would inhibit the flow of histamine. They finally succeeded in designing a molecule that would lock into a "receptor site," thereby blocking out the hormone and, in turn, the gastric secretions.

As Dr. P. Roy Vagelos, head of R&D at Merck, observed in a 1979 interview:

There has been a flowering of biomedical research. This is a fantastic time in biology. The companies with the right kinds of people and resources can capitalize on it and bring the new knowledge to bear on the right diseases and compounds [Business Week, 1979, p. 137].

The apparent trend toward closer ties between advances in scientific knowledge and new pharmaceutical products is well illustrated by recombinant DNA, or "gene splicing." This new process has been used to induce bacteria to produce human insulin and interferon, and has exciting possibilities in other areas. Several established drug firms now have research and development programs in this field and several small new firms have been founded to explore its commercial application. Even some universities are now considering the establishment of genetic engineering companies to develop the discoveries of its scientists (Time, November 10, 1980).

While, as stated, the major role of the universities in pharmaceutical R&D has been in basic research on the nature and causes of various bodily malfunctions, and on human biology in general, there are more direct links between academic and corporate researchers. The interaction of university biomedical researchers and their counterparts at pharmaceutical companies can take various forms. We list below some of these relationships:

1. Most major pharmaceutical firms use university researchers on advisory boards or as consultants.
2. Many of the clinical studies required for FDA approval are conducted at university medical centers.
3. Pharmaceutical companies provide research grants to universities. Some companies award postdoctoral fellowships to encourage the supply of scientists for the pharmaceutical industry.
4. There are many scientific organizations which have publications authored by scientists from both industry and the universities. Also, there organizations sponsor conferences which promote industrial and academic interaction. A list of some of these organizations is given below:

- Academy of Pharmaceutical Sciences
- American Chemical Society
- American Association for the Advancement of Science
- American Medical Association
- American Society for Pharmacology and Experimental Therapeutics
- Drug Information Association
- Industrial Research Institute
- The American Association of Immunologists
5. Pharmaceutical companies' scientists and university scientists often collaborate in joint research projects. As an example, NIH has recently funded a three-year project to investigate the biosynthesis and mechanism of action of an anticancer agent, CC-10-65. The research will be carried out jointly at the University of Texas and at the Upjohn Company. According to F-D-C Reports, September 14, 1981:

Upjohn's joint research with U. Texas is apparently part of a collaborative research program the firm established over two years ago. The firm has set up a full-time scientific liaison office, headed by Douglas Shepherd, PhD, to serve as a basis for interaction and coordination of joint research projects. The company now has well over 200 interactions with universities outside of clinical studies, consultancies and contracted services.

The scientific liaison office at Upjohn both funds projects through its own budget and seeks funding from other sources such as Natl. Science Foundation's Industry-University Cooperative Research Program and NIH. The U. Texas project is indicative of Upjohn's ability to extend its research activities and budget through the use of university talent and federal money.

6. A final form of interaction is where a drug is discovered by a university scientist and is then licensed to a pharmaceutical company for development and marketing. An example is the drug calcitriol, an agent used for the management of hypocalcemia in patients undergoing chronic renal dialysis.

Dr. H.F. DeLuca of the University of Wisconsin was awarded a patent for the drug calcitriol. Dr. DeLuca then assigned the patent to the Wisconsin Alumni Research Fund (WARF). In 1975, WARF licensed Roche to develop the drug and make it available to the medical community. It was recognized that substantial resources were needed to determine the efficacy, safety, and acceptability of the drug, and that an economic method for manufacturing the compound was needed. Roche was able to accomplish these objectives and gain marketing approval in 1978.

Government Drug-Development Programs

A clear exception to the tendency for government efforts to be concentrated in the basic end of the biomedical research spectrum is the National Cancer Institute's Drug Development Program. This program was established in 1955 with an initial annual budget of five million dollars. Given the nation's overriding desire to cure cancer - as expressed in the National Cancer Act of 1971 - Congress has dramatically increased support for this program over the past decade. The annual budget in 1979 was 238 million dollars (Table 6.12).

The NCI's drug-development activities in the cancer area have several components. The program screens some 15,000 potential therapeutics in animals annually. The NCI also sponsors all of the major cancer clinical trial groups in the United States. All new cancer drugs, regardless of source, must be tested in these groups. NCI's involvement at the clinical trial stage range from complete support and sponsorship to various forms of collaboration (contractual as well as informal in character) with private firms. The NCI also attempts to evaluate on a continuing basis the optimal role of all marketed drugs in the management of neoplastic diseases. The government has not become involved in the marketing of any new drugs but has licensed its developed drugs to private firms for commercial production and marketing.

Since the NCI drug-development program originated in 1955, 20 new anticancer drugs have been developed with varying degrees of government collaboration and support. (In addition there were seven new anticancer drug applications on file with the FDA in 1980.) Of these 20 marketed drug introductions, the NCI was involved with 10 of these drugs on a preclinical basis (e.g., synthesis, screening, or toxicology testing). In addition, a favorable externality of the anticancer drug developments of government and industry has been a half-dozen or so additional introductions in other therapeutic areas.

Table 6.12 indicates that the other drug-development programs of the government are very modest in size. These programs are conducted in other branches of the National Institutes of Health or the military and generally have annual
<table>
<thead>
<tr>
<th>Year Began</th>
<th>Program Name</th>
<th>Annual Budget PT 1979 (in millions)</th>
<th>NDAs</th>
<th>Target Condition or Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1955</td>
<td>Drug Development and Cancer Therapy Evaluation Programs, NCI</td>
<td>$388</td>
<td>27</td>
<td>Cancers</td>
</tr>
<tr>
<td>1956</td>
<td>Psychopharmacology Research Branch, NIH</td>
<td>17</td>
<td>1+</td>
<td>Methodology of Psychiatric Drug Development</td>
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<tr>
<td>1963</td>
<td>Army Drug Development Program, Department of the Army</td>
<td>4</td>
<td>1</td>
<td>Malaria, Leishmaniasis, Trypanosomiasis, Schistosomiasis, Radiation Sickness, Chemical Warfare Injuries</td>
</tr>
<tr>
<td>1965</td>
<td>Vaccine Development Program, NIAID</td>
<td>8</td>
<td>2</td>
<td>Prophylaxis of Viral and Bacterial Infections</td>
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<td>1968</td>
<td>Antiepileptic Drug Development Program, NINCDS</td>
<td>2.5</td>
<td>3</td>
<td>Epilepsies</td>
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<tr>
<td>1969</td>
<td>Antiviral Substances Program, NIAID</td>
<td>4.2</td>
<td>0</td>
<td>Viral Infections</td>
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<tr>
<td>1971</td>
<td>Contraceptive Development Program, NICHD</td>
<td>3.5</td>
<td>0</td>
<td>Reproductive Process</td>
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<tr>
<td>1971</td>
<td>Narcotics Abuse Treatment Drugs, NIDA</td>
<td>2</td>
<td>2</td>
<td>Narcotics Abuse</td>
</tr>
<tr>
<td>1971</td>
<td>National Caries Program, NIDR</td>
<td>1.9</td>
<td>0</td>
<td>Dental Caries</td>
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<tr>
<td>1974</td>
<td>Iron Chelator Development Program NIAMDD-NHLBI</td>
<td>0.5</td>
<td>1</td>
<td>Hemosiderosis 2° to Thalasssemia</td>
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<tr>
<td>1974</td>
<td>Blood Substitutes Program, NHLBI</td>
<td>1.3</td>
<td>0</td>
<td>Anemias</td>
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<tr>
<td>1975</td>
<td>Antisickling Agents Program, NHLBI</td>
<td>0.5</td>
<td>0</td>
<td>Sickle Cell Crises</td>
</tr>
</tbody>
</table>

*New drug applications for which the particular program has provided either scientific or financial support.

IV. ADVERSE TRENDS IN THE DRUG INDUSTRY  
DURING THE 1960s AND 1970s:  
THE ROLE OF REGULATORY AND NEW REGULATORY FACTORS

Annual Levels of New Product Introductions

Table 6.13 provides a list of the annual number of new chemical entities (NCEs) introduced in the United States between 1940 and 1978. (New chemical entities are new compounds not previously marketed and include nearly all major therapeutic advances. New products that are not NCEs include combinations of existing drugs and new dosage forms.)

The rate of introduction of NCEs has clearly declined since the late 1950s. For example, from 1955 to 1960, an average of about 50 NCEs per year were introduced. The corresponding number for the 1965 to 1970 period is only 17 NCEs, and for the most recent six-year period the average is 17 also.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
<th>Year</th>
<th>Number</th>
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</thead>
<tbody>
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<td>1940</td>
<td>14</td>
<td>1960</td>
<td>50</td>
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<td>1941</td>
<td>17</td>
<td>1961</td>
<td>45</td>
</tr>
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<td>1942</td>
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</tr>
<tr>
<td>1959</td>
<td>65</td>
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</table>


THE PHARMACEUTICAL INDUSTRY

This decline in new product introductions has been accompanied by corresponding structural trends on the input side of the innovational process. As discussed above, Hansen estimates that the current costs of developing and marketing an NCE are on the order of 24 million dollars. We may compare this finding to prior studies by Clymer (1970), and Mund (1970), and Saretz (1974) that put the uncaptured development cost of a new NCE in the one-to-two-million-dollar range in the early 1960s. Moreover, Clymer estimated that the attrition rate for drugs undergoing clinical tests was two out of three in the pre-1962 period. Current data analyzed by William Wardell and reported earlier in Figure 6.2 suggest that only one in ten clinically tested drug entities becomes a new drug introduction. Finally, the average gestation period for a successful new drug has also increased significantly from four to six years in the early 1960s to the current ten years or more.

Thus, there has been a decline in annual new drug introductions accompanied by strong upward trends in the costs, time, and risks associated with discovering and developing new drugs. In economists' terminology, there has been a shift in the "production function" for new drug innovation in the direction of lower R&D productivity— that is to say, fewer new drug introductions are emanating from larger resource commitments by the industry.

