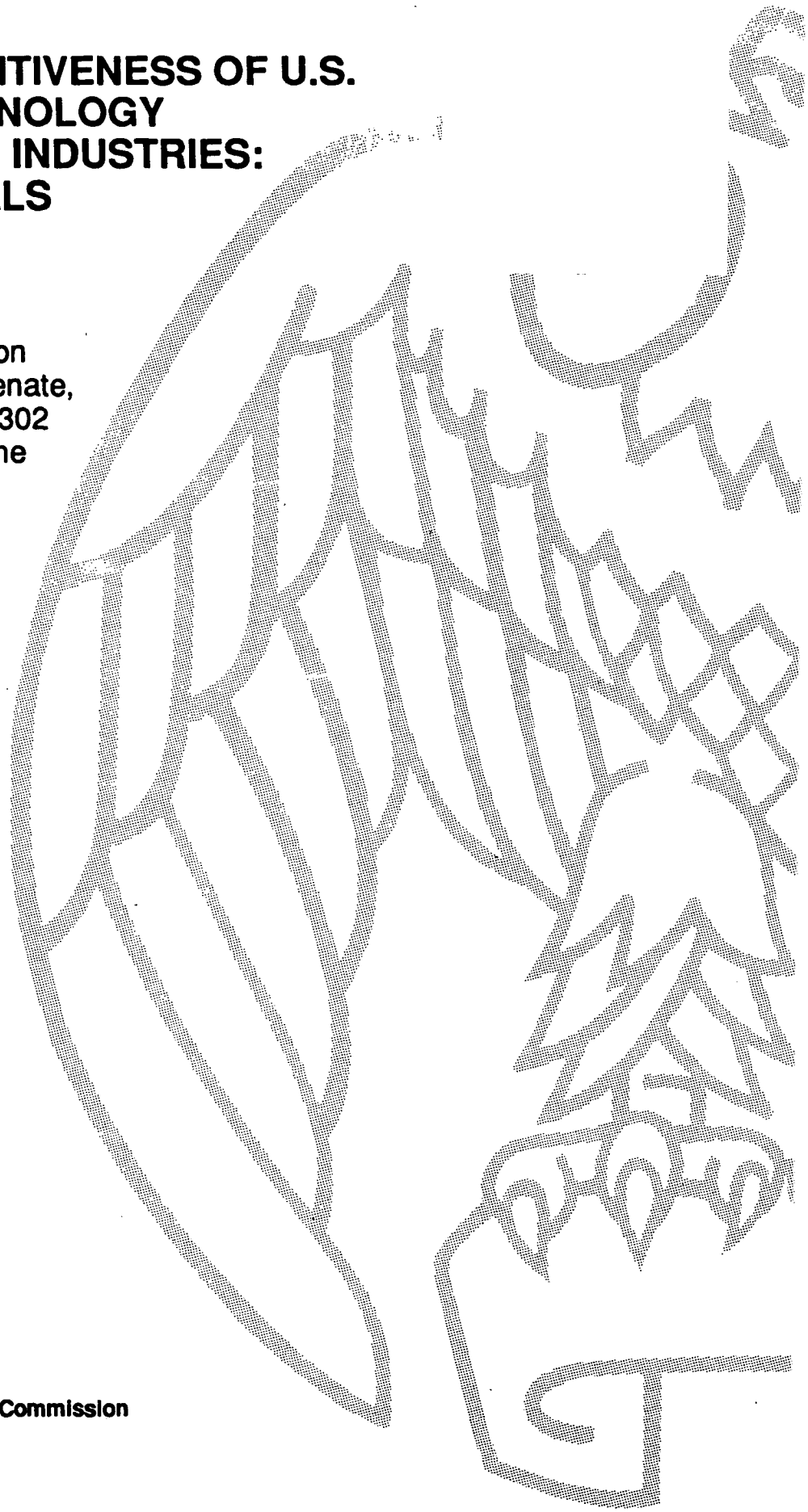
GLOBAL COMPETITIVENESS OF U.S. ADVANCED-TECHNOLOGY MANUFACTURING INDUSTRIES: PHARMACEUTICALS

Report to the Committee on Finance, United States Senate, on Investigation No. 332–302 Under Section 332(g) of the Tariff Act of 1930



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PREFACE

This report is one of three on the global competitiveness of U.S. advanced-technology manufacturing industries requested by the Senate Committee on Finance (Finance Committee). In a letter dated September 27, 1990, the Finance Committee directed the Commission, under section 332(g) of the Tariff Act of 1930 (19 U.S.C. 1332(g)), to conduct investigations on the global competitiveness of the U.S. telecommunications, semiconductor manufacturing and testing equipment, and pharmaceuticals industries, and to furnish reports on the results of the three investigations within one year. Following receipt of the letter, the Commission instituted the three requested investigations, Communications Technology and Equipment (inv. No. 332-301), Pharmaceuticals (inv No. 332-302), and Semiconductor Manufacturing and Testing Equipment (inv. No. 332-303). Notice of the Commission's institution of the investigation and scheduling of a public hearing for January 17-18, 1991, in connection with the three investigations was posted in the Commission's Office of the Secretary and published in the *Federal Register* of November 15, 1990 (55 F.R. 47812). A copy of the Finance Committee letter is reproduced in appendix A, and a copy of the Commission's notice of investigation and hearing is reproduced in appendix B.

The three investigations represent the second part of a two-step process. Initially, the Finance Committee, in a letter dated June 21, 1990, asked the Commission to identify for the purpose of monitoring, pursuant to sections 332(b), 332(d), and 332(g) of the Tariff Act of 1930, advanced-technology manufacturing industries in the United States, and from the list compiled to recommend three for in depth study. More specifically, the Committee requested that the Commission (1) within 3 months of receipt of the letter, identify for the purpose of monitoring, using criteria provided by the Committee and any additional criteria of the Commission's choosing, U.S. advanced-technology manufacturing industries, and recommend three of those industries as subjects for comprehensive Commission studies; and (2) within 12 months of the receipt of the Committee's approval (or modification) of the Commission's recommendations, submit its report on three industries the subject of comprehensive studies. In response the Commission, on July 20, 1990, instituted investigation No. 332-294, Identification of U.S. Advanced-Technology Manufacturing Industries for Monitoring and Possible Comprehensive Study. Notice of the Commission's institution of investigation No. 332-294 was posted in its Office of the Secretary and published in the *Federal Register* (55 F.R. 30530) of July 26, 1990. Although a public hearing was not held, all persons were afforded the opportunity to submit written views concerning the industries to be included on the list and that may be the subject of a comprehensive study. A copy of the Finance Committee's letter of June 22 is also set forth in appendix A.

The Commission's report on investigation No. 332-294 (USITC Publication 2319, September 1990) was transmitted to the Committee on September 21, 1990. In its report, the Commission identified ten advanced-technology industries and recommended the following three for comprehensive study: communications technology and equipment; pharmaceuticals; and semiconductor manufacturing and testing equipment. In its letter of September 27, 1990, the Committee acknowledged receipt of the Commission's report and approved the Commission's recommendation concerning the three industries for comprehensive study.

In its June 21 letter, the Committee requested that the Commission, in identifying the industries to be monitored, consider the following criteria as well as any other criteria it might choose—

(1) Industries producing a product that involves use or development of new or advanced technology, involves high value-added, involves research and development expenditures that, as a percentage of sales, are substantially above the national average, and is expected to experience above-average growth of demand in both domestic and international markets; and

(2) benefits in foreign markets from coordinated—though not necessarily sector specific—policies that include, but are not limited to, protection of the home market, tax policies, export promotion policies, antitrust exemptions, regulatory policies, patent and other intellectual property policies, assistance in developing technology and bringing it to market, technical or extension services, performance requirements that mandate either certain levels of

investment or exports or transfers or technology in order to gain access to that country's market, and other forms of government assistance.

The Committee requested that the report of the three industries to be selected include at least the following information—

Existing or proposed foreign government policies that assist or encourage these industries to remain or to become globally competitive, existing or proposed U.S. Government policies that assist or encourage these industries to remain or become globally competitive, and impediments in the U.S. economy that inhibit increased competitiveness of these U.S. industries.

A consolidated public hearing in connection with investigation Nos. 332-301-303 was held in the Commission Hearing Room on January 17, 1991. Persons appearing at the hearing were required to file requests to appear and prehearing briefs by January 3, 1991, and to file any posthearing briefs by January 31, 1991. In lieu of or in addition to appearances at the public hearing, interested persons were invited to submit written statements concerning the investigations. The Pharmaceutical Manufacturers Association of Washington, D.C., and the Industrial Biotechnology Association of Washington, D.C., were the only interested parties that presented testimony at the public hearing in connection with inv. No. 332-302 (see app. C).

The information and analysis provided in this report are for the purpose of this report only. Nothing in this report should be construed to indicate how the Commission would find in an investigation conducted under statutory authority covering the same or similar subject matter.

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EXECUTIVE SUMMARY

In 1990, the world market for ethical[1] pharmaceutical products was valued at approximately $147 billion. The top three companies in that year, in terms of ethical drug sales, were Merck (United States) with $6.4 billion, Glaxo Holdings (United Kingdom) with $5.4 billion, and Bristol-Myers Squibb (United States) with $4.9 billion. Of the top 80 pharmaceutical firms worldwide in 1989, U.S.-based companies, well established in the world market, accounted for approximately 40 percent of global sales of ethical pharmaceuticals in that year.

U.S. and Western European firms historically have had strong research programs, introducing almost 90 percent of the new products that have entered the world market during the past 50 years.[2] During 1940-88, U.S. firms accounted for about 62 percent of the new drugs introduced and Western European firms about 27 percent. Industry sources cite a number of reasons for U.S. producers' continued strength, including "an unencumbered U.S. economy" (in terms of price controls and cost-containment programs), and the fact that the United States has long been the center of R&D for the pharmaceutical industry.[3]

The competitiveness of a U.S. pharmaceutical firm hinges on its capability to develop innovative and profitable products. Between 1976 and 1990, the cost of developing a pharmaceutical product in the United States increased from $54 million to $231 million.[4] The high cost of developing a drug is attributed to several factors, including the uncertainty of success and the industry-wide trend towards development of products to treat chronic diseases. Only 1 out of every 4,000 to 10,000 compounds discovered can be marketed commercially; after which, a company has less than 10 years to partially recoup its R&D investment before its patents expire and generic manufacturers enter the market or a "me-too" drug is created by a competitor.

The pharmaceutical industry finances its R&D expenditures primarily through revenues accrued from the sales of its products. Domestic or foreign government policies that reduce such revenues can weaken the competitiveness of the pharmaceutical industry in a specific country and, therefore, strongly affect the global pharmaceutical industry. This report examines the effect of regulatory policies, intellectual property rights (IPR), pricing/cost containment, product liability, taxation, R&D incentives, export policies, and tariff barriers on the competitiveness of the U.S. industry.

In general, government policies affect all firms selling or producing in a particular country/region, regardless of parentage. It is important, however, to distinguish between policies that affect the competitiveness of the suppliers located in a given geographical area and those that affect the profitability of the industry globally. It should be noted that inasmuch as a country's industry may derive much of its profits from its home market, policies implemented in that country, such as slower regulatory approval procedures, could have more of an impact on domestic firms than on foreign firms operating there.[5] Considering these effects, this report attempts to assess the ability of the United States to maintain its preeminence in the pharmaceuticals sector, particularly its potential to retain its share of global sales and R&D productivity.

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[1] An "ethical" product is one that is available only through prescription. Ethical products can be either patented or nonpatented (i.e., generic).

[2] This study primarily examines the innovative pharmaceutical industries in the United States, Western Europe, and Japan. For the purposes of this study, Western Europe is defined primarily as the EC and Switzerland. The Japanese industry, although historically not as innovative as those in the United States and Western Europe, is expected to become a strong competitor within the next 10-20 years as a result of its efforts to develop new products and to expand globally.

[3] The U.S. industry is defined as all producers in the United States, including subsidiaries of foreign-based firms.

[4] This amount includes the costs associated with bringing the drug through discovery, clinical testing, development, and marketing approval. In the United States, approximately half of the cost of developing a drug is represented by direct, "out-of-pocket" costs, whereas the remainder represents the cost of capital, or the "opportunity cost." The values for 1976 and 1990 expressed in constant (1982) dollars are $86 million and $197 million, respectively.

[5] For example, according to a representative of PMA, U.S. pharmaceutical sales accounted for 55-57 percent of total pharmaceutical sales of U.S.-based innovative companies in 1989.

The highlights of this report are as follows:

- **The competitiveness of the U.S. pharmaceutical industry, as well as those in other countries, depends largely on the ability of firms within the industry to develop innovative products. Innovation, in turn, depends on the ability to finance R&D.**

For the purposes of this report, competitiveness in the pharmaceutical industry was determined by global market share and research and development productivity. Economic analysis revealed that high levels of R&D-correlated spending, relatively large R&D staffs, and a large number of salespersons have a positive effect on global market shares. Second, the analysis also indicated that R&D spending has a positive effect on R&D productivity, but the effect diminishes beyond some point. In addition, the size of the firm and the general level of R&D activity within a country each have a positive impact on productivity as well.

Competitive pharmaceutical firms commit many resources to developing and marketing their products around the world. More important, these firms tend to be relatively large, both in terms of their R&D staff and overall sales, which suggests efficiencies associated with large-scale operations.

- **Government policies, both domestic and foreign, have a more significant effect on the level of industry innovation than many of the other factors studied in this report in that they can reduce revenues, which fund the R&D necessary to remain competitive.**

The global industry largely finances its own R&D efforts by reinvesting a portion of its revenues. Therefore, policies that reduce such revenues, both on a domestic and an international basis, can weaken the competitiveness of individual industries. Such policies can also result in the migration of R&D facilities if companies judge that the environment is not conducive to innovation.

The period of market exclusivity for innovative products has become considerably shorter in the United States, Western Europe, and Japan during the past decade, given the increase in the time needed to bring a pharmaceutical product to market. Erosion of the product's period of market exclusivity can reduce a company's ability to recoup some of its R&D expenditures. In the United States, for example, the average development time[6] for pharmaceuticals is about 10.6 years. The speedier entry of generic products onto the U.S. market per the provisions of the Waxman-Hatch Act has also decreased product lifetimes. It is estimated that whereas in the United States the average new chemical entity (NCE) recovers its R&D investment in 19 years, the average length of the effective patent life of a pharmaceutical in the United States has declined to 10 years and 10 months from 15 years in the early 1960s.[7] Patent restoration programs enacted in the United States and Japan offset this to some extent by allowing an additional period of market exclusivity.

Price control and cost-containment programs can limit or reduce revenues to firms, thereby potentially decreasing R&D expenditures. Many industry sources have expressed concern that the U.S. industry will lose revenues due to the recent implementation of cost-containment provisions under Medicaid, citing the results of such programs in Western Europe and Japan. The actual portion of company sales affected at this time is relatively small. If, however, proposed modifications to the legislation are enacted and if third-party insurers adopt similar programs, revenues used to finance R&D will diminish and, in turn, the competitiveness of the U.S. industry could suffer.

Other U.S. Government policies that have affected the ability of U.S. industry to compete are the U.S. Drug Export Act, product liability standards, certain aspects of the U.S. tax code, and recent changes in the EC's procedure for granting duty suspensions for European exports of pharmaceuticals. The last of these may effectively limit the availability of duty suspensions for pharmaceutical products

[6] Development time includes laboratory and animal testing, clinical trials, and FDA approval of an NDA submitted for the product.

[7] An NCE, as defined by the FDA, is a drug for which the active ingredient has not been previously marketed [approved] in the United States for use in a drug product. The term has often been used in the literature and by industry, however, to refer to products that have been approved either in the United States or elsewhere. For instance, a global NCE, as referred to later in this report, is defined as an NCE that has been approved/marketed in at least 7 countries, including the major pharmaceutical markets (see footnote 4 in Chapter 5). It should be noted that the term "NCE" does not in itself designate marketing approval.

for numerous reasons. The U.S. Drug Export Act removed, at least partially, a disincentive to manufacture certain unapproved drugs domestically. Concerns exist, however, that the current structure of the Act limits the competitiveness of the industry in export markets. Other countries reportedly have not enacted similar legislation. The U.S. product liability system, according to industry sources, has resulted in a decline in the competitiveness of U.S. companies compared to foreign firms. Companies have also expressed concern about certain aspects of the U.S. tax code, including Section 861 and those actions pertaining to the research and experimentation (R&E) tax credit and the cost of capital.

- **The global industry has been undergoing increasing consolidation as companies attempt to: (1) extend geographic reach; (2) broaden product portfolios; and (3) perhaps most important, spread the risk and costs associated with R&D.**

This consolidation has ranged from mergers to strategic alliances. A number of Western European and Japanese firms are participating in strategic alliances with U.S.-based firms as a means of entering the U.S. market. In the case of Japan, continued downward pressure on prices is reportedly prompting many Japanese firms to establish operations in Western Europe and the United States. Most of Japan's recent building expansion and merger and acquisition activity has been in Western Europe, possibly in anticipation of the growth opportunities that will result from consolidation of this market after 1992. Participation in this market will allow the Japanese to learn to operate under the regulations and guidelines of EC drug regulatory authorities as well as establish the marketing forces necessary to increase their share of sales.

- **Biopharmaceuticals are expected to account for an increasing share of pharmaceuticals production in the United States, Western Europe, and Japan within the next decade.**

Biotechnology provides an alternative and promising route into the pharmaceutical market. Although biopharmaceuticals currently account for a relatively small share of the global pharmaceutical market, industry sources expect that this situation will change within the next decade. Many small new companies exploiting discoveries in biotechnology have begun to produce new pharmaceutical products.[8] This proliferation, however, has been concentrated mainly in the United States during the 1980s, as the result of the creation of a new technology; the ability of individual scientists to both discover and produce new products using this technology; and readily available U.S.-based venture capital looking for promising investment possibilities.[9] Government policies are likely to have a significant effect on the continued development of the industry, particularly in such areas as patent and environmental protection.

As the availability of venture capital declines in the United States, firms from other countries, particularly Japan, are entering through strategic alliances with U.S. producers. The Japanese biotechnology industry is reportedly in a position to become a major competitor in the world market. At present, the strength of Japan's biotechnology industry lies in its experience in process refinement. Japan's biotechnology industry is actively seeking to obtain new biopharmaceuticals from innovative world drug firms through strategic alliances such as joint ventures and cross-licensing. Once new biopharmaceuticals are obtained, the Japanese, with their experience in process refinement, could obtain a larger share of the global market. However, for Japan to become a major world competitor in the industry, more emphasis must be placed on basic research to originate more global NCEs.

[8] Office of Technology Assessment, *New Developments in Biotechnology 4: U.S. Investment in Biotechnology*, 1988.

[9] Unpublished USITC staff working paper on biotechnology, 1990.

CHAPTER 1
INTRODUCTION

The globalization of the pharmaceutical industry in recent years and ongoing concerns regarding the viability of the United States industrial base have led to an increasing focus on the activities of operations located in the United States and on the operations of U.S.-owned corporations in the international market. Although considered globally competitive by many, the U.S. pharmaceutical industry faces a number of pressures that cumulatively could have a significant adverse impact on its future competitiveness. These factors and their effects on the industry are the focus of this study.

Purpose and Approach of Report

This report, as requested by the Senate Committee on Finance, will identify, compare, and analyze the principal determinants of competitiveness in the U.S. pharmaceutical industry. The report will address such factors of competitive performance as U.S. and foreign government policies, research and development (R&D) productivity, and structural change within the industry to provide an overall assessment of the performance of the U.S. industry during the past 5 to 10 years. The report will also examine and compare these factors in Western Europe and Japan.[1]

The data required for this report have been gathered from primary and secondary sources and through extensive interviews with industry representatives, associations, and government officials in the United States, Western Europe, and Japan. Additional information was obtained from the public hearing held on January 17, 1991, at the Commission in Washington, D.C. Commission staff also met with representatives of the Pharmaceutical Manufacturers Association (PMA), which represents nearly all major pharmaceutical firms in the United States. Officials of the U.S. Food and Drug Administration (FDA) and the U.S. Department of Commerce, and representatives of the Industrial Biotechnology Association (IBA) also have been helpful in providing information.

Scope and Organization of Report

Scope of the Report

The ability of U.S. pharmaceutical and biopharmaceutical[2] firms to remain highly competitive with other global producers will depend not only on factors such as future R&D commitments by these firms, but also on the nature of national health-care programs and national and foreign government policies. Therefore, this report examines a number of government policy issues, ranging from price controls and cost-containment programs to levels of intellectual property right protection worldwide. Regulations that affect the marketing of new pharmaceutical products[3] and the development of biopharmaceuticals also are studied. Additionally, the linkage of industry performance to trends and regulations in related areas of the economy such as health care is addressed by the report.

Although this report emphasizes the U.S. pharmaceutical industry and its competitiveness, it also discusses and compares the pharmaceutical and biopharmaceutical industries in Western Europe and Japan. These geographic areas were chosen for inclusion since they are currently the most active in the global market, both in terms of sales and innovation.

In examining the competitiveness of the U.S. pharmaceutical industry, the report focuses primarily on innovative companies (i.e., companies that develop new chemical entities (NCEs)[4] through extensive R&D programs), including companies that produce biopharmaceuticals. Innovative companies usually market brand-name ethical[5] preparations, as well as other products.[6]

This report also considers the impact of competition from generic products on the pharmaceutical industry.[7] Upon expiration of a pharmaceutical product's U.S. patent, companies, including the brand-name producer, are free to develop

[1] For the purposes of this study, Western Europe is defined primarily as the EC and Switzerland. The Japanese industry, although historically not as innovative as those in the United States and Western Europe, is expected to become a strong competitor within the next 10-20 years as a result of its efforts to develop new products and to expand globally.

[2] Biopharmaceuticals are broadly defined as pharmaceutical products produced through the use of biotechnology.

[3] In this report, the terms "pharmaceutical preparations," "pharmaceutical products," and "drugs" are generally used interchangeably to refer to pharmaceuticals in dosage form. Any exceptions are explained in context in the text. The term "new chemical entity," or NCE, is used as indicated in footnote 4.

[4] An NCE, as defined by the FDA, is a drug for which the active ingredient has not been previously marketed [approved] in the United States for use in a drug product. The term has often been used in the literature and by industry, however, to refer to products that have been approved either in the United States or elsewhere. For instance, a global NCE, as referred to later in this report, is defined as an NCE that has been approved/marketed in at least 7 countries, including the major pharmaceutical markets (see footnote 4 in Chapter 5). It should be noted that the term "NCE" does not in itself designate approval has been granted.

[5] An "ethical" product is one that is available only through prescription. Ethical products can be either patented or nonpatented (i.e., generic).

[6] Brand-name products also have generic, or common, names, even if a patent is still in effect. For example, two brand-name antiulcer products are Tagamet and Zantac. The generic names for these products are cimetidine hydrochloride and ranitidine hydrochloride, respectively.

[7] "Generic" is defined as being nonproprietary and denoting a drug name that is not protected by a trademark and that is usually descriptive of the drug's chemical structure. A glossary that includes these and other terms is provided in app. G.

nonbranded (generic) versions of the formerly patented product and, pending FDA approval, market them in the United States. By 1995, the U.S. patents on approximately 200 products will expire, potentially expanding the generic market by approximately $6 billion during 1990-95.[8] Nonprescription, over-the-counter (OTC) products will not be discussed in detail in this report.

The development of the U.S. biotechnology industry is discussed with particular emphasis on the biopharmaceutical producers, who are becoming an increasingly important competitive factor and are affected similarly by many of the issues that confront the U.S. pharmaceutical industry. Biopharmaceutical manufacturers use living organisms to produce pharmaceutical products through a research-intensive, multidisciplinary range of technologies.

Products

Pharmaceuticals (medicinal drugs) are used in the prevention, diagnosis, alleviation, treatment, or cure of disease in humans or animals.[9] Pharmaceutical products can be grouped in several classes, including ethical preparations, generic products, and proprietary products.[10] Ethical products accounted for about 80 percent of sales of pharmaceuticals worldwide during 1988-89.

Pharmaceuticals are defined under the Standard Industrial Classification (SIC) code 283 "Drugs." This classification includes SIC 2833 "Medicinal Chemicals and Botanical Products" and SIC 2834 "Pharmaceutical Preparations," which traditionally have constituted the majority of shipments under SIC 283.

The production of drugs takes place in two major manufacturing stages. The first stage is the production of pure pharmacologically active chemicals in bulk form (SIC 2833), either by conventional methods or through use of bioengineering procedures. These chemicals are often called "active ingredients." The second stage is the formulation of these concentrated pharmacologically active components into dosage form, or pharmaceutical preparations (SIC 2834).[11] Pharmaceutical preparations are typically the pure chemicals plus inert substances such as diluents or extenders. Pharmaceutical preparations are available in several forms, including pills, capsules, tablets, creams, and lotions. Some major therapeutic categories in which these products are classified are:

Antihistamines

Anti-infective agents

Antineoplastic agents
(i.e., anticancer drugs)

Cardiovascular drugs

Central nervous system agents

Gastrointestinal drugs

Hormones and synthetic substitutes

Vitamins

In 1989, cardiovascular and central nervous system (CNS) products were the two leading categories of ethical drugs in terms of U.S. sales; anti-infective and cardiovascular products were the two leading categories overseas. Differences in the leading categories of products in the United States and overseas primarily reflect differences in marketing/consumer information, socioeconomic factors, and demographic factors.

The focus of R&D performed by the industry has shifted over the last 10 years. In 1977, much of the R&D underway was in the area of anti-infective drugs. More recently, however, as companies try to address the treatment of diseases such as heart disease, cancer, arthritis, and chronic geriatric diseases, the emphasis has shifted to R&D in the areas of cardiovascular products, antineoplastic products, and CNS products.

Measures of competitiveness

Market share, profits, and productivity can be used to measure the relative performance of a country's industry or individual firms in the international market. Because the pharmaceutical industry relies heavily on R&D, product innovation, assessments of the industry often focus on R&D productivity as well as output measures such as the number of globally successful NCEs.

The global pharmaceutical industry transcends geographical barriers and distinctions of geographical boundaries have been further blurred by recent mergers in the industry that have created entities such as the "transnational" SmithKline Beecham.[12] Aggregate measures of the industry's performance can be constructed on the basis of either geographic location or ownership. Many data sources evaluate the industry in terms of geographic location (i.e., by including the activities of foreign subsidiaries producing in a given location). Evaluation in terms of ownership on the other hand, is reasonable in that profits may be repatriated to the home country.[13] Most of the

[8] U.S. Department of Commerce, *U.S. Industrial Outlook 1990*, p. 50-3.

[9] *Stedman's Medical Dictionary*, 23rd edition, 1976, p. 423.

[10] Proprietary products are nonprescription, over-the-counter (OTC) products.

[11] Pharmaceutical preparations are also called pharmaceutical products in this report.

[12] Although SmithKline Beecham is considered by many to be a "transnational" company, it should be noted that the firm's global headquarters are in London. SmithKline USA is based in Philadelphia, Pennsylvania.

[13] See Henry G. Grabowski, "Innovation and International Competitiveness in Pharmaceuticals," *Proceedings of the 2nd International Joseph Schumpeter Society Meetings* (Ann Arbor, MI: University of Michigan Press, 1990), pp. 167-168.

industry-level information included in this report has been collected on the basis of geographic location, unless otherwise indicated.

In general, government policies affect all firms selling or producing in a particular country/region, regardless of parentage. It is important, however, to distinguish between policies that affect the competitiveness of the suppliers in any given geographical area and those that affect the profitability of the global industry. It should be noted that inasmuch as a given country's industry may derive much of its profits from its home market, policies implemented in that country, such as slower regulatory approval procedures, could have more of an impact on domestic firms than on foreign firms operating there.[14] Considering these effects, this report attempts to assess the ability of the United States to maintain its preeminence in the pharmaceuticals sector, particularly its potential to retain its share of global sales and R&D productivity.

Global producers

The global pharmaceutical industry is a multinational industry[15] that is highly regulated, capital intensive, and driven by large R&D expenditures.[16] The industry is primarily privately owned and is technologically sophisticated, especially in developed countries.

In 1990, the world market for ethical pharmaceutical products was valued at about $147 billion.[17] The top three companies in that year, in terms of ethical drug sales, were Merck (United States) with $6.4 billion, Glaxo Holdings (United Kingdom) with $5.4 billion, and Bristol-Myers Squibb (United States) with $4.9 billion.[18] The top 80 pharmaceutical firms worldwide accounted for about 90 percent of global sales in 1989. Of these 80 firms, U.S.-based companies accounted for approximately 40 percent of global sales of ethical pharmaceuticals (see Fig. 1-1). The European-based firms in this grouping also accounted for about 40 percent of world sales, the majority made by firms in the United Kingdom, Germany, and Switzerland.

Of the top 20 firms in the global industry in 1990, 9 were based in the United States .[19] One reason for the continuing commitment to high R&D expenditures and the productive relationship between industry and

[14] For example, according to a representative of PMA, U.S. pharmaceutical sales accounted for 55-57 percent of total pharmaceutical sales of U.S.-based innovative companies in 1989.

[15] The multinational nature of the industry is demonstrated by the number of companies that have developed facilities in foreign markets in an effort to overcome cultural differences and any barriers related to transportation, regulations, and/or import restrictions.

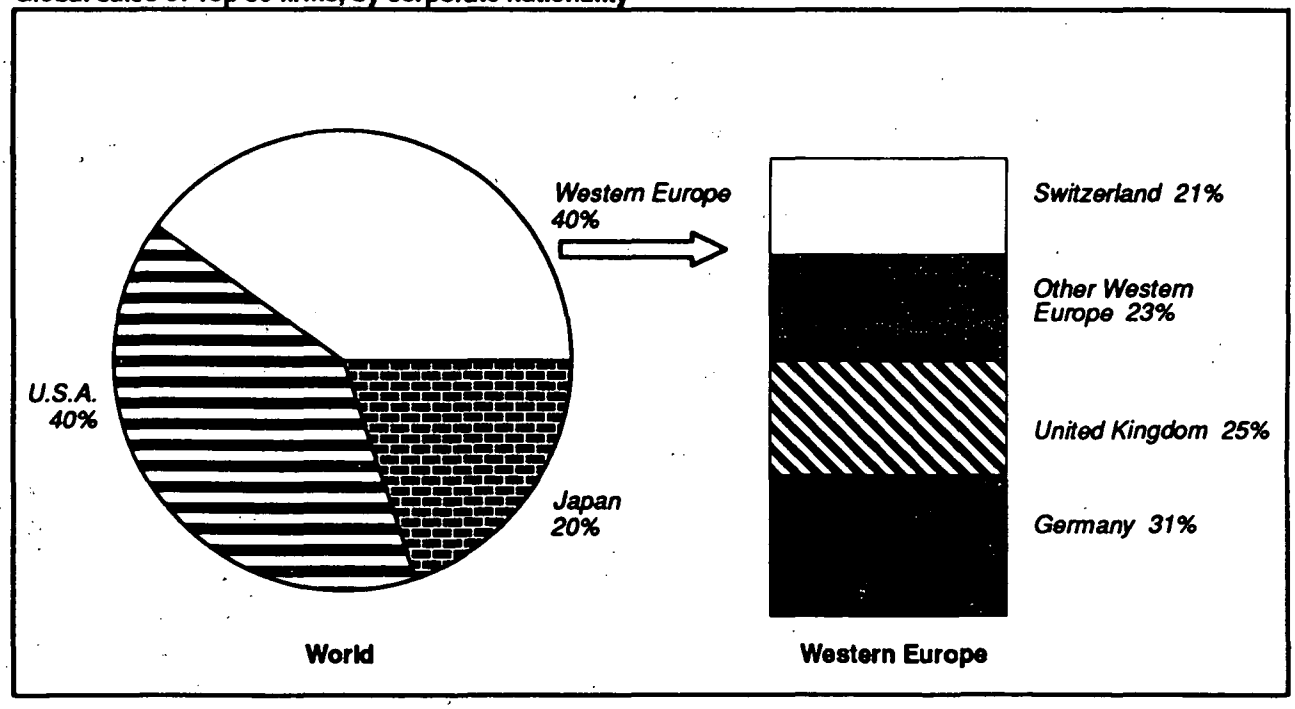
[16] The top 40 firms in the global industry spent more than $10 billion on R&D in 1988, reinvesting 15-17 percent of their revenues derived from pharmaceutical sales.

[17] Derived from the CountyNatWest Securities Ltd. rankings.

[18] The largest Japanese firm, Takeda Chemical Industries Ltd., ranked 20th in ethical drug sales.

[19] CountyNatWest Securities Co. ranking.

Figure 1-1
Global sales of Top 80 firms, by corporate nationality



Source: SCRIP League Tables, 1989.

The U.S. and Western European firms traditionally have U.S. industry's strong position in the world market is its level of innovation, which, in turn, is based on a number of factors including the domestic industry's university scientists in basic research. The U.S. pharmaceutical industry routinely allocates approximately 17 percent of its revenues from sales of ethical pharmaceuticals to R&D, or approximately three times the level allocated by the remainder of the chemical and related-industries sector.[20] had strong research programs, indicated by their having introduced about 90 percent of the new products that entered the world market in the past 50 years. During 1940-88, U.S. firms accounted for about 62 percent of the new drugs introduced and Western European firms about 27 percent.[21]

The U.S. pharmaceutical industry has invested extensively throughout the world. Investment by the industry in developed countries accounted for about 75 percent of total investment in 1986. Within this subgrouping, as shown in figure 1-2, the majority of investment was in the EC (63 percent) and Japan (16 percent).[22] A recent study indicates that of the 20 or so U.S. firms operating in Japan, 13 had wholly owned subsidiaries and 8 had majority owned subsidiaries.[23]

In 1986, it was estimated that 26 foreign pharmaceutical firms, primarily European-owned, had R&D and production facilities in the United States. Total assets of U.S. affiliates of companies based in Europe, as estimated for 1986, were valued at approximately $9.7 billion, of which $8.9 billion, or 92 percent, were accounted for by Western European-based firms.[24] Of the Western European firms, the largest share of the assets was attributed to firms with parents located in Switzerland (56 percent). In contrast, U.S. affiliates of Japanese firms represented approximately 3 percent of the total.[25] Japan, a relatively new global competitor, is approaching foreign markets on numerous fronts.

The continued increase in the cost of R&D is considered to be one of the driving forces behind the industry's current trend toward consolidation. Consolidation (i.e., mergers/acquisitions, joint ventures, or strategic alliances) allows firms to share the risks and the costs involved with bringing new products to market. It also allows firms, particularly those wishing to enter the U.S. market, to expand their geographical reach and balance product portfolios.

[20] "Changing Lineup Ahead for Global Drug Industry," *Chemical & Engineering News*, Dec. 17, 1990, p. 10. Of the 16 U.S. firms, 11 are included within the top 20 firms in the industry.

[21] Pharmaceutical Manufacturers Association (PMA) *PMA Statistical Fact Book - Facts at a Glance*, December 1989, p. 19.

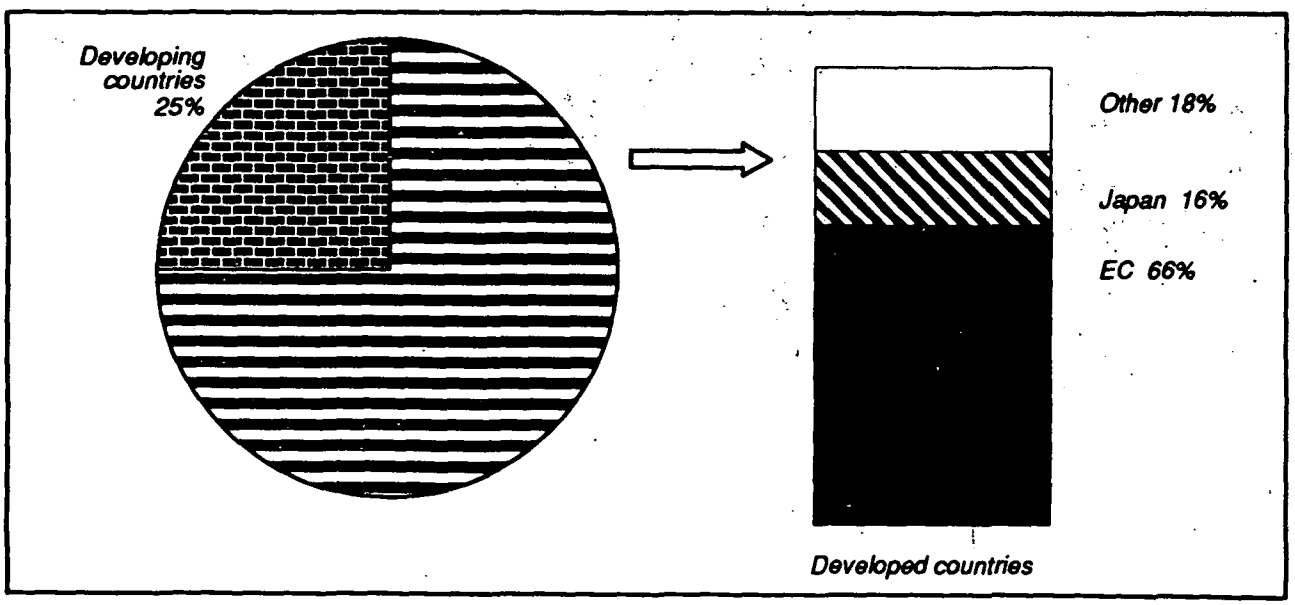
[22] This figure is defined as the "Total Assets of Affiliates, Industry of U.S. Parent by Country," U.S. Department of Commerce, *U.S. Direct Investment Abroad: Operations of U.S. Parent Companies and Their Foreign Affiliates* (Revised 1986 Estimates), July 1989.

[23] "Competition Intensifies as Japanese Lift R&D Effort," *European Chemical News*, Apr. 1, 1991, p. 18.

[24] Based on the countries indicated in U.S. Department of Commerce, *Foreign Direct Investment in the United States*.

[25] This figure is defined as the "Total Assets of Affiliates, by Industry of Affiliate by Country of Ultimate Beneficial Owner" U.S. Department of Commerce, *Foreign Direct Investment in the United States: Operations of U.S. Affiliates of Foreign Companies* (Preliminary 1986 Estimates), June 1988.

Figure 1-2
Total assets of U.S. pharmaceutical affiliates, by country/region (percent)



Source: *U.S. Direct Investment Aboard.*

Continued innovation is one way for a company to overcome (1) the loss of market share for its innovative product that results from the entry of generic products after the expiration of the company's patent or (2) the launch of a strong competitive product. As such, a company facing gaps or dry spells in its drug development pipeline is likely to enter into an alliance with another firm, thereby gaining access to new products. Figure 1-3 illustrates the dynamic structure of the industry from 1970 to 1989 that resulted from the introduction of new products, expiration of the patent(s) on others, and consolidation.

Industry consolidation takes many forms, ranging from mergers to strategic alliances. Strategic alliances including licensing agreements can be quite varied in structure, and equity investments. In the past five years there have been a number of mergers in the industry and many strategic alliances, particularly in the biopharmaceutical sector.

Organization

Chapter 2 provides a brief review of the economic literature and identifies certain determinants and measures of competitiveness in the world pharmaceutical industry. Chapter 3 identifies and discusses government policies that affect the ability of the firms in the industry to remain competitive, including regulatory policies, price controls, intellectual property protection, cost-containment programs, taxation, and product liability. It presents industry views on the effects of these policies and suggestions for change. Chapter 4 discusses the structure and performance of the pharmaceutical industry on a global and country basis. It also discusses the biopharmaceutical industry, and trends in both this sector and the pharmaceutical industry as a whole.

Chapter 5 offers an economic analysis of factors that affect the competitiveness of the U.S. pharmaceutical industry, including:

Factors influencing the demand for pharmaceuticals in the leading country markets;[26]

Factors determining the development of NCEs and the introduction of new drugs in these markets; and

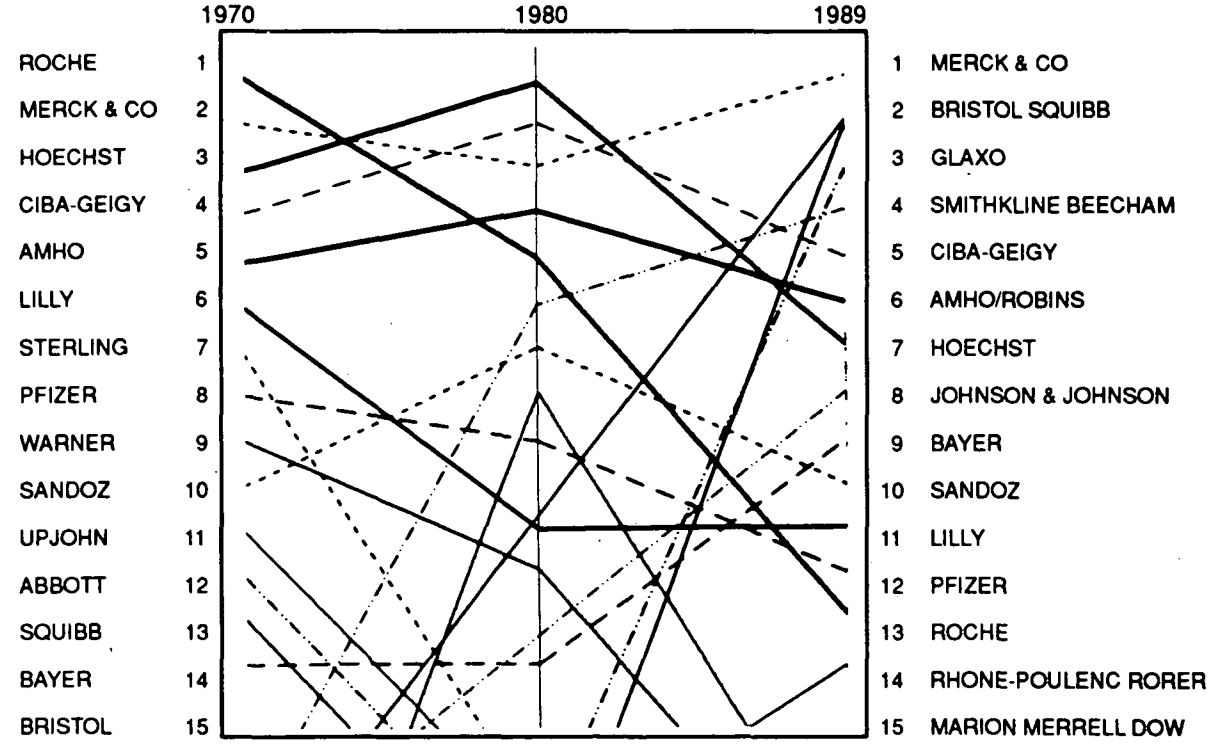
The determinants of market share and R&D productivity for the leading international producers of ethical drugs.

The analysis extends existing economic research covering this industry by using data during 1983-89.[27] Chapter 6 provides the report's principal findings.

[26] Countries included are the United States, the United Kingdom, Germany, France, Italy, and Japan.

[27] Given the focus of this study on international competition, questions regarding the social and private costs and benefits of certain types of government policies and the degree of competition within the U.S. industry are not examined explicitly.

Figure 1-3
Changes in world market rank of leading pharmaceutical companies, 1970-1989



Source: Reproduced with permission from Eli Lilly & Co.

CHAPTER 2
INTERNATIONAL COMPETITIVENESS IN THE PHARMACEUTICAL INDUSTRY

Introduction

Assessing the competitiveness of the pharmaceutical industry requires (1) developing definitions of competitiveness and measures by which comparisons across countries can be made, and (2) identifying and evaluating the determinants of competitiveness.[1] The economics literature covering this industry and the assessments and opinions of industry officials provide the basis on which such an assessment can be developed.

The first section of this chapter provides a brief review of economic analysis pertaining to the competitiveness of the U.S. pharmaceutical industry.[2] The second section provides a definition of international competitiveness and identifies potential measures of competitiveness for the pharmaceutical industry. This section also discusses several potential determinants of competitiveness and delineates factors that may affect supply and demand conditions in the market.[3]

Review of Literature

Empirical economic analysis of the industry has concentrated primarily on factors influencing the supply of ethical pharmaceutical products. Much of the analysis is related to or in response to the debate regarding the economic effects of regulatory measures and other government policies on the industry. For the most part, this research has focused on the activities of U.S. firms in the U.S. market.[4]

To date, however, empirical economic analysis of the U.S. industry's competitive position in the international market is relatively limited. A major constraint to such analysis is the lack of adequate data with which to test hypotheses concerning the differential effects of U.S. and foreign government policies on the U.S. industry and its foreign competitors. Nonetheless, the rapid globalization of the industry has prompted researchers to begin to examine international trends and identify factors that specifically affect the performance of the U.S. industry in the global market. The following sections briefly review economic research covering measures and determinants of competitiveness and the international competitiveness of the industry.

Measures and Determinants of Competitiveness

Over much of the past three decades, economic researchers have focused on conditions of competition within the U.S. market rather than the competitiveness of the U.S. pharmaceutical industry in the international market. Addressed has been the question of whether the larger pharmaceutical companies have used their market power to create effective barriers to entry (through product and price differentiation) to maintain control over segments of the market at the expense of the consumer. Conventional measures such as price, profit rates, R&D, and marketing expenditures have suggested the possibility of barriers to entry and some degree of market power for firms. Also addressed has been the question of whether the resources devoted to R&D and advertising actually add to consumer welfare, given the duplicative nature of many "new" drugs.

Other measures such as the rate of product innovation and shifts in market share have been examined to determine whether pharmaceutical companies respond to competition. Some researchers have cited these latter measures as evidence that the industry is highly competitive.[5] Moreover, the development of innovative, ethical pharmaceutical compounds generally requires more extensive R&D expenditures than either over-the-counter (OTC) products or "me-too" pharmaceutical compounds. Thus, researchers have contended that short-run monopoly profits on specific pharmaceutical products allow firms to undertake long-term R&D that entails a high degree of risk. They have suggested that policies designed to reduce profits could undermine R&D

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[1] It is important to keep in mind that this study and the literature reviewed in this chapter focus on relatively large, R&D-intensive, multinational firms that operate in the global market for ethical pharmaceuticals. Subsequent references to the pharmaceutical industry in this chapter concern this sector of the industry.

[2] Appendix D provides a brief review of recent studies that examine the issue of U.S. international competitiveness in general.

[3] The factors are those identified by the economic literature covering this industry and by industry officials. Relationships described in this section are examined empirically in chapter 5.

[4] Over the past three decades, the structure and conduct of the industry and the efficacy and cost of its products have been the subject of numerous Congressional hearings and subsequent legislation. Much of the economic analysis regarding the competitiveness of the industry relates indirectly, if not directly, to issues which were raised during these debates. Chapter 3 provides a comprehensive review of relevant legislation and government regulations related to the pharmaceutical industry.

[5] Cocks, for example, has asserted that although product competition might result in resource misallocation in the short run (through monopoly pricing), in the long run it would lead to competitive pricing behavior. Douglas L. Cocks, "Product Innovation And The Dynamic Elements Of Competition In The Ethical Pharmaceutical Industry," *Drug Development and Marketing*, Richard Helms, ed., (Washington, D.C.: American Enterprise Institute, 1975), pp. 225-254. See also, Henry G. Grabowski and John M. Vernon, "New Studies on Market Definition, Concentration, Theory of Supply, Entry, and Promotion," *Issues in Pharmaceutical Economics*, Robert I. Chien, ed., (Lexington, MA: Lexington Books, 1979), pp. 29-51.

efforts and thereby limit opportunities to develop NCEs with potentially significant social benefits.

Empirical evidence regarding the relationship between price and nonprice competition has been mixed. The results of some research indicate that in the long run non-price (i.e., product) competition leads to price competition.[6] Other, more recent research suggests that brand name recognition is an important factor; in some cases firms can maintain market share without resorting to substantial price competition.[7]

Research also has focused on factors affecting the industry's performance and the performance of individual firms within the industry. Industry trends during 1960-80 show a simultaneous decline in the number of NCEs developed by U.S. pharmaceutical companies and an increase in R&D expenditures.[8] Various estimates show R&D costs increasing significantly during this period and into the 1980s.[9] The most recent estimate of out-of- pocket R&D costs per approved NCE is $114 million (1987 dollars).[10] Including the opportunity costs of the funds allocated to R&D raises this estimate to $231 million (1987 dollars) (see Fig. 2-1).[11,12]

A number of researchers and industry officials have attributed this apparent decline in R&D productivity to the increased regulatory requirements generated by the 1962 amendments to the 1938 Food, Drug, and Cosmetic Act (FDCA).[13] Other factors may also have contributed to the increase in the cost of R&D. The shift in R&D focus to the treatment of chronic diseases is one factor cited by researchers.[14] Another factor cited, but not extensively analyzed, is increasing liability costs faced by the industry.[15] More broadly, researchers have addressed the following issues:

1. Factors driving R&D expenditures (determinants of R&D) and
2. The way in which changes in R&D costs and profitability have generated changes in the structure of the industry.

Determinants of R&D Expenditures

R&D costs reflect factor prices, regulatory requirements (primarily clinical trials to establish safety and efficacy), concern regarding corporate liability, the state of existing knowledge (i.e., how much time has to be devoted to the R&D process), and changes in technology that may result in more costly testing procedures.

The importance of R&D has prompted a number of analysts to examine the degree to which regulatory and technological changes affect R&D costs and the potential effect cost increases have on a firm's R&D decision-making process. Some studies have compared the performance of industries in other countries to evaluate the effects of regulatory changes on the U.S. industry. However, instead of evaluating industry performance across the major producer countries, the research generally has used industry performance in another country as a control measure.

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[6] See, for example, Thi D. Dao,"Drug Innovation and Price Competition," *Pharmaceutical Economics,* (Stockholm: Swedish Institute for Health Economics), 1984, pp. 207-216. In earlier research, Reekie concluded that doctors act as "price sensitive agents" on behalf of their patients and that patients also exhibit price sensitive behavior by purchasing drugs from discount sources. Reekie's empirical results suggest that the industry exhibited price competitive behavior during the period examined (1958-1975). W. Duncan Reekie, "Price and Quality Competition In The United States Drug Industry," *The Journal of Industrial Economics,* vol. XXVI, No. 3, March, 1978, pp. 223-237.

[7] Richard E. Caves, Michael D. Whinston, and Mark A. Hurwitz, "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," *Brookings Papers: Microeconomics 1991,* pp. 1-66. Caves, et. al. suggest that innovative firms may compete by developing new drugs which replace products that are about to lose patent protection. The entry of generic products does not appear to result in significant price competition between the original branded product and its generic competitors.

[8] Although the absolute number of NCEs declined, the number of therapeutically "valuable" new drugs did not decline. Henry G. Grabowski, John M. Vernon, and Lacy Glenn Thomas, "Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry, *Journal of Law and Economics,* vol. 21 (1), Spring 1978, pp. 133-163.

[9] Hansen, for example, estimated that the average cost of R&D required to develop a successful NCE during the 1963-75 period amounted to $54 million (1976 dollars). Ronald W. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics,* 1979, pp. 156 and 180. Wiggins subsequently estimated that for the 1976-85 period R&D costs per successful NCE amounted to $125 million (1986 dollars). Steven N. Wiggins, "The Cost of Developing a New Drug," Pharmaceutical Manufacturing Association, 1987, p. 18. Both estimates factor in the opportunity costs of channeling funds into R&D rather than alternative investments. Wiggins' estimate does not include failed compounds.

[10] Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna, "The Cost of Innovation In The Pharmaceutical Industry, *Journal of Health Economics,*

10—Continued

vol. 10, no. 2, July, 1991, pp. 107-142. The estimate covers NCEs first tested on humans during the 1970-82 period.

[11] Ibid. The total includes the costs of products that fail in pre-clinical and clinical testing,

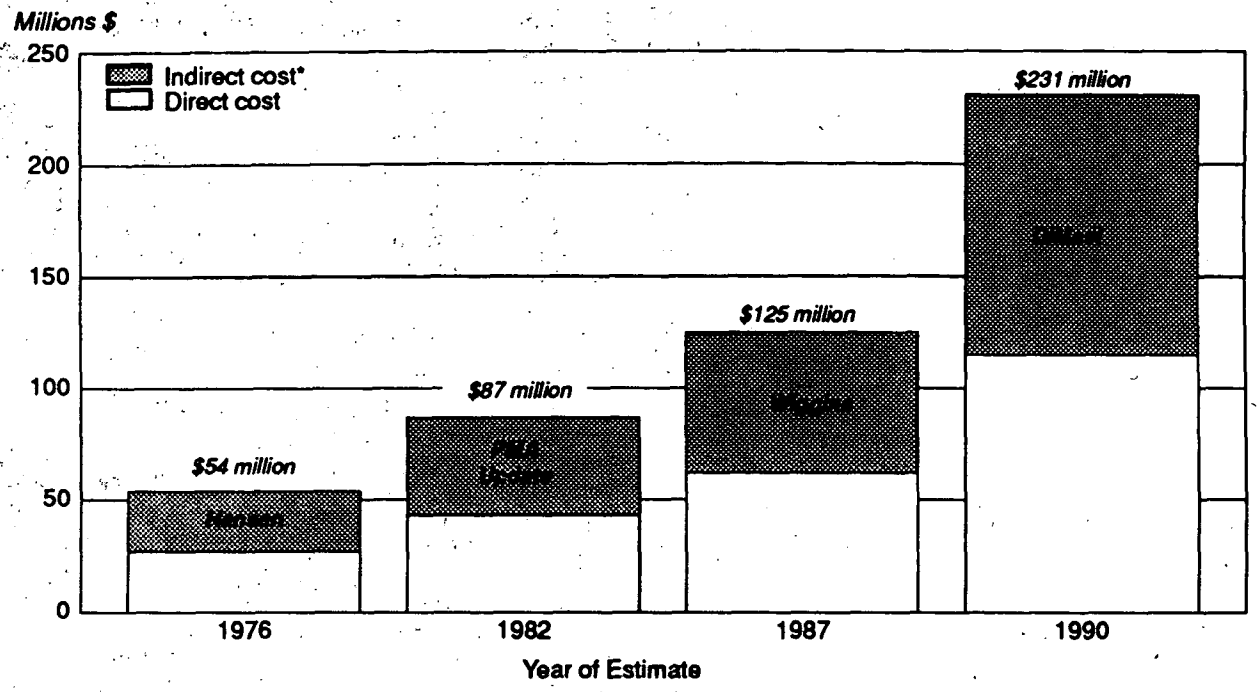
[12] It is interesting (and perhaps more accurate) to compare the individual values presented in terms of constant (1982) dollars: Hansen - $86 million; PMA - $87 million; Wiggins - $110 million; DiMasi et al. - $ 197 million.

[13] The amendments increased the scope of the Food and Drug Administration's (FDA) authority over the industry by requiring that all drugs brought to market meet efficacy as well as safety standards. See Chapter 3 for a review of government regulations affecting the industry.

[14] Wiggins, "The Cost of Developing a New Drug." The testing for products to treat chronic conditions is time consuming as a detailed understanding of the mechanism involved is required if adequate forms of treatment are to be developed.

[15] See, for example, Peter W. Huber and Robert E. Litan, eds., *The Liability Maze,* Washington, D.C.: The Brookings Institution, 1991.

Figure 2-1
Innovation: Drug development cost



* Cost of money invested over time ("opportunity costs")
Source: Reproduced with permission from PMA.

Grabowski, Vernon, and Thomas (GVT), for example, examined the effects of changes in the U.S. regulatory process on the U.S. industry's R&D productivity by comparing the performance of the U.S. and U.K. industries.[16] In addition, they examined other possible factors responsible for the observed decline in the U.S. industry's R&D productivity during the post-1962 period.[17] GVT estimated that regulatory changes accounted for approximately one-third of the total increase in average costs during the decade following the 1962 amendments. They also found that U.S. productivity declined at a faster rate than R&D productivity in the United Kingdom. They attributed the differential to changes in FDA regulations.

Other research has examined the extent to which a pharmaceutical firm's cash flow affects the level of its R&D expenditures and the impact of R&D cost increases on the firm's R&D activities. Wiggins examined the decision-making of firms at various stages in the R&D process in order to identify whether or not any fundamental changes in the process had occurred to help account for the increasing costs of R&D and the apparent decline in R&D profitability.[18] He concluded that responsibility for decisions regarding the continuation of research projects has shifted from research scientists to financial management officials within the firm at earlier stages in the R&D process. Companies have responded to increased risk by terminating research when projected profitability was in doubt. Wiggins attributed this shift to regulatory stringency.[19]

Grabowski and Vernon attempted to identify why pharmaceutical companies continued to invest in R&D, given the below-average estimated returns on R&D activity reported by some researchers.[20] They reported that the availability of internal funds appeared to affect

[16] Grabowski, Vernon, and Thomas, "Estimating the Effects of Regulation on Innovation."

[17] In addition to changes in the regulatory process, other factors included: depletion of research opportunities, liability concerns (as a result of the thalidomide episode), and technological advances that prompted additional safety testing. Ibid., p. 133.

[18] Steven N. Wiggins, "The Pharmaceutical Research and Development Decision Process," *Drugs and Health*, Robert Helms, ed. (Washington D.C.: American Enterprise Institute, 1981) pp. 55-83.

[19] See also, John R. Virts and J. Fred Weston, "Expectations and the Allocation of Research and Development Resources," *Drugs and Health*, Robert Helms, ed. (Washington, D.C.: American Enterprise Institute, 1981) pp. 22-45; Steven N. Wiggins, "The Impact of Regulation on Pharmaceutical Research Expenditures: A Dynamic Approach," *Economic Inquiry*, vol. XXI, January 1983, p. 126; and, William M. Wardell and Lorraine E. Sheck, "Is Pharmaceutical Innovation Declining?: Interpreting Measures of Pharmaceutical Innovation and Regulatory Impact in the USA, 1950-80," *Pharmaceutical Economics* (Stockholm: Swedish Institute for Health Economics, 1984), pp. 177-189.

[20] Henry Grabowski and John Vernon, "The Determinants of Research and Development Expenditures in the Pharmaceutical Industry," *Drugs and Health*, Robert Helms, ed., (Washington, D.C.: American Enterprise Institute, 1981) pp. 3-20.

firms' decisions regarding future R&D investment. In addition, perceived opportunities for future NCE development affects R&D funding. In general, firms respond gradually to past poor R&D performance. They concluded that these factors tend to moderate observed declines in R&D intensity.

Subsequent research indicates that the impact of regulation on R&D activity and the relationship of the various other factors influencing the R&D process is not as clear as indicated by earlier research. For example, when Wiggins examined data that were disaggregated by therapeutic category, he found that the number of NCEs in different classes declined at different rates.[21] On the basis of these differences, he concluded that nonregulatory factors had contributed to the decline in NCE development by U.S. firms.

Effects of Regulation on the Structure of the Industry

More recently, Thomas examined the differential effects of changes in FDA regulations after the 1962 amendments on the U.S. industry by using data covering trends in the U.K. industry as a basis for comparison.[22] He concluded that the regulatory changes generated by the 1962 amendments had a direct negative effect on smaller U.S. pharmaceutical companies because many of these companies produced drugs that were not subject to extensive clinical review under pre-1962 FDA regulations. This change shifted the comparative advantage to larger firms that already had the requisite infrastructure to conduct extensive clinical research. Thus, the regulations have reduced competition for these companies in the short run.

Thomas noted, however, that these structural changes might have occurred in the absence of increased regulatory stringency. Prior to 1962, physicians were beginning to demand increased testing and marketing information in order to evaluate the efficacy claims of the pharmaceutical manufacturers. In addition, pharmaceutical companies were beginning to respond to potential liability risks by increasing clinical testing. Changes in technology already underway in the early 1960s allowed for more sophisticated but more costly testing. Because of the high risk associated with the development of successful NCEs, companies had begun to evaluate the potential marketability of NCEs at earlier development stages.

Thomas concluded that FDA regulations have increased the competitiveness of larger U.S. pharmaceutical companies relative to smaller companies in the U.S. market. His research suggests, however, that delays in the review process compared to the review process in the United Kingdom may have a negative impact on U.S. companies' efforts in the international market.[23]

International Competitiveness

Although some of the research reviewed above points to the potential effects of regulatory and other policy changes on the U.S. pharmaceutical industry's activities in the international market, research completed during the 1980s addresses this issue more explicitly. In 1983, the National Academy of Engineering (NAE) conducted a study that evaluated the competitive status of the U.S. industry in the international market.[24] The NAE examined trends for six measures of industrial performance: research effort, innovative output, production, sales, market structure, and international trade. The researchers distinguished between those macroeconomic factors that tended to affect manufacturing industries in general and those that were particular to the pharmaceutical industry. Two trends unique to the pharmaceutical industry were identified: the decline in U.S.-based drug production as a percentage of world drug production and the decline in the U.S. share of world pharmaceutical R&D.[25] The study identified the following factors as contributors to these trends:

1. Foreign nontariff trade barriers;
2. U.S. Food and Drug Administration regulations;
3. Patent laws;
4. Liability regimes for consumer product claims;
5. Antitrust policies that may reduce the ability of U.S. firms to achieve economies of scale; and
6. Tax incentives for R&D.[26]

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[21] Steven N. Wiggins, "Effect of U.S. Pharmaceutical Regulation on New Introductions," *Pharmaceutical Economics*, B. Lindgren, ed. (Stockholm: Swedish Institute for Health Economics, 1984) pp. 191-205. Wiggins tested hypotheses concerning the extent to which: 1) the decline in NCEs was the result of a decline in research opportunities; 2) innovation was hampered by an increase in caution on the part of the industry and physicians as a result of the thalidomide tragedy; 3) technological advancement allowed for more elaborate, expensive testing; and, 4) changes in regulations following the 1962 amendments contributed to escalating R&D expenditures.

[22] By comparing the experiences of the U.S. and U.K industries, Thomas distinguished between regulatory and other (e.g. technological) changes. Lacy Glenn Thomas, "Regulation and firm size: FDA impacts on innovation," *RAND Journal of Economics*, Vol. 21, No. 4, Winter 1990, pp. 497-517.

[23] Ibid., p. 514.

[24] National Academy of Engineering, *The Competitive Status of the U.S. Pharmaceutical Industry: The Influences of Technology in Determining International Industrial Competitive Advantage*, Washington, D.C.: National Academy Press, 1983, pp. 21-52.

[25] The study noted that the decline in U.S. drug production was not matched by a comparable decline in the production of other sectors of the U.S. chemical industry. The decline in the U.S. share of world pharmaceutical R&D during the period under evaluation was more rapid than that of other U.S. industries.

[26] Ibid., pp. 4-5.

The NAE concluded that although the U.S. industry was likely to remain a significant force in the international market, decreases in various measures of industrial performance relative to other major international pharmaceutical producers suggested that the industry would lose its dominant position.[27]

The U.S. Department of Commerce's International Trade Administration (ITA) conducted an assessment of the U.S. industry's international competitiveness the following year and concluded that the United States was, and would continue to be, internationally competitive.[28] Despite the generally positive assessment of the industry, the study did identify a number of policy issues that could affect the global position of the industry. For example, the report noted that efficacy and safety regulations tend to produce positive, as well as negative, effects. The report concluded that although U.S.-produced pharmaceutical products had gained a worldwide reputation for quality, U.S. companies were likely to be at a disadvantage because of significantly longer U.S. regulatory review periods.

Research based on more recent data than either the NAE or ITA studies provides a more favorable assessment regarding the competitive position of the U.S. industry. For example, Thomas compared the performance of the U.S. industry to that of other countries' industries on the basis of a ten-nation sample.[29] He concluded that firms competing successfully in the international market do so by developing innovative new drugs that can be successfully marketed in most major country markets. He suggested that a critical factor contributing to a company's ability to compete successfully in the international market is the degree of competition in the company's home market. Three factors contribute to competitive home country markets: rigorous quality restrictions on market access; high levels of publicly funded biomedical research; and unregulated domestic prices. Thomas argues that public policies that encourage the emergence of smaller pharmaceutical producers (e.g., lack of product patents, quantitative and other nontariff barriers, and pricing policies) can hamper the long-run competitiveness of the country's industry.

Recently, Grabowski updated and extended the data reviewed in the NAE study and evaluated more recent trends reflecting sales and R&D productivity for the major producer countries.[30] His assessment is similar to that of Thomas.[31] In terms of both ownership and location, the United States has continued to be a leading source of consensus drugs (i.e., those which gain worldwide market acceptance) and should continue to dominate the global market over the next decade.[32] Grabowski concludes, however, that changes in government policies (such as the adoption of cost-containment measures) could have a significant adverse impact on R&D incentives, which would subsequently influence the U.S. industry's performance in the future. A recent report issued by the Council on Competitiveness also highlights issues cited by both Thomas and Grabowski.[33] The report emphasizes that factors such as science education, funding for R&D, and relative freedom from price control are important to the continued competitiveness of the U.S. industry.

Although researchers have begun to examine the effect of government policies on the international competitiveness of the U.S. industry, many issues remain unresolved. Two issues stand out: (1) the impact of existing U.S. health policies and the potential effects of various cost-containment proposals; and (2) the impact of product liability exposure on industry decisions regarding R&D.[34] An examination of these issues requires understanding the interaction of the demand and supply sides of the pharmaceutical market and the relationship of the pharmaceutical market to the overall health-care markets.

Descriptive analyses of differences in health-care policies provide a starting point from which to examine the effects of health-care policies on the pharmaceutical industry. However, these analyses do not measure the actual effects of particular government policies.[35]

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[27] Ibid., p. 51

[28] International Trade Administration, *A Competitive Assessment of the U.S. Pharmaceutical Industry* (Washington, D.C.: U.S. Department of Commerce, 1984).

[29] Lacy Glenn Thomas, "Spare the Rod and Spoil the Industry: Vigorous Competition and Vigorous Regulation Promote Global Competitive Advantages," unpublished, October 1989. Thomas reiterates one of the concerns expressed by ITA in its assessment: namely that the lengthy regulatory review periods of the FDA were not necessary and should be reduced.

An earlier study by Parker attempted to rank regulatory stringency and measure effects of diffusion of drugs into 19 country markets. The results indicated that a greater degree of regulation in a country did not seem to affect pharmaceutical companies' decisions to introduce drugs into that country. A number of intervening variables such as intellectual property rights protection, the size of the market and other exogenous factors may have affected the results. John Parker, "Regulatory Stringency and the International Diffusion of Drugs," *Pharmaceutical Economics* (Stockholm: Swedish Institute for Health Economics, 1984) pp. 139-159.

[30] Henry Grabowski, "Innovation and International Competitiveness in Pharmaceutical," *The Proceedings of the 2nd International Joseph Schumpeter Society Meetings* (Ann Arbor, MI: University of Michigan Press, 1990), pp. 167-185.

[31] Thomas, "Spare the Rod and Spoil the Industry."

[32] However, measures of R&D expenditures and innovation during the 1979-83 period show that the Japanese industry has improved its capacity to conduct innovative research and produce consensus drugs.

[33] Council on Competitiveness, *A Competitive Profile of the Drugs and Pharmaceuticals Industry,* Washington, D.C.: Council on Competitiveness, March, 1991.

[34] To the extent possible, these and other issues will be examined in chapter 3.

[35] European researchers have begun to examine the economic effects of various countries' cost-containment policies. For example, Huttin provides a descriptive

Weisbrod, examining the interdependence of health insurance coverage and technological development, suggests potential effects that cost-containment efforts may have on the pharmaceutical industry.[36] The nature of insurance coverage and changes in coverage can create incentives for certain types of R&D. At the same time, efforts to reduce the cost of pharmaceutical products could provide disincentives to R&D aimed at pharmaceutical products that complement specific medical technologies. Because of the length of time required to develop medical and pharmaceutical technologies, the decision to undertake particular types of R&D may be influenced by anticipated changes as well as by current insurance coverage.[37] Although this research does not examine international competitiveness issues directly, it does suggest potentially positive and negative affects that changes in government health-care policies may have on the industry's development. To the extent that the U.S. or foreign industries rely on particular country markets, such changes can affect their competitive positions in the global market.

Research covering the effects of generic competition in the pharmaceutical market also illustrates the difficulty of assessing the impact of cost-containment policies on the industry. Caves, et. al., for example, contend that generic competition does little to depress pharmaceutical prices.[38] Although price competition does result from the entry of generic competitors, price decreases are more pronounced among the various generic products, rather than between the branded and generic products. Factors that influence competition include the life cycle of the innovative drug and the role that physicians and pharmacists play with respect to the choice of drugs to supply.[39]

Liability has been cited by researchers and industry officials (see below) as a factor that increasingly may reduce industry R&D efforts. To date, empirical and anecdotal evidence for this view is somewhat mixed. The literature suggests that R&D innovation focusing on particular types of products (birth control devices, oral contraceptives, and vaccines) has been negatively affected.[40] For example, two products (the Dalkon Shield and Bendectin) accounted for 60 percent of the total number of liability suits affecting pharmaceutical producers during 1973-86.[41] For other products, the evidence to date is less clear. Some researchers and industry analysts have concluded that the negative impact of liability on R&D innovation may be exaggerated,[42] while others suggest that the effects may be more profound than these data imply.[43]

Commission Research Framework

Measures of Competitiveness for the U.S. Pharmaceutical Industry

An important measure of international competitiveness for any industry is the degree to which it can achieve profitability and growth relative to its foreign rivals. These goals require the ability to sustain and increase market share, either by lowering costs and prices through continuous improvements in factor utilization or by improving the quality of product. Measures of competitiveness therefore usually include market share, profits, and productivity. A firm (or industry) that is more productive is likely to increase its market share relative to its competitors. Although productivity is clearly a determinant of competitiveness, it can be used also as a measure of future potential competitiveness.

For the pharmaceutical industry, maintaining profitability requires the ability to develop innovative drugs which, because of their unique therapeutic value,

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35—Continued

comparison of policies in the U.K., Germany, France, and the United States. Christine Huttin, "More Regulation or More Competition in the European Pharmaceutical Market: Some Europe-US price control comparisons," unpublished paper, 1991. See also, Organization for Economic Cooperation and Development, *Health Care Systems in Transition: The Search for Efficiency*, (Paris: OECD), 1990.

[36] Burton A. Weisbrod, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature*, vol. XXIX, June 1991, pp. 523-552. The technological innovation examined includes the pharmaceutical as well as the medical equipment industry.

[37] Ibid. In particular, see discussion on pp. 530-541.

[38] Caves, Whinston, and Hurwitz, "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry. See also, Norman V. Carroll, Chanaporn Siridhara, and Jack E. Fincham, "Factors Affecting Market Acceptance of Generic Drug Products: An Examination of Inherent Risk, Price, and Maximum Allowable Cost Coverage," *Akron Business and Economic Review*, vol. 18, no. 1, pp. 11-18.