The causes and importance of this decline in new drug introductions has been the subject of considerable controversy. This debate has centered around the effects of increased regulation resulting from the 1962 Kefauver-Harris amendments as a major cause of this decline in innovation.

An initial response by the FDA was to argue that the observed decline in pharmaceutical innovation was in fact actually compositional rather than real in character:

The relevant question is not and never has been how many new drugs are marketed each year, but rather how many significant, useful and unique therapeutic entities are developed. . . . The rate of development and marketing of truly important, significant, and unique therapeutic entities in this country has remained relatively stable for the past 22 years [Alexander Schmidt, 1974a].

It is difficult, however, to substantiate the FDA claim that the observed decline in new drug introductions has been largely confined to marginal-type drugs. As discussed above, it is true that the much higher costs and risks of developing new drugs have caused firms to focus less on their research programs on innovative "me too" drugs. These drugs do appear to have declined disproportionately over time. Nevertheless,
there is also evidence that suggests a decline in therapeutically significant drugs as well. Most classifications of important therapeutic advances by academic analysts show such a decline, as does at least one prior FDA ranking of important drugs. (7)

Furthermore, measures of pharmaceutical innovation based on economic criteria also suggest a real decline has occurred. For example, if we examine a "market share" type measure (8) that indicates the relative importance of NCE sales to total ethical drug sales, we find that the share of NCEs has fallen from 20 percent in 1957-1961 to 8.6 percent in 1962-1966, and to 6.2 percent in 1972-1976 (Grabowski and Vernon, 1976). Of course, known economic measures will tend to give little weight to major therapeutic advances for relatively rare diseases. It is unlikely, however, that the downward trend can be primarily explained by an increasing proportion of such innovations over time given the adverse economic shifts in the costs of discovering and developing new drugs that occurred over this period.

Sam Peltzman (1973) has analyzed a related drug quality issue as to whether the large decline in NCE introductions could be explained by fewer ineffective drugs entering the marketplace after the 1962 amendments were passed. His analysis of data from three groups of experts - hospital panels employed by state public assistance agencies, and the American Medical Association's Council on Drugs - does not support this view. These data suggest that only a small fraction of the pre-1962 and post-1962 NCE introductions could be classified as ineffective. (9)

In sum, the hypothesis that the observed decline in new product introductions has largely been concentrated in marginal or ineffective drugs is not generally supported by empirical analyses. If one accepts that a significant decline in drug innovation occurred in the 1960s and 1970s, the question still remains as to the role of regulatory versus nonregulatory factors in explaining this decline. In the remainder of this section we consider various possibilities in this regard and the evidence from various aggregate analyses of this issue.

Regulatory Developments in the 1960s

As noted above, a major legislative change occurred in 1962 with the passage of the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act. This law was passed following the well-documented and tragic events associated with the drug thalidomide (a drug introduced in several foreign countries but not the U.S.). The 1962 amendments had two basic provisions that directly affected the drug innovational process - a proof of efficacy requirement for new drug approval and establish-

ment of FDA regulatory controls over the clinical (human) testing of new drug candidates. (10)

With regard to the efficacy requirement, the amendments required firms to provide substantial evidence of a new drug's efficacy based on "adequate and well controlled trials." Subsequent FDA regulations interpreted this provision to mean using experimental and control-group samples to demonstrate a drug's efficacy as statistically significant. The preferred mode of study was "double blind" control where neither patient nor physician was aware whether he was receiving the experimental drug or a standard therapy of placebo. According to industry sources, these substantial evidence criteria led to large increases in the amount of resources necessary to obtain an NDA approval, especially in therapeutic areas where subjective analyses of patient responses are necessarily involved (such as analgesics or antidepressants).

The second major change in the 1962 amendments influencing the drug innovational process were the Investigational New Drug (IND) requirements on clinical testing. Prior to any tests on human subjects, firms were now required to submit a new drug investigational plan giving the results of animal tests and research protocols for human tests. Based on its evaluation of the IND and subsequent reports of research findings, the FDA may prohibit, delay, or halt clinical research that poses excessive risks to volunteer subjects or does not follow sound scientific procedures. Hence, as a result of the IND procedures the FDA shifted in the post-1962 period from essentially an evaluator of evidence and research findings at the end of the R&D process to an active participant in the process itself. This is another potentially important factor leading to the higher development costs and times observed over more recent times.

In addition to these two major changes in the 1962 legislation, the external environment surrounding FDA decisions on new drug approval also changed significantly. The thalidomide disaster received wide publicity in the popular press. This in turn galvanized congressional and media attention on new drug approvals.

Former FDA Commissioner Schmidt has emphasized the problem these external pressures create for the maintenance of a balanced and rational decision-making structure. He notes:

For example, in all of FDA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. . . . The message of FDA staff could not be clearer. Whenever a controversy over a new drug is resolved
The expanded attention from Congress and the media thus tended to reinforce the natural incentives of FDA officials to err on the side of caution or delay rather than the alternative type of error of allowing a drug with excessive risks into the marketplace.

A final set of factors influencing R&D costs and regulatory delays relates to FDA resource capabilities and its management procedures. The FDA's regulatory responsibilities expanded dramatically after the 1962 amendments. Little thought was apparently given, however, to the resource and management problems that might arise in implementing the new law. This point has come up repeatedly in outside and intraagency reviews of the FDA over the past two decades.

The most recent analysis of this question was a recent General Accounting Office study(11) that focused on the NDA approval process. Despite the fact that over 90 percent of all NDAs are eventually approved, the FDA now takes between two to three years on the average to approve an NDA. The GAO cited the following problems in FDA procedural reviews:

1. FDA guidelines are imprecise.
2. Reviewers of the NDA change, slowing the process.
3. Scientific and professional disagreements between FDA and industry are slow to be resolved.
4. FDA feedback to industry about deficiencies is slow.
5. Chemistry and manufacturing control reviews are especially slow.
6. Industry submits incomplete NDAs.

In responding to the GAO report, the FDA has indicated the goal of reducing over a three-year period the processing time on NDAs by 25 percent for drugs that represent important or modest gains and 15 percent for all other drugs.

To sum up, over the post-1962 period, there has been a substantial increase in both the scope and the intensity of regulatory controls on ethical drugs. As a consequence, it has been postulated that the costs of discovering and developing a new drug, along with the risk and uncertainty of drug innovation, have increased and that this in turn has been a major factor underlying the observed decline in new drug innovation in the United States.

Alternative Hypotheses for Explaining Declining Innovation Levels

Several other factors have been advanced in the literature as explanations for the decline in drug innovation over the past few decades.

Depletion of Research Opportunities

This hypothesis has been given the most attention in the literature as an alternative to increased regulation. Adherents of the research depletion hypothesis argue that major drug innovations tend to occur in waves or cycles and that in many major therapeutic areas we have currently reached a point where the probability that a new discovery will be an advance over existing therapies is quite low. They further argue that we are on a research plateau because the major diseases areas left to conquer are the ones where we have the least adequate scientific understanding of the underlying biological processes. Former FDA Commissioner Schmidt has expressed the research depletion hypothesis in the following terms:

Today's world includes a great number of important therapeutic agents unknown a generation ago. These include antibiotics, antihypertensive drugs, diuretics, antipsychotic drugs, tranquilizers, cancer chemotherapeutic agents, and a host of others. ... In many of these important drug groups there are already a large number of fairly similar drugs. As the gaps in biomedical knowledge decrease, so do the opportunities for the development of new or useful related drugs. As shown by the declining number of new single entity drugs approved in the U.S., England, France and Germany, this is an international phenomenon. This does not reflect a loss of innovative capacity, but rather reflects the normal course of a growth industry as it becomes technologically more mature [Schmidt, 1974b, p. 272].

This hypothesis, advanced by the FDA and others, has been received with considerable skepticism in many scientific quarters. Some have challenged the hypothesis on conceptual grounds. Others have pointed to the vast expenditures on basic biomedical research by the National Institutes of Health and other organizations as creating a renewed pool of basic knowledge which should offset any tendency toward a depletion of opportunities from prior drug discoveries (Bloom, 1976).
Changing Expectations

In addition to the factors of increased regulation and research depletion, Lebergott (1973) p. 9843 has pointed to the effects of the thalidomide tragedy on the behavior and expectations of physicians and drug firms as further confounding factors. In particular, he argues:

Do any of us believe that after that catastrophe, consumers were quite as likely as before to prefer new drugs to ones tested by experience? Were physicians henceforth quite as likely to prescribe new drugs – with the prospect of acute toxicity (and malpractice suits) when the one chance of 10,000 ran against them? Which of our leading pharmaceutical firms would henceforth endanger its reputation (and its entire existing product line) on behalf of a new drug on quite the same terms as it did in the days when biochemists could do no wrong? . . . Such massive changes in the U.S. perspective on drugs – we may call them shifts in both supply and demand curves – had to cut the number of more venturesome drugs put under investigation since 1962. It would have done so if the entire FDA staff had gone fishing for the next couple of years.

Thus, Lebergott argues that strong shifts in the incentive structure facing physicians and manufacturers occurred after thalidomide and that this would independently operate to increase R&D costs and lower the number of new drug introductions. His analysis points out the analytical difficulties in trying to identify the effects of regulatory and nonregulatory factors that changed simultaneously as a result of the thalidomide incident.

Advances in Pharmacological Science

Dr. Pettinga (1975) and others have also pointed to scientific advances in pharmacological science over the past few decades as another potentially important factor. In particular, he suggests that these advances, which have made teratology and toxicological studies much more sophisticated and costly in nature, would have been incorporated into drug-firm testing procedures even in the absence of regulatory requirements to do so. That is, drug firms would undertake many of these increased tests in their own self-interest, in order to reduce the likelihood of future losses in good will and potential legal liabilities.

Several plausible hypotheses have thus been advanced with respect to the observed downward trend in drug innovation. These hypotheses are not mutually exclusive and may all have contributed significantly to declining innovation in ethical drugs. In the next section we discuss the empirical evidence concerning the relative importance of increased government regulation versus these alternative explanations of declining drug innovation.