[39] Researchers have examined the effect physicians and pharmacists have on the demand for pharmaceuticals. The extent to which cost considerations affect the choice of drugs is one hypothesis examined. For example, physicians may not have information on the costs of drugs; therefore,

39—Continued

drug prices may not influence their decisions. In contrast, pharmacists may have an incentive to prescribe generic products because often the mark-up on these products is higher than that for branded drugs. Liability considerations also reportedly affect drug choice. Physicians and pharmacists reportedly favor "safer" branded products, particularly for therapeutic classes associated with higher risk. See Caves et al., "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," for a review of this literature.

[40] See, for example, Council on Competitiveness, *A Competitive Profile of the Drugs and Pharmaceuticals Industry*, and Judith P. Swazey, "Prescription Drug Safety and Product Liability," in Peter W. Huber and Robert E. Litan, eds., *The Liability Maze* (Washington, D.C.: The Brookings Institution), 1991, pp. 291-333.

[41] Swazey, "Prescription Drug Safety and Product Liability."

[42] Ibid., pp. 293-298.

[43] See, for example, Louis Lasagna, "The Chilling Effect of Product Liability on New Drug Development," pp. 334-359 and Henry Grabowski, "Product Liabilty in Pharmaceuticals: Comments on Chapters Eight and Nine," *The Liability Maze*, pp. 360-366.

can capture a significant share of the global market. Thus, one measure of competitiveness for the U.S. industry is the number of "global" ethical pharmaceutical products that it develops in comparison to its foreign counterparts.[44] However, this measure may not necessarily reflect the current productivity of the industry.

Productivity can be measured in terms of output per worker. The pharmaceutical industry's reliance on R&D to produce and market NCEs suggests another productivity indicator that may be more accurate in terms of measuring international competitiveness: R&D productivity. R&D productivity in the pharmaceutical industry can be measured by the number of R&D compounds or R&D compounds per R&D employee.

Determinants of International Competitiveness

A number of factors related to demand and supply conditions contribute to the ability of the pharmaceutical industry to develop, produce, and market innovative ethical drugs. Figure 2-2 illustrates the major determinants of competitiveness discussed in the economic literature and indicated by industry officials during staff interviews.

The demand for ethical pharmaceuticals is determined by demographic and socioeconomic factors. For example, factors such as the composition of the population in terms of age as well as socioeconomic factors such as diet or access to health care can affect the demand for drugs in a particular region or country. Government policies and programs such as cost-containment, degree of health-care financing, and support for health-related education may also affect the demand for drugs, directly or indirectly.

An important factor affecting the supply of ethical pharmaceuticals is R&D activity, i.e., the level and productivity of R&D spending. Such activity requires sufficiently high profits, the ability to secure external financing, or both. Government actions ranging from macroeconomic policies, treatment of product liability, tax policy, and regulatory controls exert indirect and direct effects (positive and negative) on the ability of firms and the industry as a whole to produce pharmaceuticals.[45]

The ability to fund R&D is only one element of the picture, however. The industry also requires access to a highly developed research base in order to develop innovative pharmaceutical products and improve the productivity of its R&D efforts. Access to new technology and highly trained scientists affords companies not only the opportunity to develop new products but alsothe means to reduce the risk associated with pharmaceutical R&D. Consequently, government support for education and pharmaceutical R&D contributes directly and indirectly to industry productivity.

Because the U.S. industry operates worldwide, government policies in other countries may have an impact on the activities of U.S. pharmaceutical firms. For the most part, these issues have not been the subject of empirical economic analysis. Researchers are hampered by the lack of available international data that would allow them to evaluate the differential effects of foreign government policies on the U.S. industry. Nonetheless, industry officials have identified issues such as the protection of intellectual property rights, tax policy, and pricing policies as being of major concern to the U.S. industry.

To the extent possible, these and similar issues are addressed in the chapters that follow. In particular, chapter 5 provides the results of empirical analysis conducted by Commission staff to examine the major determinants of international competitiveness that affect the U.S. pharmaceutical industry.

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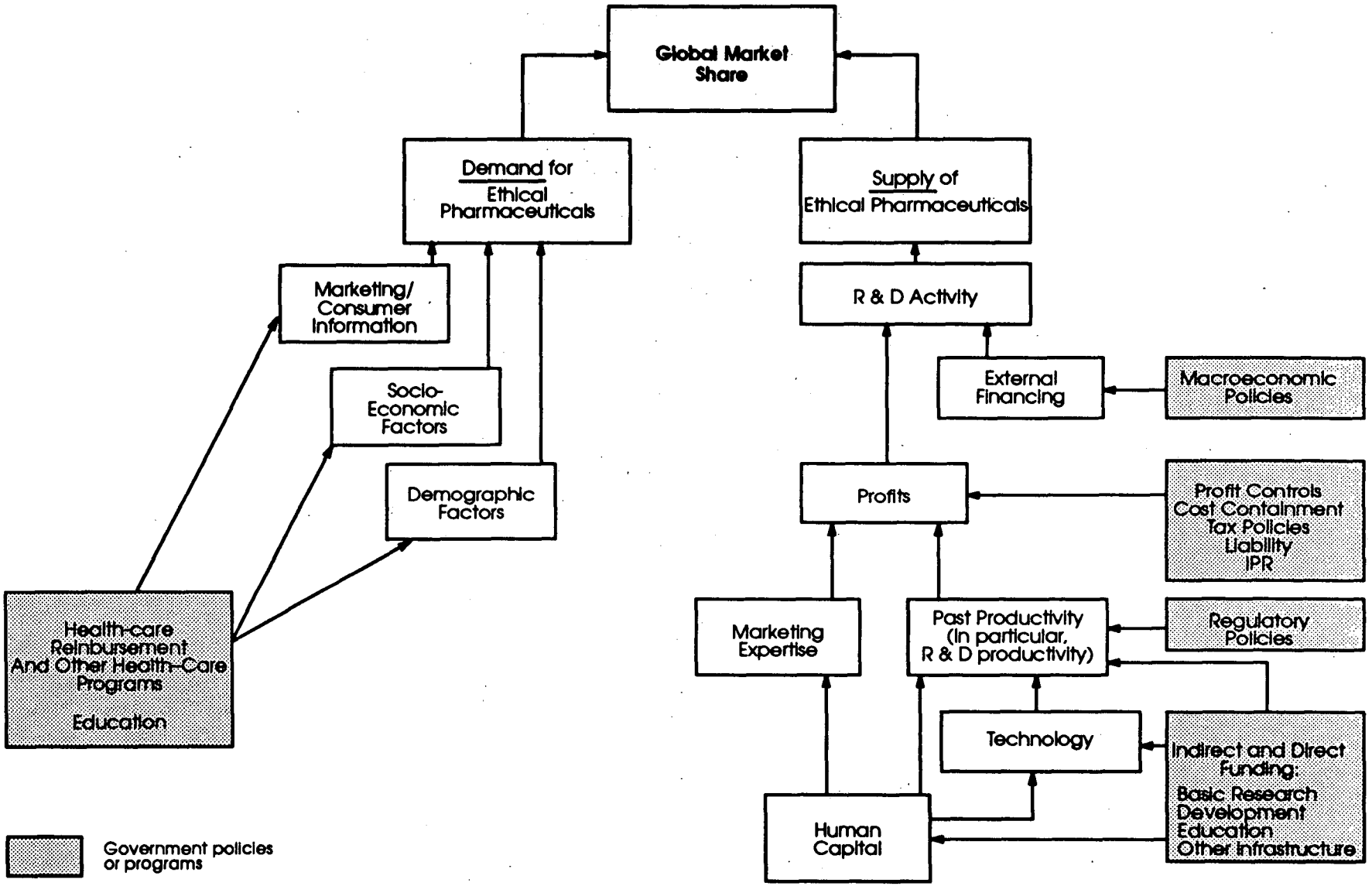
[44] An alternative measure is the total number of new chemical entities (NCEs) developed by the industry. This measure is fundamentally flawed because it is not always a good proxy for global market share. Many NCEs do not capture a significant share of the market outside of the country in which they are developed.

[45] Figure 2-2 presents a simplified view of the various factors that may influence the development and sale of pharmaceutical compounds. R&D activity, as shown in the figure, includes the level and productivity of current R&D. Just as past R&D productivity is influenced by a number of government policies and programs, so also is current R&D activity.

Figure 2-2
Determinants of global market share



CHAPTER 3
COUNTRY-SPECIFIC GOVERNMENT POLICIES

Government policies, whether domestic or international, have a significant impact on the global pharmaceutical industry, given the nature of the industry. Issues of concern to the industry that pertain to country-specific government policies include regulatory issues, pricing policies, cost-containment efforts, intellectual property rights, and tariff-related matters such as the granting of duty suspensions.[1] To fully understand the significance of government policies, particularly regulatory policies, to the global pharmaceutical industry requires some familiarity with the evolution of the industry (see figure 3-1). Milestones ranging from the discovery of new products to the implementation of laws and regulations in the United States and other countries have had a significant impact on the industry's development. The cumulative effect of these milestones has been to shape the global industry as we know it today.

This chapter, then, will first discuss the industry's beginnings to place current policies in context. The legal aspects of the government policies noted above and their impact on the global pharmaceutical industry are presented in the second section of the chapter. National tax policies, export controls, and R&D subsidies are also considered. Antitrust regulation and environmental policies were not found to have a significant influence on the competitiveness of the U.S. pharmaceutical industry at this time.[2]

Industry Evolution

One of the earliest milestones in the development of the global pharmaceutical industry was the Pre-World War II development and commercial marketing by the German chemical industry of a number of synthetically derived pharmaceutical products. Many of the early chemical companies, such as those in Switzerland and Germany, found that their technology to make synthetic dyes was readily transferable to pharmaceuticals, resulting in the development and commercialization of a number of new pharmaceutical products between 1908 and World War II. For example, Salversan, used in the treatment of syphilis, and aspirin were among the first pharmaceuticals manufactured commercially by the German chemical industry.[3]

A number of the sulfa drugs, including sulfanilamide, were developed around 1935 by the German and French industries in their search for better anti-infective agents. The discovery of these products was said to be the result of a massive effort to screen chemicals undertaken by the German industry during World War I. The U.S. industry joined in the search for better sulfa drugs during 1930-50, and also performed considerable research on vitamins and hormones. The continued development of synthetically derived medicinals occurred concurrently with advances in organic chemistry, thus establishing early the connection between new products and the results of basic research. Advances in pharmaceutical production technology also developed during this time. Although long produced via extraction from beef pancreases, the synthetic production of insulin was one of the early applications of techniques used in what was later to become known as the biotechnology industry.

The U.S. industry began to evolve fairly rapidly after World War II, primarily as the result of its commercialization of penicillin. An Englishman, Alexander Fleming, discovered penicillin in 1928, but lacked the time and money to develop his discovery. Research on the product was continued by scientists from universities and the chemical industry in the United States during World War II as part of a wartime project to develop penicillin and to produce it in large quantities to supply the allied forces. The U.S. Government sponsored much of the research, investing about $3 million in the project. The penicillin plants were then sold to private firms at half cost after the war.[4] Given the relatively rapid development in the field of antibiotics during 1938-53, this period was known as the "Age of Antibiotics."[5]

The revenues accruing from the sales of many of these pharmaceutical products allowed for increased R&D to develop other such products and the beginning of the worldwide expansion of the U.S. industry.[6] The Swiss industry had established facilities early in the United States, becoming one of the first to become truly multinational in an effort to compensate for their relatively small domestic market. After World War II, however, many firms constructed production facilities in Western Europe, primarily as a result of restrictions on imports imposed by national governments.[7] Some expansion also occurred in Japan. Early foreign expansion in Japan was generally in the form of joint

[1] PMA submission, p. 2.

[2] It should be noted that the government policies discussed were chosen on the basis of Commission interviews with the industry and by an extensive review of the literature.

[3] Prior to the discovery of such products, doctors had relied primarily on naturally-occurring medicinals.

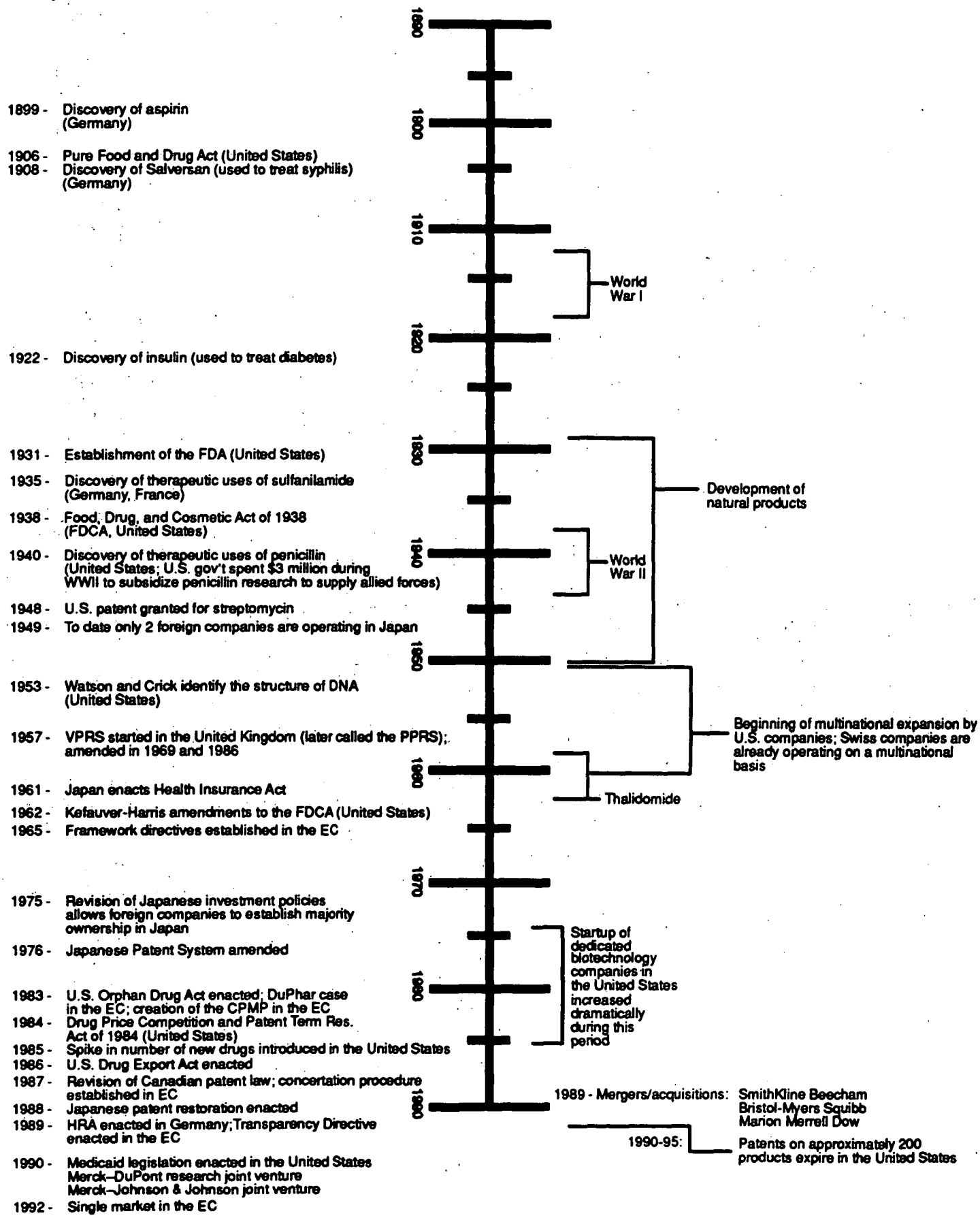
[4] *The Competitive Status of the U.S. Pharmaceutical Industry: The Influences of Technology in Determining International Industrial Competitive Advantage*, 1983, p. 9.

[5] In 1948, the U.S. Patent Office granted a patent on streptomycin, paving the way "for a new form of competition—competition through product development." (*The Competitive Status of the U.S. Pharmaceutical Industry: The Influences of Technology in Determining International Industrial Competitive Advantage*, 1983, p. 9.)

[6] It should be noted that many German, Swiss, and U.S. pharmaceutical firms have had marketing organizations in European countries since the early 1900s.

[7] *The "Cost of Non-Europe" in the Pharmaceutical Industry,"* Commission of the European Communities, Volume 15, p. 93.

Figure 3–1
Certain Milestones in the Evolution of the Pharmaceutical Industries in the United States, Western Europe, and Japan



ventures or non-majority agreements because Japan's investment policies prohibited the establishment of majority ownerships by foreign firms until 1975. Although reconstruction costs slowed the worldwide expansion of the German and Japanese industries after World War II, the global pharmaceutical industry continued to develop relatively rapidly in the Post-World War II period, resulting in an increased number of products available to the consumer and in significant advancements in the development and production of pharmaceutical products.

As the pharmaceutical industry evolved globally, so did government policies regulating various aspects of the pharmaceutical industry. For example, regulations to ensure public health and safety were implemented in most developed countries, often requiring that new drugs be approved by a national regulatory authority before they can be marketed to the public. Since a pharmaceutical company cannot compete in a market where its product is not approved for sale, national regulatory approval laws have a direct effect on the competitiveness of pharmaceutical firms. The requirements for regulatory approval usually involve extensive preclinical and clinical testing to provide required data, and the approval process can be expensive and time-consuming. The sections below discuss the regulatory marketing approval laws for the United States, the European Community, Japan, and Switzerland, as these apply to new drugs.

Regulatory Approval for New Drugs

United States

U.S. Marketing Approval Procedure

One of the first regulatory procedures in the United States, the Pure Food and Drug Act, was enacted in 1906. This Act called for increasing emphasis on the purity of pharmaceutical products, particularly what were then termed "patent medicines." The Act was intended to eradicate pharmaceutical products which were fraudulent and dangerous and to abolish unsanitary conditions in many manufacturing facilities. The deaths of nearly 100 people in the United States in the late 1930s, said to be associated with "sulfanilamide elixir," prompted the passage of the Federal Food, Drug and Cosmetic Act (FDCA) in 1938, revising the 1906 Pure Food and Drug Act.[8]

The FDCA is the major statute regulating marketing approval for new drugs on a Federal level in the United States.[9] The FDCA, thought to be the most extensive law of its kind in the world, is administered by the Food and Drug Administration (FDA), a part of the Public Health Service, which is, in turn, part of the Department of Health and Human Services.[10]

The FDCA has been amended several times, including substantial amendments in 1962 and 1984. In 1962, the FDCA was modified by the Kefauver-Harris Amendments to restrict experimentation with new drugs in the United States. Senator Kefauver originally focused on possible price collusion between pharmaceutical companies, a perceived "suboptimal degree of competition" within the industry, a perception of excessive profits within the industry, and the relatively low number of generic products prescribed by physicians.[11] A number of restrictions were added to the proposed legislation during the 26 months of hearings, including the requirement that data on efficacy and safety be presented as part of the drug approval process. Although Congressional support for the amendments waned, causing many to believe that they would not be enacted, the subsequent discovery that the drug thalidomide[12] was a teratogen[13] prompted unanimous passage.[14]

The Kefauver-Harris Amendments raised national safety standards in the United States in that they established the current investigational new drug (IND) procedure discussed below as a prerequisite to filing a new drug application (NDA). They also established the requirement for post-approval adverse reaction reports. Under the new procedures, manufacturers

[8] According to one source, the deaths were attributed primarily to a solvent used in the preparation of the anti-infective product.

[9] 21 USC 301 et seq.

[10] The FDA has issued implementing regulations on drugs for human use at 21 CFR 300 et seq. The FDA was established within the U.S. Department of Agriculture in 1931 by the passage of the Agricultural Appropriation Act. Prior to its founding, the duties of the FDA had been performed by a number of other agencies. The creation of the FDA allowed for a centralized system of drug approval and oversight in the United States. In 1940, it was transferred to the Federal Security Agency. The FDA was then integrated in 1953 into the Department of Health, Education, and Welfare, which became the Department of Health and Human Services in 1979.

[11] "Congress, the FDA, and New Drug Development: Before and After 1962," *Perspectives in Biology and Medicine*, 32, 3, Spring 1989, pp. 322-343.

[12] Thalidomide caused birth defects in about 4,000 infants born during 1959-62 in Germany and the United Kingdom to mothers who had taken the product during their pregnancy. Although the drug was never marketed in the United States, many U.S. patients were given thalidomide while the product was in the final stages of the approval process. The thalidomide discovery prompted many, if not all, of the developed countries to strengthen their regulatory systems so that products were shown to be of good quality, safe, and efficacious prior to being approved for marketing. The United Kingdom, for example, established the Committee on Safety of Drugs in 1963 and implemented the "Medicines Act 1968." The latter called for the creation of new regulatory procedures that were intended to prevent such occurrences, establishing in the process a number of legally required reporting mechanisms (many of which were formerly performed on a voluntary basis).

[13] A teratogen is an agent or influence that causes physical defects in the developing embryo (*Dorland's Pocket Medical Dictionary* (22nd ed., p. 658)).

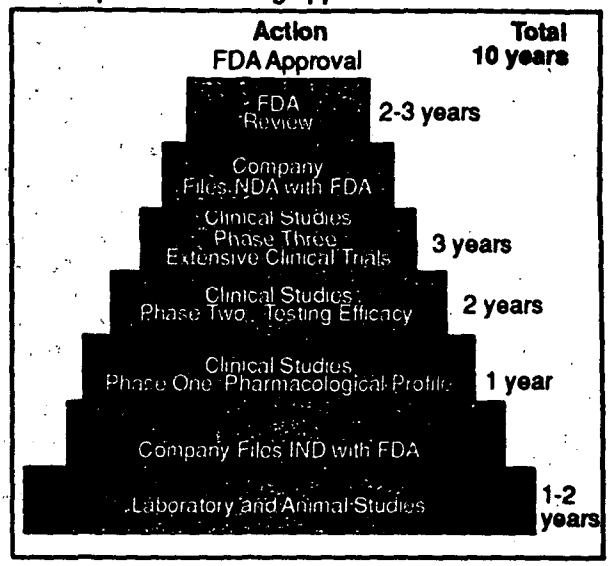
[14] "Congress, the FDA, and New Drug Development: Before and After 1962," *Perspectives in Biology and Medicine*, 32, 3, Spring 1989, pp. 322-343.

were required to report the start of experimental testing of new pharmaceuticals to the FDA; qualified investigators had to perform the tests; and detailed records, accessible to the FDA, had to be maintained. Sponsors were also required to demonstrate the efficacy of their product(s).[15] By 1970, the approval process took an average of about 10 years, compared with an average of 3 years in 1960.[16]

Smaller, imitative firms producing generic and "me-too" products in the United States reportedly felt the effect of the increased testing requirements much more severely than the larger firms, since the smaller firms had to conduct increased premarket testing for safety and efficacy (as compared to before 1962) and then market the products based on these results.[17] As a result, many of them reportedly ceased innovation after 1962.[18] One source contends that any benefit that accrued to larger U.S. firms from this decrease in domestic competition was offset by a competitive disadvantage when compared to large foreign firms.[19]

Generally, under the FDCA, a new drug may not be commercially marketed in the United States, imported, or exported from the United States, unless it has been approved as safe and effective by the FDA.[20] Such approval is based on an NDA submitted by the sponsor of the drug (usually, but not always, the manufacturer) (see Fig. 3-2). The NDA must contain acceptable scientific data, including the results of tests to evaluate its safety and substantial evidence[21] of effectiveness for the conditions for which the drug is offered.

Figure 3-2
The steps towards drug approval



Source: Reproduced with permission from the *Pharmaceutical Manufacturers Association.*

Once a drug is approved, its chemical formula, manufacturing process, labeling, packaging, recommended dosage, methods of testing, etc., generally may not be changed from those stated in the NDA unless a supplemental application has first been filed and approved. However, changes to increase assurance of safety and effectiveness are to be put into effect at the earliest possible time, without waiting for approval. Drugs that are not "new," as defined by the law, are not subject to the "new drug" procedure, but must comply with all the other drug requirements, including registration, labeling, and requirements as to manufacturing practices.

The 1962 amendments applied special rules to investigational drugs. These are new drugs intended solely for investigational use by qualified scientists. Such a drug may be distributed in the United States, or imported, even though there is no approved NDA.

[15] "A Primer on Postmarketing Surveillance," p. 77; "The Political Economy of the Pharmaceutical Industry," *Journal of Economic Literature*, Vol. 24, September 1986, pp. 1179.

[16] "Regulation and Firm Size: FDA impacts on Innovation," RAND Journal of Economics, Vol. 21, No. 4, Winter 1990, p. 501. It is noted that many of the new regulations were phased in during the late 1960s and early 1970s.

[17] "Regulation and Firm Size." A "me-too" product, broadly defined, is one that is similar, either therapeutically or chemically, to an existing pharmaceutical product.

[18] Given the impact of the Kefauver-Harris amendments, it will be interesting to follow developments with the regulation of generic products as a result of the recent generic drug industry scandal (the term "generic drug scandal" is used both within the industry and the FDA. For example, the term appears in the *Final Report of the Advisory Committee on the Food and Drug Administration* (HHS, May 1991, p. 1)). The scandal reportedly involved the acceptance of bribes by several FDA employees and the falsification of test data for new drugs by several generic manufacturers. ("Under Siege," *The Economist*, Aug. 12, 1989, p. 60; "Why the FDA Needs a Miracle Drug," *Business Week*, Feb. 19, 1990, p. 108; "Generics Charges, Sentence Handed Out to Five by US," Chemical Marketing Reporter, Sept. 16, 1991, p. 3.) Generic manufacturers, who currently have to prove that their products are chemically identical and bioequivalent to the innovative products under consideration, could be required to prove that their products are also therapeutically equivalent in patients. If so, sources believe that the prices on many generic products will increase over time ("The Price of No-Name Drugs May Soon Be Hard to Swallow," *Business Week*, Oct. 2, 1989, p. 67).

[19] Ibid. The disadvantage is said to be "at minimum, of radically greater U.S. delays."

[20] In certain instances, export of new drugs which have not received such approval is permissible, but certain conditions must be met and a special approval must be obtained. 21 USC 382.

[21] "Substantial evidence" is defined by the law as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" 21 USC 355(d).

However, investigational drugs may not be distributed or imported for trial on humans unless the sponsor has filed an acceptable "Notice of Claimed Investigational Exemption for a New Drug" (the "IND" already referred to) as specified by the FDA regulations.

As a matter of practice, the approval procedure for new drugs begins with preclinical testing by the drug's sponsor. Such testing, as noted above, is necessary for filing an IND, which in turn is a prerequisite for conducting the clinical tests that are required for submission and approval of an NDA. Once an NDA is filed, the FDCA requires that action on approval (actual approval or notification of an opportunity for a hearing on approvability) be made within 6 months. The average approval time is approximately 2 years.[22] Approvals are generally in force until revoked.

Drug sponsors are required to keep the FDA informed of any developments that may affect the safety and effectiveness of their products ("adverse reaction reports"), during clinical study or following FDA approval for marketing.

In 1984, the FDCA was amended under the Drug Price Competition and Patent Term Restoration Act (also known as the Waxman-Hatch Act). Under this Act, innovative drug firms received partial restoration of their patent term by up to 5 years on new products, depending on the amount of time lost during regulatory review, in return for greater market accessibility for generic products, through new procedures for abbreviated new drug applications (ANDAs) for generic versions of previously approved drugs.[23]

Orphan Drug Act

A unique feature of the FDCA is the Orphan Drug Act (ODA), enacted in 1983.[24] The ODA is intended to promote development of new drugs for rare diseases or conditions (i.e., those affecting less than 200,000 persons in the United States, or affecting more than 200,000 persons, but for which the drug sponsor has no reasonable expectation of recovering development costs through U.S. sales). The ODA provides technical assistance and economic incentives to pharmaceutical manufacturers to develop and market such drug products. If the FDA agrees that a drug meets the statutory definition for a designated orphan drug, the sponsor is entitled to a tax credit (and certain other assistance) for the cost of clinical trials.[25] Upon the date of new drug approval or biological licensure, another sponsor's application for marketing the same drug for the same orphan use may not be approved for a period of 7 years. In order to maintain exclusivity, the sponsor must ensure an adequate supply of the drug.

There is no such legislation in Western Europe or in Japan. Since the ODA was introduced, 265 of 380 requests for such designation have been approved and 36 of the designated products were approved for marketing. Many of the products are for treatment of rare cancers and AIDS.

Recently, controversy arose over an unsuccessful attempt to amend the ODA. The amendments would have allowed market competition if two drugs are developed concurrently, and allowed for the loss of marketing exclusivity for a product if the disease it treats is no longer considered rare. Two companies withdrew from the Industrial Biotechnology Association (IBA), citing, as one of their reasons, the association's opposition to any changes in the Orphan Drug Act.[26] According to the Association of Biotechnology Companies (ABC), erythropoietin (EPO) and human growth hormone are cases where "the Orphan Drug Act has been misused to obtain market exclusivity for products which are clearly not orphans, and would have been developed even without the Orphan Drug Act."[27]

Biological Products

Special provisions also apply to biological products (e.g., vaccines, sera, and blood products), which have been required to be licensed under Federal law since 1902. Under the Public Health Service Act, a manufacturer wishing to ship a biological product for sale in interstate commerce or for import or export must obtain a U.S. license for both the manufacturing

[22] Special rules for antibiotics provide that they be treated as new drugs; they must have the equivalent of an approved NDA. Antibiotic manufacturers are no longer required to submit batch samples for testing and certification by the FDA to assure safety and effectiveness, but the statutory authority for this remains and batch certification could be resumed if necessary. The FDA still establishes master standards for new antibiotics. In effect, the regulation of antibiotics is now very similar to that of all new drugs.

Special rules for insulin subject it to batch testing and certification by the FDA. These requirements apply to both insulin crystals and finished dosage forms. Approval of an NDA is a prerequisite for acceptance of samples for certification by the FDA.

[23] "Implementation of the Drug Price Competition and Patent Term Restoration Act of 1984: A Progress Report," *Journal of Clinical Research and Drug Development*, 1, 1987, pp. 263-75. The Japanese Government enacted similar legislation in 1988, adding five years to existing patents. This results in an average patent life of about 13 years.

[24] 21 USC 360aa-ee.

[25] 26 USC 28, 21 USC 360ee.

[26] "Walkout at Biotech Group," *Chemical Week*, Apr. 4, 1990, p. 8; "Two Biotech Companies Quit Trade Association," *Chemical and Engineering News*, Apr. 2, 1990, p. 6.

[27] "ABC Seeking Individual Changes to the Orphan Drug Act, wants to break HGH and EPO Monopolies," *FD&C Reports Pink Sheet*, Oct. 9, 1989, p. 27; "Walkout at Biotech Group," *Chemical Week*, Apr. 4, 1990, p. 8; "Two Biotech Companies Quit Trade Association," *Chemical & Engineering News*, Apr. 2, 1990, p. 6. It should be noted that one source indicates that the IBA represents a much larger share of the industry, in terms of the number of firms, than does ABC.

establishment and the product intended for shipment.[28] These licenses are granted following a showing that the establishment and the product meet specific standards to insure continued safety, purity, potency, and effectiveness.

To apply for licensure, the manufacturer must submit protocols detailing affirmative proof that the manufactured product meets the standards, and must successfully complete a prelicensing inspection by the FDA inspectors, followed by annual inspections. Prior to release by the manufacturer of each lot of a licensed product, specified materials must be submitted to and cleared by the FDA. The requirements for filing an IND application for a biological product are essentially the same as for drugs.

Implementation of the U.S. Regulatory Procedure

One study states that the average break-even lifetime for new products (i.e., the time needed to recover costs associated with bringing a product to market) can be reduced by about 3-4 years if regulatory delays are reduced by about 1 year.[29] The drug development process, from discovery to FDA approval, takes approximately 10 years; U.S. patents on pharmaceutical products, generally sought fairly early in the development process, usually have a lifetime of 17 years. Any delays in the development and marketing approval process thereby shorten a product's effective patent life, reducing the period in which a company can recoup its R&D expenditures.

The average FDA review time for the 20 new drugs approved in the United States in 1988 was about 31 months, compared with an average of approximately 15 months for foreign review of those of the 20 products that were first approved overseas.[30] The mean approval time for the 23 NCEs approved in 1990 was 27.7 months.[31] Comparison of review times in the United States and abroad can be difficult, however, because of factors such as: (1) differences in defining the length of approval time, i.e., when "the clock is started," and (2) because, in some cases, testing performed in the United States is not included in the foreign review period.[32] Industry sources state, however, that a perceived differential in approval times prompts many companies to seek market approvals overseas first. In 1989, 18 of the 23 products approved in the United States had received their first marketing approval in countries other than the United States.[33] During 1984-88, 88 of the 113 products introduced in the United States were first approved in a foreign country.[34]

U.S. Drug Export Amendments Act

The U.S. Drug Export Amendments Act (DEAA), passed in 1986, allows U.S. pharmaceutical and biopharmaceutical manufacturers, under certain conditions, to export drugs and biologics for commercial purposes to any of the 21 developed countries specified under the Act, provided that the drug or biologic has been approved for sale by the importing country. This legislation is important to the industry because of the increasing tendency of U.S. firms to seek marketing approval overseas prior to or during application for such approval in the United States (see the section in this chapter entitled "Export Policies" for further discussion of the DEAA).

European Community

Marketing Approval Procedure

The national regulatory authorities of the European Community (EC) member states are responsible for acting on applications for marketing authorizations for new drugs. An EC institution, the Committee for Proprietary Medicinal Products (CPMP), made up of the heads of national authorities, acts under the so-called concertation procedure and the multistate procedure, described below. It is expected that a European Pharmaceuticals Agency will be established to oversee member states' assessment and surveillance activities.

While the actual procedure for approval of marketing authorizations varies among the member states, much of the procedure must conform to standards set forth in various EC directives, recommendations and decisions. Among other things, these directives set time limits for processing applications and require the member states to prepare an assessment report for products containing a new chemical entity which are subject to a request for a marketing authorization for the first time. The criteria for assessing applications are quality, safety and efficacy. Applications must be acted on within 120 days (extendable to 210 days), not counting time spent by the applicant in obtaining and furnishing additional information. Once granted, marketing authorizations are good for five years and are renewable for further five-year periods.

The EC has established a multistate procedure which permits extending a marketing authorization issued by one member state to at least two other member states.[35] To qualify for this procedure, the

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[28] 42 USC 262.

[29] The break-even point is considered to have a built-in return on capital that is commensurate with what could be earned in other parts of the economy for a risky venture. (Dr. Henry G. Grabowski, *Health Care Cost Containment and Pharmaceutical Innovation*, Dr. Henry G. Grabowski, 1986, p. 26.)

[30] PMA, *PMA Facts at a Glance*, 1989, p. 7.

[31] Data provided by Mr. Gerald Meyer, Deputy Director, Center for Drug Evaluation and Research, FDA. The total approval time is calculated from the official receipt date of the NDA to the approval date.

[32] Per a conversation with a representative of the FDA.

[33] *The Pharmaceutical Industry*, p. 43.

[34] "Facts at a Glance," *PMA Statistical Fact Book*, December 1989, p. 17.

[35] The multistate procedure was created by the Second EC Council Directive of May 20, 1975 (75/319/EEC), which has since been amended.

product must have been authorized by one member state in accordance with the EC directives governing national procedures. The application is submitted directly to the national authorities of the member states to which extension is sought, with notice to the CPMP and the national authority of the member state granting the first marketing authorization.[36]

The member states to which extension is sought must either grant authorization or forward objections to the CPMP and the applicant within 120 days. Generally, the CPMP must give its opinion within 60 days, and the member state then has 60 days itself to decide what action to take.

A different Community-level procedure is the concertation procedure[37] which is intended to enable questions relating to the quality, safety and efficacy of biotechnology and other high technology products to be resolved within the CPMP before any national decision is taken.