Aggregate Analytical Studies of Pharmaceutical Innovation

Time Series Studies by Peltzman and Bally

Sam Peltzman’s 1973 study of the effect of the 1962 amendments has received considerable attention in both economic and policy circles. Peltzman (1973) employs a "demand pull" model in which the supply of new drugs in any period responds with a lag to shifts in demand-side factors. The model is estimated on preamendment data (1948–1962) and is then employed to forecast what the number of NCEs would have been in the post-1962 period in the absence of regulation. The effects of the 1962 amendments are computed as the residual difference between the predicted and actual flow of NCEs. Using this approach, Peltzman concludes that "all the difference between the pre-1962 and post-1962 new chemical entity flow can be attributed to the 1962 amendments" (Peltzman, 1973). However, his approach never formally includes or considers any of the supply–side factors in the hypotheses cited above. All of the observed residual difference after 1962 is attributed to increased regulation. Since this residual difference can plausibly reflect the affects of a number of the other factors cited above (i.e., research depletion, changing expectations, and scientific factors), it probably encompasses various nonregulatory phenomena as well.

Martin Bally (1972) employed a production-function model of drug development that does try explicitly to separate the effects of regulation from the depletion of scientific opportunities. He postulates that the number of new chemical entities introductions in any period will be a function of lagged industry R&D expenditures and that both regulation and research depletion effects operate to shift this R&D production function over time. Regulation is captured explicitly in Bally's model by a time intercept shift variable and depletion by a moving average of past introductions. Both variables were quantitatively and statistically significant when his model was estimated over the period 1954 to 1969. However, when the model was later estimated for the period extending through 1974, the research depletion variable became insignificant and unstable over time.

Thus, the early time series studies of this issue by Peltzman and Bally both found strong negative impacts of
regulation on new drug innovation. Neither study, however, provided very satisfactory approaches for isolating the effects of regulation on innovation from other confounding effects discussed above. This is a difficult econometric problem to handle in the context of aggregate time series analysis of U.S. introductions.

**Wardell’s Drug Lag Analysis**

In order to separate the effects of increased regulation from other hypothesized factors, one would ideally perform an "experiment" involving two different states of the world: one with the 1962 amendments in effect and one where they are not. Given the impossibility of this experiment, a second-best type of analysis may be to find another country that is as similar to the United States as possible, but which differs significantly in terms of regulatory controls and procedures.

With this kind of methodological approach in mind, William Wardell, a clinical pharmacologist, performed a series of comparative analyses of drug introduction in the United States and the United Kingdom in the post-1962 period. The United Kingdom is similar to the United States in terms of high standards of medical training and practice and also has a very research-intensive multinational drug industry. However, the regulatory systems in effect in the United Kingdom and United States have important differences in the post-1962 period. Premarket safety reviews of new drugs essentially began in 1963 in the United Kingdom as a response to the thalidomide tragedy. The safety reviews in the United Kingdom have been characterized as high quality in terms of the depth of review process and the type of evidence necessary to gain approval (FDA, 1975). At the same time, the United Kingdom did not require formal proof of efficacy until its Medicine Act was implemented in 1971; before this the task of evaluating a drug's efficacy was essentially left to the market mechanism. Furthermore, the U.K. IND procedure was on a voluntary basis until 1971. Third, the British system utilized the judgment of external committees of academic medical experts in making approval decisions and emphasized postmarketing surveillance of new drugs to a much greater degree than the United States. As a result, the British system has been characterized as less adversarial and bureaucratic than the U.S. system, which relies to a greater extent on the decisions of career civil servants, congressional oversight hearings, and the judicial process.

Wardell’s first comparative study (12) of new drug introductions in the United States and United Kingdom covered nine therapeutic classes for the period 1962–1971. For this period he finds that the number of new chemical entities introduced into the United Kingdom was roughly 50 percent higher than the number introduced into the United States (159 NCEs compared to 103 for the United States). Moreover, for the drugs that were mutually available in both countries by 1971, twice as many were introduced first in the United Kingdom as were introduced first in the United States. This "drug lag" was found to be the greatest in the areas of cardiovascular, diuretic, gastrointestinal, and respiratory medicine. On the other hand, in cancer chemotherapy, Wardell found both countries had comparable availability of new therapies.

In a related paper, Wardell attempted to assess the therapeutic consequences of these different rates of introduction through a detailed discussion of the individual drugs available in the two countries. He concludes:

> From the present study, it is clear that each country has gained in some ways and lost in others. On balance, however, it is difficult to argue that the United States has escaped an inordinate amount of new-drug toxicity by its conservative approach; it has gained little else in return. On the contrary, it is relatively easy to show that Britain has gained by having effective drugs available sooner. Furthermore, the cost of this policy in terms of damage due to adverse drug reactions have been small compared with the existing levels of damage produced by older drugs. There appear to be no other therapeutic costs of any consequence to Britain. In view of the clear benefits demonstrable from some of the drugs introduced into Britain, it appears that the United States has, on balance, lost more than it has gained from adopting a more conservative approach than did Britain in the post-thalidomide era (Wardell, 1974 p. 90).

In a follow-up study (13) to his original drug lag study, Wardell found comparable trends for the 1972–1976 period in the aggregate numbers of exclusive introductions and comparable lags in mutually available drugs. However, he also noted some tendency for the largest clinical differences to narrow over time. He attributed this convergence in part to more "realistic" regulatory standards in the United States in some (but not all) areas and a trend to more conservative practices abroad.

**Further International Comparative Analyses**

In a recent paper, Grabowski (1980) analyzes the time pattern of all NCE introductions in the United States for the period 1963 to 1975 relative to three European countries - the United
Kingdom, Germany, and France. He finds a significant lag has characterized NCE introductions in the United States relative to the United Kingdom and Germany in the post-1962 period. This is true for both NCEs discovered in this country and those discovered abroad. For France, the data indicate that the United States still generally leads that country in the introduction of U.S.-discovered NCEs, but not foreign-discovered ones. Second, his analysis also indicates that the lag with Europe is not confined to drugs with little or modest medical gain, but also includes drugs ranked as significant therapeutic advances (as classified by the FDA itself). Third, there is evidence, from a regression analysis performed in the paper, that regulatory approval lags have been an important factor contributing to this introduction lag. Finally, the analysis further indicates that regulation has had an especially strong impact on the introduction lag for foreign-discovered drugs over this period.

The recently released GAO study(14) of the FDA drug-approval process discussed above also examined the availability of 14 therapeutically important drugs in the United States and five other countries (Canada, Norway, Sweden, Switzerland, and the United Kingdom). This study focuses on drugs introduced in the United States between 1975 and 1978. They found that all but 1 of these 14 drugs were available first abroad with lags ranging from 2 months to 13 years in length. Furthermore they found the average FDA approval time on these drugs of 23 months was significantly greater than that for all other countries except Sweden (with England and Switzerland having average regulatory approval times of 5 and 12 months respectively).

While a pattern of lagging U.S. NCE introductions (including therapeutically important drugs) thus emerges from a number of recent studies, a broader issue is the effect of regulation on the level, rather than the timing, of introductions. This may be characterized as the issue of "drug loss" rather than "drug lag." This is the issue addressed by the earlier econometric analysis of Peltzman and Bally. As noted above, however, these aggregate times-series studies had substantial difficulties in separating the effects of regulation from other confounding factors such as research depletion.

One, of course, may view the drug lag findings as symptomatic of broader impacts of regulation on the innovational process; that is a scenario of regulation leading to greater costs, development times, and commercial uncertainties for new drugs and hence to fewer annual NCEs being developed and introduced each year. The magnitude of these impacts, however, is arguable and remains an important issue for empirical research.

In a study(15) that we performed jointly with Lacy Thomas, we have examined aggregate "R and D productivity" changes in the United States and the United Kingdom to gain some insights into the effects of regulation on the level of innovation. Our strategy in this analysis was to structure the analysis in terms of an econometric model and to use international data as a means of separating confounding regulatory from nonregulatory factors. We found in this analysis that American R&D "productivity" - defined as the number of new chemical entities discovered and introduced in the United States per dollar of R&D expenditure - declined to about 1/6 of its former level between 1960-1961 and 1966-1970. The corresponding decrease of R&D productivity in the United Kingdom was to about 1/3 of its former level. On the basis of a regression analysis that used these and other data, we concluded that increased regulation in the post-1962 period has probably at a minimum doubled the cost of obtaining an NCE. At the same time, nonregulatory factors (such as research depletion, scientific advances in detecting toxicology, changing expectations) also apparently have significantly increased costs here and in the United Kingdom. However, the specific mechanisms and magnitudes of these different regulatory and non-regulatory factors await a more extensive and disaggregative analysis.

Summary and Implications

The various empirical studies discussed above do not provide definitive conclusions on the exact role of regulatory versus nonregulatory factors in explaining the lower levels of drug innovation experienced in the 1960s and 1970s. On analytical grounds, it is difficult to separate the effects of these contemporary factors. Nevertheless, the studies do provide a number of different analytical approaches to the problem and a consistent finding is that increased regulation is one of the important explanatory factors in this regard.

From a policy standpoint, the evidence has been sufficient to shift the perception of law makers quite dramatically compared with the situation in the early 1960s. At the time of the passage of the 1962 amendments, apparently little thought or credence was given to the notion that increased regulation could have unintended or undesirable side effects on innovation. However, given the industry's experiences of the past two decades, and the evidence from various academic studies (especially the drug lag studies), even the proposed regulatory reform laws of liberal congressmen include at least provisions for improving regulatory performance so that useful new drug therapies can be obtained by patients on a speedier basis.
In the last section of this chapter, we provide a detailed analysis of current legislative proposals in this regard. Before doing so, however, we turn in the next two sections to some more microeconomic-oriented studies on the returns and determinants of pharmaceutical R&D investment. Using a more microeconomic framework, we also attempt to analyze the effects and interactions of other government policy variables on firm R&D investment behavior.