In the case of biotechnology products, the applicant requests the first member state to act as rapporteur for the application. For other high technology products, the applicant must first obtain the agreement of the first member state that the product is suitable for the procedure.

The rapporteur refers the application to the CPMP and to the member states for which a marketing authorization is sought. The time table for review is set by the rapporteur, usually 210 days. The rapporteur prepares an evaluation report within 45 days and files it with the member states and the company. The member states provide comments, and any questions, within 60 days and the rapporteur, within a further 45 days, consolidates the total response. The applicant is usually given 3 months to respond, and, 30 days later, the member states send the rapporteur and the CPMP their conclusions. The CPMP opinion, which is not binding, is then sent to all member states. Those member states in which marketing authorizations have been requested have 30 days in which to notify the Commission as to what action will be taken.

Implementation of the EC Regulatory Procedure

In the EC, the delay in processing applications for authorization through the multistate option varies among member states under the present market approval system. France is said to adhere the most to registration deadlines, averaging about 6 months; applicants in other countries experience delays of up to 2 to 3 years. One industry source estimated that delays in approval of registration under the current system accounts for about 0.5 to 1.0 percent of EC industry costs. These costs include loss of revenue from a decrease in effective patent life, loss of working capital, and the staff costs to process multiple registrations.[38] The proposed single-market authorization system, which would combine centralized and decentralized procedures, is viewed by industry representatives as allowing companies more flexibility in choosing an approval route. The new system could also decrease delays in approval on a member-state level and reduce the possible backlog of applications that would probably result from implementation of just one central route for approval.[39]

European Agency for the Evaluation of Medicine

The EC is reportedly proceeding carefully in establishing an institutional body to regulate the approval of new pharmaceutical products in an effort to avoid a proliferation of spinoff agencies. In late October 1990, the EC Commission issued a proposal to create the European Agency for the Evaluation of Medicines (the Agency). The Agency would be responsible for all marketing approvals of new biotechnology and certain high-technology products by the year 2000. The new Agency would have three principal duties: the evaluation of new medicines, arbitration of international disputes within the EC concerning the authorization of existing pharmaceuticals, and coordination of national inspection systems. The Agency would also manage an alert system by which information could be quickly distributed and dangerous products withdrawn from the EC market. Beginning in 1996, a manufacturer would no longer have to apply for 12 different approvals to market pharmaceuticals within the EC, as is now required. The Agency is viewed by some as a version of the U.S. Food and Drug Administration.[40]

Switzerland

The major laws regulating marketing approval for new drugs in Switzerland are the Intercantonal Convention on the Control of Medicaments and its implementing regulations. The national approval authority for pharmaceuticals is the Intercantonal Office for the Control of Medicaments (IOCM). The Federal Office of Health regulates biologics. Applications for marketing approval are filed with the IOCM and are assessed with respect to quality, safety, efficacy, and price (i.e., the price must not be

[36] A format for applications under the multi-state procedure and, optionally, for national applications, is set out at Annex 2 to the Notice to Applicants, which is reproduced in Volume II of the EC Commission's Rules Governing Medicinal Products in the European Community. The application has five sections: documentation; toxicological and pharmacological documentation; clinical documentation; special particulars.

[37] The concertation procedure was established by EC Council Directive of December 22, 1986 (87/22/EEC).

[38] Paolo Cecchini, *The European Challenge 1992*, p. 67.

[39] USITC, *The Effects of Greater Economic Integration Within the European Community on the United States: Second Follow-up Report*, September 1990, Chapter 22.

[40] USITC, *The Effects of Greater Economic Integration Within the European Community on the United States—Third Follow-Up Report*, USITC Publication 2368, March 1991, p. 4-37.

"excessive"). Data required for new drugs include chemical and pharmaceutical data, experimental and biological data, and clinical data. There is no fixed approval time. Marketing authorizations are in force for five years and may be renewed for additional five-year periods. After marketing, the manufacturer must report adverse reactions to IOCM.

Japan

Marketing Approval Procedure

The major law regulating the marketing of pharmaceuticals in Japan is the Pharmaceutical Affairs Law (Law No. 145 of August 10, 1960, as amended) and its related regulations. Under the law, the application for approval of an ethical drug must proceed through various steps of local and Federal government agencies. The first step is application to the local prefectural government of the sponsoring company. The application is then filed with the Ministry of Health and Welfare (MHW or Koseisho).

Koseisho, established in 1938, is responsible for the administration, promotion and development of social welfare, social security and public health. The Ministry is divided into nine bureaus, two of which affect the pharmaceutical industry; the Pharmaceutical Affairs Bureau (PAB), which enforces regulations concerning drugs, and the Health Insurance Bureau, which sets drug prices.

The application for drug approval is forwarded, with regard to its therapeutic category, to a New Drug Expert Committee of the Central Pharmaceutical Affairs Council (Chuikyo), an advisory council to Koseisho, consisting of authorities from the academic, medical and research fields. At this stage, any issues in question are discussed with the applicant.

At the same time, the National Institute of Hygienic Sciences and the National Institute of Health verify the specifications and analytical methods for the products involved in the application. The applicant is given an explanation of the results of the Council's deliberation. A hearing may be held on additional documents in answer to directions issued by the Council. The approval of new products is issued by the Minister, based on the report of the Council. The average time required for processing an application is 18 months for prescription drugs, 10 months for nonprescription drugs, and six months for in vitro diagnostics, excluding the time needed by the applicant to meet supplementary requests by the Koseisho. In 1967, post-marketing regulations to ensure the continued safety and efficacy of approved drugs were implemented. Koseisho required firms to collect all adverse drug data on a drug, re-examine the NCE clinical data after six years and 10,000 cases, and re-evaluate the drug every five years.

There are specific requirements for applications. For example, for products containing a new chemical entity, the following information is required: origin of the drug, background of its discovery, and conditions of use in foreign countries; physicochemical properties, standards and test methods; stability; toxicity and teratogenicity; pharmacology; absorption, distribution, metabolism, and excretion; and clinical trial results. This means, among other things, that the applicant must have conducted preclinical and clinical trials prior to filing the application. Preclinical studies include physicochemical studies and animal studies, which must be conducted in accordance with Good Laboratory Practice as established by Japanese law. Foreign preclinical data reportedly are now acceptable in Japan as a result of mutual recognition agreements with the United States, the United Kingdom, Germany, France and Switzerland.[41] Plans for clinical trials (i.e., trials conducted on humans) for NCEs are subject to submission to Koseisho. Foreign clinical trial data are, in principle, acceptable. However, data prepared in Japan are required, at least to some degree, in the clinical trials. For example, for new drugs, data prepared in Japan are required for absorption, metabolism and excretion tests, dosage determination tests and comparative clinical trials. The law requires that after marketing, adverse reactions be reported by the manufacturer to Koseisho within 30 days.

Implementation of the Japanese Regulatory Procedure

Until the late 1960s, Japanese companies could easily license foreign products, get them approved in Japan for production or import, and then sell the drugs domestically at large profits. Relatively low barriers to entry existed for Japanese firms to introduce foreign drugs that were already approved overseas. Prior to 1967, Japan did not require domestic clinical trials on safety or efficacy for foreign products listed in an accepted official pharmacopoeia. These products were excluded from the definition of "new drugs" and therefore received rapid approval. Consequently, the main strategic emphasis of Japanese pharmaceutical companies, until the mid-1960s, focused on seeking licenses for the manufacture or importation of various foreign products. Drug approval policy in Japan provided strong incentives for importing foreign pharmaceutical technologies, and domestic companies responded eagerly.

Drug approval regulations also helped keep foreign firms out of the Japanese market. Foreign firms were prohibited by regulatory policy from applying on their own for the first step of drug approval, i.e., the demonstration of efficacy and safety review, and clinical trials had to be conducted in Japan on native citizens. Both policies remained in effect until the mid-1980s, when discussions with the United States in bilateral trade negotiations resulted in changes that allowed foreign firms to apply directly and permitted the submission of the results of foreign clinical trials.

[41] USITC staff field interviews in Japan with representatives of Japanese and U.S.-based firms, representatives of industry trade associations, and government officials in April 1991.

Japan's pharmaceutical market in 1989 was only slightly smaller than that of the United States, the world's largest market for pharmaceuticals, or approximately $33 billion.[42] One trade journal states that under the recent revisions of Japanese law concerning the approval of drugs for the market, foreign firms are becoming increasingly attracted to Japan.[43] The more favorable legal environment includes faster approval for new drugs and a strengthened patent system.[44]

Industry Position

United States

At least one industry source believes that U.S. drug regulation has "evolved in a direction contrary . . . to the intent of the statute and its legislative history . . . and has forced the drug development process into an excessively lengthy, expensive, and wasteful mode as pharmaceutical sponsors and researchers try to meet increasingly onerous FDA requirements and bring new medicines to a waiting public."[45] However, the Council on Competitiveness has stated that the FDA, "while criticized by some as being too slow at approving drugs, has a generally good record for maintaining public confidence in the safety and efficacy of drugs."[46] The U.S. pharmaceutical industry, although cognizant of the role that the FDA must play in safeguarding the health of the American public, has expressed concern about the time lag involved in the U.S. marketing approval process. Such delays result in changes in a company's marketing strategies, since it cannot depend on a set approval time period. In some cases, it has taken 5 years for a product to go from the NDA stage to approval at the FDA, compared with the average 2-3 years.[47] In 1987, of the 27 NDAs approved by the FDA, only three were reportedly approved in less than a year.[48] The delays at the FDA have been attributed by the industry to a number of factors, including personnel shortages at the FDA; the recent generic drug industry scandal; the reportedly increasing amount of data required by the FDA to demonstrate the safety of the product under consideration; and, in some cases, the failure of industry to submit sufficient information to the FDA promptly and in a complete and thorough fashion.[49] For example, given two applications for two specific pharmaceutical products, the total FDA review time for one was 10.1 months (1988-89), compared with 77.1 months for the other (1983-89).[50] One of the main reasons cited for the disparity in approval time was the number of amendments that had to be made to the applications in each case.[51]

It has been suggested that for FDA to function more efficiently, it should be given the "requisite resources," including human resources, material resources, and additional funding.[52] In 1989, the Advisory Committee on the FDA was established to examine FDA's mission, responsibilities, and structure and to recommend ways to improve operations. The primary findings of the Committee were as follows:[53]

1) The FDA must define its mission and set program priorities that "govern its resource allocations, policy directives, and enforcement activities, in a manner consistent with its mission";

2) The Department of Health and Human Services should enhance the status of the FDA and increase the authority of the Commissioner of the FDA;

3) The enforcement capabilities of the FDA must be strengthened;

4) The FDA's management systems must be improved; and

5) The resources of the FDA should be augmented. "Additional resources, specifically targeted and keenly managed, are crucial."

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[42] PMA submission, p. 30.

[43] "Japan: the Pharmaceutical Market Here is the World's 2nd Largest," Medical Marketing, August, 1990, pp. 22-34.

[44] Ibid.

[45] "Congress, the FDA, and New Drug Development: Before and After 1962," *Perspectives in Biology and Medicine*, 32,3, Spring 1989, p. 341. The PMA, in *Better Health Through New Medicines and an Improved FDA* (Sept. 13, 1990; p. 1), states that the FDA has "drifted far from the basic intent of Congressional legislation."

[46] Council on Competitiveness, *A Competitive Profile of the Drugs and Pharmaceuticals Industry*, Mar. 1991, p. 3.

[47] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[48] "Health Care Innovation," p. 27. The approval times for the 3 products cited were 3 months, 4 months, and nine months.

[49] *Health Care Innovation: The Case for a Favorable Public Policy*, Merck & Co., 1988, p. 23; *Better Health Through New Medicines and an Improved FDA: Statement to the Subcommittee on Drugs and Biologics of the Advisory Committee on the Food and Drug Administration, Department of Health and Human Services*, PMA, Sept. 13, 1990, pp. 1-5; USITC staff field interviews in the United States and Western Europe with representatives of EC- and U.S.-based multinational firms and representatives of industry associations during January-April 1991.

[50] Information provided to Commission staff by Mr. Gerald F. Meyer, Deputy Director, Center for Drug Evaluation and Research, Food and Drug Administration.

[51] Ibid.

[52] *Health Care Innovation, p. 23; Better Health Through New Medicines and an Improved FDA, pp. 1-5; A Competitive Profile of the Drugs and Pharmaceuticals Industry*, p. 3.

[53] U.S. Department of Health and Human Services, *Final Report of the Advisory Committee on the Food and Drug Administration*, May 1991, pp. i-ii.

European Community

In regard to the single-market authorization procedure, U.S. pharmaceutical industry representatives stated that its opinion was sought in the creation of the EC system and that the EC Commission has already addressed a number of the issues raised by the U.S. industry.[54] One concern of the industry, however, is the possible elimination of the national approval systems for EC-wide access by 1996, except for local companies who want to market a product in one member state. The U.S. industry currently uses the national systems fairly extensively. Representatives of the U.S. industry have suggested that all the systems remain in place until 1996, at which time the systems and their use could be reviewed and modified appropriately.[55]

PMA has stated that it agrees with the EC Commission that a system should be established which "ensures the rapid and efficient review and approval of new medicines in the Community."[56] The industry expressed concern, however, about the oversight of the proposed European Agency for the Evaluation of Medicines (the Agency) and about arrangements for transition to the new single-market authorization procedure.[57]

PMA recommends that oversight of the Agency be dually controlled by both the Commission and by a "strengthened" Management Board. In regard to the establishment of the new registration system, PMA has stated that the industry would like to see the implementation of a transition period during which the new registration system could be phased in. This transition period, which would have to be of sufficient duration to allow the new registration system to be tested and proven, would be expected to reduce the potential overload of the new system.[58]

Other issues important to the industry in regard to the registration procedure include decision making procedures, consultation with applicants, and pharmacovigilance. In regard to the evaluation process, PMA welcomes the fact that a uniform period of 210 days has been proposed for the evaluation of submissions under either the centralized procedure or for the first member state approval under the decentralized procedure. PMA proposes, however, that "companies should have the right to appeal before the Management Board at any stage of the process if time limits are being exceeded unjustifiably." PMA states that "as it is unrealistic to expect applicants to resort to legal action against member states or Community institutions, it is essential that the Commission should develop further proposals for effective, speedy, and acceptable enforcement mechanisms."[59]

Japan

Industry sources state that they are concerned that the relationships between Koseisho, physicians, and the industry often seem to violate conflict-of-interest rules as applied in the United States. Clinical trial investigators, they assert, may also serve as reviewers on New Drug Expert Committees, or on Chuikyo, which sets prices for drugs. Companies may fund research foundations to do clinical trials and finance journals where clinical results are often published, independent of peer review.

Industry representatives also stated concern about the absence of informal contact between companies and the Pharmaceutical Affairs Bureau during the approval process. Company representatives want more transparency to facilitate the examination process. The practice in Japan of not requiring written informed consent for subjects in clinical trials, contrary to the custom in other countries, makes the data unsuitable for ethical reasons by other regulatory agencies in the world.

In the past, some U.S.-based firms were critical of the differences between Japanese regulatory procedures and U.S. and European standards.[60] Harmonization of standards has been a much discussed topic, but to date no positive actions have been taken to modify these procedures, and this is viewed by foreign-based firms as a substantial obstacle to doing business in Japan.

In 1985, changes were made, in part, as a result of the MOSS talks. However, incompatibility of data is still an issue in many areas. Some human clinical studies must still be performed in Japan, to Japanese standards, resulting in duplication of effort for foreign firms. The Japanese have stated that clinical trials must be performed on native Japanese rather than other races because of possible physiological differences in their native population.[61] Most U.S. firms consider this requirement simply a cost of doing business in this market. They note that most of the other clinical trial work can be done elsewhere, which some feel represents a reasonable compromise. The Japanese firms and certain representatives of the Japanese Government stated that future scheduled talks should resolve any remaining problems pertaining to this matter.

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[54] USITC, *The Effects of Greater Economic Integration Within the European Community on the United States—Second Follow-Up Report*, USITC Publication 2318, September 1990, p. 22-18.

[55] Ibid.

[56] USITC, *The Effects of Greater Economic Integration Within the European Community on the United States—Third Follow-Up Report*, USITC Publication 2368, March 1991, p. 4-37.

[57] Ibid.

[58] Ibid.

[59] Ibid.

[60] USITC field interviews in Japan with representatives of U.S.-based multinational firms and representatives of industry associations during April, 1991.

[61] USITC field interviews in Japan with representatives of Japanese pharmaceutical producers, industry associations, and Japanese Government officials.

Mutual Recognition

Bilateral talks on the topic of mutual recognition are currently underway between the EC and the United States and the EC and Japan. Mutual recognition, or the acceptance by one country of regulatory requirements, such as inspections and clinical trial data, that are generated in another country, is an ongoing goal of these negotiations. Most industry contacts felt that some degree of mutual recognition is inevitable, given the increasing globalization of the industry and the fact that duplication of effort shortens patent life. Industry sources believe that inspections will be the first area of acceptance. Complete reciprocity for clinical trial data, however, while possible in the long term, is not likely to come about soon. Acceptance of foreign data alone to support an NDA submission, while desirable, is the exception rather than the rule. While the FDA does not routinely approve products based solely on foreign data, its regulations provide that it will accept these data under certain conditions and has urged other countries to do the same under these conditions.

Patent Law and the Protection of Intellectual Property Rights

The following is a synopsis of the patent and trademark laws of the United States, the European Community, Switzerland, and Japan. Patents and trademarks are the most important of the statutorily created forms of intellectual property[62] for the pharmaceutical industry. Points of applicability to the pharmaceutical industry are noted in the text.

United States

Patents

There are three categories of patents: utility patents (by far the most common and most important), design patents, and plant patents. Utility patents are by far the most numerous and the most important for the pharmaceutical industry. They are issued for a 17-year term, and cover new and useful processes, machines, manufactures, compositions of matter, and improvements thereof.[63]

The term of any individual patent may be extended by Act of Congress, though this is rare. The term of a utility patent for certain pharmaceutical products (as well as certain medical devices, food additives, and animal drug products) subject to regulatory approval prior to marketing may, in some circumstances, be extended for a limited period through an administrative proceeding at the Patent and Trademark Office (PTO). Through fiscal year 1990, the PTO had issued 90 certificates of patent-term extension since enactment of the Drug Price Competition and Patent Term Restoration Act of 1984.[64] Periodic maintenance fees must be paid to the Patent and Trademark Office to keep utility patents in force for their full term.

The average length of time to process a biotechnology-related patent in the United States is 27-28 months, compared with 43 months in Japan, 28 months in Europe, and 23 months in Canada.[65] In an effort to speed up the patent process, the PTO has recently created the "Biotechnology Institute," to "enhance" the training and skills of biotechnology patent examiners.[66] The PTO estimates that it will take 4 years to reduce the average processing time to 18 months.

Actions for patent infringement are begun in United States district courts, with appeal to the United States Court of Appeals for the Federal Circuit. Further appeal is by way of a petition for writ of certiorari to the United States Supreme Court. Remedies include preliminary injunctions, permanent injunctions, and damages. A patent owner may also bring an administrative preceding for infringement by imported articles before the U.S. International Trade Commission under section 337 of the Tariff Act of 1930, which may result in those articles being excluded from entry into the United States and/or a cease and desist order.

H.R. 5664,[67] introduced during the 101st Congress in 1990, was an attempt to "close [a] 'loophole' in

[62] As used here, a Federally created intellectual property right refers to a patent, a nationally registered trademark, copyright, and mask work protection.

[63] Design patents, issued for a 14-year term, are granted for new, original, and ornamental designs for articles of manufacture. Plant patents, issued for a 17-year term, are granted for distinct and new varieties of plants.

[64] This Act, known also as the Waxman-Hatch Act, not only amended the patent law to provide for patent-term extension for pharmaceutical products under certain conditions where FDA action on an NDA had been delayed, it also amended the FDCA to provide for abbreviated new drug applications (ANDAs) for generic versions of previously approved drugs.

[65] "Biopesticide Producers Concerned Over Patent Protection," p. 11; *Biotech90*, p. 95; a staff telephone conversation with a representative of the U.S. Department of Commerce, Patent and Trademark Office (PTO), on August 5, 1991. The average "patent pendency" time, in general, for utility, reissue, and plant patents was about 18 months (above-mentioned staff telephone conversation and the U.S. PTO's *Annual Report Fiscal Year 1990*, p. 20).

[66] "GEN's 10 Crucial Biotech Issues in the Next Decade," p.6. According to one industry source, one of the reasons for the backlog in approvals of biotechnology patents at the PTO is turnover in staff; the turnover, in turn, is attributed to a number of factors, including a reported negative differential in pay between PTO staff and private industry. The PTO has implemented the "13-Point Biotechnology Catchup Plan of 1987" and the "8-Point Biotechnology Catchup Plan of 1990."

[67] H.R. 5664 was a revised version of previous legislation (H.R. 3957) introduced by Reps. Rick Boucher (D-VA) and Carlos Moorhead (R-CA) in June 1990. Per the PTO's *Annual Report Fiscal Year 1990*, p. 10, "the Administration supported only those provisions of H.R. 3957 and S. 2326 that would have permitted the patenting of processes using patented materials . . . [and] recommended that this concept be extended to processes that make patented products." H.R. 5664 is said to address the concerns of the Administration.

U.S. law currently enjoyed by foreign competitors" and to improve the competitiveness of U.S. firms.[68] The bill would have amended the United States Code such that a process would not be considered obvious if an "essential material used in the process is novel and otherwise non-obvious."[69] The legislation was the result of recent rulings that have been perceived by some in the industry to be obstructions to the development of the domestic biotechnology industry. The legislation was not enacted during the 101st Congress. Representative Boucher (D-Va) and Senator DeConcini (D-Ariz) introduced H.R. 1417 and S. 654 in the 102nd Congress in March 1991. The latter two bills are said to be identical to H.R. 5664.[70]

Trademarks

The trademark law of the United States is the Lanham Act of 1946, as amended, title 15, U.S. Code. In addition, most of the States have their own trademark laws, based on both statute and the common law.

The Federal law provides for registration of trademarks, service marks, certification marks, and collective marks. There are two registers, the principal register and the supplemental register, with the principal register being the more important. Registration on the principal register is accomplished by application filed with the U.S. Patent and Trademark Office, which is examined for formal and substantive compliance with the law. Use in interstate commerce is prerequisite for registration, but under certain circumstances, intent to use is sufficient providing it is eventually followed by actual use. Before actual registration on the principal register, a mark which has been examined and found to be otherwise entitled to registration must be published for opposition. Registrations under the Federal law are for 10 years, renewable for succeeding terms of 10 years.

Actions for federally registered trademarks are usually begun in the United States district courts, with appeal to the appropriate United States Court of Appeals. Further appeal is by way of a petition for writ of certiorari in the United States Supreme Court. Remedies include preliminary injunctions, permanent injunctions, and damages, as well as seizure and destruction of infringing articles. A criminal action for trademark counterfeiting may also be brought. A trademark owner may also bring an administrative proceeding for infringement by imported articles before the U.S. International Trade Commission under section 337 of the Tariff Act of 1930, which may result in those articles being excluded from entry into the United States and/or a cease and desist order. A trademark owner may also record a trademark registered on the principal registrar with the U.S. Customs Service, which may bar and/or seize infringing imports.

European Community

Patents

There is no EC-wide patent law. However, the EC has concluded (but not yet ratified) a Community Patent Convention that would create a comprehensive, Communitywide patent law. Furthermore, most of the EC member states (and several nonmember states) are signatory to the European Patent Convention, which sets procedures for centralized examination for patents, under uniform standards, at the European Patent Office. However, what the European Patent Office issues is not a supranational European patent but a bundle of national patents.

All of the member states grant patents, whose issue is based on an application, which is given at least a formal examination in the national patent office. The criteria for patentability in most member states is novelty, inventive step, and capability of industrial application. Some member states exclude certain subject matter from patentability. The most important examples are computer programs and certain biotechnology inventions. However, the national laws of many member states provide for copyright protection for computer software, and the EC Council has adopted a directive which requires all member states to provide such protection. Further, the EC Commission has proposed a directive which, if adopted, would require national patent laws to be amended to permit patenting of many kinds of biotechnology inventions.

With few exceptions, the term of patents in the member states is 20 years from the date of filing. Recently, France enacted a law which would, under certain conditions, permit some patents on pharmaceutical products to be extended for limited periods where the marketing of those products has been delayed because of required regulatory marketing approvals. The EC Commission has proposed a regulation which, if adopted, would create a similar system for the entire EC.

Actions for infringement are usually begun in the national trial courts, with the possibility of two levels of appeal. The grounds for the final level of appeal are usually limited. Remedies for infringement usually include a permanent injunction and damages and may include a preliminary injunction and seizure and destruction of the infringing articles as well. In some member states, criminal proceedings may be brought for patent infringement.

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[68] "Patent Protection Act Seeks to Improve Competitiveness of U.S. Firms;" "Bill Seeks Stronger Protection Against Foreign Infringement of Biotech Patents," *International Trade Reporter*, Feb. 14, 1990, Vol. 7, p. 220; "Biotech and Copyright Renewal Bills Are Endorsed at Senate Panel Hearing," *BNA's Patent, Trademark & Copyright Journal*, June 20. 1991, p. 184.

[69] "Biotech and Copyright Renewal Bills Are Endorsed at Senate Panel Hearing," *BNA's Patent, Trademark & Copyright Journal*, June 20. 1991, p. 184.

[70] Ibid.

Trademarks

There is at present no comprehensive, Communitywide trademark law. However, the EC Commission has proposed several regulations which would create a Community trademark regime, which would exist side by side with the national trademark laws of the member states. In addition, the EC Council has adopted a directive which would achieve a partial harmonization of national trademark law in the member states. The directive sets out minimum substantive standards for refusing registration, for the exclusive rights to be obtained on registration, for use, and for invalidation. The procedure for registration and invalidation and the effect of invalidation would be governed by national law.

In general, the trademark laws of the member states provide for the creation of trademark rights by registration. Registration is by application to the national industrial property office. Applications are given at least a formal examination, and, in some member states, may be subject to an opposition procedure. The term of registration varies; most member states have a 10-year period and provide for indefinite renewal for additional 10-year periods.

Actions for trademark infringement are brought in a trial court, with the possibility of an appeal. Remedies include a permanent injunction and damages. In some member states, a criminal action for trademark infringement may also be brought.

Switzerland

Patents

Switzerland grants patents on application to and examination by the Swiss patent office. To be patentable, an invention must be novel and capable of industrial application. Certain subject matter may not be patented, e.g., medical and therapeutic methods or species of or procedures to breed plants and animals. Alternatively, since Switzerland is a signatory to the European Patent Convention, application may be made to the European Patent Office designating Switzerland as one of the countries for which grant is sought. The normal term of Swiss patents is 20 years from the date of filing. Infringement consists of unauthorized industrial use of the patented invention and may subject the infringer to liability for compensation and other punishment.

Trademarks

Swiss trademark law permits the registration of trademarks but not service marks. Registration is only evidence of prior use, and it is prior use, not registration, that determines whether a trademark can be enforced. Registration is by application to the Swiss Trademark Office. A registration once granted extends for 20 years and may be renewed for periods of 20 years. Infringement entitles the trademark owner to compensation. The infringer may also be liable to other punishment.

Japan

Patents

Japan grants patents on most subject matter.[71] Applications for patents are made to the Japanese Patent Office, which conducts a formal and, after request by the applicant, a substantive examination. If the applicant does not file a request for substantive examination within 7 years of the application date, the application will be deemed abandoned. If, after substantive examination, the application appears otherwise allowable, it will be published for opposition prior to grant. In any event, the application will be laid open for public inspection 18 months after application. Certain rights accrue to the applicant on publication. The average time for issuance of a Japanese patent is about 5 years from application, compared with about 20 months in the United States. Among the reasons for this is the relatively small number of examiners in the Japanese patent office and the pregrant opposition procedure.

The claims allowed in Japanese patent applications tend to be narrower than those allowed in U.S. applications and the doctrine of equivalents, as it is known in the United States, is not applied in Japan.[72] The narrowness of the claims allowed in an individual application opens the possibility that competitors may obtain numerous patents on relatively minor variations of the claimed invention, a practice referred to by some as "patent flooding." This practice can result in a patentee being hemmed in by a competitor's patent even in a technology in which he has pioneered, preventing the patentee from effectively exploiting that technology and thereby inducing him to enter into cross-licenses. An alternative course for the patentee is to himself apply for several patents to obtain more complete coverage of his technology.

The term of Japanese patents is 15 years from date of publication but no longer than 20 years after application. Since 1988, Japan has had in force patent term restoration legislation. Patents for products (including pharmaceuticals), the marketing of which has been delayed because of required regulatory approvals (and perhaps other reasons) may be extended for up to 5 years. Annual maintenance fees must be paid to keep the patent in force. Compulsory licenses may be granted if the patented invention is not worked or if necessary in the public interest. Actions for patent infringement are begun in the high court. There is the possibility of appeal. Remedies include permanent injunctions and damages.

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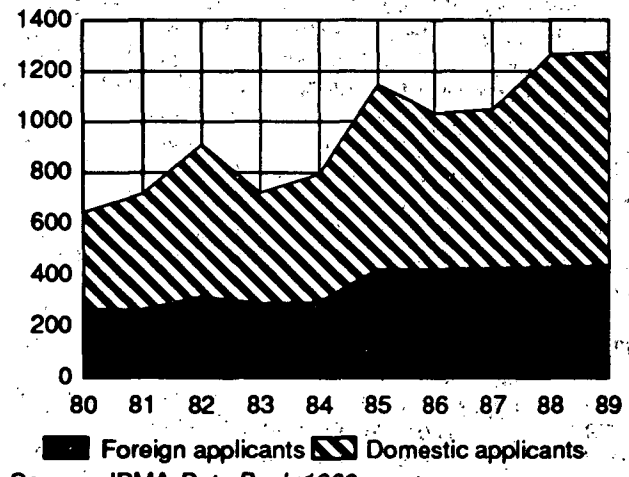
[71] Japan also grants utility models (sometimes called "petty patents") for subject matter not rising to the level of patent protection, but justifying some protection.

[72] Under United States practice, an accused device may be found to infringe even if it does not precisely meet the terms of a patent claim, if the patented can show that the accused device performs substantially the same function in substantially the same way to achieve substantially the same result.

In 1976, the Japanese patent law was changed from providing protection to only process patents to encompassing compound patents. As a result of this increased protection, many foreign firms began to patent an increasing number of their products in Japan. According to some sources[73], one of the reasons the Japanese Government changed its patent law was that an increasing number of Japanese pharmaceutical firms were beginning to develop unique products in the 1970s as a result of their increased R&D efforts. They wanted stronger protection for their products. The strengthened patent system allowed large Japanese companies to become more research oriented. During 1984-85, the number of patents examined in Japan for pharmaceutical products increased from 797 to 1,144, or by 44 percent, as shown in Figure 3-3:[74]

There are data which indicate that the average time it takes for the Japanese Patent Office to grant a patent is about 5 years from date of filing (about 3 years from examination under the deferred examination system), compared to about 20 months in the United States. This may in part be due to the fact that there are significantly fewer examiners in the JPO, though the number of applications filed is much higher than in the United States. The Japanese Government is aware of this problem and is said to be taking steps to hire new examiners. The Government is also in the process of converting to a paperless system. It is hoped that these new improvements will reduce the time required to obtain a patent to 24 months within the next 5 years.[75]

Figure 3-3
Total patents examined in Japan



Source: JPMA *Data Book 1990*.

[73] USITC staff field interviews in Japan with representatives of Japanese and U.S.-based firms, representatives of industry associations, and government officials during April, 1991.

[74] *Data Book 1990*, p. 68.

[75] "Japan Patents Wrapped in Red Tape," *The Japan Times*, August 27, 1990, p. 20. It is noted in the article that a representative of a U.S. company operating in Japan said that although foreign companies aren't deliberately discriminated against in the Japanese patent system, Japanese firms can use the patent system to obtain foreign technology.

Trademarks

In Japan, trademark rights are created by registration. Marks that can be registered include trademarks and tradenames. Service marks are now registrable as a result of recent legislation. Registration is by application to the Patent Office. The term of registration for trademarks is 10 years, but may be renewed indefinitely for further 10-year periods.

Actions for infringement are commenced in the high court, with the possibility of a limited appeal. Remedies include a permanent injunction and damages. A criminal action for trademark infringement may also be brought.

Patent Term Restoration

Patent term extension legislation was enacted in the United States in 1984 and in Japan in 1988. According to industry sources, such legislation was prompted, in part, by the decline in the average length of the effective patent life of a pharmaceutical to 10 years and 10 months. The decline in turn, was attributed to a number of factors, including the increase in the average development time of a product to about 10.6 years.[76] Industry sources in both the United States and Japan cited increases in the testing and registration procedures required by both Governments for approval of new products as one reason for the lengthened development times of new products.

In Japan, as in the United States, the Patent Restoration Act allowed for the extension of patent terms by up to five years, depending on the length of time needed for regulatory review and approval procedures. Since the Act in Japan was passed, approximately 92 patents have been extended covering 45 products. The average length of time for the extensions granted in Japan was three years and eleven months. In the United States, as of April 1990, 85 innovative products had their patents extended. However, no products were able as yet to take advantage of the full five-year extension permissible under the Waxman-Hatch Act.[77]

Decreases in the period of market exclusivity of a product reduce the amount of time during which a company may recover its investment in the product thereby potentially decreasing a company's competitiveness. The patent term extension process in the United States and Japan was considered to put the Western European industry at a competitive disadvantage,[78] thus prompting new legislation under

[76] European Federation of Pharmaceutical Industries' Associations, *Memorandum on the Need of the European Pharmaceutical Industry for Restoration of Effective Patent Term for Pharmaceuticals*, p. 7; USITC staff field interviews in the EC with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during Jan. 8-19, 1990.

[77] PMA, *The Pharmaceutical Industry: Transition to the 1990s*, 1990, p. 18.

[78] Ibid., p. 28.

the EC92 program. This legislation is expected to allow for an additional variable period of market exclusivity, capped such that the sum of the effective patent life of the product and the added time would equal 16 years.[79]

Comparison of The Impact of Patent Protection On the Industries in Two Countries

The influence of IPR on the pharmaceutical industry can best be shown through the experiences of two countries, Canada and Italy. Although many countries have strengthened their patent system or are in the process of doing so, industry representatives have stated that the Canadian patent system remains the weakest of any industrialized country and some developing countries.[80]

Compulsory licensing for bulk active ingredients (covered by Canadian patent claims) used in the preparation or production of a medicine has been in effect in Canada since 1923.[81] In 1969, the Canadian Patent Act was amended to include bulk active ingredients that were imported, rather than produced in Canada.[82] This resulted in an increase in the compulsory licensing of patented medicines[83] and a reduction in the annual growth rate for pharmaceutical research in Canada during 1970-77 to 7 percent from 18 percent during 1963-69.[84] Many pharmaceutical companies reportedly closed or moved their Canadian research facilities to the United States in response to the 1969 amendments.[85] The near demise of a Canadian research based industry resulted primarily because of (1) the concern of non-Canadian innovative companies that their patented products would be licensed, thereby earning, at most, a 4 percent royalty,[86] and (2) because of the growing dependence of many of the Canadian firms on licensing products rather than on innovation.