V. STUDIES OF THE RETURNS TO AND DETERMINANTS OF PHARMACEUTICAL R&D

Rate of Return Studies

Several empirical studies of the rate of return to drug innovation have been performed in recent years. We will discuss two of the most influential studies first and then turn to our own recent work on this topic.

David Schwartzman 1975 Study

Schwartzman (1975) begins his analysis by computing the annual sales revenues generated by the new chemical entities introduced in the United States in the 1966–1972 period. In order to calculate an expected rate of return to discovering and developing these drugs, he further estimated (1) the level and time pattern of research and development costs incurred to obtain these NCEs, and (2) the current and expected future profits generated by these new product sales.

Schwartzman’s estimates on the average cost and revenues streams over this period yielded an after-tax rate of return on pharmaceutical R&D of only 3.3 percent. Schwartzman’s analysis clearly embodies a number of important assumptions. Perhaps the weakest link in his chain of assumptions concerns his procedures for estimating expected profit margins for new drugs and expected product lifetimes (see Grabowski, 1976). Schwartzman, however, does perform a sensitivity analysis to see how his rate of return results change with different assumptions on these parameters. Other things constant, a 40 percent profit margin (instead of 25.6 percent) and a 20-year product life (instead of 15 years) yields an after-tax return for this period studied by Schwartzman of 7.5 percent (instead of 3.3 percent). This is still a very low rate of return for what is generally considered to be a very risky activity.

Perhaps the most interesting finding of Schwartzman’s analysis is not his absolute estimates on the rate of return to drug innovation but the rate of change that he observes in this measure when his methodology is used on data from an earlier period. Specifically, Schwartzman found an after-tax rate of return of 11.4 percent in 1960 (compared to 3.3 percent in 1966–1972) using conservative estimates of the model’s parameters. This is generally consistent with findings of higher returns in prior analyses by Bally (1972) and Clymer (1970) for this earlier period. In contrast to Schwartzman’s approach, Bally constructed a two-equation econometric model from which he calculated the rate of return. Hence these two studies, despite the use of quite different methodologies, seem to be in general agreement.

The Virts and Weston 1980 Study

Virts and Weston (1980) p. 107 were concerned with the expected rate of return for pharmaceutical R&D in 1976. While they did not explicitly calculate a rate of return estimate, they did provide estimates of the present value of net revenues. These estimates were then compared with the present value of R&D costs taken from the Hansen study (discussed above). According to Virts and Weston:

The implications are that the average return on investment (ROI) to pharmaceutical R&D has been significantly less than 8% and that these results have varied markedly among individual NCE’s. Clearly, the owners of those NCE’s failing in the top 25% in terms of market performance have achieved much higher returns and the average ROI to R&D for those companies exceeds the average for the drug industry and for all manufacturing industries. On the other hand, most NCE’s have apparently failed to generate cash flows sufficient to earn a conservative estimate of the cost of capital.

Grabowski and Vernon 1982 Analysis

Because studies of returns to R&D require numerous important assumptions about such variables as product life, profit margins, etc., we have performed a sensitivity analysis (Grabowski and Vernon, 1982) of expected profitability for 37 NCEs discovered and introduced in the United States over the 1970–1976 period. A brief description of our analysis is given below.

The primary data used in the analysis are U.S. sales and promotion expenses for each NCE and R&D costs by therapeudic class. Two additional important types of data were not available: the cost of producing the NCEs after FDA approval and the net revenues resulting from sales in foreign countries. In both cases we have relied on estimates made by Celia Thomas as part of her Ph.D. dissertation at Duke University.
For example, her best estimate for production costs (16) as a fraction of sales is .30. However, because of the uncertainty about this estimate, we have also examined the effect of estimates of .20 and .40. A similar approach was taken with respect to Thomas' estimate of 1.75 as the ratio of worldwide net revenues to U.S. net revenues. That is, estimates of 1.5 and 2.0 were also used in a sensitivity analysis.

The R&D cost estimates are based on a study by Hansen. As described earlier, Hansen (1979) obtained survey data from 14 pharmaceutical firms on the R&D costs for a sample of NCEs first tested in humans from 1963 to 1975. The average discovery cost was $19.8 million and the average development cost was $41.4 million, for a total of $57.3 million. The $57.3 million represents the capitalized value (at 10 percent interest and in 1967 dollars) at the date of marketing approval.

At our request, Hansen (1980) estimated the costs per NCE on a therapeutic class basis. These are the cost estimates used in this analysis and as will be shown, reveal a rather large variation across classes. We should also note that Hansen's estimates include the costs of NCEs that enter clinical testing but are not carried to the point of NDA approval. Hence, the estimates should be interpreted as the average expected cost of discovering and developing a marketable NCE.

As observed above, Hansen's estimates are expressed as capitalized values at the date of marketing. For example, the capitalized expected cost of discovering and developing a cardiovascular drug at the date of marketing is $30.6 million in 1967 dollars. Because he worked with constant dollars, Hansen used real interest rates; in the example above, the interest rate is 10 percent. The natural measure for comparison with Hansen's cost estimate is the present value of the new revenue stream resulting from the NCE. To be consistent, of course, the net revenue stream must be deflated to 1967 dollars and discounted to the date of marketing at the same real interest rate. The ratio of present value of net revenue to capitalized R&D cost is termed the profitability index (PI) in the finance literature, and it will be the measure of expected returns used here. Clearly, a PI = 1 implies a project that just breaks even.

Before turning to the results of our analysis in Figures 6.3, 6.4, and 6.5, we provide some general information about the data in Table 6.14. What is particularly striking about Table 6.14 is the relatively low estimate of the expected present value of R&D costs for a new chemical entity in antiinfectives (19.1 million dollars) compared to therapeutic classes such as psychopharmacology (70.0 million dollars), metabolic-antifertility (65.3 million dollars) and antiinflammatory (68.3 million dollars). This is consistent with a significant regulatory effect on the cost of developing new entities since antiinfectives is the easiest area to establish efficacy using the "large and well controlled trials" criterion of the FDA.

The Pharmaceutical Industry


<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Hansen's R&amp;D Cost (10%, 1967 dollars)</th>
<th>Number of US NCEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cardiovascular</td>
<td>30.6</td>
<td>4</td>
</tr>
<tr>
<td>B. Neurologic, Analgesic</td>
<td>36.3</td>
<td>6</td>
</tr>
<tr>
<td>C. Psychopharmacology</td>
<td>70.0</td>
<td>3</td>
</tr>
<tr>
<td>D. Metabolic, Antifertility</td>
<td>65.3</td>
<td>5</td>
</tr>
<tr>
<td>E. Antiinfective</td>
<td>19.1</td>
<td>12</td>
</tr>
<tr>
<td>F. Antiinflammatory</td>
<td>68.3</td>
<td>1</td>
</tr>
<tr>
<td>G. Gastrointestinal,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, Surgery</td>
<td>28.5</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>

Figure 6.3 shows the PI versus Product Life relationship for four alternative real interest rates (cost of capital). As stated, the PI variable is a weighted average PI for the 37 NCEs, where the weights applied are the R&D costs. The fraction of production cost to sales is held at .30 and the ratio of world net revenues to U.S. net revenues is taken to be 1.75. If we assume that the appropriate real cost of capital (inclusive of a risk premium) is 10 percent, then the product life necessary to break even on average is 19 years. An 8 percent cost of capital reduces the break-even life to 12 years.

Since the assumptions about production costs and foreign sales are uncertain, Figure 6.4 was prepared to reflect this uncertainty. Given the subjective probability distributions shown in Figure 6.4, a band of one standard deviation in width about the weighted average PI is presented. The one standard deviation band brackets the break-even life between approximately 14 and 30 years.

Figure 6.5 focuses on a different type of uncertainty. It shows a frequency distribution of the PIs of the 37 NCEs. Clearly, the distribution is highly skewed - with only 13 of the 37 projects breaking even or better. The letters are codes for the innovating firms and indicates that firm "A" had three "winners," while the remaining ten were spread over ten different firms.

Of course, the 34 NCEs that have PIs of less than unity fail to break even only in the sense of not covering fully allocated discovery and development costs, including a share of
Fig. 6.3. Weighted average P.I. vs. life for various interest rates (weights are R&D costs).

Fig. 6.4. Weighted Average P.I. vs. Life with Uncertainty Bands (Uncertainty due to estimate of M.F.)
Table 6.15 also presents the time pattern of foreign research and development expenditures for the period 1965–1978. While it is not clear how to deflate these outlays, it is clear from these data that slower growth rates in domestic R&D have been offset in part by faster growth in foreign R&D expenditures. The proportion of total R&D accounted for by foreign R&D roughly doubled from 7.5 percent in 1965 to 16.9 percent in the most recent year. This is consistent with the greater percentage of revenues from foreign markets and also the possibility of incurring less stringent regulatory controls in early clinical trials abroad. It may, of course, reflect other economic factors as well.

The final column in Table 6.15 gives the time trend in the ratio of global R&D expenditures to sales (i.e., including both domestic and foreign pharmaceutical activities) for U.S. firms. This ratio has been quite stable over the period, ranging between 8 and 9 percent.

One other trend in industry behavior is also worth noting at this point. Specifically, U.S. firms have been increasing their degree of participation in nonpharmaceutical activities in recent years. This is reflected in Virts and Weston’s analysis (17) of changes in the aggregate percentage of pharmaceutical to nonpharmaceutical sales for eight leading firms over the period 1975–1978. This measure declined from 58.9 to 55.3 percent for this six-year period. Moreover, analyzing the longer period 1962–1975, we found a significantly declining trend in overall, corporate R&D to sales ratios (that is, including pharmaceutical and nonpharmaceutical corporate activities). This trend is also consistent with increased firm diversification into less research-intensive activities such as specialty chemicals and cosmetics.

In sum, the larger firms seem to be exhibiting a mixed strategy in their investment behavior in recent years—maintaining their R&D activity in pharmaceuticals with low rates of growth in real terms, while devoting somewhat more managerial and financial resources to nonpharmaceutical areas. While these trends may be viewed as providing some support for the findings of low rates of returns on pharmaceutical R&D by Schwartzman and others, they are much less than one might expect if firms really expected the low rates of returns observed by Schwartzman to hold on their current R&D activity. There is thus an apparent paradox. If current rates of return are so low, why do pharmaceutical firms continue to invest such substantial sums of money in R&D?

In our recent study (18) of the determinants of R&D expenditures, we attempted to answer this question.

Basically, we performed a multiple regression analysis on a sample of ten firms over the period 1962–1975. The dependent variable was the firm’s R&D to sales ratio. The two primary explanatory variables were measures of past R&D success and cash flow.

THE PHARMACEUTICAL INDUSTRY

The measure of past R&D success was essentially a moving average of firm’s introductory sales of NCEs over a prior five-year period divided by its R&D expenditures over this period. It, of course, was intended to reflect the firm’s expected rate of return from R&D investment. The cash flow measure, lagged profits plus depreciation, was included to test the hypothesis that firms impute a lower cost to internal funds, because of the lower transactions costs and risks, than they impute to external funds. Cash flow also seemed especially important for investment in activity characterized by such great uncertainty as pharmaceutical R&D.

Our regression results indicated that firms do react to lower realized returns on R&D activity in the expected manner, but the adjustment process is a very gradual one with relatively long lags. This is perhaps not surprising given that new product innovation historically has been a central and quite profitable mode of competition for the industry dating back to the pre-World II era. Moreover, the high degree of uncertainty and serendipity that characterizes discovery research and early clinical development trials in pharmaceuticals is also consistent with a cautious response to lower realized returns on prior R&D efforts. Future returns may be very different from current or past returns, especially at the individual-firm level.

In this regard, it is worth mentioning once again that many firms apparently expect that industry returns from new drugs will be much greater in the coming decades as a result of several basic research "breakthroughs" discussed in Section III above. It is, of course, expectations about future rather than past returns that ultimately count in terms of firm investment behavior. It remains to be seen, however, whether these basic research advances can be translated into profitable new drugs in the foreseeable future.

Our regression results also indicated that the general availability of internal funds or cash flow is another important factor that influenced R&D behavior over this period. We found a statistically significant stable positive relation between firm research intensities and their lagged cash flow margins. Moreover, these margins were relatively high over much of the period under study as a result of the record number of products introduced in the 1950s. These products remained under patent protection and generated high cash flows for the innovating firm well into the 1960s and even the 1970s in many cases.

Hence, we can infer from our analysis that the relatively high levels of internal cash flow over much of post-1962 period operated to moderate what would otherwise have been a more dramatic decline in R&D investment patterns.

In sum, our regression analysis indicates that both expected returns and cash flow are two major economic factors
influencing firm willingness and ability to invest in R&D outlays for new drug products. From a policy standpoint, these results therefore indicate that R&D expenditures will be sensitive to the spectrum of government policies that impact on these variables. The remainder of this chapter is concerned with an analysis of various policy impacts in this regard.

VI. GOVERNMENT'S IMPACTS ON INNOVATION

Many different government laws and regulations affect the process of pharmaceutical innovation. Some regulations directly affect innovation, e.g., the FDA's regulations concerning safety and efficacy testing increase the costs of developing new drug compounds. On the other hand, some laws are less direct in their impact. A good example is the current movement to repeal state antisubstitution laws.

State antisubstitution laws prohibit pharmacists from substituting generic products for brand-name products prescribed by physicians. Repeal of these laws should lead to increased competition for the innovator's drug by imitative drug products, thereby reducing expected returns to innovation.

Important interdependence can exist among the various laws and regulations. For example, the effects of the new substitution laws on innovation incentives must be considered in light of government patent or regulatory policies. Since substitution laws alter the expected revenues of a new drug only after the patent expires and alternative suppliers enter the market, their impact on innovation returns depends on the patent protection. The effective patent life for new pharmaceuticals is typically much shorter than the legal life of 17 years owing to the long gestation period that is required to develop and gain regulatory approval for a new drug entity. Hence, drug substitution, patent, and regulatory policies have potentially significant interactive effects on the incentives for drug innovation investment.

From a normative or policy perspective, these public policies are also obviously interrelated. If changes in drug substitution laws were seen as leading to suboptimal incentives for drug innovation, policy makers have the option of adjusting patent life to increase incentives. It would not be necessary to maintain substitution restrictions on all pharmaceuticals in order to maintain sufficient incentives with respect to drug innovation. This latter objective could be accomplished by changing the patent life on new drugs. This point is developed in more detail later.

The objective in this section is to provide a comprehensive discussion of how government laws and regulations affect the expected return to R&D investment. Ideally we would also provide an assessment of the relative importance of these various laws and regulations in stimulating or retarding innovation. Unfortunately, adequate evidence does not exist for such an assessment in many cases. This is necessarily the case for policies, such as the new substitution laws, which are just now becoming operational. Hence, our assessments in such cases will necessarily be somewhat speculative.

It will be useful to organize our discussion around the standard investment model of the firm.

Suppose that an NCE is expected to be introduced in year t. It will involve R&D costs over m years and earn positive profits for n years after introduction, p of which are subject to patent protection. Then the rate of return, r, for this particular product introduction is found by solving the equation that equates the present value of investment outlays to net revenues generated after the product is commercially introduced. (19)

This expected rate of return calculation abstracts from potential differences in risk associated with specific development projects. The expected return from each project would have to be adjusted for such risk differentials across projects (unless the firm is risk neutral). The firm's decision to invest in a particular development project would depend on whether its adjusted rate of return exceeds or falls below the firm's capital cost, which reflects the opportunity cost of alternative investments for the firm and its shareholders.

The firm is assumed to make such calculations for all possible new drug-development opportunities. It then uses this information to construct a marginal rate of return (MRR) schedule by arranging projects in order of decreasing rates of return. The intersection of MRR and the marginal cost of capital schedule (MCC), which reflects the opportunity cost of alternative investments for the firm and its shareholders, determines the optimal level of R&D investment, R. This is shown graphically in Figure 6.6.

We now begin an analysis of how various government policies can be expected to affect R&D investment decisions.

Funding of Basic Biomedical Research

In Section III the large expenditures on basic biomedical research made by the federal government were shown. We concluded that while it is impossible to quantify precisely the impact of advances in basic science on pharmaceutical innovation, the impact is undoubtedly of great importance.

In terms of Figure 6.6, it is useful to view such advances as shifting the MRR schedule rightward as new opportunities for drug development are made possible.
Given the lengthy discussion in Section III of the role of government-supported basic research in drug discovery and development, we shall not discuss it further here. It might be recalled, however, that many experts believe that a revolution is now taking place in molecular biology and this might make the social payoff to funding of basic research especially high at this time.

**FDA Regulation**

FDA regulation affects both the cost and revenue sides of the rate of return calculation. Earlier we gave a brief description of Hansen’s estimates of R&D costs. FDA regulations exert important effects on these costs, e.g., by specifying the number of tests and the amount of evidence on safety and efficacy that must be accumulated. And, as described above, the two-to-three year period of FDA review of the NDA adds significantly to the cost. (Earlier we referred to our 1978 study which concluded that the increased FDA regulation resulting from the 1962 amendments more than doubled R&D costs.)

FDA regulations also exert effects on the expected revenues from an NCE. There are several possibilities here, some of which have opposite implications for expected revenues.

Regulatory controls will reduce the probability of commercialization for many compounds and lower expected revenues.

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One of the primary benefits of regulation is the extent to which the regulatory agency screens out and deters drug entities that present risks that the majority of consumers would not knowingly and willingly undertake. Evaluating whether the FDA has been too conservative in its risk/benefit decisions is one of the most difficult and controversial areas of regulatory analyses.

There are also several ways that regulation can operate to increase the expected revenues of drugs approved for marketing by the FDA. First, regulations serve a certification function. Stringent regulatory processes provide physicians and patients with confidence in a new drug’s safety and efficacy, thereby facilitating rapid market diffusion and penetration for new drugs. Second, drugs that are approved in a stringent regulatory regime face less actual and potential competition than is the case in an unregulated market. This is true for two basic reasons. First, many marginal drugs will be undeveloped, given the greater costs of developing drugs under regulation. Second, the minimum scale at which R&D can be profitably undertaken will tend to increase under regulation, lowering the number of firms engaged in pharmaceutical innovation.

Regulation also affects the effective patent life for a new drug entity. Since the average time to develop an NCE and gain regulatory approval now far exceeds the time necessary to obtain a patent, regulatory-derived increase in development or approval times will operate to lower the effective life of a drug patent. While the length of patent protection has been of secondary import historically in the drug industry, this situation could change dramatically with the repeal of antisubstitution laws.

How do these regulatory effects balance out and what is their new impact on the rate of return to innovation? Of course, there is no definitive answer to this question, but the evidence surveyed earlier suggests that increased regulation has been at least one important factor underlying the declining trend in average innovation returns. We should emphasize that these studies all dealt with past time periods; the likely impact of FDA regulation in the future is less certain given various proposed legislative and administrative reforms currently under active consideration.

**Substitution Laws**

As noted earlier, the repeal of antisubstitution laws might result in increasing the importance of the length of patent protection. To see how this might come about, some background on the antisubstitution laws should be useful.
GOVERNMENT AND TECHNICAL PROGRESS

These laws were enacted in the early 1950s in response to the drug "counterfeiting" problem, i.e., the dispensing by pharmacists of drugs similar in size, color, and packaging to popular brand-name products, but of unknown quality or origin. Antisubstitution laws were adopted by all 50 states and generally prohibited any form of substitution for the brand written on the prescription.

The laws made it possible for innovating firms, through strong brand loyalties, to maintain dominant market positions for their products even after patent expiration. Hence, even though lower-cost generic products became available upon patent expiration, in many cases physicians have continued to prescribe the original brand-name product.