The Patent Act was amended again in 1987 by legislation frequently referred to as C-22.[87] The amendments, which somewhat tempered, but by no means eliminated, the compulsory licensing provision, were reportedly made in an attempt to foster a stronger Canadian industry. C-22 allowed for a deferral of the use of a compulsory license granted to a company intending to make its own brand of the product.[88] In return for this extended period of market exclusivity, innovative companies operating in Canada agreed to increase their ratio of R&D expenditures to sales in Canada to 10 percent by 1996.[89] As of 1990, the ratio of R&D expenditures to sales revenues for the industry was 8.8 percent, compared with a low of 3 percent in 1979.[90] Industry representatives, however, state that further amendments to the Canadian system will be necessary if this level of reinvestment is to be sustained.[91]

C-22 also created the Patented Medicine Prices Review Board (PMPRB). The PMPRB, an independent quasi-judicial agency, was intended to protect consumer interests by "ensuring that the prices of patented medicines are not excessive."[92] Under the aegis of the PMPRB, the price of existing patented products cannot increase more than the CPI, whereas new products are monitored by comparison to prices in other markets.

Italy, on the other hand, is an example of a country that has taken a progressive approach in regard to pricing and patent protection, thereby strengthening its industry.[93] In 1978, Italy amended its patent system to provide increased protection for pharmaceutical

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[79] U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States: First Followup Report*, Inv. No. 332-267, March 1990, p. 6-80; "14-Year Compromise on SPCs?" *Scrip*, June 19, 1991, pp. 2-3.

[80] Testimony of Gerald J. Mossinghoff, President, Pharmaceutical Manufacturers Association, before the U.S. International Trade Commission on January 17, 1991.

[81] Patented Medicine Prices Review Board, *Third Annual Report*, June 1991, p. 5; John W. Rogers, III, "The Revised Canadian Patent Act, the Free Trade Agreement, and Pharmaceutical Patents: An Overview of Pharmaceutical Compulsory Licensing in Canada," *EIPR*, 1990, p. 351.

[82] Ibid. Also, under this provision, only pharmaceutical processes, not products, could be patented.

[83] Ibid. It has been reported that between June 1969 and January 31, 1985, 599 applications for the grant of compulsory licenses to import and sell were applied for, 306 of which were granted, 15 were refused or terminated, 96 were abandoned or withdrawn, and 142 were still pending. The Report of the Commission of Inquiry, H.C. Eastman, Commissioner, cited in John W. Rogers, "An Overview of Pharmaceutical Compulsory Licensing in Canada."

[84] According to one source, compulsory licenses were granted almost routinely. Generic manufacturers simply applied for the license.

[85] "The Revised Canadian Patent Act, the Free Trade Agreement, and Pharmaceutical Patents," p. 351.

[86] Compulsory licensing affected the innovation of these companies in that it reduced their revenues, thereby potentially reducing their R&D expenditures.

[87] "The Revised Canadian Patent Act, the Free Trade Agreement, and Pharmaceutical Patents," p. 351. The amendments to the patent system were applicable only to the pharmaceutical industry. The article states that Bill C-22 was of the 33d Parliament, 2nd session, 35-36 Eliz. II (1986 to 1987). "Royal assent to Bill C-22 was given on 19 November 1987, and most sections thereof have been proclaimed."

[88] Although the companies seeking the compulsory licenses are called "generic" companies, compulsory licenses are applicable to products that are still patented (i.e., non-generic products).

[89] Patented Medicine Prices Review Board, *Third Annual Report*, p. 19.

[90] Ibid.

[91] *The Pharmaceutical Industry*, p. 49; USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[92] *Third Annual Report*, p. 3. It should be noted that the PMPRB has no regulatory authority over nonpatented pharmaceuticals.

[93] *The Pharmaceutical Industry*, p. 47; USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

products. According to industry sources, domestic and international investment in the industry, traditionally comprised of mid-sized, family-owned firms, has grown since that time, with the international share in the Italian market increasing to about 60 percent. The number of strategic alliances between Italian firms and multinational firms has been increasing, allowing foreign firms broader access to the Italian market. According to some sources, the alliances are also entered into so that foreign firms can have increased access to Italian Government agencies involved with the approval and pricing of new products.[94] Five of the top ten products in the Italian market are co-marketed.[95] In addition, Merck and Sigma Tau have entered into a research joint venture.[96] In view of these developments, the Italian industry is viewed as developing a stronger research base.[97] R&D investment in the Italian industry increased from about 133 billion lira in 1978 to about 856 billion lira in 1987.[98]

Industry Position

Industry representatives have generally been very positive about recent advancements in U.S. policy on both domestic and international IPR issues. They also viewed very favorably the potential implementation of an additional variable period of market exclusivity in the EC.[99] They expressed concern, however, about a number of issues associated with IPR worldwide.

Waxman-Hatch Act

Although generally positive about the patent restoration provisions of the Waxman-Hatch Act, industry representatives said that one aspect of the Act, i.e., the accelerated approval process for generic copies of innovative products, is disadvantageous to the industry. One source believes that the effect of the Act on the industry is similar to that of a cost-control measure.[100] Generic products can now enter the market more quickly than prior to 1984, reportedly reducing the market share of many innovative products by 35 percent in one year and by as much as 50 percent within two years.[101] This results, they said, in a compression of the time in which companies can recover their R&D expenditures. According to at least two sources in the generic industry, however, many innovative manufacturers have offset the impact of Waxman-Hatch by increasing the prices of their branded products shortly before the patents on the products expired.[102] According to industry sources in innovative firms, however, such increases help a firm to manage a product's life cycle, given pressures such as decreases in product lifetimes and increasing R&D expenditures.[103] Faced with the fast-growing challenge by generics to displace drugs near the end of their patent life, drug companies reportedly are beginning to by-pass this threat by considering the production of branded generic products and by converting their ethical drugs to OTC status, usually by alliances with other companies that already are strong in the OTC market.[104] Companies also try to introduce modified versions of the products going off patent, thereby allowing doctors a choice in products.[105]

International

According to one source, losses from patent, copyright and trademark infringement, estimated to cost the pharmaceutical industry $6 billion in 1986, could result in a decrease of $720-900 million in R&D spending.[106] PMA states that "the U.S. Trade Representative (USTR), acting on its own initiative, and the pharmaceutical industry, with the indispensable assistance of the USTR, have threatened or initiated a number of such [Section 301] actions that have enabled the government to negotiate improved patent protection in a number of countries — including Argentina, Chile, Mexico, Korea, and, most recently, in Eastern Europe. But much more remains to be done."[107] According to PMA, "hostile Governments, lack of patent protection and well-entrenched patent pirates are reducing the market share and presence of U.S. pharmaceutical companies" in countries such as Bolivia, Colombia, Ecuador, and Peru.[108] Although PMA has also stated

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[94] "Drug Alliances Increase as Margins Are Squeezed," *European Chemical News*, Dec. 3, 1990, p. 26; Merck & Co., *1990 First Quarter Report*, p. 20.

[95] Ibid. Some examples cited are: (1) Menarini and Glaxo's agreement to co-market ranitidine hydrochloride; (2) Menarini and Squibb's agreement to comarket captopril; and (3) Sigma Tau's agreement with Merck, initiated in 1982, to comarket products such as enalapril, famotidine, and simvastin.

[96] Merck & Co., *1990 First Quarter Report*, p. 20.

[97] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[98] *The Pharmaceutical Industry*, p. 47. The value for 1978 is said to be normalized in terms of 1985 lira.

[99] USITC staff field interviews in the United States, Western Europe, and Japan with representatives of multinational and domestic firms and representatives of industry associations during January-April 1991.

[100] *PMA's Three Major Areas of Focus*, p. 31.

[101] Ibid.; "A New Look at the Returns and Risks to Pharmaceutical R&D," p. 806.

[102] U.S. Senate Special Committee on Aging, *Prescription Drug Prices: Are We Getting Our Money's Worth?*, August 1989, Appendix G; "Future is Sunny for Generics as Popular Rx's Come Off Patent," *Drug Topics*, Oct. 22, 1990, p. 14.

[103] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[104] "Prescription for Cost Containment," *Chemical Marketing Reporter - Pharmaceuticals '91*, Mar. 11, 1991, p. SR4; "Future is Sunny for Generics as Popular Rx's Come off Patent."

[105] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991. The introduction of modified versions of products reportedly help a firm to maintain a good profit level.

[106] *Health Care Innovation*, p. 21.

[107] PMA submission, p. 17.

[108] Ibid., p. 22.

that the pharmaceutical industry has "strongly supported" the Trade-Related Intellectual Property negotiations underway concurrently with the Uruguay round of negotiations on the General Agreement on Tariffs and Trade (GATT), the industry "would rather have no overall GATT agreement than an agreement that fails to provide for adequate intellectual-property protection."[109]

The prehearing submission of the PMA identified Canada, Latin America, East Asia, and the Pacific Rim as being countries or regions where inadequate patent protection is of the greatest concern. In regard to Canada, the U.S. pharmaceutical industry seeks to eliminate all compulsory licensing laws. Industry representatives are primarily concerned about the compulsory license provisions of Canadian patent law which, under the 1987 amendments, can be triggered by what a Canadian government panel may determine to be excessive prices for pharmaceutical products. The industry would like to delink prices from intellectual property. They believe that IPR protection should not be based on prices.[110] Industry representatives are also concerned about differentiations in the terms of market exclusivity for products researched and developed in Canada compared with those discovered elsewhere. Products researched and discovered in Canada are granted a 20-year patent term and are exempt from compulsory licensing. Other products, however, although eligible for full protection under a Canadian patent, often realize limited terms of market exclusivity under the compulsory licensing system. For example, products discovered elsewhere in the world and produced and patented in Canada are granted market exclusivity for 7 years (i.e., domestic companies granted a compulsory license must delay marketing the product). Marketing is deferred for 10 years if the product is imported. Compulsory licenses for products intended for export are reportedly granted immediately, allowing for the immediate marketing of the product by the licensee in a third country.

Concern has also been expressed by industry representatives about the pricing guidelines developed by the Canadian authorities. The PMPRB compares the price of the product in Canada with the median price of the product in seven other countries.[111] If the price of a product is found to be "excessive," the PMPRB has the option of either ordering a price reduction or it can cancel the deferral period for the product and one other product (the latter product is said to be chosen arbitrarily by the Canadian government).[112] Canada implemented the median price system contrary to an agreement between the Canadian government and industry reached during C-22 negotiations whereby the prices of new products were to be based on a range of prices in the same 7 countries.[113] Areas of concern as cited by another source include (1) "the retention of the four-percent royalty rate" and (2) "the ability of generic manufacturers to import and stockpile patented pharmaceuticals during the deferral period."[114]

In Latin America, the main problem cited by PMA is the lack of patent coverage for pharmaceutical products, as is the case in East Asia and the Pacific Rim, especially India and Thailand. The Philippines was specially mentioned because of an ongoing effort there to remove patent protection for pharmaceuticals. New Zealand was mentioned for its compulsory license provisions.

The submission of the IBA made general references to lack of patent coverage for pharmaceuticals and particularly biotechnology products and to so-called working requirements and compulsory license provisions of the patent laws of unspecified foreign countries.

Biotechnology

In its prehearing submission, the IBA stated that while the U.S. patent system was superior in most areas affecting biotechnology inventions, it had certain drawbacks with respect to availability of protection and enforcement. The availability problem relates to process patents, where, according to IBA, a 1985 decision of the U.S. Court of Appeals for the Federal Circuit has made it difficult to obtain process patent protection for genetic engineering inventions.[115] The

[109] Ibid., p. 18.

[110] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[111] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[112] "The Revised Canadian Patent Act, the Free Trade Agreement, and Pharmaceutical Patents: An overview of Pharmaceutical Compulsory Licensing in Canada," p. 357. The article cites the following statutes: Can. Rev. Stat. §41.12(2)(e)(1987); Can. Rev. Stat. §41.12(2)(d)(i)(1987); Can. Rev. Stat. §41.12(2)(d)(ii)(1987); *Third Annual Report*, p. 6. To date, according to industry sources, the compulsory licensing option has not been exercised by the PMPRB. The *Third Annual Report* of the PMPRB states that, except for the cases still pending, many were resolved either by voluntary action on the part of the patentee or by expiration of the Canadian patent on the product. (p. 14).

[113] According to PMA.

[114] "The Revised Canadian Patent Act, the Free Trade Agreement, and Pharmaceutical Patents," p. 358.

[115] The case referred to is *In re Durden*, 763 F. 2d 1406 (Feb. Cir. 1985). *Durden* was a traditional organic chemistry case, not a biotechnology case. The holding in *Durden* is a narrow one, i.e., the fact that starting materials or final product are patentable does not itself mean that a claim to the process of making the product is also patentable. Nevertheless, examiners have cited *Durden* in rejecting biotechnology process claims. The narrowness of *Durden* has been made clearer by such recent cases as *In re Pleudemann*, 910 F. 2d 823 (Feb. Cir. 1990) and *In re*

enforcement problem relates to the manufacture of an unpatented product abroad using U.S.-patented biological materials (e.g., cells) and importing that end-product into the United States. Under present U.S. law, this does not constitute patent infringement, nor is it reachable under section 337 of the Tariff Act of 1930 as an unfair practice in the import trade. The IBA also stated that the U.S. Patent and Trademark Office has had great difficulty retaining trained personnel to examine biotechnology patent applications and to conduct timely examinations.

A more fundamental issue in pharmaceutical and biotechnology patent protection (and which arises in other technologies as well) is that of the permissible scope of patent claims. For example, in the biotechnology area, patent protection has been granted to purified versions of products that exist in nature. In such cases, the patent may cover all embodiments of the product itself, even though the patent may actually teach how to make and use that product only in embodiments of relatively low purity. When another party subsequently develops and uses a new method to make that same product in very high purity, it may be found to infringe the first party's product patent, notwithstanding that (1) the product is per se a naturally-occurring substance, (2) the patent issued to the first party may not enable those in the art to make and use the product at the purity level achieved by the second party, and (3) the very high purity product of the second party may be the more commercially viable of the two.[116] Whether a finding of infringement is justified in these cases has been criticized in a recent law review article.[117] In a recent important biotechnology patent case decided by the United States Court of Appeals for the Federal Circuit, the court was presented with the question of whether a claim to a naturally-occurring product of a specified degree of purity was invalid because the patent did not teach how to make and use that product of that degree of purity. The Federal Circuit did find the patent to be invalid, but limited its decision to the specific circumstances of that case. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991).

The Boucher bill (discussed earlier in this section in more detail) is controversial. Many favor the legislation, particularly the provision about the "obviousness" of a process. A representative of IBA has stated that ten of the top eleven biotechnology companies in the United States have endorsed this legislation. Two companies withdrew from the IBA, however, citing the association's support of such legislation as one of their reasons for withdrawing.[118] The bill is opposed by the Intellectual Property Owners Association, the American Bar Association's Section on Patent, Trademark and Copyright Law, and the American Intellectual Property Law Association. According to another source that opposes the legislation, the legislation is considered to be "special interest legislation sponsored by Genentech and Amgen to protect their products and give them rights not given under patent law."[119] Others believe that "additional uncertainty" in patent law will be generated, resulting in the expenditure of additional time and money by the industry.[120]

In regard to Japan, industry sources have indicated that the Japanese Government has generally been responsive to the needs of foreign firms in the area of IPR. There are, however, still some areas of concern.[121] The prehearing submission of the IBA specifically referred to two problems with the Japanese patent system as it relates to biopharmaceuticals. First, IBA stated that patent applications languish for years in the Japanese Patent Office before they are acted on and that during this time Japanese companies are selling these pharmaceuticals in their market, with the U.S. innovator having no recourse. Second, IBA stated that even when such patents are finally granted, they are so narrow in scope that they are easily circumvented. This can result in more cross-licensing, which reduces profits for the firm that originated the product.

Pricing and Cost-containment Policies

The enactment of cost-containment programs, price controls, or both, on a national level may result in decreased levels of R&D spending in that such programs can reduce revenues that can be reinvested in R&D programs. In turn, the implementation of policies that significantly restrict R&D efforts in a country could result in a decrease in the international competitiveness of that country's pharmaceutical industry.[122]

115—Continued

Dillon, 919 F. 2d 688 (Fed. Cir. 1990) (en banc.). Indeed, for biotechnology cases, the favorable decision in *In re Mancy*, 499 F. 2d 1289 (CCPA 1974) is widely regarded as the better and more definitive statement of the law.

[116] The issue of patent scope has arisen several times in biotechnology patent litigation. For the viewpoint of one biotechnology firm on this subject, see David Beier and Robert H. Benson, *Biotechnology Patent Act*, 68 Denver University Law Review 173, 174-76 (1991).

[117] Robert P. Merges and Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 Columbia Law Review 839 (1990).

[118] "Walkout at Biotech Group"; "Two Biotech Companies Quit Trade Association." The companies that withdrew termed the original legislation to be "protectionist" and stated that it would "distort U.S. patent law." Concerns have also been expressed about S. 654, companion legislation to H.R. 1417, which, in turn, is identical to H.R. 5664. "Biotech and Copyright Renewal Bills Are Endorsed at Senate Panel Hearing."

[119] "Patent Protection Act Seeks to Improve Competitiveness of U.S. Firms."

[120] Ibid.

[121] USITC staff field interviews in Japan with representatives of U.S.-based multinational firms and representatives of industry associations during April, 1991.

[122] Heinz Redwood, *The Price of Health*, 1989, pp. 45-6; Schnell Publishing Co., "Pharmaceuticals, 1989," *Chemical Marketing Reporter*, Mar. 20, 1989, p. SR10.

Pricing

Pricing is considered one of the "main determinant[s] of margins, research capacities, and internationalization."[123] The primary factors involved in the pricing of pharmaceutical products include costs of production, profit, and perceived therapeutic value to recoup research and development costs. As such, pricing policies have a significant impact on the industry, particularly on R&D expenditures. It has been noted by industry sources that pharmaceutical industries in countries with higher prices for pharmaceuticals, and, thereby, more revenues to reinvest in R&D, generally have well-established and stronger R&D programs as compared with industries in countries with lower-priced products (see Chapter 5 for a discussion of pharmaceutical prices and the demand for pharmaceuticals). The United States, for example, has not to date implemented price controls on pharmaceuticals and is considered by many to be the country with "the last of the free pricing."[124] Consequently, the industries in countries with higher prices are generally stronger and more competitive in that they account for a larger share of globally-successful NCEs and have been able to maintain and/or enhance their internationalization efforts.

[123] "Pharmaceutical Pricing: A Cause for French Concern," *European Chemical News*, Mar. 20, 1989, p. 20.

[124] USITC staff field interviews in the United States with representatives of multinational firms and representatives of industry trade associations during February-March, 1991.

The comparative (although not absolute) strength of the pharmaceutical industries in several OECD countries is reflected, according to one industry source, in the relative size of the pharmaceutical trade balances of the individual countries.[125] As shown in figure 3-4, Switzerland, Germany, the United Kingdom, and the United States have historically maintained the largest positive trade balances in pharmaceuticals and are considered to be the strongest industries on a worldwide basis, whereas the industries in Spain, France, and Italy have relatively weaker trade balances.[126] France and Italy have traditionally been very dependent on their home market; the United Kingdom and Germany have been less so. Japan, not yet a major player, has had negative trade balances during the past five years.

Western Europe

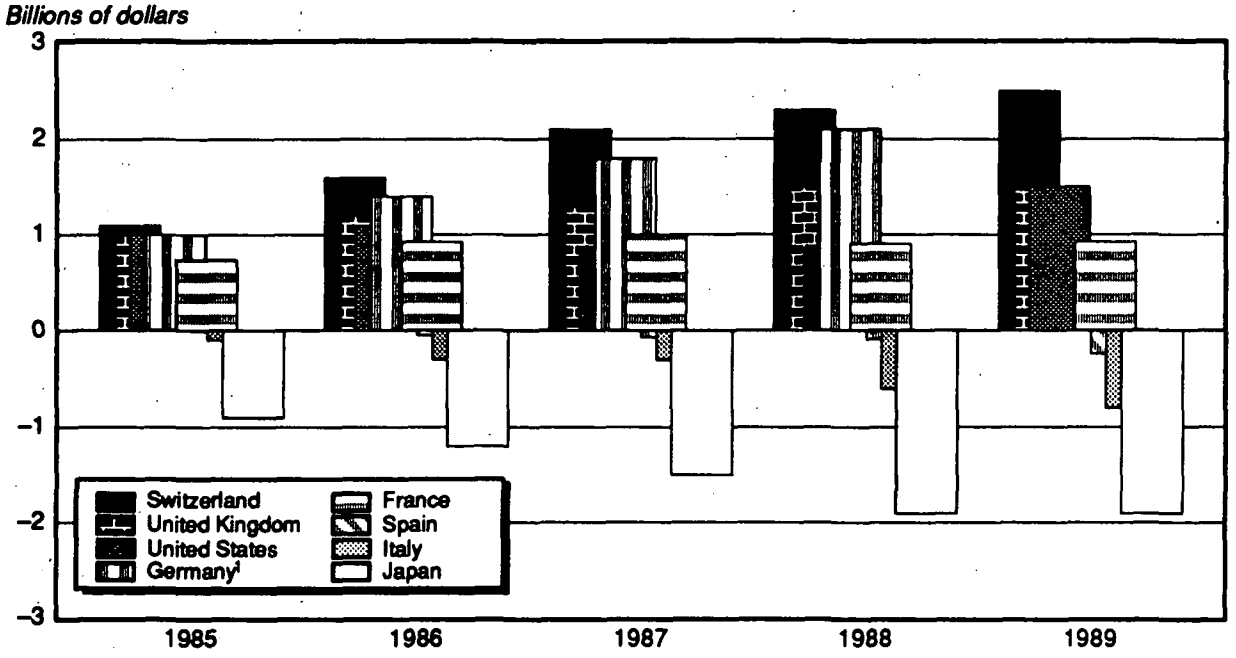
Pricing controls on pharmaceutical products marketed in the EC are implemented by almost all of the member states. In 1983, the European Court of

[125] Heinz Redwood, *The Pharmaceutical Industry: Trends, Problems, and Achievements*, 1987, p. 135; USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[126] It is interesting to note that the countries with the larger trade surpluses are those that have traditionally had higher prices for pharmaceuticals.

[127] Duphar and others vs. Netherlands (ECJ case 238/82, 1984).

Figure 3-4
Annual pharmaceutical trade balances (SITC 541)



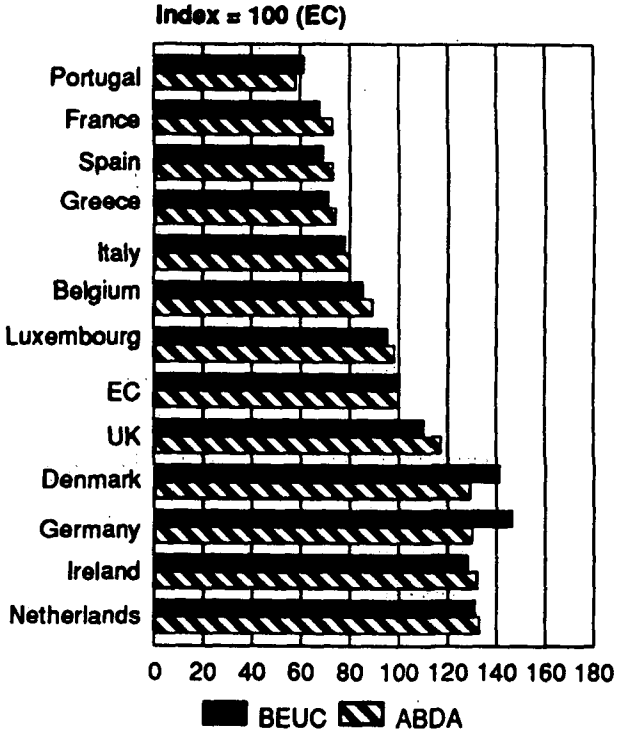
[1] 1989 data for Germany not available.

Source: U.N. Trade Data System.

Justice ruled in the Duphar case that individual member states can organize their health care and social security systems so as to increase the financial stability of these systems.[127] As such, price and profit controls were declared legal and not in conflict with the Treaty of Rome.[128] This ruling made the idea of price controls more acceptable in the EC.[129]

Decisions on pricing by public authorities are said to be influenced by "factors such as investment commitment, employment impact, and export potential." These individual pricing systems and other factors result in different prices for pharmaceutical products in each of the member states.[130,131] It is estimated that the final prices to consumers for products in member states with the highest prices and those with the lowest can vary as much as 500-1,000 percent (see Fig. 3-5).[132] Industry sources indicate that the differences in the prices generally result from differentials in such factors as: national reimbursement systems, distribution margins,[133] exchange rates, inflation rates, value-added tax (VAT) rates,[134] and the standards of living, in individual countries.[135] For example, if one assumes identical from about 40 percent higher than the manufacturer's price (Portugal) to about 270 percent higher (Denmark).[136] The pharmacist's margin in each manufacturers prices, differences in the VAT rates and in the "allowable" distribution margins in each member state can cause the price to the final consumer to range member state reportedly accounts for a large share of this difference.[137]

Figure 3-5
Relative prices of pharmaceuticals in the European Community



Source: *World Pharmaceutical Standards Review*, June 1991.

The implementation of the price controls takes many forms, ranging from actual price setting to controls on profitability to systems in which the reimbursement program implemented in a given country influences prices (cost-containment programs), as shown in the following tabulation:[138]

[128] *1992 and the Regulation of the Pharmaceutical Industry*, p. 41.

[129] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[130] According to a recent article in *European Chemical News*, (Feb. 12, 1990, pp. 11-12), the member states are ranked as follows in regard to drug pricing (in order of increasing prices): Greece, Portugal, Spain, Italy, France, Belgium, the United Kingdom, Ireland, Denmark, the Netherlands, and Germany. The article states that the president of France's pharmaceutical industry trade association believes that "the current low prices [in France] have the perverse effect of pushing firms to compensate through increased sales." According to EC Commission *Main Statistics on the Community's Pharmaceutical Industry*, (p. 11), in 1987, France accounted for about 36 percent of households' consumption of pharmaceutical products on a EC-wide basis, compared with 29 percent in Italy and 18 percent in West Germany.

[131] U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States: Second Followup Report*, Inv. No. 332-267, September 1990, p. 22-13.

[132] Leigh Hancher, *The European Pharmaceutical Market: Problems of Partial Harmonization*, p. 9. Higher prices generally exist in the northern countries, whereas lower prices generally exist in the southern countries; "Wide Differences Among Nations Pose Problems for Harmonization," *World Pharmaceutical Standards Review*, June 1991, p. 5. The data was compiled by the European Bureau of Consumers' Union (BEUC) and the German pharmacists organization (ABDA).

[134] The standard VAT rate for pharmaceuticals, for example, can range from 14 percent in Germany to zero in the United Kingdom.

[135] USITC staff field interviews in the EC with representatives of EC-based and U.S.-based multinational firms and representatives of industry trade associations during Jan. 8-19, 1990.

[136] Shearson Lehman Hutton, *A Controversial Vision of the Future: Challenges Posed by Pharmaceutical Deregulation*, February 1989, pp. 66, 76 and *EC Commission, Main Statistics on the Community's Pharmaceutical Industry, 1989*, p. 14. Many member states limit maximum margins for wholesalers and pharmacists.

[137] "*A Controversial Vision of the Future*," p. 76; "Main Statistics on the Community's Pharmaceutical Industry," p. 14. According to *A Controversial Vision of the Future*, (p. 76), this margin is generally higher in countries in which local regulations allow pharmacists to own only one store (countries cited as examples of this are Denmark, Germany, and France).

[138] *1992 and the Regulation of the Pharmaceutical Industry*, p. 29.

Country	Control of individual drug prices	Better price for local activities?
Belgium	Yes	Yes
Denmark	Effectively no	No
France	Yes	Yes
Germany	(1)	No
Greece	Yes	(2)
Ireland	No	No
Italy	Yes	Yes
Netherlands	No	No
Portugal	Yes	(2)
Spain	Yes	Yes
United Kingdom	(3)	Yes

[1] Germany instituted the Health Reform Act in 1989 (see below).
[2] Unknown.
[3] A profit control system is used in the United Kingdom (see below).

In the United Kingdom, for example, the voluntary system used is called the Pharmaceutical Price Regulation Scheme (PPRS).[139] The PPRS, enacted in 1957 as the Voluntary Price Regulation Scheme and renamed the PPRS in 1978, only addresses those brand name ethical pharmaceutical products that are sold to the Department of Health and does not apply to generic or OTC products. The PPRS is intended to maintain price levels that allow for a "reasonable return on capital" and to ensure that prices of pharmaceutical products are not raised arbitrarily.[140] The level of return on capital, or the target profit, is established through industry-government negotiations and is based on factors such as the company's degree of investment, its levels of employment and exports, associated long-term risks, and earlier financial returns.[141] The permitted returns on capital over the past 7 years are as follows:

Year	Permitted returns on capital
	Percent
1984-86	15-17
1986 (Oct.)	16-18.5
1987 (Oct.)	17-21
1988-89	Linked to the average return on capital of British industry per the "Financial Times 500" index

[139] The system, amended in 1969 and 1986, was the result of recommendations from a number of investigative committees that were created to suggest ways to limit the cost of drugs to the National Health Service (NHS). The majority of the pharmaceuticals consumed in the United Kingdom are provided through the NHS. (David G. Green, *Medicines in the Marketplace*, The IEA Health Unit, 1987, p. 8.)
[140] Shearson Lehman Hutton, *A Controversial Vision of the Future: Challenges Posed by Pharmaceutical Deregulation*, February 1989, p. 51.
[141] "UK PPRS is a Model in Europe," *SCRIP*, Mar. 29, 1991, p. 4.

Companies can maintain profits in excess of their limits in any given year if these profits result either from the launch of a new product or from the reduction of a company's costs through manufacturing efficiencies. Increased profits from external factors such as changes in exchange rates cannot be retained. If profits are too high, however, the Department of Health may (1) negotiate price reductions; (2) delay the approval of price increases; or (3) seek repayment of "excessive past profits."[142] The prices of new products are set freely by companies upon entry to the market. The PPRS also calls for a cap on promotional spending by companies. The latter is said to have more of an impact on small- and medium-sized companies because of the higher ratio of promotional spending to sales generally incurred by these firms, as compared to that of larger firms.

France, Italy, Belgium, Portugal, and Spain generally set prices based in part on negotiation and in part on consideration of factors such as exports, investments, research, wages, raw material costs, and employment levels. National price approval for products is required in Belgium, Italy, Portugal, or Spain before products can be put on the market in any of those countries.

In the EC, the Transparency Directive, which became effective January 1, 1990, sets forth procedural provisions relating to the time limits for member states making pricing decisions, the citing of criteria used by member states in making the decision, and the rights of appeal and publication of the decisions.[143] Industry sources have suggested that the directive could reduce discriminatory practices, particularly overt national practices associated with factors such as investment, that have been associated with some past official pricing decisions.

Japan

The prices for pharmaceutical products in Japan are set by the Government. In the early 1980s, the Japanese Government reportedly selected the domestic pharmaceutical industry for international expansion, "an action that lays the groundwork for coordination of trade, pricing, and health-care policies to promote overseas expansion."[144] Reportedly, however, the Japanese Government also systematically lowers pharmaceutical reimbursement prices biennially, resulting in decreased revenues to companies operating in Japan, thereby limiting the competitiveness of the Japanese industry.[145]

Prices for pharmaceuticals in Japan are set by the Special Committee on Drug Prices, part of the Central Social Insurance Medical Council (Chuikyo). The

[142] Ibid.
[143] Ibid.
[144] New York Academy of Sciences, *The Competitive Status of the U.S. Pharmaceutical Industry*, p. 76.
[145] PMA submission, p. 31.

Chuikyo acts as the Minister of Health and Welfare's advisory body on diagnosis and treatment reimbursement and drug price standards under the National Health Insurance Act and the Health and Medical Services Act for the Elderly.[146] Prices for all drugs are included in the Pharmacopeia, the official registry of approved-for-use drugs in Japan.

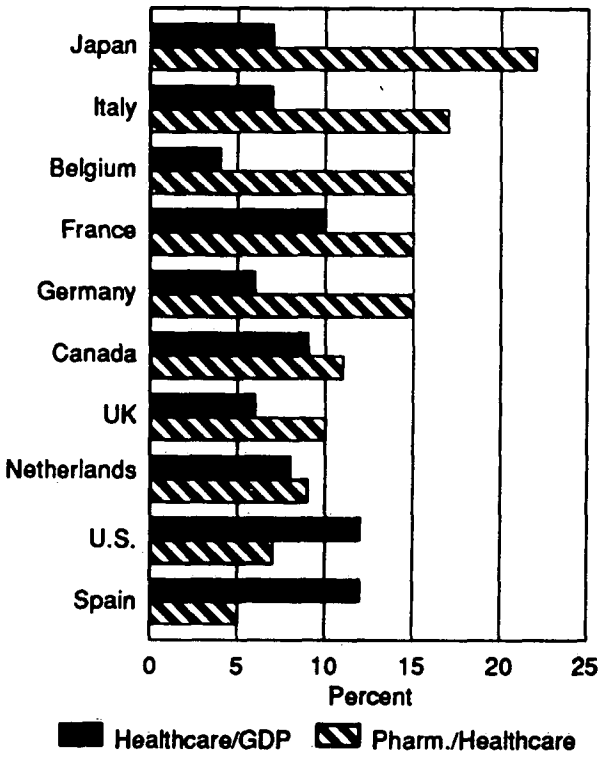
The price for a new drug is set by comparison with the National Health Insurance (NHI) price for a drug with similar properties (i.e., efficacy, structural formula, pharmacological action, etc.) already listed by the Koseisho. Should the new drug have no similarities to other listed drugs, then the Working Group receives from manufacturers detailed information on the cost of manufacturing the drug (including R&D payback) and sets the new drug price. This will be the highest price at which the drug will ever be sold in Japan. Once a pharmaceutical is given an NHI price and sold in the Japanese market for two years, its price is subject to downward revision by the Special Committee. No formal discussions are held with either sellers or consumers to incorporate their views into the decision to set a rate for price reduction.

Based on suggestions made in the Ryukinkyo report, Chuikyo has proposed certain revisions to the price setting mechanism which will enable industry to present its views as well as take into account international prices and make provisions for a special evaluation of revolutionary new drugs and orphan drugs.[147] Drugs and their prices will continued to be listed quarterly.

Cost Containment

A number of countries, including many EC member states and Japan, have implemented cost-containment programs for health care expenditures. Among other things, these programs are intended to lower the portion of health-care expenditures accounted for by pharmaceuticals. The implementation of such programs is becoming more prevalent worldwide as national health-care expenditures continue to increase in many countries. Figure 3-6 shows health expenditures as a percent of GDP in a number of developed countries in 1987 and the relative shares of these expenditures accounted for by pharmaceuticals.[148]

Figure 3-6
GDP spending on healthcare; Healthcare spending on pharmaceuticals



Source: Eli Lilly & Co.

In the United States, for example, health-care spending as a percent of GNP has increased from less than 4 percent in 1929 to about 12 percent in 1989. The percentage of the total accounted for by pharmaceuticals, however, has decreased from almost 14 percent in 1960 to less than 7 percent in the 1980s. The Japanese government, despite the full coverage afforded by the National Health Insurance, was able to keep the ratio of national health expenditures to GNP at around 6 percent, compared with 10 percent in the United States and Germany.

Although the Japanese Government's efforts to contain costs were successful during the 1970s because the GNP was growing at the rate of national health expenditures, the Japanese government started to limit the rise in health expenditures in the early 1980s. In June 1981, the official reimbursement price of drugs was reduced by nearly 18 percent. By 1986, the price reimbursement level had been reduced by nearly 50 percent, and in 1988, prices were reduced by another 10 percent. The result of this policy has been a reduction in the growth rate of pharmaceutical sales. More recently however, pharmaceutical sales have grown annually at 2 percent and are expected to continue at this rate.

United States

The Omnibus Budget Reconciliation Act of 1990 contains regulations intended to reduce Medicaid's

[146] *Health and Welfare in Japan*, Ministry of Health and Welfare, Tokyo, Japan, 1989.

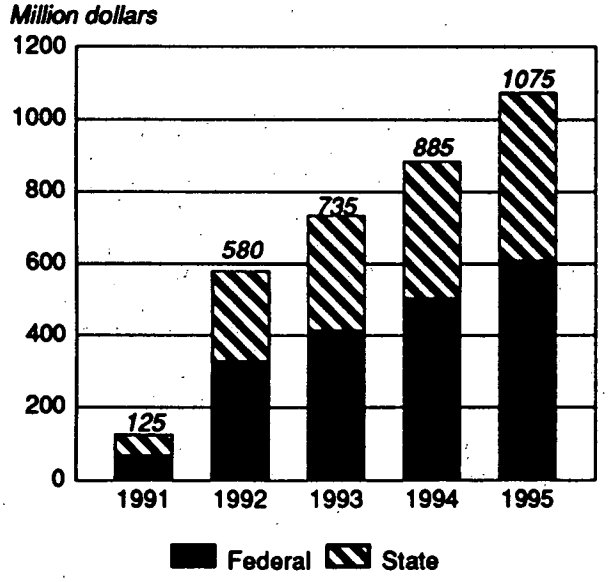
[147] The method employed by the MHW to set prices is called the 90 percent bulk-line method. Under the proposed changes to the pricing procedure, it is the goal of the Government to gradually reduce (over a ten-year period) the discrepancy allowance between the NHI listed price and the market price to 10 percent. To accomplish this end, the bulk-line method will be replaced by a weighted-average method for calculation so that official prices may better reflect the overall sales performance of a drug.

[148] Obtained during USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during Feb.-April 1991. It should be noted that the data in the chart for Japan and the United States is updated to 1989.

outlay for prescription drugs in the United States. Pharmaceutical companies are required to provide rebates to the Medicaid program in order to have their prescription drugs reimbursed by the Government. The amount of the rebate is based upon a percent of the average selling price paid to the manufacturer. The percentage paid varies on a product basis (see Fig. 3-7). Under current provisions, companies will have to rebate from 12.5 to 25 percent of their sales to Medicaid in 1991. The cap on the rebate depends on the percent of the discount provided to Medicaid. The maximum level of the rebate will increase to as much as 50 percent of a company's Medicaid sales in 1992. In 1993, the minimum rebate will increase to 15 percent, whereas the maximum rebate will be as great as that given to any other customer, regardless of the percentage of sales that customer represents.

Another Medicaid reimbursement policy currently practiced in the United States is the use of formularies as criteria for such reimbursement by about 19 states.[149] The use of formularies reportedly can result in delays within states ranging from 12-40 months before a product is granted formulary approval. These delays can, in turn, result in decreased revenue accruing from these products, thereby reducing the expected lifetime return on the new product.[150]

Figure 3-7
Expected company rebates under the Medicaid Rebate Law



Source: CBO, PMA.

[149] The number of states with formularies is current as of July 1990. "Drug Costs Hold Steady as Percent of Medicaid," *Drug Topics*, Oct. 22, 1990, p. 66.

[150] Henry Grabowski, "The Changing Economics of Pharmaceutical Research and Development," *The Changing Economics of Medical Technology*, 1991, pp. 35-52.

Western Europe

Individual member states have reimbursement systems that vary from country to country. State funding ranges from 50 percent to almost 80 percent of the total bill for pharmaceuticals under individual member state health-care systems. Pharmaceutical spending in the EC, on the average, represents about 10 to 20 percent of a country's health-care expenditures. Therefore, national authorities in some member states are implementing reforms in an effort to control expenditures. For example, Germany—traditionally a country with high prices and free pricing—recently enacted the "Health Reform Act" (HRA). The HRA fixes reimbursement levels for products that are off patent and that have a relatively high volume at a level between the generic price and the original manufacturer's price (reputedly closer to the former than the latter). The HRA does not, however, set an absolute price. Under phase 2 of the HRA, a reference price will be introduced for products that are "chemically related and are pharmacologically and therapeutically comparable," whereas in phase 3, a reference price will be introduced for "products in particular combinations of products, which are not necessarily chemically related, but which are pharmacologically and therapeutically comparable." The system has reportedly already resulted in an average decrease of about 25 to 30 percent in the prices of West German pharmaceutical products.

In the United Kingdom, there is control on profits from the sale of drugs to the public sector. The state-funded National Health Service (NHS) provides free treatment for more than 90 percent of the population. Overall, in 1986, generics accounted for 12 to 13 percent of the total value of $3.3 billion worth of drugs dispensed under the NHS. Since 1988, family physicians, in a "drug budgeting" scheme, have received regular figures showing how their prescribing patterns (generics vs. original products) compare with those of their local colleagues and with national trends, along with pricing information on the two types of drugs. The generic companies reportedly have not been happy with cost-containment measures in the United Kingdom or in general; if measures like the above cause ethical drug companies to lower prices on their drugs too far, the generic drugs will lose their competitiveness.[151]

In France, much of the costs of drugs for individual patients is reimbursed by the country's social security fund. Since French governments reportedly have kept drug prices artificially low and the industry has traditionally been dependent on its home market for a large share of its revenues, the flow of research funds to companies has been reduced. Higher drug prices were permitted in some cases, depending on companies' agreement to build plants in France. The relatively low level of R&D expenditures by French

[151] *Chemical Marketing Reporter*, Mar. 20, 1989, p. SR12.

companies has generally resulted in a reduction in the number of global NCEs developed by the French industry since 1979.[152]

As of August 1991, in a continuing effort to reduce national expenditures on pharmaceuticals, the French Government will reportedly reduce sales of French pharmaceutical companies by 2.5 percent and increase patient's copayments. The methods used to reduce companies' sales will include: (1) decreasing the prices of products; (2) removing products from reimbursement lists; and (3) withdrawing products from the market. The reduction is expected to primarily affect companies with sales of over $16.9 million.[153]

In Italy, the government reportedly removed around 900 drugs from the reimbursement list in 1990[154] and reclassified many other medicines so that patients will have to pay for 30 to 40 percent of their costs. The Government also reportedly lifted a price freeze on drugs in line with the above-noted EC directive, which could trigger a long-term increase in pharmaceutical prices in that country.[155]

Japan

The Japanese National Health Plan, initiated in 1961, promoted rapid growth in public health expenditures and increased drug sales. Under the National Health Insurance system, Japanese patients are required to pay only a fraction of the full cost of a prescription drug; the balance is paid by National Health Insurance. By the mid 1980s, drugs accounted for between 30 and 35 percent of Japan's national health expenses and the Japanese Government reportedly began lowering both the prices of domestic pharmaceutical products and reimbursement levels. Prices have decreased by approximately 8-9 percent a year over the past decade.[156] In 1984, the plan was amended to introduce 10 percent patient cost-sharing for insured people.[157] As a result, the growth rate of pharmaceutical sales has declined. There was a 1.6 percent drop in the value of Japanese drug production in 1984. More recently however, pharmaceutical sales have grown annually at 2 percent and are expected to continue at this rate.

Japan also established the Health and Medical Services System for the Elderly program, in which disparities in medical costs for the elderly were rectified, and, as a result of subsequent amendments, allowed for an element of "cost-sharing and apportionment" for elderly insured persons.[158]

The Effect on Industry R&D

Levels of R&D spending in the pharmaceutical industry often decline as the result of the enactment of price controls and/or cost-containment programs on a national level in that these controls can reduce revenues that can be reinvested in R&D programs.[159] According to one source, "No country that has practiced cost-containment in health care at the expense of its pharmaceutical industry has managed to nurture a pharmaceutical industry that can compete globally."[160]

In the EC, individual pricing systems and other factors in member states result in different prices for pharmaceutical products in each of the member states.[161,162] This price differentiation in the individual Western European countries can result in increased parallel trade, particularly from the southern member states, trade barriers, or both. Parallel importation is the importation of a product from a low-priced country into a higher-priced country.[163]

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[152] "European Drug Makers Face Major Shake-Out," *Chemical Marketing Reporter - Pharmaceuticals '90*, Mar. 19, 1990, p. SR34.

[153] "French Want Sales Cuts by August," *SCRIP*, No. 1628, June 26, 1991, p. 2. According to "European Drug Makers Face Major Shakeout," many in the industry expect the implementation of the Transparency Directive to result in higher prices in France, thereby making it necessary to increase patient's copayments and/or to take products off the reimbursement list. The latter option could hit small-to-medium sized companies the hardest, particularly those making "low-cost, relatively ineffective medicines." Conversely, according to the article, higher prices would help the industry's effort to internationalize by providing funding for the development of globally successful pharmaceutical products.

[154] Italy, like France, has one of the highest per-capita rates of drug consumption in Europe.

[155] Ibid.

[156] "Japan," *Business Week*, p. 70; *Time*, Jan. 8, 1990, pp. 56-58.

[157] Ministry of Health and Welfare, *Health and Welfare in Japan*, 1989, p. 16.

[158] Ibid.

[159] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[160] Heinz Redwood, *The Price of Health*, 1989, p. 45.

[161] According to a recent article in *European Chemical News*, (Feb. 12, 1990, pp. 11-12), the member states are ranked as follows in regard to drug pricing (in order of increasing prices): Greece, Portugal, Spain, Italy, France, Belgium, the United Kingdom, Ireland, Denmark, the Netherlands, and Germany. The article states that the president of France's pharmaceutical industry trade association believes that "the current low prices [in France] have the perverse effect of pushing firms to compensate through increased sales." According to EC Commission *Main Statistics on the Community's Pharmaceutical Industry*, (p. 11), in 1987, France accounted for about 36 percent of households' consumption of pharmaceutical products, compared with 29 percent in Italy and 18 percent in Germany.

[162] U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States: Second Followup Report*, Inv. No. 332-267, September 1990, p. 22-13.

[163] *The European Pharmaceutical Market*, p. 9. It should be noted that in the EC, through parallel trade, patented products can move between countries regardless of whether they are patent protected in the country in which they are ultimately sold. It would not be possible to have similar movement of patented products between a lower priced country and the United States, however, since

Several countries that have implemented cost-containment programs have seen their industries shift from within their borders. Japanese companies, for example, are now said to be facing pressure to enter foreign markets. Innovation in Canada reportedly declined as a result of its compulsory licensing program. Price and promotion controls in France apparently weakened the domestic industry.[164] Since the French Government owns about one third of the French industry, the Government must perform the dual task of balancing its industrial policy to develop the pharmaceutical industry while controlling prices of pharmaceutical products.[165]

In some cases, national governments can regulate pharmaceutical pricing and reimbursement in such a way as to favor domestic industries. The PPRS, for example, has resulted in increased investment in the UK industry. France is said to provide indirect R&D incentives for local firms or foreign-based firms with significant investment levels in France by allowing for such things as more rapid product approval and better domestic prices.

In light of this, many companies believe that it is necessary to enter into comarketing agreements with French partners and to maintain production and/or research facilities in France to compete there. However, at least one company, citing discrimination in regard to pricing negotiations, is said to be considering the option of building a new factory in another Western European country rather than adding investment in France.[166]

Industry Position

The United States is considered to be one of the last countries in the world with a relatively unencumbered economy in regard to pharmaceuticals. As of 1990, however, legislation was enacted that requires pharmaceutical companies "to provide steep rebates to the Medicaid program in order to have their prescription drugs reimbursed by the Government. The rebate is less for the makers of generic copies than for the pioneering manufacturers."[167] This legislation is perceived by representatives of the pharmaceutical industry as the first stages of cost-containment efforts in the United States in that the level of rebate directly affects a company's profits.[168] Some industry sources have suggested that the cost-containment program was prompted, in part, by increases in the prices of pharmaceuticals during the 1980s that reportedly exceeded the increase in the inflation rate.[169] These increases are perceived to have been the industry's "main strategic response" to a combination of pressures facing the industry, including higher R&D costs and shorter product life cycles.[170]

Although the Medicaid market currently represents a relatively small share of the domestic pharmaceuticals market (about 10-15 percent by value), industry sources believe that a significantly larger portion of a company's revenues could be subject to the rebate provisions by 1993, given the expected increase in the rebate level to about 15-50 percent and higher, as described earlier in this section. If state and third-party programs then implement similar procedures, a company's profits could decline by a significantly larger amount since a larger portion of its sales would be affected.[171]

The Medicaid system is said to be similar in concept to the reference pricing system in Germany, which uses the concept of therapeutic clustering.[172] Therapeutic clustering is the grouping of drug products for similar indications at similar price levels for reimbursement by either health insurance plans or national health systems, regardless of whether the products are patent protected.[173] Therapeutic clustering is expected to exacerbate the impact of cost-containment programs. If the products are patent protected, the companies essentially lose revenues, in spite of being granted national market exclusivity for the product. Consequently, one industry representative indicated that cost-containment efforts are viewed as undercutting domestic IPR protection.[174]

163—*Continued*

products that have U.S. patents cannot be imported into the United States by anyone other than the patent holder(s) and/or any U.S. licensees of the patent holder(s).

[164] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991; *Medicines in The Marketplace*, p. 16.

[165] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[166] USITC staff field interviews in the United States and Western Europe with representatives of European-based and U.S.-based multinational pharmaceutical firms and other sources during January-April, 1991; "Multinational Drug Firms Said Hesitant to Invest," *World Pharmaceutical Standards Review*, June 1991, p. 6.

[167] PMA submission, p. 14. The Medicaid market constitutes about 10 percent of the U.S. prescription drug market. Concern exists, however, that any program implemented for Medicaid could eventually be adopted by other domestic health insurers.

[168] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[169] USITC staff field interviews in the EC with representatives of EC-based and U.S.-based multinational firms and representatives of industry trade associations during Jan. 8-19, 1990.

[170] "The Changing Economics of Pharmaceutical Research and Development," p. 35-52.

[171] USITC staff field interviews in the United States and Europe with representatives of EC-based and U.S.-based

[172] The HRA has reportedly already resulted in an average decrease of about 25 to 30 percent in the prices of West German pharmaceutical products.

[173] Such clustering is expected to be implemented in future phases of the West German cost-containment system.

[174] The decrease in revenues would also have an impact on R&D expenditures.

Industry sources have stated that, if it is necessary to have price controls, the PPRS (described earlier in this section) is probably one of the best, particularly if compared to the reference pricing system implemented under the Health Reform Act in Germany.[175] The PPRS is credited with having increased investment in the UK pharmaceutical industry and balancing cost-containment measures with industry policy. One source argues, however, that despite the fact that the U.K. industry "has a good record of investment and innovation, . . . it is likely that it could have been still more successful if it had not been for the curtailment of profits through the PPRS."[176] The French Government is reportedly considering the implementation of a "French-style PPRS" with the goal of increasing the profitability of the French industry.[177]

In regard to the Duphar case,[178] according to industry sources, a positive feature of the ruling is the provision that member states, when making decisions in regard to either pricing or reimbursement, must do so based on objective and verifiable criteria. This wording, also used in the Transparency Directive, allows firms operating in the EC to do so on a more level playing field, regardless of parentage, and to anticipate with more certainty the national conditions that must be met.[179]

The industry has also expressed concern about the increase in parallel imports that could occur as the result of continued differentials in price in the EC. Industry sources expect that the increase in parallel trade, which, under this scenario could result in as much as a 10-20 percent decrease by value in the EC market, would affect primarily the multinational firms that market products throughout the EC. According to the European Federation of Pharmaceutical Industries Associations (EFPIA) and the Pharmaceutical Manufacturers Association (PMA), the undercutting in price that results from parallel trade would decrease revenues and thus potentially have a negative impact on R&D. As prices are considered the "main determinant of margins, research capacities, and internationalization," the enactment of price controls leads pharmaceutical firms to question the economic merit of introducing new products.[180]

The Transparency Directive, which became effective January 1, 1990, addresses part, but not all, of the industry's concern on the pricing of pharmaceutical products in the EC. Industry sources have suggested that the directive could reduce discriminatory practices, particularly overt national practices associated with factors such as investment, that have been associated with some past official pricing decisions. The industry "questions any implication, however, that the directive would in any way positively impact trade." Industry representatives stress that the directive does not address the issue of restrictive price controls or the effect of parallel imports on prices once the single market is created.[181] All member states are considered "free to keep such restrictions in place or, if they so choose, to impose even more onerous restrictions."[182]

Product Liability

United States

Product liability law in essence deals with the right of a consumer to sue the manufacturer of a product for injuries caused by a perceived defect in the product. Lawsuits about defective products are particularly prevalent in the field of pharmaceuticals. One source estimated that liability insurance and litigation defense costs account for over 95 percent of the price of a childhood vaccine.[183] In recent years, injury awards have increased steadily, with the average payment topping the $1 million mark in 1986, due in part to the rise in punitive damage awards.[184] Liability concerns have led to the practice of "defensive medicine" — taking steps not considered clinically necessary in order to defend against charges of negligence — and substantial increases in health care costs.[185] Product liability litigation has driven at least one U.S. pharmaceutical firm into bankruptcy.[186] Although product liability concerns generally affect all companies operating in a given geographical area, it is possible to argue that the domestic industry bears a large share of the impact inasmuch as the domestic industry often incurs a major portion of its revenues from its home market.[187]

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[175] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[176] David G. Green, *Medicines in the Marketplace*, The IEA Health Unit, 1987, p. 30.

[177] "The Big Squeeze," *Chemical Marketing Reporter - Pharmaceuticals '91*, Mar. 11, 1991, p. SR44.

[178] See section on price control in Western Europe for more details on the case.

[179] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[180] U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States*, p. 22-13; USITC staff field interviews in Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry trade associations during April, 1991.

[181] Ibid.; Intradepress, *Eurobrief*, Feb. 23, 1990, p. 142.

[182] Ibid.

[183] P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 3.

[184] Merck & Co., *Health Care Innovation: the Case for a Favorable Public Policy*, p. 33; P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 127.

[185] W. Olson, *The Litigation Explosion* (New York, 1991), pp. 6, 218.

[186] USITC staff interview with representative of U.S. industry during April 1991.

[187] For example, according to a representative of PMA, U.S. pharmaceutical sales accounted for 55-57 percent of total pharmaceutical sales of U.S.-based innovative companies in 1989.

Common Law

In the United States unlike many other countries, product liability law is mainly common law determined by the courts rather than statutory law passed by legislatures.[188] It is made particularly complex by the fact that it is mostly governed by the courts of the fifty States rather than the Federal Government. A dispute over the safety or efficacy of a drug can lead a manufacturer into extended and costly litigation in fifty separate jurisdictions, so that defenses have to be proven again and again.[189]

Strict Liability

The last two decades have seen a significant shift in the way the law deals with defective products. Originally, a manufacturer could be held liable only if an injured consumer could prove that the producer was negligent in making its product. Now, under the legal theory of strict liability, applicable in many jurisdictions, a plaintiff must prove that the product was defective and that it caused injury, but need not prove that the manufacturer acted negligently.[190]

Attempts have been made to accord pharmaceuticals special treatment on the grounds that drugs often have dangerous side-effects but can be of great benefit to human health. One court held that prescription drug manufacturers are not strictly liable for injuries caused by their products so long as the drugs were properly prepared and accompanied by warnings of their dangerous propensities that were either known or reasonably scientifically knowable at the time of distribution.[191] The U.S. pharmaceutical industry supports that holding and hopes that other courts will follow it. However, the holding has not been adopted on a nation-wide basis, leaving the industry with a large degree of uncertainty about how courts will handle pharmaceutical cases.[192]

Government Approval Defense

Some countries permit a manufacturer to defend against a product liability suit on the ground that a governmental authority such as the FDA has tested and approved the product as safe. This governmental approval defense insulates a manufacturer from liability provided the firm has not practiced fraud in its application for approval and has manufactured the product according to the government's standards. U.S. courts generally do not recognize such a defense, and producers face potentially enormous liability even after the government has declared the product to be essentially free of defects.[193] In at least one instance,[194] a drug was driven off the market entirely by product liability suits even though the FDA had approved, and continued to approve, it, and most of the lawsuits were won by the drug manufacturer. An industry source suggested that the drug might be available to consumers if U.S. law had a governmental approval defense.[195]

A clear indication of the difference between U.S. and foreign liability laws came with the attempt by several British plaintiffs in one drug liability dispute to sue the drug maker in U.S. courts. These individuals found that British law was not favorable to their claim because the British Government's Health Ministry had approved the drug and such approval was a defense against liability suits. As noted above, U.S. courts generally do not permit a drug manufacturer to defend against product liability claims based on governmental approval. In this instance, the British plaintiffs did not succeed in bringing their suit in the U.S., but they showed that such transatlantic claims may be made in the future.[196]

Insurance

Drug companies seek to protect against liability through insurance. Industry sources state that this option has become increasingly difficult to exercise in recent years. Insurance companies have become wary of pharmaceuticals because of the significant number of large awards that courts and juries have made to plaintiffs in suits involving drugs. One drug manufacturer has found that its insurers dispute many claims, particularly the amount of legal defense expenses, and pay slowly, requiring the manufacturer to engage in expensive collection procedures.

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[188] P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 3.

[189] USITC staff interview with representative of U.S. industry during June 1991.

[190] Merck & Co., *Health Care Innovation: the Case for a Favorable Public Policy, p. 29; P. Huber, Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 37. See also *Greenman v. Yuba Power Products*, Inc., 59 Cal. 2d 57, 27 Cal. Reptr. 697, 377 P.2d 897 (1963), and *Evans v. General Motors Corp.*, 359 F.2d 822 (7th Cir. 1966), *cert. denied*, 385 U.S. 836 (1966).

[191] *Brown v. Superior Court (Abbott Laboratories)*, 44 Cal. 3d 1049, 751 P.2d 470, 245 Cal. Rptr. 412 (1988). See also *Restatement (Second) of Torts*, section 402A, comment k (Some products currently cannot be made safe; these are especially common in the field of drugs).

[192] USITC staff interview with representative of U.S. industry during June 1991. Firms have been held liable in spite of extensive warnings. In one case, a jury found a manufacturer liable for failing to warn of a danger even though the FDA had considered and disapproved that warning. *Wooderson v. Ortho Pharmaceutical Co.*, 235 Kan. 387, 681 P.2d 1038, *cert. denied*, 469 U.S. 965 (1984), cited in R. Kingham, Pharmaceutical Manufacturers Association, statement to the Senate Committee on Commerce, Science, and Transportation, May 10, 1990.

[193] An opponent of such a defense might argue that regulatory agencies provide only minimum standards that may not prevent behavior that is in compliance with those standards from also being negligent. P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 48.

[194] Industry sources state that there have been other instances as well.

[195] USITC staff interview with representative of U.S. industry during June 1991.

[196] Ibid.

Some insurers have gone bankrupt. Others now write more restrictive policies and rule out entirely coverage of such products as birth control drugs and vaccines, which creates a significant disincentive to undertake the development of new products in these areas.[197]

Legislative Action

Some jurisdictions have attempted to limit the impact of product liability litigation. Eighteen states have imposed by statute a ceiling on the amount of damages, variously punitive or non-economic, that a plaintiff can collect. Twenty-one states permit the imposition of penalties on plaintiffs filing frivolous complaints.[198] Utah, Arizona, and Oregon have adopted a governmental approval defense, and New Jersey and Ohio have passed broader bills covering that and other issues.[199]

Seeking an overall solution for a decade, pharmaceutical companies have pressed Congress to take action. In partial response, Congress passed the National Childhood Vaccine Injury Act of 1986.[200] As live biological agents, vaccines usually must contain a risk of disease in order to be effective. Consequently they are particularly vulnerable to product liability claims. Industry sources state that concern over liability has resulted in fewer companies making vaccines, and fewer vaccines being made. Under the Vaccine Injury Act, the Department of Health and Human Services runs a National Vaccine Injury Compensation Program which maintains a fund for paying victims for vaccine-related injury and death. To collect, a victim must file a petition with the U.S. Claims Court.[201] Although the statute does not preclude suing the vaccine manufacturer in another court, limitations on damages are placed on such suits. For example, a manufacturer cannot be held liable if injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and accompanied by proper directions and warnings.[202] The Vaccine Act is seen as a constructive step, but as having been hampered at first by lack of funding and administrative delay. Also, plaintiffs have not been eager to take advantage of the fund because awards tend to be smaller than those in normal liability suits, particularly with respect to attorneys' fees.[203]

Several liability reform bills have been introduced in Congress over the past few years. Among them were H.R. 1115, introduced in 1987, and S.1400, considered in 1990. S.1400 would have, among other provisions, introduced a government approval defense under which drug manufacturers could defend against punitive damage claims by showing that their product was approved by the FDA.[204] No broad federal liability reform bill has been passed, however, and industry sources see little hope of passage in the near future.[205]

Western Europe

In 1985, the European Community (EC) issued Directive 85/374 on liability for defective products.[206] In the recitals prefacing that directive, the EC found that differences among member state liability laws distort trade and hamper the free movement of goods and the formation of a common market for consumers.[207] In 1988, the EC issued a related decision on a system for rapid information exchange on dangers arising from the use of consumer products.[208] In 1989, the EC Commission proposed a directive, complementary to the liability directive, on general product safety.[209] The EC Commission has also proposed a directive establishing rules on liability of polluters for waste, and plans a directive on liability for defective services.[210]

The product liability directive (Directive 85/374) aims at harmonizing EC member state laws, many of which deny redress to an aggrieved consumer unless he can prove that a producer has been negligent. In contrast, the EC directive instituted a form of strict liability, requiring an injured consumer only to prove that a product was defective and that the defect caused

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[197] Particular products adversely affected by product liability have been thalidomide, intra-uterine birth control devices, and tetracyclines. USITC staff interview with representative of U.S. industry during April and June 1991. Deductibles tend to be set high, often in the $ 15-20 million range. Merck & Co., *Health Care Innovation: the Case for a Favorable Public Policy*, p. 30.

[198] Merck & Co., *Health Care Innovation: the Case for a Favorable Public Policy*, pp. 34-35; P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 202.

[199] USITC staff interview with representative of U.S. industry during June 1991.

[200] Pub. L. 99-660, Title III, § 301, Nov. 14, 1986, 100 Stat. 3755, 42 U.S.C. § 300aa-1 et seq..

[201] 42 U.S.C. § 300aa-11.

[202] 42 U.S.C. § 300aa-22(b).

[203] USITC staff interview with representative of U.S. industry during June 1991.

[204] *Washington Post*, May 23, 1990, p. C1; R. Kingham, Pharmaceutical Manufacturers Association, statement to the Senate Committee on Commerce, Science, and Transportation, May 10, 1990.

[205] USITC staff interview with representative of U.S. industry during June 1991.

[206] Directive 85/374 of July 25, 1985, *OJ* No. L 210/85; see U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States* (Investigation No. 332-267), USITC Publication 2204, July 1989, pp. 6-37 to 6-38, and USITC, *The Effects of Greater Economic Integration Within the European Community on the United States—First Follow-Up Report*, USITC Publication 2268, March 1990, pp. 6-120 to 6-124.

[207] Utz Toepke, address to ABA-EC conference, "Europe 1992," June 8, 1990.

[208] Decision 89/45 of Dec. 21, 1988, *OJ* No. L 17/89.

[209] *OJ* No. C 193/89.

[210] Fourth Progress Report of the Commission to the Council and the European Parliament concerning the implementation of the Commission's White Paper on the completion of the internal market. COM (89) 311 final (June 20, 1989).

injury. A producer can use certain defenses, such as the fact that the product's defect was due to compliance with mandatory regulations issued by public authorities. Under the directive, a consumer can also bring suit against the importer of a defective product, and, if the producer cannot be identified, against the supplier of the product.[211] Although the directive has instituted strict liability, one source opined that the EC liability standard will remain more limited than the U.S. standard even if Congress passes one of the proposed reform measures it has considered.[212]

Once a directive is passed by the EC, it must then be implemented by each member state before it can become fully effective. The product liability directive had an implementation deadline of July 30, 1988. Since then, after a slow start, most member states have attempted to comply with the implementation requirement. However, the EC Commission has brought actions before the European Court of Justice to seek revision of the United Kingdom's Consumer Protection Act[213] and a measure passed by Italy,[214] which the EC Commission considered to not comply with the directive.[215]

Even after full implementation, differences among member states will remain. These differences involve the types of damages covered, the jurisdiction of various national courts, and court procedures. For example, the United Kingdom and Ireland permit "preaction discovery," a milder counterpart to U.S. pretrial discovery, by parties in lawsuits, whereas many other EC countries do not.[216] Moreover, by the terms of the directive itself, member states may pass implementing legislation that is more stringent than the directive, in that the legislation may cover more products and exclude some defenses provided in the directive.[217]

In Switzerland, the Code of Obligations covers most product liability claims. This code, covering contracts, extra-contractual relations, and commercial matters, was enacted over 60 years ago and is considered by some to be outdated in that it does not fully address the issue of product liability.[218] Various articles of the Code of Obligations permit suits that in the United States might be termed product liability claims.[219] Although Swiss law provides for strict liability in certain areas,[220] medical drugs, narcotics, and vaccines fall under a series of statutes that do not impose such liability.[221] Instead, drugs must be registered with the authorities and must comply with regulations covering such aspects as packaging.

Certain aspects of Swiss law suggest that product liability claims would be less prevalent in Switzerland than in the United States. As discussed above, strict liability applies with respect only to a limited number of products, and not at all to drugs. In most cases, negligence must be proved. The defense of contributory negligence is usually available. Unlike the United States, Switzerland has a relatively short statute of limitations, under which a plaintiff must sue within one year after learning of the claim.[222] Indeed, compared to U.S. law, the corpus of Swiss product liability law is relatively modest, although a significant case law exists in which injured consumers have sued manufacturers for defective products.[223] Because product liability is a relatively small area of law, most Swiss companies, aside from operators of railways and other sectors covered by special liability statutes, have seen little need for liability insurance.[224]

In general, liability suits are brought less frequently in Europe than in the United States. In Europe, unlike in the United States, attorneys generally cannot conduct extensive discovery, obtain jury trials, or collect contingency fees. In the European Community, British courts see the largest number of such suits; however, in the United Kingdom, a victorious defendant can collect attorneys' fees from the plaintiff, thus discouraging frivolous claims.[225]

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[211] The consumer's chance of success is increased under the Brussels Convention, which provides EC plaintiffs with a choice of jurisdictions in which to sue. Convention on Jurisdiction and the Enforcement of Judgments in Civil and Commercial Matters, signed at Brussels Sept. 27, 1968.

[212] Wendell Wilkie II, General Counsel, U.S. Department of Commerce, address to ABA-EC conference, "Europe 1992," June 7, 1990.

[213] Consumer Protection Act 1987, Part 1, effective Mar. 1, 1988.

[214] Presidential Decree No. 224 of May 24, 1988, effective July 30, 1988; Report drawn up on behalf of the Committee on Legal Affairs and Citizens' Rights, Apr. 28, 1989, p. 9.

[215] EC-US Business Report, Vol. 2, No. 4, Apr. 1, 1990, pp. 7-8.

[216] Utz Toepke, address to ABA-EC conference, "Europe 1992," June 8, 1990.

[217] For example, Germany, Greece, Portugal, and Spain have imposed a cap on the amount of damages a plaintiff can receive; the other member states have not. Utz Toepke, address to ABA-EC conference, "Europe 1992," June 8, 1990, and conference materials, Tab H, p. 5.

[218] The Swiss Department of Justice established a study commission to comprehensively revise Swiss civil liability law. ORGALIME, *Product Liability in Europe: A Practical Guide for Industry*, April 1989, p. 46. That effort has not yet affected product liability. USITC staff interview with representative of the Swiss Government during June 1991.

[219] *See* Articles 41, 55, 97, and 184-215. W. Freedman, *Products Liability: An International Manual of Practice*, Oceana Group, Switzerland, pp. 2-3.

[220] Article 58 of the code imposes strict liability for fixtures such as a high crane temporarily erected on a construction site. Statutes outside the code impose strict liability on certain areas such as nuclear power plants, pipelines, and motor vehicles.

[221] For example, vaccines are covered by four statutes, at SR 812.21, 812.24, 812.111, and 812.112. If a drug contains a poison, it must also comply with the Poisons Act.

[222] ORGALIME, *Product Liability in Europe: A Practical Guide for Industry*, April 1989, p. 47.

[223] USITC staff interview with representative of Swiss Government during June 1991.

[224] W. Freedman, *Products Liability: An International Manual of Practice*, Oceana Group, Switzerland, p. 58.

[225] USITC staff interview with representative of U.S. industry during June 1991.

Japan

Traditionally, product liability claims have been dealt with in Japan under the general law of torts as codified in Article 709 of the Civil Code.[226] This law requires a plaintiff to prove negligence to recover for injuries based on a defective product. Japanese law generally does not impose strict liability for defective products.[227]

In recent years, product liability has received more attention in Japan, largely due to the influence of the U.S. experience.[228] Nevertheless, pharmaceutical companies have found in general that they are sued much less frequently in Japan than in the United States.[229] Product liability claims, even in instances of mass injury, apparently are often settled by negotiation rather than litigation, partly because Government consumer centers set up throughout Japan encourage and assist in settlement of disputes.[230]

Lawsuits based on allegedly defective drugs do occur, however. One U.S. pharmaceutical manufacturer noted that it was involved in a major lawsuit in Japan that had lasted for several years and that threatened a significant exposure, but had not actually resulted in large awards. A source at that firm stated that Japanese consumers traditionally have not been eager to sue, but the legal climate is changing and that more frequent litigation was likely in the future.[231]

The Japanese Government has sought ways other than litigation to handle injured consumers. In 1979, a law was passed establishing the Drug Fund for Adverse Reaction Relief. In 1987, the law was amended to add to the fund's activities the promotion of research into such areas as drugs and medical equipment.[232] Since 1980, the fund has provided benefits to individuals harmed by adverse reactions to drugs. Pharmaceutical firms in Japan are required to make monetary contributions to the maintenance of the fund,[233] and the Japanese Government subsidizes it as well.

Industry Position

The U.S. product liability system, according to industry sources, has resulted in a decline in the competitiveness of U.S. companies compared with foreign firms.[234] Unlike non-U.S. companies, U.S. pharmaceutical manufacturers must factor the cost of liability claims into the price of their products. Foreign companies operating in the United States face the same risk of litigation as U.S. companies, but the size of their exposure is much less because only their U.S. assets can be seized.

Industry sources state that several aspects of the U.S. product liability system, that usually do not exist overseas, lead to larger numbers of lawsuits and larger awards to plaintiffs. Contingency fees permit a plaintiff with few financial resources to hire a lawyer, who receives no fee unless he wins the case. In the U.S. industry's view, the contingency fee arrangement increases the lawyer's incentive to seek a large award and to resist settlement. Product liability cases can be tried by juries, who often are unversed in complex technology. The U.S. legal system permits extensive, and to the industry excessive, discovery, which gives a plaintiff's attorney license to examine a drug company's files for evidence of imperfect methods of drug design and production.[235]

Innovation in the U.S. industry is stunted by concern over potential liability because juries are more likely to find a new product defective than an old, familiar one.[236] According to some sources, the specter of product liability exposure has led pharmaceutical companies to shy away from research, particularly into areas such as obstetrics and birth control.[237] The United States has experienced a vaccine shortage and refusals by physicians to vaccinate.[238] Also, U.S. pharmaceutical companies find it more attractive now to make their products outside the U.S. in order to escape U.S. liability law.[239]

One pharmaceutical company noted that withdrawing a drug from the U.S. market because of liability concerns can often lead to withdrawal from overseas markets as well even though the risk of liability in other countries can be far less than in the United States. The need to withdraw overseas comes from the need to maintain an image as a good corporate citizen. When a drug is pulled from U.S. store shelves but not withdrawn in other countries, the manufacturer may encounter criticism that it is discriminating against

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[226] If a breach of contract is involved, Article 415 of the Civil Code is the relevant law.