A major structural change taking place in the pharmaceutical industry today is the repeal of state antisubstitution laws. Over 40 states have passed product selection, or drug substitution laws. While the state-enacted laws have significant differences, essentially all enable pharmacists to substitute generic products (some mandate substitution) unless a physician prevents substitution by checking a preprinted box or writing "dispense as written" (DAW) on the prescription form.

If substitution laws foster increased competition for the innovator's product, then the degree of patent protection assumes a critical role in the appropriability of drug returns. A shorter effective patent life shifts the impact of drug substitution forward in time, amplifying the impact of revenue losses on the expected return to innovation. Table 6.15 shows that the effective patent life for pharmaceuticals has been declining and is currently in the range of nine to twelve years.

We can show the sensitivity of the expected profitability of R&D to changes in the effective patent life and the degree of substitution by using the profitability index (PI) analysis described in the first part of Section V. Recall that we calculated the average PI for 37 NCEs introduced over the period 1970 to 1976 for a number of alternative assumptions about product life, real interest rate, etc. The results were shown graphically in Figure 6.3. Here, using this same sample, we take as our benchmark case a product life of 20 years and a real interest rate of 10 percent. The PI corresponding to these assumptions is 1.029.

In order to study the sensitivity of this PI of 1.029 to changes in the effective patent life and the impact of substitution on net revenues, we imposed selected values of these parameters on our data and recalculated the PIs. One case examined was an effective patent life of eight years and a 50 percent reduction in U.S. net revenues after patent expiration. (21) The PI for this case was only .863 as compared with the benchmark of 1.029. The results for all cases are given in Table 6.17.

**Table 6.16. Average Effective Patent Life for New Chemical Entities Introduced into the United States from 1966 to 1977**

<table>
<thead>
<tr>
<th>Year</th>
<th>Average Effective Patent Life (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>13.6</td>
</tr>
<tr>
<td>1967</td>
<td>14.4</td>
</tr>
<tr>
<td>1968</td>
<td>13.5</td>
</tr>
<tr>
<td>1969</td>
<td>12.7</td>
</tr>
<tr>
<td>1970</td>
<td>14.4</td>
</tr>
<tr>
<td>1971</td>
<td>12.2</td>
</tr>
<tr>
<td>1972</td>
<td>10.9</td>
</tr>
<tr>
<td>1973</td>
<td>12.1</td>
</tr>
<tr>
<td>1974</td>
<td>13.0</td>
</tr>
<tr>
<td>1975</td>
<td>11.4</td>
</tr>
<tr>
<td>1976</td>
<td>11.3</td>
</tr>
<tr>
<td>1977</td>
<td>9.6</td>
</tr>
<tr>
<td>1978</td>
<td>10.5</td>
</tr>
<tr>
<td>1979</td>
<td>9.5</td>
</tr>
</tbody>
</table>

*Effective patent life refers to the length of time from the date of FDA approval until the date of patent expiration.

Source: University of Rochester, Center for the Study of Drug Development, Department of Pharmacology and Toxicology. See Eisman and Wardell (1981).

As one would expect, the calculated PIs in Table 6.17 are lower for shorter effective patent lives and for greater percentage reductions due to substitution. Under the most unfavorable conditions for R&D activity considered here - an eight year patent life and a 50 percent reduction in U.S. net income - the rate of return is reduced to .863, or by about 16 percent from the 1.029 benchmark. On the other hand, when a 30 percent net income reduction and a 12-year patent life are assumed, the PI is .974, or roughly a 5 percent reduction due to substitution. These estimated effects are not negligible and, other things constant, may be expected to make some R&D projects no longer attractive to pharmaceutical manufacturers.

The results in Table 6.17 underscore the fact that the effects of substitution on R&D returns are highly sensitive to the length of patent protection. If the patent life for drugs...
Table 6.17. Sensitivity Analysis Showing Profitability Index for Alternative Assumptions About the Impact of Substitution and the Effective Patent Life

<table>
<thead>
<tr>
<th>Percentage Reduction</th>
<th>Effective Patent Life</th>
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<tbody>
<tr>
<td></td>
<td>8 Years</td>
</tr>
<tr>
<td>U.S. Net Income upon Patent Expiration</td>
<td></td>
</tr>
<tr>
<td>-10</td>
<td>.996</td>
</tr>
<tr>
<td></td>
<td>(-3.2)</td>
</tr>
<tr>
<td>-30</td>
<td>.930</td>
</tr>
<tr>
<td></td>
<td>(-9.6)</td>
</tr>
<tr>
<td>-50</td>
<td>.863</td>
</tr>
<tr>
<td></td>
<td>(-16.1)</td>
</tr>
</tbody>
</table>

Notes: 1. The standard against which the above Profitability Indexes (PIs) should be compared is 1.029. This is the PI for a 20-year commercial life with no reduction in U.S. net income. It is also assumed that the ratio of production cost to sales is .3, the ratio of world net revenues to U.S. net revenues is 1.75, and the real interest rate is .10.

2. It is assumed that at the end of the effective patent life, substitution will result in the alternative reductions in U.S. net income given above for the remaining years of the 20-year commercial life.

3. The numbers in parentheses are the percentage reductions for each PI from the standard PI of 1.029.

actually equalled the legal life of 17 years, the effects of increased substitution on R&D returns would be quite modest. For example, with a 17-year life, a 50 percent reduction in U.S. net income from substitution causes R&D profitability to decrease by only 3 percent in the present example. On the other hand, as patent lives decrease, the effects of drug substitution are magnified.

The results in Table 6.17 are somewhat tentative in character. The analysis is based in aggregative data sources and contain the simplifying assumptions discussed above. Nevertheless, the results suggest that the effects of substitution laws on innovation incentives are consequential in nature and are quite sensitive to the longevity of patent lives over the

ranges considered (i.e., 8 to 17 years). These issues are considered further in the final section on current policy initiatives.

Other Laws and Regulations

To conclude this analysis of the effects of various government policies on the incentives to undertake R&D, we briefly discuss the Maximum Allowable Cost (MAC) program and the federal income tax code.

The MAC program(22) is somewhat similar to the new substitution laws in the way it affects the expected rate of return to pharmaceutical innovation. Specifically, MAC is a program designed to limit federal government third-party reimbursement, primarily under Medicaid, for prescription drugs. It limits reimbursement to the lowest price at which a particular multisource drug is generally available. Since MAC is only applicable to multisource drugs, it is similar to the substitution laws in acting to reduce an innovator's net revenues after patent expiration. On the other hand, MAC only applies to drug purchases that qualify for government reimbursement. Medicaid prescriptions, for example, account for only about 15 percent of all prescriptions.

Since the first maximum cost limit for a drug product was set for penicillin in 1977, it is clear that this program is just getting started. Hence, it is too early to assess the overall impact of MAC on innovation incentives.

The U.S. Internal Revenue Code has been designed by Congress to assist U.S. possessions in obtaining employment-producing investments by U.S. corporations. Through Section 936, so-called "possessions corporations" can be exempt from federal tax on income from operations in Puerto Rico, American Samoa, Guam, and the Panama Canal Zone. As a result, many pharmaceutical firms have set up operations in Puerto Rico and thereby obtained large tax savings.

The tax savings are, in fact, quite substantial and are concentrated especially in the pharmaceutical industry. For example, the Treasury Department has estimated that in 1977, 45 percent of all tax savings to U.S. corporations accrued to the pharmaceutical industry. It also reported that 16 drug firms had a total of $344 million in tax savings in 1977 under Section 936.(23) This sum represents about 10 percent of the pretax income for these firms.

The sizable tax savings from Puerto Rican operations add significantly to industry cash flows. Given the importance of cash flows as a determinant of R&D expenditures as noted earlier, a change in tax policy to reduce this tax advantage could have a significant negative effect on R&D incentives. Just such a change is possible if the IRS successfully argues
in a current court case that Lilly has allocated excessive profits to its Puerto Rican subsidiary. A ruling in favor of the IRS could possibly be applied to the other pharmaceutical firms. In addition, various legislative proposals to amend these tax provisions have been introduced into Congress recently.

To summarize briefly, we have examined how six government laws and regulations affect the expected rate of return to pharmaceutical innovation. These six policies are funding basic biomedical research, FDA regulation, patent policy, state substitution laws, the MAC program, and the corporate income tax. A key point that has been made throughout the discussion is that these policies are interdependent and that policy changes must be considered in light of that interdependence.

It is clear that public policies have had both significant positive and negative incentive effects on innovation. Historically, it appears that the main positive effects have been derived from government funding of biomedical research while the main negative effects have been associated with health and safety regulations. Other public policies, currently in an evolutionary state, such as MAC and state substitution laws, could also have significant negative impacts on the economic returns to innovation over future periods. This will be so if the effective patent lives for new drugs continue to trend downward over time and these evolving new laws and regulations cause a dramatic increase in generic drug usage after patents expire. These negative incentive impacts could be offset by various compensatory policy actions. These are discussed in our final section on current policy initiatives.

VII. CURRENT PUBLIC POLICY INITIATIVES

In the final section of this chapter we consider current policy issues in the areas of regulatory reform, patent legislation, and government funding of research and development.

Regulatory Reform

In 1979, the Carter administration introduced parallel bills into the House of Representatives and Senate with several co-sponsors that would have comprehensively overhauled all stages of the drug regulatory process. This legislation came to be known as the Drug Regulatory Reform Act of 1978. In addition, bills with similar (but not identical provisions) were introduced into the Senate by Senator Kennedy and the House of Representatives by Congressman Rogers.

These regulatory reform measures were introduced during a period of changing attitudes toward drug regulation and attempted to balance a number of somewhat conflicting objec-

tives. Among the apparent objectives of the bills were: (1) to speed up the approval of significant new drug therapies; (2) to increase the degree of public participation in the drug approval process and make it more open to outside scrutiny; (3) to facilitate the entry of generic producers into the market after patent expiration by removing duplicative testing requirements; and (4) to expand FDA regulatory controls over the postmarketing period.