[227] Z. Kitagawa, *Doing Business in Japan* (1989), Vol. 7, § 4.01.

[228] Ibid.

[229] USITC staff interview with representative of U.S. industry during April 1991.

[230] Z. Kitagawa, *Doing Business in Japan* (1989), Vol. 7, § 4.10.

[231] USITC staff interview with representative of U.S. industry during June 1991.

[232] Law No. 55, 1979, amended by Law No. 32, 1987.

[233] All firms who manufacture or import and market drugs contribute annually, and all drug firms whose products have caused injury that resulted in payments by the fund contribute an additional amount. Z. Kitagawa, *Doing Business in Japan* (1989), Vol. 7, § 4.08[3].

[234] USITC staff interview with representative of U.S. industry during April and June 1991; P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 229.

[235] USITC staff interview with representative of U.S. industry during June 1991.

[236] P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), pp. 14, 157.

[237] Research expenditures by U.S. companies working on contraceptives peaked in 1973 and plummeted 90 percent in the next decade. P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), p. 155.

[238] The number of U.S. companies producing childhood vaccines went from 13 in 1981 to three at the end of the decade. According to one of them, the drop was due to liability costs. Merck & Co., *Health Care Innovation: the Case for a Favorable Public Policy*, pp. 3, 31.

[239] USITC staff interview with representative of U.S. industry during April and June 1991.

non-U.S. consumers by selling them defective drugs, even if there is nothing wrong with the drug. In addition, the U.S. is often the largest market for a drug, so that the non-U.S. world market is too small to make production of the drug worth the manufacturer's investment.[240]

Tax Law

United States

The U.S. corporate tax system is complex, and a comprehensive description or analysis is well beyond the scope of this section. Accordingly, this section is limited to a brief description of key features of U.S. corporate tax law, with special emphasis on those provisions identified by the U.S. pharmaceutical industry as important to the well-being of the industry. This section focuses only on Federal tax law. However, it should be noted that States and localities impose taxes of various kinds, including income taxes, which, though generally less than Federal taxes, can be significant and may affect the competitiveness of firms and industries.

The Tax Reform Act of 1986 substantially revised U.S. income tax laws. In general, rates on taxable income of both individuals and corporations were substantially reduced, but numerous deductions and credits were either eliminated or made less generous. The 1986 Act also repealed certain exclusions, in effect in various forms since 1921, applicable to most longterm capital gains. Since passage of the 1986 Act, most capital gains have been taxable at ordinary income rates.

Rules regarding depreciation of tangible personal and real property have changed significantly several times since 1981. The Accelerated Cost Recovery System (ACRS), which applied to tangible depreciable property placed into service after 1980, was amended in 1986 by the Tax Reform Act of 1986 and is now generally known as the Modified Accelerated Cost Recovery System (MACRS). The MACRS, which generally is not as generous as the original ACRS, applies to all tangible depreciable property placed into service after 1986. In general, the time for tax cost recovery under MACRS is longer than under ACRS. As a result, annual tax deductions available to all firms, including pharmaceutical firms, are effectively reduced.[241]

One tax law of particular interest to the pharmaceutical industry is the research and experimentation (R&E) tax credit. In general, a 20-percent tax credit is allowed for qualified research[242] expenses paid or incurred by a taxpayer during a taxable year that exceed the average amount of the taxpayers's yearly qualified research expenses in the base period, which is generally the preceding 4 taxable years.[243] The credit also applies to certain payments to universities for basic research.[244] The law is temporary rather than permanent and is presently scheduled to expire on December 31, 1991. It is this temporary aspect of the law that is of particular concern to the domestic industry. Pharmaceutical research generally involves a long-term commitment of funds and personnel by a firm. This requires long-term planning, which can be inhibited by the uncertain future of this law.

Research eligible for the credit must be undertaken for the purpose of discovering information that is technological in nature, the application of which may help in the development of a new or improved business component of the taxpayer.[245] Substantially all of the research must constitute elements of a process of experimentation related to a new or improved function, performance, or reliability or quality.[246] There are a number of activities for which the credit is not allowed, including research after commercial production, marketing surveys, and foreign research.[247]

Another concern of the U.S. pharmaceutical industry is section 861 of the U.S. tax code. Section 861 contains detailed rules for allocating, among other things, R&D and certain other expenses in the case of multinational corporations. Until 1986, U.S. multinationals could deduct up to 100 percent of their U.S. R&D against U.S. source income even when they had significant foreign source income from the same category of products to which the R&D was directed. Under Treasury regulations issued in 1977 (regs. section 1.861-8, but on which Congress had placed a moratorium through 1986), U.S. multinationals would have been able to deduct automatically only 30 percent of their U.S. R&D against U.S. source income, with the remainder to be allocated between foreign source income and U.S. source income. In the Tax Reform Act of 1986, Congress set the percentage at 50 percent for a two-year period, and has subsequently annually set the percentage at 67 percent, overriding the 30-percent provision in the Treasury regulations. The current temporary provision, which U.S. firms would like to see made permanent,[248] is set to expire at the end of 1991, after which the 30-percent provision in the Treasury regulations will come into effect. Because some foreign countries do not allow deductions under their tax laws for expenses of R&D activities conducted in the United States, multinational firms with significant foreign source income but which perform a disproportionately high share of their R&D in the United States are unable to fully deduct their

[240] USITC staff interview with representative of U.S. industry during June 1991.

[241] 26 U.S.C. 168(b)(4).

[242] The term "qualified research" covers both in-house research and contract research expenses.

[243] 26 U.S.C. 41(a) and (c).

[244] 26 U.S.C. 41(a)(2).

[245] 26 U.S.C. 41(d)(1)(B).

[246] 26 U.S.C. 41(d)(1)(C) and (d)(3)(A).

[247] 26 U.S.C. 41(d)(4).

[248] See, e.g., submission to the USITC of the Pharmaceuticals Manufacturers Association, Feb. 8, 1991, p. 2; and Merck & Co. publication "Health Care Innovation: The Case for a Favorable Public Policy, p. 61 (1988).

U.S. R&D expenses either directly against U.S. source income or indirectly against foreign source income and through any unused foreign tax credits. Generally, the smaller the percentage that can be deducted automatically (and thus the larger the percentage that must be allocated), the greater the amount of R&D expense deduction that is likely to be lost. This, some U.S. firms argue, encourages U.S. firms to shift R&D operations from the United States to countries which allow deductions for R&D expenses but do not allow deductions for R&D activities conducted in the United States.[249]

One provision of the tax code that has been beneficial to the pharmaceutical industry is section 936. Basically this section grants tax preferences to U.S. firms operating in Puerto Rico and was also designed to encourage reinvestment of profits to stimulate economic development in U.S. possessions. Under section 936, qualified domestic corporations may receive a credit equal to the portion of earnings from subsidiaries in U.S. possessions, such as Puerto Rico. To be eligible, at least 75 percent of this income must be derived from the active conduct of business; the remainder may be passive income derived from investments in "eligible" activities. As a result of section 936, a number of the major U.S. pharmaceutical firms have manufacturing facilities in Puerto Rico.

It should also be noted that the United States taxes U.S. persons on their worldwide income, including their foreign income. However, a tax credit generally allows U.S. taxpayers to reduce the U.S. tax on their foreign income by the foreign income taxes that they pay on that income. In the case of foreign business operations that are conducted directly, as through a foreign branch, income for such foreign operations would be reported on U.S. tax returns for the year in which it was earned and it generally would be taxed currently along with U.S. income. In general, in the case of indirect foreign operations, a U.S. shareholder of a foreign corporation defers payment of U.S. taxes on the imcome from those operations until the foreign corporation repatriates its income.

Foreign Countries

Like U.S. tax law, foreign tax laws tend to be intricate and reflect social custom, practical considerations in collection, and government policy. Direct comparisons between U.S. and foreign tax laws, particularly with respect to general corporate tax rates or industry-specific deductions, such as depreciation, tend to be very difficult and can be meaningless if not placed in the broader context of the whole tax system. For example, a country with a high nominal rate on taxable income but with many opportunities for deductions and credits may have a lower effective rate of tax than another country with a much lower nominal rate but fewer opportunities to take deductions or credits. Similarly, a liberal system of deductions and credits directed at an industry may be of little or no benefit, and thus provide little inducement for additional investment if the industry has little in the way of profits or taxable income. Moreover, local taxes levied on corporations are often significant: the trade tax levied on corporate income by localities in Germany raises about the same amount of revenue as the German Federal corporation tax. In addition, some countries (e.g., in the EC) rely relatively heavily on indirect taxes, such as value-added and excise taxes, and are less dependent on direct taxes, such as corporate and personal income taxes.

Unlike the United States, most developed countries either do not tax individuals on their long-term capital gains (e.g., Germany, Switzerland, the Republic of Korea, Taiwan, Italy, Belgium, and the Netherlands), or tax them at a rate substantially below that for ordinary income (e.g., Japan taxes long-term capital gains at a rate of 5 percent, and Sweden taxes gains on assets held over 2 years at a rate of 18 percent). However, most developed countries tax corporations on their long-term capital gains at ordinary income rates. With respect to corporate dividends, some countries (e.g., the Netherlands and Switzerland) follow the classical system (used in the United States) and in effect tax dividends twice, once at the corporate level and once at the individual shareholder level. However, Italy and the United Kingdom follow an imputation system, under which shareholders receive a tax credit, and Germany follows a "split-rate" system, under which distributed profits are taxed at a lower rate than undistributed profits. Some countries, such as Japan, follow the U.S. approach and tax domestic taxpayers on their worldwide income, but others, such as Switzerland, generally do not.

Like the United States, Japan has adopted tax policies designed to stimulate research and development, but Japanese incentives tend to be more directed to specific sectors.[250] Apparently the dispensation of tax incentives permits MITI to allocate incentives as it deems appropriate, a practice which reportedly favors high-technology industries. Japan reportedly has 19 different tax incentive systems to encourage technological innovation, including an R&D tax credit similar to that of the United States. In addition, it had in effect between 1985 and 1988 a Key Technologies Tax Credit, equal to 7 percent of the acquisition cost of assets used in specified technologies or 20 percent of the corporate income tax, whichever is greater.

Industry Positions

Several industry groups have addressed tax issues of interest to the industry. In general, industry groups identified three areas in the field of taxation that would

[249] Merck publication, p. 61. For a summary of arguments, see also *Tax Reform Act of 1986: Report of the Committee on Finance [on] H.R. 3838 . . .*, Rept. No. 99-313, 99th Cong., 2d Sess., p. 705.

[250] The material in this paragraph is from T. Howell et al., *The Microelectronics Race: The Impact of Government Policy on International Competition*, 1988, pp. 67, 132-33.

strengthen the pharmaceutical industry: (1) restructuring the R&E tax credit and making it permanent; (2) reducing the cost of capital by reducing the tax on capital gains and encouraging long-term savings and investment; (3) resolving issues raised by section 861 by permanently setting a percentage of R&D expenditures for allocation against U.S. income.

In submissions in conjunction with the Commission's hearing in this investigation, both the IBA and the PMA asserted that the R&E tax credit should be made permanent.[251] PMA explained that "Continued double-digit increases in pharmaceutical R&D investment shows that the credit has been effective."[252] In addition, IBA called for a restructuring of the R&E credit to make it more effective in helping small biopharmaceutical companies to fund research activities. IBA called for removal of the cap limiting the credit to 50 percent of the increase in qualified R&E over the base period, explaining that the cap "serves to penalize the very high growth companies whose R&D investment will improve American competitiveness."[253] IBA also said that the limitation of credit availability to investments incurred "in carrying on" existing trade or business effectively precludes new trades and businesses from using the credit:

> Because of the "in carrying on" restriction, the R&E expenses leading to many of America's most significant small business innovations would not have been eligible for the credit, including for example the R&E leading to human growth hormone. In fact, the most significant innovations by definition involve a new line of business and would not be eligible for the existing credit.[254]

IBA asserted that the costs of capital for U.S. firms "far exceed" the costs to foreign competitors, and advocated that government policy focus "on encouraging investors to take a long-term perspective by enacting a capital gains differential that emphasizes long-term investments."[255] IBA said that this would "increase the availability of 'patient' capital that research-oriented companies need, and it will tend to make the market less volatile."[256] IBA noted several major trading countries where capital gains either are not taxed (e.g., the Republic of Korea, Germany, Italy, Belgium, and the Netherlands) or are taxed at rates substantially below the rates on ordinary income (e.g., Japan).[257]

[251] IBA statement submitted Dec. 28, 1990, p. 19; and statement of PMA President Gerald Mossinghoff, received Jan. 3, 1991, p. 15.
[252] PMA statement, p. 15.
[253] IBA statement, p. 20.
[254] Ibid., p. 21.
[255] Ibid., pp. 8-9.
[256] Ibid., p. 9.
[257] Ibid., pp. 8-9.

R&D Incentives

All the major pharmaceutical producer countries provide at least some government support for pharmaceutical R&D through funding of basic medical research. However, the nature and scope of the support as well as funding mechanisms vary considerably. In addition, many governments support pharmaceutical R&D indirectly through funds allocated to higher education and through specific tax incentives designed to encourage private sector R&D.[258]

In general, R&D is an important factor affecting a country's ability to sustain economic growth.[259] Industrial R&D generates technological changes that allow for the development of new products and improvements in manufacturing and services production. As a result, successful R&D generates real growth in national income. Government R&D policies generally focus on the support of basic research because it is likely to affect a variety of industries and may be underfunded by the private sector. Less direct funding is provided for product development activities because the private sector is more likely to allocate levels of funding consistent with private and social efficiency.[260]

Government funding of pharmaceutical R&D, particularly in the United States, follows this general pattern. Governments may focus on certain areas as a result of health or economic development priorities, but tend to concentrate funding on basic research rather than product development.[261] Assessing the effectiveness of government-funded pharmaceutical R&D is difficult because of spill-overs from and into other sectors and because of the relatively small percentage of total R&D funded by government.

International Comparisons of Government R&D

Cross-country R&D data developed by the Organization for Economic Cooperation and

[258] For example, the U.S. Government allows for a 20 percent tax credit for certain R&D expenses. The efficacy of the credit is questionable because of its temporary nature, according to some industry sources.
[259] See, for example, R.M. Solow, "Technical Change and the Aggregate Production Function," *Review of Economics and Statistics*, 39, 1957, pp. 312-320.
[260] Basic research and, to some extent, precompetitive product development run the risk of being underfunded in the private sector for three reasons. First, firms cannot always appropriate the output of R&D. Because private returns may be considerably lower than public returns, under-investment may occur. Second, basic research generates externalities; other firms can act as free-riders. Finally, in some cases the scale of a research effort may be too extensive (either in terms of economies of scale or in terms of time) to be undertaken by a single firm. OECD, *Industrial Policy in OECD Countries: Annual Review, 1990*, p. 108.
[261] For example, government support for R&D in the biotechnology sector is motivated by biotechnology's numerous backward and forward linkages to other industries.

Development (OECD) exist for the 1970s. However, the categories used include health research outside of pharmaceutical development and also include some government funding of higher education.

Comparable data do not exist for more recent years and are difficult to estimate. Expenditures on pharmaceutical research are often included in broader categories and are not easily disaggregated. Measuring government support for biotechnology R&D (related to pharmaceutical development) is even more difficult because much of the research deals with areas unrelated to pharmaceutical or medical research. In addition, funding for pharmaceutical and biotechnology research is managed by a variety of agencies in different countries and often includes joint private-public activities.[262] The remainder of this section will review trends in the United States, the EC, and Japan.

United States

Federal Government support for medical research continues to exceed funds allocated by other national governments.[263] This support is directed through grants and programs largely administered by the Department of Health and Human Services (HHS); the majority of this activity is carried out by the National Institutes of Health (NIH). In addition, the National Science Foundation (NSF) supports research directly or indirectly related to medical/biotechnology research. Although total R&D conducted by HHS accounts for less than 15 percent of total U.S. Government-sponsored R&D, basic research conducted or managed by HHS accounts for about 41 percent of total U.S. Government-funded basic research. Table 3-1 shows Government research funds for fiscal years, 1988-92, excluding general Federal Government support to universities. NIH is the primary vehicle for direct U.S. Government support for pharmaceutical R&D. Funding is allocated to R&D conducted by NIH and for grants administered by NIH.

Europe

The various European Governments provide funds for health-related R&D and higher education. In addition, the EC provides separate funding for R&D through its framework programs,[264] which fund basic or precompetitive research. Table 3-2 shows funding for health and biotechnology R&D during 1987-91 and 1990-94 under the EC Framework Programs.

During 1987-91, the EC allocated 65 million ECU for a medical and health research program that was to increase the efficiency of the Community's medical research and health-care efforts.[265] EC funding for the

[262] Lower funding of health R&D on the part of these countries relative to the United States may be explained, in part, by the free-rider concept. Just as the private sector tends to under-invest in basic research, so too may other governments, perhaps hoping to benefit from spill-overs in U.S. funded research.

[263] Based on incomplete information.

[264] The framework programs were established to coordinate R&D projects that among other criteria were too large and/or complex to be conducted by individual countries. USITC, *The Effects of Greater Economic Integration Within the European Community On The United States: Second Followup Report*, p. 16-16.

[265] Ibid.

Table 3-1
U.S. R&D funding (obligations) for medical and health research and other science support, fiscal years, 1988-92

Agency	1988[1]	1989	1990	1991[2,3]	1992[4]
	Millions of dollars				
HHS:					
Total R&D	7,161	[3]7,892	[3]8,506	9,273	9,836
NIH R&D	6,612	[1]7,145	[1]7,576	8,277	8,775
Basic research:					
Total	4,086	[3]4,417	[3]4,714	5,101	5,477
NIH				4,634	4,968
R&H facilities	22	[3]14	[3]77	130	186
NSF (total R&D)	1,722	[1]1,886	[1]1,944	2,239	2,643
Total Federal Government R&D	58,773	[3]63,051	[3]63,712	64,111	72,078
HHS as percent of total	12	[3]13	[3]13	14	14
Total Federal Government basic	9,468	[3]10,487	[3]11,397	12,320	13,314
HHS as percent of total	43	[3]42	[3]41	41	41

[1] Actual.
[2] Enacted.
[3] Estimate.
[4] Proposed.
Source: *Chemical and Engineering News*, various issues.

Table 3-2
EC Research Funding for Life Science Research Under the Framework programs

Framework program	*Sums in million ECU*	*Proportion of total budget (percent)*
1987-1991:		
Health	80	1.5
Biotechnology	120	2.2
1990-199:		
Biotechnology	164	2.4
Biomedical and health	133	2.3

Note.—One ECU equalled approximately 1.2 dollars during 1987-91

Source: *The Effects of Greater Economic Integration Within the European Community On The United States: Second Followup Report*, USITC Publication 2318, September 1990, p. 16-7.

BRIDGE (Biotechnology Research for Innovation, Development and Growth in Europe) program amounted to 100 million ECU (1990-94). The program's purpose is the facilitation and promotion of communitywide biotechnology research and establishment of Community regulations for biotechnology.[266]

Outside of its framework programs, the EC funds programs or organizations that focus on product or process development, such as EUREKA.[267] EUREKA extends beyond the EC and includes the EFTA countries and Turkey. EUREKA coordinates private sector and institutional R&D efforts. Project areas include medical technology and biotechnology.

Japan

Because of differences in the structure of funding, it is extremely difficult to draw comparisons between the level of the Government of Japan's (GOJ) funding and that of other governments. Funding data are incomplete, but indicate that the GOJ continues to allocate significantly less to medical research than levels supported by the U.S. Government.

The GOJ funds medical and general life sciences (including biotechnology) research through the Ministry of Health and Welfare (MHW), the Science and Technology Agency (STA), the Ministry of International Trade and Industry (MITI)[268] and the Ministry of Education, Science, and Culture (Monbusho). Preliminary estimates of R&D funding for the life sciences in fiscal year 1991 amount to approximately 99 billion yen.[269] These funds are allocated among the above agencies.

The 99-billion yen budget understates total government expenditures because it does not include items such as personnel expenditures, basic research grants (under control of Monbusho), and special coordination funds (STA). However, the "life sciences" category includes areas of research unrelated to medical (and, more specifically, pharmaceutical) R&D. Thus, it overstates "pharmaceutical R&D."

The GOJ, through its various agencies, funds research in areas such as cancer control, human genome, the clarification of biomechanisms, and AIDS control. Much of the GOJ support for R&D is channeled through various institutes and organizations such as the Research Development Corporation of Japan. (JRDC). Some of these organizations, such as the JRDC, receive funds from the private sector as well.

Export Policies

The domestic pharmaceutical industry has been concerned about certain U.S. export policies for some time. Until recently, a provision in the FDCA effectively banned the export of a new drug that had not been approved in the United States, even when the country of destination had already approved the product. This provision was thought to restrict U.S. competitiveness and to encourage overseas manufacturing by U.S. firms.

As a result of the export restriction, companies had an incentive to establish manufacturing facilities abroad for unapproved drugs, particularly since drugs were often approved overseas prior to being approved in the United States. These overseas manufacturing facilities could then service all other foreign markets in which the drug was approved and might eventually be used to supply the U.S. market as well, since other countries generally have not imposed export bans.

The export ban was thought to be especially troublesome for biotechnology companies with interests in biopharmaceuticals. Such companies tend to be relatively small and often lack the capital to establish foreign manufacturing facilities when their new products are approved overseas in advance of being approved in the United States. If such firms enter into foreign marketing agreements and cannot manufacture in the United States, they may be obliged

[266] Ibid., pp. 16-14.
[267] European Research Cooperation Agency. EUREKA is not EC-controlled.
[268] Research is limited to biotechnology.
[269] Over $700 million, at a conversion rate of 135 yen to the dollar. Source: U.S. Department of State.

to transfer their technology so that the foreign partner can manufacture and market the product overseas.

Drug Export Amendment Act of 1986

In 1986, the law was amended via the Drug Export Amendment Act of 1986 (DEAA). The DEAA expressly authorizes exports of unapproved pharmaceuticals to certain countries that are deemed to have effective drug approval regimes when certain conditions are satisfied.[270] It removed, at least partially, a disincentive to manufacture certain unapproved drugs domestically.

Under the DEAA, the exporter must apply to the Secretary of Health and Human Services (i.e., the FDA) for permission to export 90 days prior to shipment. The exportation of certain unapproved drugs can be allowed by the Secretary if: domestic approval of the drug is being actively pursued and the drug has not been previously disapproved; the ultimate country of destination is one of those expressly enumerated in the law[271] and the drug has been approved in that country; the drug is manufactured in accordance with "good manufacturing practice"; the label lists the countries for which export is authorized; and the manufacture of the drug is not contrary to the public health and safety of the United States.

The law effectively limits the exportation of an unapproved drug to those countries that have effective drug approval and regulatory regimes[272] and that have actually approved the particular drug. If a drug is actually disapproved in the United States, then it cannot be exported under the DEAA even if the foreign country of destination has an effective regulatory regime and has approved the drug.

The DEAA restricts reexports, but it does not really provide for the effective means of policing and enforcing such restrictions. France, the United Kingdom, Germany, and Switzerland reportedly do not ban the export of unapproved drugs.[273] Thus, U.S. firms may be at a relative disadvantage, and, moreover, the controls themselves may not be entirely effective in preventing unapproved drugs from reaching their final destinations.

Industry Position

Absent the DEAA, many companies would have to abandon foreign markets or build plants abroad, leading to the export of technology from the United States.[274] The pharmaceutical industry has, however, expressed concern about three aspects of the Act. First, a number of important markets are believed to have been omitted from the eligible list, including countries in South America, the Middle East, and Eastern Europe.[275] Second, a company cannot export a product that, although approved for marketing overseas, would not be approved in the United States because it includes an inert substance that is currently not allowed in the United States (i.e., certain food dyes, etc.). One solution suggested by industry representatives is to grant approval on the basis of the active ingredient, rather than on a specific formulated product.[276]

Third, the process to obtain FDA approval to export products under this Act is considered cumbersome. Industry sources state that since foreign marketing approvals for new products can be granted within a span of a few months and such exports require prior FDA approval on a country-by-country basis, companies can end up submitting duplicate applications to the FDA every few months, particularly when approvals are sought in EC member states.[277] One suggestion to improve this process, in regard to the EC, would be to grant a company approval to market a product in the EC on an overall basis once the product is approved in a predesignated number of member states, eliminating the need for 12 separate applications. This concept could be extended to approval to market to the rest of the world, assuming that approval is granted for a predesignated number of countries/regions. Industry sources said that modifying the Act in regard to these issues would help companies make decisions as to where to establish future production facilities.[278]

Tariff Barriers

United States

Customs' tariff rates on pharmaceutical products are generally low and are not considered to affect international trade flows significantly.[279] The

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[270] Pub. Law 99-660, 100 Stat. 3743 (21 U.S.C. 382).

[271] The countries to which an unapproved drug can be exported include the countries of the European Economic Community (not including Greece), the countries of the European Free Trade Association, and Australia, Canada, Japan, and New Zealand.

[272] Section 802 of the Food, Drug and Cosmetics Act (21 U.S.C. 382(b)(4)(B)) sets forth the criteria that should be considered in determining whether a country has an effective drug approval and regulatory regime.

[273] Senate Report No. 99-225, reprinted in 1986 U.S. Congressional and Administrative News, p. 6331.

[274] OTA, *New Developments in Biotechnology 4: U.S. Investment in Biotechnology*, July 1988, pp. 104, 179, 180.

[275] Within the EC, Greece was omitted.

[276] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during January-April 1991.

[277] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991 and per a conference, entitled "American Pharmaceuticals in the Global Village: International Implications of National Regulations," co-sponsored by the American Foreign Service Association and PMA, on June 13, 1991.

[278] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[279] See, e.g., *The Competitive Status of the U.S. Pharmaceutical Industry* (National Research Council 1983), p. 681.

increased globalization of the pharmaceutical industry has meant that tariffs operate as less of a protective trade mechanism and more of a nuisance simply adding to the cost of a final product. Nontariff barriers (such as the overall regulatory regime, which is covered elsewhere in this chapter) are considered to be more important in affecting competitiveness. Nevertheless, all customs tariffs, regardless of level, influence trade and competitiveness to a degree, and certain pharmaceutical products may be subject to relatively higher tariff rates.

Accordingly, the United States and the EC authorize the temporary suspension of import duties under certain circumstances. In 1990, for example, the temporary suspension of import duties by the United States amounted to approximately $200 million. In addition, the U.S. pharmaceutical industry has been supporting an effort in the GATT Uruguay Round negotiations to eliminate global pharmaceutical tariffs entirely. In December 1990, the United States, the EC, EFTA, Canada, and Japan announced their support to eliminate tariffs on pharmaceuticals (the so-called zero-for-zero proposal).

Thus, although tariffs are seen generally to be relatively less important in influencing competitiveness, efforts have been and are being undertaken to suspend individual tariffs temporarily or to eliminate them entirely. The unilateral and multilateral efforts in this regard are indicative of the globalization of the industry.

Western Europe

Because of the large volume of trade in pharmaceuticals to Western Europe, recent changes in the EC's procedure for duty suspensions have been of particular interest to the industry. In August 1989, the EC Commission issued a communication containing new guidelines.[280]

According to the guidelines, the Community, in principle, will not grant duty suspensions when identical, equivalent, or substitute products are manufactured in sufficient quantities within the Community; when the subject goods are finished products intended for sale to consumers without further processing; when the goods are subject to an exclusive trading agreement; when the benefits are unlikely to be passed on to Community processors, producers, and consumers; and when the suspension could distort competition or conflict with other Community policy. Despite the fact that the procedure is mainly for raw materials and the like, the communication provides that the suspension of tariffs on components imported for "pure-and-simple assembly" should be avoided.

[280] See EC Commission, *Communication Concerning Autonomous Tariff Suspensions*, Official Journal of the European Communities, No. C 235 (Sept. 13, 1989) [Communication], p. 2.

Industry Position

The U.S. industry has argued that the new EC guidelines are tougher and that the EC Commission has indicated that they will enforce and scrutinize applications for duty suspensions more carefully and more stringently than they have in the past. PMA stated that the "tougher guidelines . . . will result in reduced access to duty suspension for the U.S. pharmaceutical industry operating in Europe. . . .These guidelines pose a cost to U.S. companies importing into Europe [and] may force some to consider relocating production facilities (and jobs) to the European Community."[281]

These duty suspension guidelines may effectively limit the availability of duty suspensions for pharmaceutical products for numerous reasons. The guidelines indicate that the Community generally will not grant duty suspensions for goods subject to an "exclusive trading agreement." Pharmaceutical firms often rely on restrictive trading arrangements for international trade in active ingredients in order to protect their patent rights. It remains to be seen how these criteria will be interpreted and administered, but it could effectively exclude from eligibility goods under patent, or goods subject to an exclusive license or distribution agreement. In addition, applying the criteria of "substitutable product" may also be problematic because very different pharmaceuticals may have the same or similar applications or uses. The Community has tended to interpret what is substitutable broadly.[282] The increased difficulty in obtaining duty suspensions in Europe may increase the possibility that U.S firms will move production facilities to Europe.

Summary

Because of the complexity of the policies examined in this chapter and the fact that several of these are in force at any given time, thereby compounding their impact, it is difficult to rank them on a quantitative basis. Anecdotal information from Commission interviews with the industry is not sufficient to rank them qualitatively because of the different emphasis placed on the individual policies by each firm, depending on the firm's size, focus, or both.[283] Whereas these policies may have some positive features, several also have the potential to reduce industry revenues, thereby potentially decreasing the industry's level of innovativeness. Decreases in the R&D productivity of the industry can decrease the competitiveness of the industry.

In the United States, for example, the increased regulatory requirements of the FDA generated by the Kefauver-Harris amendments to the FDCA were primarily intended to protect consumers from products

[281] Written submission from the Pharmaceutical Manufacturers Association.

[282] Based on conversations with industry sources in May 1991.

[283] The firms did all agree, however, that all of the policies discussed were significant to the industry.

that are fraudulent, unsafe, and not efficacious.[284] Most developed countries developed similar regulatory requirements in the wake of the thalidomide tragedy.[285] Lengthy delays in granting product approval in any one country, however, can shorten a product's patent lifetime in that market, thereby decreasing the time a company has to recoup its R&D investment. Such delays are said to result in changes in companies's marketing strategies, since they can't depend on a set time period to complete the approval process. Although comparison of review times in the United States and abroad can be difficult, industry sources state that a perceived differential in approval times between the United States and other countries prompts many companies to seek market approvals overseas first.

If a U.S. company seeks or receives approval to market its product(s) in one or more countries prior to receiving approval in the United States, the company is faced with a decision as to how to best supply the foreign market. Although the U.S. Drug Export Act removed, at least partially, a disincentive to manufacture certain unapproved drugs domestically, the U.S. industry is concerned that the current structure of the Act limits the competitiveness of the industry in that it omits a number of markets and precludes exportation of products that might never be approved in the United States because of differences in standards. Because other countries reportedly have not enacted similar legislation, U.S. pharmaceutical firms believe that they are placed at a competitive disadvantage.

Delays in regulatory approvals can be partially offset by patent restoration programs. To date, such programs have been implemented in the United States and Japan; legislation on the issue is pending in the EC.[286] In the United States, although the Waxman-Hatch Act extends a product's period of market exclusivity, it also allows for faster approval and market entry of generic products. Industry sources estimate that generic products now decrease the market share of branded products by almost 50 percent in the first two years after being launched on the market.[287]

In general, although the patent systems in the United States, Western Europe, and Japan are viewed as offering comparable protection and enforcement, some concern has been raised by industry representatives as to certain administrative aspects of the Japanese patent process. They have also expressed concern about countries and regions with inadequate patent protection.

Price controls, cost-containment programs, or both, have been implemented throughout Western Europe and in Japan, primarily in an effort to offset growing national health-care expenditures. Although the impact attributed to them might be contributed to, in part, by other factors, price control and cost-containment programs can limit or reduce revenues to firms, thereby potentially decreasing R&D expenditures.

National industries are affected differently, depending on the type of program implemented. In France, for example, the government has reportedly kept drug prices artificially low, thereby reducing the flow of research funds to companies. The UK industry has traditionally had a good record of innovation despite the implementation of the PPRS. Although some believe that the industry's level of innovativeness could have been higher in the absence of the PPRS and that the program will result in decreased innovativeness in the future, others cite the increased investment in the industry that resulted from the PPRS as a positive feature. Industry sources maintain that, if it is necessary to have price controls, the PPRS is probably one of the best systems, particularly if compared with the reference pricing system implemented under the Health Reform Act in Germany.

The United States, considered by many to be one of the last countries in the world with a relatively unencumbered economy in regard to pharmaceuticals, recently enacted legislation under the Omnibus Budget Reconciliation Act of 1990 that requires pharmaceutical companies to provide rebates to the Medicaid program to have their prescription drugs reimbursed by the Government. The Medicaid system is said to be similar in concept to the reference pricing system in Germany. Programs such as the HRA, which utilize the therapeutic clustering concept, result in companies losing revenue on patent-protected products, despite the fact that these products have been granted national market exclusivity.

The U.S. product liability system, according to industry sources, has resulted in a decline in the competitiveness of U.S. companies compared to foreign firms.[288] Unlike non-U.S. companies, U.S. pharmaceutical manufacturers must factor the higher cost of liability claims into the price of their products. Foreign companies operating in the United States face the same risk of litigation as U.S. companies, but the size of their exposure is much less because only their U.S. assets can be seized.

In regard to taxation, companies generally commented only on the U.S. tax system. Industry

[284] In the *Final Report of the Advisory Committee on the FDA*, the FDA is described as the oldest federal consumer protection agency. (p. 2)

[285] Companies operating in the United States, or in a country that has similar requirements, are subject to these requirements, regardless of their parentage.

[286] The proposed EC regulation would allow for the creation of a supplementary protection certificate for medicinal products. The certificate is regarded by many as a device (i.e., a means to confer an additional period of market exclusivity) rather than a patent. France has independently enacted similar product protection as part of its national law.

[287] It should be noted that the patent system and patent enforcement in the United States is generally regarded to be very good.

[288] USITC staff interview with representative of U.S. industry during April and June 1991; P. Huber, *Liability, The Legal Revolution and Its Consequences* (New York, 1988), P. 229.

groups identified three areas in the field of taxation that would strengthen the pharmaceutical industry: (1) restructuring the R&E credit and making it permanent; (2) reducing the cost of capital by reducing the tax on capital gains and encouraging long-term savings and investment; (3) resolving issues raised by section 861 by permanently setting a percentage of R&D expenditures for allocation against U.S. income.

The primary tariff barrier identified as affecting the U.S. industry is the recent changes in the EC's procedure for granting duty suspensions. The new duty suspension guidelines may effectively limit the availability of duty suspensions for pharmaceutical products. The increased difficulty in obtaining duty suspensions in Europe may increase the possibility that U.S. firms will move production facilities to Europe.