As one might expect, none of the interested parties here— the drug manufacturers, consumer advocates, practicing physicians, pharmacists, and the academic medical community—was completely satisfied with all sections of these proposed drug regulatory reform bills and they worked vigorously to amend certain provisions. In September 1979, after extensive hearings, the Senate passed an amended drug regulatory reform act that contained some important compromise features and omitted some of the more controversial provisions of the original bill. However, the Drug Regulatory Reform Act was never reported out of committee in the House and thus the bill died when the 96th Congress expired.

With the inauguration of the Reagan administration in January 1982, primary attention has shifted from legislative to administrative reform of the drug regulatory process. The new administration announced its intention to examine all the major regulations that evolved from the broad statutory authority granted under the Food, Drug and Cosmetic Act and its amendments. In fact, many of the main features the Drug Regulatory Reform Act of 1978 would have codified FDA procedures already adopted through administrative rules or internal policy decisions. With a few exceptions (primarily involving postmarketing controls), administrative rule making could have been used to accomplish all of the major reforms embodied in the Drug Reform Act. Administrative rule-making changes of course do not necessarily have the same permanence as legislative changes. The new administration has chosen the former approach for its initial strategy in pursuit of a speedier and more efficient regulatory process.

In the remainder of this section we consider some of the major proposed policy changes of the drug regulatory process that have been discussed in various recent academic and government studies and task forces. These involve both administrative and legislative reform proposals.

More Flexible Controls over Early Clinical Trials

Regulatory delays in the early stage of clinical research process can have an especially significant effect on resource costs and time because of the uncertain recursive nature of the research process. Generally, about ten substances are tested clinically for every one that is taken through full development to an NDA with the FDA. However, the information garnered
from testing the unsuccessful compounds on a small number of individuals in phase I and II provides a cumulative feedback effect that is incorporated into successful drug therapies. Delays in the early stages of clinical process therefore have a compound effect on outcomes and tie up the most creative part of a firm's research organization.

Clinical trials are currently approved and supervised by institutional review boards at the medical centers where they are performed in addition to the controls exercised by the FDA in the IND process. The safety record in these early trials is very good. This is because of the intensive monitoring and highly controlled nature of early clinical trials. Cardon, Donnell, and Trumble (1976) of the National Institutes of Health have reviewed the injury data to research subjects and concluded in this regard that "the data suggest that risks of participation in nontherapeutic research may be no greater than those of everyday life and in therapeutic research, no greater than those of treatment in any other setting."

Decentralizing primary responsibility for early clinical trials into the hands of institutional review boards is a recommendation of several recent studies of the drug process including the GAO and the Staff Report of House Subcommittee on Science Research and Technology. The Drug Reform Act (which passed the Senate but not the House in the last Congress) would have had the FDA issue general regulations and then certify certain delegated health institutions (such as research hospitals) to approve and supervise phase one and two clinical investigations. The FDA would still retain oversight authority, however, to revoke any drug investigations approved by these delegated institutions. Current regulations governing initial clinical trials are part of the general administrative review of the drug regulatory process being undertaken by the new administration.

More Reasonable Premarketing Standards Combined with Increased Postmarketing Surveillance

Drug regulation in the current system has an all or nothing character. Before approval, candidate drugs are restricted to small patient populations under highly controlled experimental conditions. After approval, usage often increases with minimal regulatory surveillance. Under such circumstances, it is not surprising that regulatory officials tend to err on the side of conservatism in new drug approvals. At the same time, despite very great preapproval conservatism, many of the adverse side effects of drugs, those that occur with frequencies of less than 1 in 1,000 or are longer term in nature, can realistically be discovered only after a drug has been consumed by large patient populations.

The FDA premarketing approval conservatism has manifested itself by an evolving expansion over time in its inter-

pretation of what constitutes "adequate and well controlled" investigations of a drug's effectiveness. This frequently puts investigators at the FDA in the position of delaying a drug's entry into the market until the pivotal scientific studies are performed, even where there is little doubt about a drug's safety or effectiveness and where the new drug offers some very significant advances over existing therapies. Furthermore, low incidence risks (less than one per thousand) cannot be generally detected in these pivotal clinical studies. The best way to detect these is through more extensive and effective postmarketing surveillance.

An alternative approach to the current "all or nothing" system of drug approvals would be to allow new drugs on the market sooner based on significant evidence of safety and efficacy while expanding postmarketing surveillance on these drugs after they enter the marketplace. This is an approach favored by a large number of academic and medical experts as a principal means of getting new drugs to patients sooner consistent with present safety objectives. There is less than complete consensus, however, on how to change existing procedures to accomplish this general objective. Some specific policy changes in this regard are discussed further below.

Greater Acceptance of Foreign Clinical Data on Safety and Efficiency

The most serious drug lag cases generally occur for important new drug therapies discovered or developed in foreign countries. One of the basic reasons for this drug lag is the limited acceptability of foreign data trials as proof of safety and effectiveness for U.S. approval. Prior to 1975, the FDA did not accept foreign data at all as positive evidence in support of an NDA's approval. Since that time, the FDA has begun accepting foreign data. Nevertheless, since 1975, no drugs have been approved by the FDA on the basis of foreign data alone, irrespective of the amount of evidence in support of a drug's safety and efficacy from foreign experiences. The usual requirement is that at least two U.S. studies be conducted to supplement and verify foreign evidence.

A general recommendation, endorsed by a wide number of academic and government studies, is to have the FDA place greater reliance on foreign data as a way of speeding the availability of new drug therapies to U.S. patients. This appears to be an important step for improved regulatory performance. Drug discoveries from foreign laboratories now account for approximately 40 percent of U.S. introductions and U.S. firms are now conducting an increasing percentage of their research and development abroad (Wardell, 1978). The GAO further found that in technically advanced countries, drug sponsors design clinical trials to meet the most stringent standards.
The documented case history on sodium valproate presented in hearings of the House Subcommittee on Science Research and Technology (1980) p. 66 is instructive on this issue:

There were over 200 favorable reports in the medical literature on the effectiveness of sodium valproate in the treatment of epilepsy. Thirty of these were clinical scientific studies involving a total of more than 1,300 patients. It is extremely unusual for even a U.S. drug to have undergone such wide-spread investigation before marketing. FDA's Neurological Drug Advisory Committee reviewed these studies, and the committee's chairman reviewed them. Both reviews found that at least two studies were adequate and well controlled and clearly demonstrated valproic acid's effectiveness and safety in controlling absence seizures in epilepsy and unanimously recommended that the FDA immediately approve the drug.

FDA staff questioned aspects of the studies and required that at least one U.S. study be conducted. When completed this study showed nothing significantly different from the foreign well controlled studies. The result was several more months delay in the approval of the drug in the United States. Sodium valproate is one of a few, if not the only drug which the FDA has approval on the basis of just one U.S. study accompanied by foreign studies.

The subcommittee concluded that a mechanism was needed within the FDA to evaluate foreign clinical data to determine on a drug-by-drug basis whether it meets the intent of U.S. criteria and can be used in lieu of domestic tests.

Conditional Release of New Drugs

A concept that has been frequently advocated in the literature is a conditional type of approval process for new drugs. Under this concept, new drugs could be marketed when significant evidence of safety and efficacy become available, subject to continued testing and monitoring and FDA authority to stop product sales quickly if warranted. Some of the variants of this proposal would also have initial marketing restricted to particular institutions or particular medical specialties.

There have been precedents for this type of regulatory approval. The FDA has granted some important drugs (for example, L-DOPA) early release for marketing on the condition that manufacturers monitor and report effects on a given number of patients. In addition, the NIH with its network of clinical centers for patients trials in the cancer area has something like a conditional availability of promising new anticancer drugs prior to formal approval by the FDA for marketing. This involves liberal use of the IND procedures to undertake treatment of patients in terminal situations. This is not, however, typical in other therapeutic areas.

The Drug Reform Act of 1978 contained a provision allowing the conditional release of "breakthrough" drugs for use in life-threatening, severely disabling, or severely debilitating situations. This provision would have relaxed the standard of evidence from "substantial" to "significant" to allow patients access to such breakthrough drugs while final testing on them was being performed. The statute was designed, however, to restrict the discriminatory use of this provision to only a small portion of new drug introductions.

The breakthrough drug approach for conditional approval was criticized in hearings for its narrowness of application and also because it relied heavily on FDA judgment to determine breakthrough status. The FDA, for example, initially classified valproic acid as a moderate therapeutic advance while the NIH Anti-Epileptic Drug Program was actively campaigning for its rapid approval as a significant advance over established therapies. It was also argued that scientific advances in the drug areas, as in other fields, are more often incremental in character and frequently accumulate only gradually over time to major gains in social welfare. This has been the case historically for example, in antihypertensive therapy and combination chemotherapy for cancer. Furthermore, the "breakthrough" status of a new drug sometimes becomes apparent only after a drug is in general use and often for a purpose different from what was originally intended (e.g., the diuretic qualities of the sulfa drugs). These factors often make forecasting of the significance of medical advances difficult.

It should be noted that the FDA has already begun implementing a program of "fast-tracking" certain drugs in the allocation of its resources during both the IND and NDA phases. In particular, all INDs are now classified at a fairly early stage in the development process into three basic categories - drugs likely to be (a) an important advance, (b) a modest advance, or (c) little or no advance. The intention is to have priority reviewing in accordance with how a drug is placed under this classification scheme. While this approach may get some important therapies into public hands sooner, it is also subject to similar problems as discussed above for the Breakthrough Drug Provision. In particular, if the FDA's judgment on a new drug's therapeutic value is in error, it may delay rather than speed up the time required for a drug to clear regulatory hurdles (i.e., by putting an important drug on a slower track). This is an area where further research on FDA performance seems desirable.
Regulatory Incentives and Accountability

As noted earlier in the chapter, FDA incentives are strongly skewed toward officials avoiding the acceptance of a "bad" drug while being much less concerned about rejection or delay of a "good" drug. The agency's authority evolved as a response to a few widely publicized drug tragedies. Its mandate is drawn in very narrow terms — i.e., to insure the safety and efficacy of new drug products. All of the burden of proof rests on the sponsoring firm to demonstrate this to the satisfaction of the regulatory authorities. There is also the absence of any effectively functioning appeals process in the case of scientific or other kinds of agency firm conflict short of a full-fledged suit in the judicial system.

In view of these characteristics, it is not surprising that the drug approval process is a long and costly affair or that the GAO and others have found a number of management deficiencies in the agency that contribute to this outcome. While these regulatory problems are receiving increasing attention by Congress and the general public recently, there seems to be little popular support for removing the basic system of premarket controls in pharmaceuticals in favor of other forms of government protection. Nevertheless, there is clearly a desire being manifested in many quarters for a more balanced regulation structure that will get approvable drugs into the hands of the public without long delays and one that also puts minimal restraints on the innovative process. The congressional sessions on drug lag and in related areas seem to be having a growing impact in this regard.

Obviously, the incentive structure at the FDA is not an easy matter to change through either legislative or administrative action. The Drug Reform Act attempted a beginning by declaring the encouragement of innovation to be an important objective of public policy along with basic safety protection. Beyond stating this objective, however, Congress might consider some specific institutional mechanisms for insuring that a more balanced perspective will in fact be reflected in regulatory decisions.

One idea that has been advanced is to create a distinguished panel of scientists and medical experts from elsewhere in the health community to review annually the FDA's progress on new medicines as well as to consider potentially valuable new drug therapies already in use abroad. This type of body would be a logical extension of the FDA advisory committees. In contrast to the latter, however, which become involved only in the later stages of the approval process for specific medicines, the proposed panel would have a broader oversight function and would be designed to bring the perspective of scientists and medical prescribers of drugs into the regulatory decision process in a more complete and systematic way. The greater use of outside experts has been one of the more successful aspects of the British system of drug regulation.

A related measure is the development of an effective appeals process for scientific disputes between the FDA reviewers and sponsoring firms. Such an appeals mechanism exists in many other countries. For example, in the United Kingdom, applicants can appeal an adverse decision of the Licensing Committee to the Medicine Commission, a 14-member body composed of scientists, physicians, veterinarians, and representatives of the pharmaceutical industry (Dunlop, 1973). A similar kind of appeals mechanism might be considered in the United States as an additional check on regulatory decision making.

While the effectiveness of such policies in the United States is open to question, it would seem worth experimenting with such measures is order to try to generate a more balanced decision-making environment.

Patent Protection

Patent protection in the pharmaceutical industry has been another major area of interest for policy makers. As discussed above, the period of patent protection in drugs now averages about ten years in length and has been trending downward in recent years as a result of the long development periods and regulatory approval times for new drugs. Furthermore, there is the prospect of increased substitution and market penetration by generic products after patents have expired in the future periods as a result of the spread of state substitution laws and the growth of programs like MAC. Given these trends, a number of policymakers have advocated restoring part or all of the effective patent term lost during the IND and NDA regulatory periods.

Proposals embodying the basic concept of patent restoration in ethical drugs and other similarly affected industries have been introduced recently into Congress. For example, a bill (S255) introduced by Senator Mathias into the 97th Congress, and passed by the Senate, would add back to the patent life at the time of FDA approval, any time lost during the clinical testing and FDA review period, up to a maximum of seven years. The bill would also be applicable to other industries with premarket approval of new innovations (e.g., food additives, pesticides, and medical devices). A similar bill (HR1937) is being considered by the House of Representatives.

The selection of any specific number of years for patent protection necessarily gives rise to difficult tradeoffs (i.e., the possibility of too little incentive for innovation versus the encouragement of too much market power). These tradeoffs must be evaluated under considerable uncertainty. Neverthe-
less, there appears to be growing concern among policy makers about the potential adverse implications of passively allowing the continued downward drift in effective patent lives for drugs.

In our sensitivity analysis of the mean profitability of new drugs introduced in the period 1970-1976 (Grabowski and Vernon, 1982) we estimated an average product life of 12 to 19 years was needed by firms to cover R&D costs and provide a real rate of return on investment of 8 to 10 percent. Average effective patent life is therefore currently considerably less than average product life necessary for profitable operation. In the emerging environment of increased competition from generic producers after patent expiration, the length of patent protection is likely to become an increasingly important economic incentive factor influencing R&D investment decisions.

It is quite difficult to say, however, what type of innovation activity would be most stimulated by increased patent protection. On theoretical grounds, patent restoration can be expected to have a greater impact on the R&D incentives for products with longer expected product lives before being made obsolete by rival innovations. (If a drug had a very short expected life before technological obsolescence occurs, it would be essentially unaffected by patent restoration.) One class of drugs that should be positively affected by patent restoration are "breakthrough" type drugs with above-average riskiness but also longer expected product lives before technological obsolescence. Another class of drugs positively affected would be marginal type drugs with a small but stable market share niche. The exact size or quantitative impacts of patent restoration on specific kinds of innovative outputs is very uncertain, however.

Government Support of R&D

As we discussed earlier, the most relevant government-funded R&D activities for the pharmaceutical industry have been in the basic scientific research area. Several of the industry's most promising current R&D projects are the outgrowth of basic discoveries in such diverse scientific fields as immunology, enzyme chemistry, recombinant DNA, and prostaglandins. New pharmaceuticals has become one of the most important applications of the government's basic biomedical research activities.

Except in the cancer area, the government role in the direct development of new pharmaceuticals has been limited. As discussed above, Congress dramatically increased the budget of the National Cancer Institute for new drug development during the past decade. The annual budget in this respect, now over 200 million dollars annually, is larger than the total R&D budget of any of the major U.S. pharmaceutical firms.

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The large-scale government funding to find a cure for cancer has been controversial from the start. In the case of applied programs like new drug development, scientists warned that targeted budgeted outlays might outpace promising scientific opportunities. In addition, some of the major areas of government funding, such as the work on interferon, are areas where commercial firms are also very active. Thus, there is always the danger of significant duplication of private development efforts.

The record to date of the anticancer development program has been somewhat mixed. There have been some notable successes in treating cancer through government-aided drug therapies, particularly in Hodgkin's disease and childhood leukemia. At the same time there have not been the dramatic advances or "magic bullet" cures that the most ardent congressional supporters of the "War on Cancer" anticipated (perhaps naively) when budget outlays were rapidly increased in the early 1970s. It is still too early, of course, to judge the overall success of the government anticancer efforts but there remain many skeptics in the scientific community who emphasize the heavy opportunity costs, in terms of the diversion of scarce scientific human resources, associated with this program.

Another issue that has recently been receiving considerable attention is government support for the development of so-called "orphan drugs." As discussed above, this label is variously used to describe drugs of limited commercial value, either because they treat rare diseases or because they are for some reason nonpatentable. The orphan drug problem is in considerable part an outgrowth of the large development costs and times necessary to satisfy all the regulatory hurdles for a new drug entity. This in turn significantly limits the willingness of firms to undertake development projects with small expected revenues.

To the extent that the problem results from the inability to patent a compound that otherwise would have a sufficiently large market to be commercially viable, there are a number of possible property-rights-type solutions that could be used to deal with the problem. For example, some countries such as Japan grant an exclusivity period to the firm that undertakes the initial development of the data necessary to gain regulatory approval. The Drug Reform Act also had a provision that would have prohibited imitators from relying on the innovator's scientific data on safety and efficacy for a five-year period. This was included specifically to provide some incentives for the development of drugs without patent rights. Another approach might be to strengthen the applicability of use patents in situations where a firm discovers a new use of an existing chemical compound. Currently, use patent exist but their degree of protection and enforceability is subject to a number of problems.
A more difficult category of orphan drugs involves the case of disease areas whose incidence is too small to warrant commercial development and regulatory approval. If such diseases are to be the subject of systematic targeted R&D, some kind of subsidy to producers appears necessary. While orphan drugs are not public goods in the normal use of this term, government subsidies for them can be rationalized as expenditures for "merit" wants or goods in common with other expenditures in the social welfare area (e.g., food and medical treatment for low-income individuals, special provisions for the handicapped, etc.). However, orphan drug development must compete with other social welfare outlays for a limited (and contracting) budget for such expenditures.

As noted above, there are currently a few drug-development programs in the NIH directed at orphan-drug-type problems. There has been some success to date in facilitating development of antiepileptic drugs. The proposed Drug Reform Act would have expanded government R&D efforts in this regard by creating a Center for Drug Science with one of its main functions being targeted R&D on rare diseases. A recent government task force has recommended the creation of an independent government advisory board to coordinate and fund orphan drug research in both the government and the private sectors. Some congressmen in hearings have also mentioned requiring private firm R&D projects on rare diseases through regulation, although very obvious significant administrative and enforcement problems are associated with this.

The appropriate degree of government support for orphan drugs is obviously highly debatable. In the present period of contracting government size, the likelihood of any major new funding programs for orphan drugs (or for other types of merit wants) appears slight. At the same time, the orphan drug question remains an understandable area of intense concern for certain groups. Perhaps some novel solutions could be fashioned through the charitable giving process. Some of the relevant disease areas are the subject of sizeable charitable campaigns currently and some of these funds might be channelled toward the development of new therapies. This and related approaches appear to warrant further consideration in the current period of reduced government expenditures in the social welfare area.

### Notes

1. For a historical account of the regulation of drugs, see Wardell and Lasagna (1975), chap. 1, and Temin (1980).

2. See, for example, U.S. Senate (1960).
where

\[ C_{t-1}, C_{t-2}, \ldots, C_{t-m} \] are R&D costs and other investment expenditures:

\[ R_t \ldots R_{t+p} = \text{net income stream before patent expiration}; \]

\[ R_{t+p+1} \ldots R_{t+n} = \text{net income stream after patent expiration}. \]

\[ m = \text{gestation period} \]

\[ n = \text{product life} \]

\[ p = \text{patent life}. \]


21. In terms of the present value, equation (1) in note 19, \( p \) was set equal to 8 and all the \( R_s \) in the second summation term were reduced to reflect a 50 percent reduction in U.S. net revenues.


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