CHAPTER 4
STRUCTURE AND PERFORMANCE OF THE PHARMACEUTICAL INDUSTRY IN THE WORLD MARKET

Major Global Producers

The U.S. Industry

Producers, Shipments, and Production

In the United States today, approximately 750 innovative firms discover, manufacture, and market ethical and proprietary pharmaceutical products.[1] Approximately 180,000 people were employed by these firms in 1990.[2] About 300 domestic firms, including a number of innovative firms, manufacture generic pharmaceutical products.[3] Drug manufacturing facilities are concentrated principally in New Jersey, New York, Pennsylvania, Ohio, Indiana, Illinois, Michigan, Missouri, California, and Puerto Rico.[4]

Pharmaceutical products are made available to patients in more than 6,800 hospitals and 68,000 pharmacies nationwide through distribution networks including wholesale distributors.[5] Industry sources estimate that wholesalers distribute about 69 percent of the dosage-form pharmaceuticals (pharmaceutical products) sold domestically to hospitals, health maintenance organizations (HMOs), and pharmacies. The remaining 31 percent is sold directly to institutions by manufacturers.[6]

The value of U.S. drug shipments, which includes bulk active ingredients and pharmaceutical products, increased from $31.1 billion in 1986 to an estimated $49.6 billion in 1990 (table 4-1). Average annual growth in shipments for this period was 12.3 percent.[7] Pharmaceutical products accounted for the majority of shipments during these years, averaging about 76 percent of the total.

The increase in value of U.S. drug shipments has been attributed to a number of factors, including the large number of generics that entered the market after the implementation of the Waxman-Hatch Act[8] and the growing geriatric population in the United States.[9] Production of bulk medicinal chemicals,[10] or active ingredients, increased from 120.0 million kilograms in 1986 to 130.3 million kilograms in 1989 (the most current year with available data), or an average annual increase of 2.8 percent.[11]

Production capacity and capacity utilization statistics are not very meaningful for pharmaceutical products since most are made by batch processes, in which in-place equipment is used frequently to manufacture a variety of products. The processes are

[1] *PMA Statistical Fact Book 1989*, p. 3. Many of the firms that manufacture ethical drugs also produce OTC products. For a more complete definition of many of the terms used in this chapter (i.e., ethical, proprietary, etc.), please see Chapter 1, the Glossary, or both.

[2] Department of Commerce, *U.S. Industrial Outlook*, 1991, p. 45-2; PMA, *Annual Survey Report, 1988-90*, p. 16.

[3] Per a telephone conversation with a representative of the Generic Pharmaceutical Industry Association on June 17, 1991. This number includes some PMA member firms as well. According to "The Price of No-Name Drugs May Soon Be Hard to Swallow," (*Business Week*, Oct. 2, 1989, p. 67), innovative companies produce about 60 percent of the generic products marketed in the United States.

[4] Puerto Rico is considered part of the United States for tax and tariff purposes.

[5] *PMA Statistical Fact Book*, December 1989, p. 2.

[6] PMA, *Facts at a Glance*, 1989, p. 9.

[7] Since 1982, the value of product shipments increased by an annual average of 10.2 percent, partially due to inflation; the average annual increase in constant 1987 dollars was 3.3 percent. (Department of Commerce, *U.S. Industrial Outlook*, 1986-91; "Drugs."

[8] The Waxman-Hatch Act, which provided an accelerated approval process for generic products, is discussed later in this chapter and in chapter 3.

[9] USITC field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[10] The data for bulk chemicals do not include finished pharmaceutical preparations and products put up in dosage form.

[11] *Synthetic Organic Chemicals*, U.S. Production and Sales, 1989, USITC publication 2338, p. 6-1.

Table 4-1
SIC 283, Drugs: Product data for the U.S. pharmaceutical industry, 1986-90[1]

	1986	*1987*	*1988*	*1989*	*1990*
Shipments (million dollars)	31,118	35,283	39,857	44,384	49,605
Exports (million dollars)	3,087	3,229	3,934	4,401	5,252
Imports (million dollars)	2,322	2,795	3,485	3,513	4,190
Consumption (million dollars)	30,353	34,849	39,408	43,496	48,543
Imports/consumption (percent)	7.7	8.0	8.8	8.1	8.6
Exports/shipments (percent)	9.9	9.2	9.9	9.9	10.6
Consumption domestically produced (percent)	92.3	92.0	91.2	91.9	91.4

[1] U.S. Industrial Outlook 1989-Drugs, 1990-Drugs, 1991-Drugs.

generally complex and require careful monitoring if products of acceptable activity and purity are to be obtained. Companies that have idle or excess capacity may perform contract work for other firms.[12] Because production runs often are small, companies face a constant challenge of balancing the use of available capacity with cyclical demand to operate flexibly and achieve economies of scale.[13]

The U.S. pharmaceutical industry has shown continuous improvement in employee productivity (as measured in terms of output per employee hour) since 1971. From 1977 to 1987, pharmaceutical productivity increased by 24 percent, compared with 9 percent for all nonfarm business.[14] This largely reflects increased automation in many production facilities and streamlined operations. However, some industry spokesmen indicated that the measurement of output per employee hour may not accurately represent productivity changes within the pharmaceutical industry.[15] Several important indicators, such as the added value of innovative therapies that replace older, less effective drugs and more expensive forms of health care, are not reflected in employee productivity statistics.

Market Share and Concentration

As of 1990, 9 of the 20 largest pharmaceutical corporations in the world, in terms of ethical drug sales, were based in the United States. The top three American firms in 1990, ranked by share of world market sales, were Merck (4 percent), Bristol-Myers Squibb (3 percent), and Eli Lilly (3 percent).[16] Total pharmaceutical sales of the top 10 U.S. companies in 1990, valued at about $33 billion, accounted for approximately 22 percent of world sales.[17]

During 1986-90, pharmaceutical firms operating in the United States supplied between 91 percent and 93 percent of apparent U.S. consumption of pharmaceutical drugs. Approximately 30 percent of these shipments were by U.S. affiliates of European-based firms. As shown in table 4-1, U.S. producers have maintained a consistently high share of the domestic market.

The average four-firm concentration ratio (on the basis of sales) in the United States was 25 percent from 1958 to 1982 (see table 4-2). In 1989, sales of the four largest innovative firms again accounted for about 25 percent of the U.S. market.[18] Continuing industry consolidation may eventually increase the level of concentration.[19] As shown in table 4-2, the number of pharmaceutical firms has steadily declined from 1958 to 1982; however, the trend has reversed since 1982.

Trade

The U.S. pharmaceutical industry has historically maintained a positive trade balance. The surplus in drug trade flows (see table 4-1) increased from $0.8 billion in 1986 to an estimated $1.1 billion in 1990, and is forecast to reach $1.2 billion in 1991.[20] Since 1987, the value of drug imports has increased at an annual rate of 15 percent by value.

[12] OECD, *The Pharmaceutical Industry: Trade Related Issues*, Paris, 1985, pp. 7-17; and, Bert Spilker, Ph.D., M.D., *Multinational Drug Companies: Issues in Drug Discovery and Development*, New York, 1989, pp. 470-478.

[13] Ibid.

[14] PMA, *Statistical Fact Book*, December 1989, p. 22.

[15] USITC field interviews in United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February and March 1991.

[16] "Changing Lineup Ahead for Global Drug Industry," *Chemical & Engineering News*, Dec. 17, 1990, p. 10. Also compiled from CountyNatWest Securities Ltd. rankings. SmithKline Beecham, which ranked fifth with a world market share of almost 3 percent, has its headquarters in London.

[17] The sources of this data are company annual reports, Shearson Lehman Hutton's *PharmaProfiles 1989*, and CountyNatWest Securities Ltd. industry rankings.

[18] PMA submission, p. 4. According to the submission, the eight largest PMA member firms accounted for less than 50 percent of the U.S. market, whereas the top 21 firms accounted for 75 percent of the domestic market.

[19] Consolidation is discussed in the section of chapter 4 entitled "Consolidation in the Global Pharmaceutical Industry".

[20] U.S. Industrial Outlook, 1991-Drugs, p. 45-2.

Table 4-2
Drugs: Concentration ratios for U.S. firms manufacturing drug preparations (SIC 2834) selected years, 1958-82

Year	Number of establishments	Percent of value of shipments accounted for by— 4 largest companies	8 largest companies	20 largest companies
1958	1,114	25	43	71
1963	1,011	22	37	71
1967	875	24	40	70
1972	756	25	43	73
1977	756	25	41	70
1982	683	26	41	67

Source: 1982 Census of Manufacturers, Pub. MC77-Sr-9, Subject Series, Bureau of Census, U.S. Department of Commerce, 1986.

Annual growth in exports for the same period was 18 percent by value. Export growth of 20 percent is projected for 1991 by the U.S. Department of Commerce.[21]

Demand for bulk active ingredients by the United States and its trading partners is the main component of drug trade. U.S. export growth reflects increased shipments of active ingredients and intermediate products that are processed into finished drugs and packaged in the countries where they will be sold. The passage of the Drug Export Amendments Act in 1986 has aided export growth by permitting the export of drugs not yet approved by the FDA to a select list of countries (see Chapter 3).

The major markets for U.S. drug exports in 1989 were Japan (21 percent of total), Germany (10 percent), Canada (8 percent), and Italy (6 percent).[22] Major sources of U.S. drug imports during 1989 were the United Kingdom (19 percent of total), Germany (15 percent), Japan (12 percent), and Switzerland (11 percent).[23]

Industry Characteristics

The U.S. pharmaceutical industry has a highly developed research infrastructure, has the capability for rapid technological diffusion, has established a highly structured marketing network, and displays a relatively high degree of vertical integration.[24] The industry also has relatively high R&D outlays, since R&D spending is considered to be the foundation for growth. A company that wishes to have a broad-based, fully integrated research and development function competitive on a world-wide basis generally has an annual R&D budget valued at greater than $300 million.[25] R&D spending among PMA member firms in the United States has approximately doubled every 5 years, from $0.6 billion in 1970 to an estimated $8.2 billion in 1990. The rising cost, complexity, and uncertainty of successful pharmaceutical research have made it much more difficult for medium-sized drug companies with research budgets of less than $200 million annually to remain competitive,[26] prompting some medium-size firms to seek alliances with larger firms to better develop new products.[27]

R&D commitment can also be measured as the ratio of research personnel employed to the total labor force of the industry. Between 1986 and 1988 the number of scientists and engineers engaged in R&D in the pharmaceutical industry increased from 24,500 to 27,230. Their ratio to the total labor force of the industry remained relatively constant at 15 percent during 1986-88.[28]

In the United States, consumers receive ethical pharmaceutical products from a number of sources, including hospitals and retail pharmacies. In turn, these sources receive the products either through wholesalers or directly from the manufacturer. Wholesalers account for the majority of the distribution, or about 69 percent. Given that promotional activity is considered a significant form of competition, particularly in the early stages of market entry, and that many companies believe that "detailing"[29] is the most effective way to communicate with doctors, pharmaceutical companies generally try to optimize their sales activities. One analyst reported that, since 1984, the pharmaceutical industry sales force in the United States increased by 50 percent to 30,000. This expanded force made some 30 million calls (details), and at $100 per call, the direct cost of detailing in 1989 was some $3 billion.[30]

Generic Drugs

Generic drugs are direct substitutes for innovative products. Their presence on the market generally either stabilizes pricing for a particular drug or causes prices to decline by directly competing with brand-name products. Industry sources estimate that in 1995, sales of generic products will be valued at $13.2 billion, or about 27 percent of the U.S. ethical drug market, compared with about $4 billion, or about

[21] Ibid.

[22] Compiled from official statistics of the U.S. Department of Commerce.

[23] Compiled from official statistics of the U.S. Department of Commerce.

[24] More pharmaceutical firms are expanding their production facilties to include capacity for some of the raw materials needed to produce the pharmaceutical products. In addition, some major U.S. chemical companies are entering the industry, including Dow, Monsanto, and DuPont. Pharmaceutical sales for these multinational chemical firms, many of whom are back-integrated to basic petrochemicals, generally represent less than 30 percent of annual sales. These firms, in some cases, entered the industry through mergers and acquisitions with small- to medium-sized pharmaceutical firms, as the chemical giants have the capital to sustain the increasing pharmaceutical R&D costs.

[25] USITC field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[26] USITC field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[27] Ibid.

[28] PMA Annual Survey Report, 1988-90, p. 29. The ratio for the pharmaceutical industry is considered to be among the highest of those in any of the industry sectors in the United States.

[29] "Detailing" has been defined as calls made by a company's sales force on physicians to describe a product's efficacy and the benefits to the patient that would accrue through use of the product. ("Pharmaceutical Industry Faces Pressure on Prices," *European Chemical News*, Aug. 20, 1990, pp. 34 and 54.)

[30] *Ranitidine Hydrochloride: The Potential Impact on Domestic Competition in the Antiulcer Drug Market of a Temporary Duty Suspension on Imports*, January 1991, p. 10. "Detailing" has been defined as calls made by a company's sales force on physicians to describe a product's efficacy and the benefits to the patient that would accrue through use of the product. ("Pharmaceutical Industry Faces Pressure on Prices," *European Chemical News*, Aug. 20, 1990, pp. 34 and 54.)

13 percent, in 1989. This expected increase reflects such factors as the expiration by 1995 of the patents on approximately 200 brand name-products, valued at about $8.1 billion in 1989;[31] the growing number of chain drugstores in the U.S. market which, compared to independent stores, experience larger margins on high-volume sales of generics;[32] and implementation of the Waxman-Hatch Act.

By providing an accelerated approval process for generic products, the 1984 Waxman-Hatch Act made it easier for generics to enter the market.[33] As a result of this law, in order to receive FDA approval to market generic products after patent expiration, producers of generic products had only to demonstrate bioequivalence to the innovative product. Producers did not have to duplicate the innovative producer's clinical trials, so there was a significant increase in the number of generic products on the market. One source, however, recently suggested that the number of generic firms operating in the United States could decline in the future if generic products are subject to increased testing requirements as a result of the generic drug industry scandal.[34]

The Western European Industry

Producers And Production

The pharmaceutical industry in Western Europe, as represented by the EFPIA, consists of about 2,000 plus firms located in 16 countries.[35] The number of firms cited, however, includes some over-counting of the actual number of firms operating in these countries in that many of the international firms are located in almost every country in Western Europe. Except for a few state-owned operations, like Rhone-Poulenc SA of France, most of the major pharmaceutical firms in the EC and Switzerland are privately owned.

Subsidiaries or jointly-owned affiliates of U.S. pharmaceutical companies in Europe, important contributors to the local European pharmaceutical market, are also included in the EFPIA total. These firms, sometimes called "European firms of American parentage," perform local R&D and manufacture active ingredients for both patented and generic prescription products. Several industry sources have stated that the majority of a U.S.-base company's sales in Western Europe is often accounted for by a company's facility in Western Europe.

In 1988, Europe represented about 32 percent of the world's pharmaceutical production. Production of pharmaceuticals in the 16 European countries of EFPIA was valued at $60.3 billion in 1988, an increase of 89 percent from $31.9 billion in 1985 (an average annual rate of growth of 24 percent).[36] In 1988, pharmaceutical production in the EC was reported at $54.5 billion, or 90 percent of the EFPIA total. In terms of value of production, the leading pharmaceutical-producing countries in Europe in 1988 as reported by the EFPIA were: Germany (22 percent of the total), France (21 percent), Italy (16 percent), the United Kingdom (17 percent), Spain (7 percent), and Switzerland (5 percent).[37] These 6 nations accounted for an aggregate total of 88 percent of total EFPIA production in 1988. In terms of EC pharmaceutical production, the 5 EC members in the above total represented 90 percent of the value of total EC pharmaceutical production in 1988. In that year, Germany alone represented, as stated above, 22 percent of the value of EFPIA production and 24 percent of EC pharmaceutical production. The 5 EFPIA nations that are not EC members had an aggregate production of $5.8 billion in 1988; Switzerland accounted for $3.1 billion in 1988, or 54 percent of the total.[38] Employment in the Western European industry was estimated to be 501,000 in 1989. R&D personnel represented about 15 percent of the total.[39]

Market Share/Concentration

The leading pharmaceutical firms in Western Europe are located in the United Kingdom, Switzerland, Germany, France, and Sweden, and sales data for these firms are shown for 1988 (unless otherwise noted) in Table 4-3.[40] The twelve largest European-based pharmaceutical firms had aggregated pharmaceutical sales of $23 billion in 1988, or

[31] Industry sources estimate that within the next ten years, patents on an estimated $18 billion worth of pharmaceutical products will expire.

[32] Christine Huttin, "More Regulation or More Competition in the European Pharmaceutical Market," First Workshop on Strategies for the European Pharmaceutical Industry and Patient Interests, Brussels, Jan. 31-Feb. 1, 1991, p. 35.

[33] Although market statistics differ as to the actual share of the ethical market currently held by generic products (ranging from 13 to 30 percent), they do indicate that the share held by generic products increased significantly after 1984.

[34] "The Price of No-Name Drugs May Soon Be Hard to Swallow," *Business Week*, Oct. 2, 1989, p. 67.

[35] The EFPIA represents the pharmaceutical industry in Europe and is a federation of the national pharmaceutical industry associations in 16 European countries. These countries are as follows: Austria, Denmark, France, Greece, Italy, Norway, Spain, Switzerland, Belgium, Finland, Germany, Ireland, the Netherlands, Portugal, Sweden, and the United Kingdom.

[36] EFPIA, *EFPIA in Figures, 1986-1987*, Brussels, pp. 8 and 13; and, EFPIA, *EFPIA in Figures: The Pharmaceutical Industry in Europe, 1987-1989*, Brussels, pp. 8-17.

[37] Ibid.

[38] Ibid.

[39] EFPIA, *EFPIA in Figures, 1990*, p. 23.

[40] Dun & Bradstreet International, *Dun's Europa-Supplement*, 1990, pp. 47-50; "Test Tube Tribulations," *Financial World*, May 30, 1989, pp. 76 and 77. Since this article was published, SmithKline Beckman of the United States merged with Beecham Group; EFPIA, *EFPIA in Figures: The Pharmaceutical Industry in Europe, 1986-1987*, Brussels, pp. 7-9, 13; EFPIA, *EFPIA in Figures: The Pharmaceutical Industry in Europe, 1987-1988*, Brussels, pp. 20 and 21; and, PMA, *PMA Statistical Fact Book*, December 1989, pp. 2-14.

Pharmaceuticals: Data on the twelve leading firms in Western Europe, 1988

Company	Country	Pharmaceutical sales	Total sales	Pharmaceutical sales as percent of total sales	Earnings	Return on sales	Research and development	Stock price	Price cash flow	World pharmaceutical market share 1983	1988
		— Million dollars —			Million dollars	Percent	Million dollars	Per share		— Percent —	
Glaxo Holdings	United Kingdom	3,160	3,520	89.8	976	22.4	405	23-1/4	16	1.40	3.00
Ciba-Geigy	Switzerland	3,020	12,730	23.7	865	6.5	440	2,054	15	3.20	2.80
Hoechst	Germany	2,700	23,530	11.5	973	5.3	330	161	9	3.00	2.50
Bayer	Germany	2,370	23,650	10.0	954	4.7	480	161	11	2.00	2.20
Sandoz	Switzerland	2,230	7,260	30.7	493	6.6	390	6,578	53	2.00	2.10
Hoffman-LaRoche	Switzerland	1,940	5,790	33.5	427	4.2	470	97,387	2	2.20	1.85
Imperial Chemical Industries	United Kingdom	1,450	21,060	6.9	1,586	18.1	240	80-3/4	10	1.60	1.35
Beecham Group	United Kingdom	1,400	4,680	29.9	458	10.5	140	21-3/8	14	1.40	1.35
Wellcome	United Kingdom	1,340	2,110	63.5	215	10.1	205	8-1/4	41	1.10	1.25
Rhone-Poulenc	France	1,300	10,720	12.1	342	3.0	250	90-3/8	3	1.30	1.20
Astra	Sweden	1,050	1,080	97.2	122	22.0	200	37	14	0.70	0.80
Sanofi	France	1,046	2,400	43.6	161	5.8	200	129	8	0.50	0.60
Selected total/averages		23,006	141,536	37.7	7,572	9.9	3,750	8,894-1/4	16.3	20.40	22.35

Source: "Test Tube Tribulations," *Financial World*, May 30, 1989, pp. 76 and 77. Since this article was published, a number of significant mergers have occurred in the industry. For example, SmithKline Beckman of the United States merged with the Beecham Group (United Kingdom).

57 percent of the $40 billion total pharmaceutical sales in Western Europe in that year.[41] These firms represented 22.4 percent of total world pharmaceutical sales in 1988, versus 20.4 percent in 1983. As shown in Table 4-3, the largest world market share for any one European pharmaceutical firm did not exceed 3 percent in 1988.[42]

Factors affecting the competitive position of European pharmaceutical companies include product lines, sales revenue, the quality of the products marketed, and the level of Government intervention.[43] European firms have discovered that, in recent years, both physician and product loyalty have been declining and that their largest customers are increasingly institutions (such as hospitals and health-care groups), national health-care programs, and mail order pharmaceutical companies. Also, brand-name loyalty has been declining because of increased Government demand for lower prices through the use of generic products.

Trade

In recent years, the EC pharmaceutical industry has accounted for over half of the world's drug export activities.[44] Average export sales for all EFPIA members in 1988 represented about 34 percent of the value of production; for 7 of the 16 member countries of EFPIA, export sales represented more than 60 percent of the value of pharmaceutical production in 1988.[45] Although a large share of these exports are to other Western European countries (see Fig. 4-1), imports of pharmaceutical products from Western Europe have accounted for the majority of total U.S. imports of these products during the past five years (see Fig. 4-2). The EFPIA members enjoyed a balance of trade in pharmaceutical products of $6.8 billion in 1988, up 11 percent from a trade surplus of $6.2 billion in 1987.

The share of a firm's sales represented by domestic sales depends on the home market for the EFPIA firm. For example, major French pharmaceutical firms have traditionally depended mainly on their home market, which accounts for 40 to 70 percent of their sales.[46] On the other hand, Switzerland is at the other end of the scale for major producing nations in Europe, as the leading Swiss pharmaceutical firms obtain only about 3 percent or so of their annual sales domestically.[47]

Characteristics of The Industry

Many of the larger European firms, like Ciba-Geigy, Hoechst, and Bayer, are vertically integrated into other chemical fields. Some of the leading pharmaceutical firms in Western Europe, as in the United States, have integrated horizontally into areas such as surgical supplies, medical supplies, medical devices, and OTC medicines. This allows them to serve the complete needs of their customers, thereby making them a more valuable supplier. However, many of the OTC products as well as the generic (or multisource) pharmaceuticals are produced by small, noninnovative firms, many of whom sell only to domestic or regional markets.

A number of Europe's leading pharmaceutical firms, including such firms as Glaxo Holdings, Sandoz, and Hoffmann-LaRoche, have traditionally received 30 percent or more of their annual sales from pharmaceutical operations.[48] However, some of the major chemical companies in Europe have either entered or are entering the pharmaceutical field. Major European-based chemical firms that have important pharmaceutical operations include ICI (United Kingdom), Bayer (Germany), and Hoechst (Germany).[49]

The Japanese Industry

Producers and Production

Statistics published by the Japan Pharmaceuticals Manufacturers Association (JPMA) show that the total number of pharmaceutical producers decreased from 1,359 in 1975 to 1,315 in 1986.[50] In 1986, about 80 percent of the firms were medium- to small-sized companies specializing in traditional medicinal products, generic drugs, and OTC preparations, and employing fewer than 30 workers each. A large

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[41] Pharmaceuticals: Sorting Out the Market," *Chemical Week*, June 13, 1990, pp. 40 and 44.

[42] The largest pharmaceutical firm in the world, Merck (United States), accounted for only 3.95 percent of the world pharmaceutical market in 1988.

[43] USITC field interviews in the United States with representatives of European-based and U.S.-based multinational pharmaceutical firms and other sources during January-February, 1991.

[44] "Patent Term Restoration on EC Agenda, EFPIA Told," *Marketletter*, London, June 12, 1989, pp. 10 and 11. From a speech by Martin Bangemann, EC Commission vice president to general assembly conference of the EFPIA in Paris during the first week of June 1989; and, EFPIA, *EFPIA in Figures, 1986-1987*, Brussels, pp. 11, 13, 15, and 17; and, EFPIA, *EFPIA in Figures, 1987-1988*, Brussels, pp. 11, 13, 15, and 17.

[45] EFPIA, *EFPIA in Figures, 1987-1988*, Brussels, p. 13; PMA, *Facts at a Glance*, 1989, pp. 17-19; and, PMA, *PMA Statistical Factbook*, December 1989, Chapter 11, pp. 8 and 9.

[46] "European Drug Makers Face Major Shake-Out," *Chemical Market Reporter*, Mar. 19, 1990, pp. SR34 and SR35.

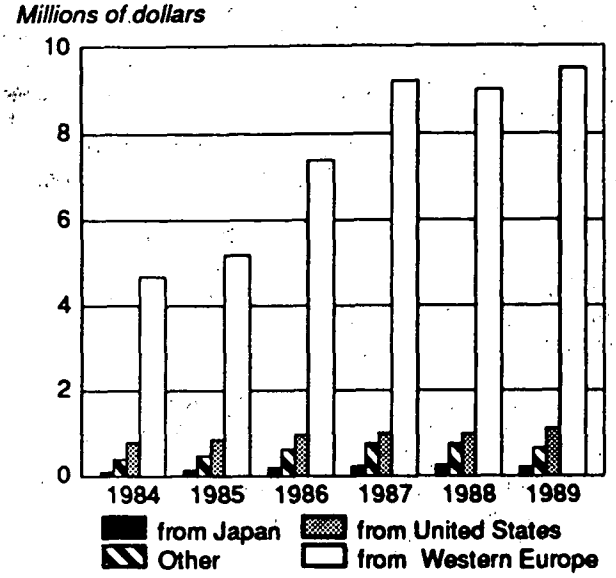
[47] "Pharmaceuticals," *Financial World*, May 30, 1989, pp. 54-71.

[48] "Pharmaceuticals: A story of Research and Survival," *Chemical Business*, November 1990, pp. 8-10.

[49] John Lidstone, *Market Planning for the Pharmaceutical Industry*, Wiltshire, England, 1987, p. xiv; OECD, *The Pharmaceuticals Industry: Trade Related Issues*, Paris, 1985, pp. 9-17; "In the Pink-Except for a Case of Nerves," *Business Week*, Jan. 1990, p. 102; "The New World of Drugs," *The Economist*, Feb. 4, 1989, pp. 63 and 64; "Pharmaceuticals: Sorting Out the Market," *Chemical Week*, June 13, 1990, pp. 40 and 44; and, "The New World of Drugs," *The Economist*, Feb. 4, 1989, pp. 63 and 64.

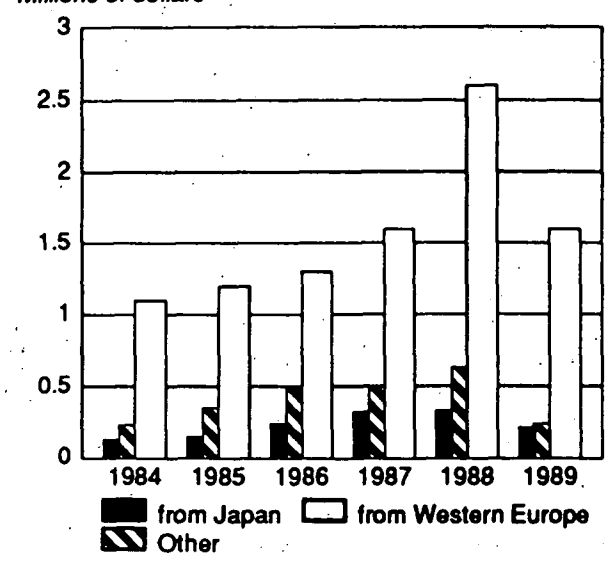
[50] Japan Pharmaceutical Manufacturers Association, *Data Book 1990*, p. 2.

Figure 4-1
Western European imports: Pharmaceutical products (SITC 54)



Source: Official U.N. statistics. (1989 data may be incomplete)

Figure 4-2
United States imports: Pharmaceutical products (SITC 54)



Source: Official U.N. statistics. (1989 data may be incomplete)

number of the Japanese pharmaceutical firms have been in operation for many years and began as wholesalers from the Osaka area of Japan. Takeda Chemical Industries Ltd., for example, Japan's leading pharmaceutical company, is 210 years old. Although traditionally family owned, many of these firms are now held publicly.[51]

The Japanese Economics and Trade Research Organization (JETRO) has classified Japanese pharmaceutical companies into the following categories: manufacturers of ethical drugs; exclusive manufacturers of OTC drugs; family drugs; bulk manufacturers; and manufacturers of drugs for door-to-door distribution. Of these, manufacturers of ethical drugs are primarily engaged in the production of drugs for medical practitioners. Most major pharmaceutical producers are classified in this category, along with many small- and medium-sized companies. The total number of ethical drug manufacturers, including subsidiaries of foreign firms, increased from 330 firms in 1975 to to 436 in 1986.[52] A survey conducted by Japan's Koseisho showed that as of May 1987, there were 452 manufacturers of ethical drugs.[53] The number of persons employed by the pharmaceutical industry in 1987 was 187,940, or about 0.3 percent of total employment in that year.[54]

Pharmaceuticals production in Japan increased from $26 billion in 1986 to $40 billion in 1989,[55] with ethical drugs constituting the greatest segment of the Japanese pharmaceuticals market. Cardiovascular drugs represented the largest part of Japanese production by value in 1989 (14 percent), followed by antibiotics (13.2 percent).[56] Increases in the production of gastrointestinal, respiratory, central nervous system, and cardiovascular products have occurred in recent years due to the rapidly increasing elderly population in Japan.[57]

Manufacturers belonging to the family drug group concentrate mainly on Japanese and Chinese medicine. Their products, which have a long tradition in Japan, are still popular. Many of these producers specialize in producing only one drug.

Market Share and Concentration

According to the most recent statistics available, the top 10 leading Japanese pharmaceutical firms accounted for 41.5 percent of the total value of

[51] USITC field interviews in Japan with representatives of multinational firms and representatives of industry trade associations during April, 1991.
[52] *Data Book 1990*, p. 2.
[53] *Standards and Certification Systems Concerning Drugs in Japan*, 2nd edition, edited by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Yakugyo Jiho Co., Ltd., Tokyo, Japan.
[54] P. Reed Maurer, *Competing in Japan*, The Japan Times, Ltd., Tokyo, Japan, 1989.
[55] *Data Book 1990*, p. 38.
[56] *Japan's Pharmaceutical Industry: Update, Internationalization for Renewed Growth, March 27, 1991*, Credit Suisse, Research Department, Tokyo, Japan.
[57] Ibid.

production in Japan in 1986.[58] The following tabulation shows sales data for the six largest Japanese pharmaceutical firms (based on total value of sales) for the 1989 Japanese fiscal year.[59] Takeda, the largest wholly owned Japanese pharmaceutical manufacturer ranked 20th worldwide in 1990. The 2nd largest, Sankyo, ranked 23rd.[60]

Top Six Japanese Pharmaceutical Companies, 1989

Company	Total Sales	Profits
	Million of dollars	
Takeda Chemical	4,905	277
Sankyo	3,043	101
Shionogi	2,082	84
Yamanouchi Pharmaceutical	1,790	21
Tanabe Seiaku	1,655	68
Fujisawa Pharmaceutical	1,606	22

Source: Forbes, Jan. 22, 1990

Recent additions to the domestic industry are the food and beverage producers, Mitsubishi-Kasei, and Kirin Brewery, both members of the Mitsubishi Group, and Ajinomoto, the world's largest producer of synthetic food seasonings.[61] Ajinomoto established a 100-percent-owned firm, Lenti-Chemico Industry, Inc., and applied for FDA approval to market its AIDS drug, Lentinan, in the United States.[62] Ajinomoto also signed an agreement with Bristol-Myers Squibb for exclusive sales of DDA and DDI, two products under development by Bristol-Myers for AIDS treatment. Finally, it joined with a U.S. firm, Biotech Research Laboratories, Inc., in basic research on the AIDS virus and other viral agents, as well as cancer treatment.[63] Kirin Brewery plans to apply its expertise in biotechnology to the development of anticancer agents.[64]

Government restrictions on foreign direct investment began to be eased in the 1970s, allowing many European and U.S. companies to enter the industry. Many domestic nonpharmaceutical Japanese companies also entered the pharmaceutical industry during this time period. Prior to the easing of the Government restrictions, the level of multinational competition in Japan was relatively low, giving the Japanese industry the opportunity to expand and increase its R&D capacity through concentrating on its domestic market. This domestic focus reduced the incentive for the Japanese industry to develop its export potential.[65]

Driven by the size of the market (the second-largest worldwide) and the ability of well-established foreign pharmaceutical manufacturers to distribute their products directly to wholesalers, (eliminating the need for a Japanese partner), a recent trend is toward wholly owned foreign firms in Japan.[66] Almost all major U.S. and European pharmaceutical manufacturers maintain Japanese subsidiary operations.[67] As of 1987, 97 firms had more than 50-percent non-Japanese ownership, including 28 from the United States, 13 from Germany, 8 from Switzerland, and 8 from the United Kingdom.[68] Another study found that of 21 U.S. firms, 13 had wholly owned subsidiaries in Japan and 8 had majority-owned subsidiaries.[69] In 1989, it was estimated that 24 U.S. companies in Japan accounted for about 15 percent, or about $5 billion, of the Japanese market.[70] The following tabulation shows the proportion of the market for ethical pharmaceuticals accounted for by selected foreign firms operating in Japan:

Selected Foreign Firms Percentage Share of Market-1989

Bayer	2.3
Banyu-Merck	2.3
Sandoz	1.7
Pfizer	1.4
Ciba-Geigy	1.2
Hoechst	1.2
Lederle	1.2
Nihon Schering	0.9
ICI Pharma	0.8

Source: "Japan's Pharmaceutical Industry, Emergence of the Second Wave," *Investment Research*, Goldman Sachs and Co., Tokyo, Japan, Dec. 7, 1990, p. 25.

Japanese-origin products have consistently accounted for about 60 percent of the Japanese market over the last 10 years; although 2 United States and 2 European firms were ranked in the top 20 in 1987, no foreign firm ranked in the top 10.[71] About 66 percent

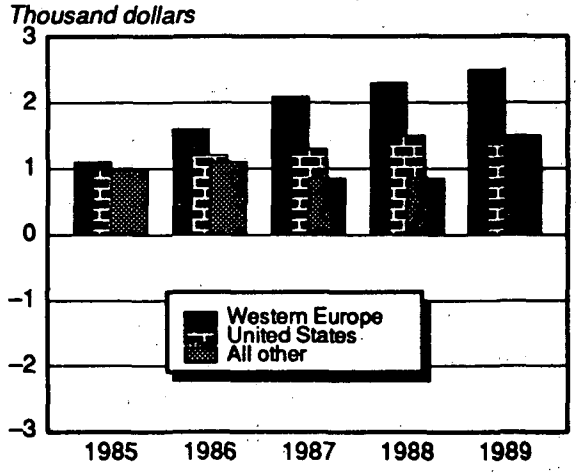
[58] *Data Book 1990*, p. 16.
[59] "A Different Kind of Drug Problem," *Forbes*, Jan. 22, 1990, pp. 40-41.
[60] "Japan: the Geta on the Other Foot," *Financial World*, May 30, 1989, p. 70; CountyNatWest Securities Ltd. industry ranking.
[61] "Biotech Companies Turn Toward Tokyo," *The Washington Post*, Sept. 23, 1991, p. B1.
[62] "Ajinomoto Co., Strengthening its Processed Food Position via M&A," *Tokyo Business Today*, May 1989, p. 48.
[63] Ibid.
[64] "Biotechnology, the Trump in Diversification," *Tokyo Business Today*, April 1986, pp. 60-61.
[65] "Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy," *California Management Review*, Winter 1990, p. 144.
[66] "Japan's Next Battleground: the Medicine Chest," *Business Week*, Mar. 12, 1990, p. 68.
[67] "Multinationals Take to the Offensive," *Tokyo Business Today*, June 1987, p. 52.
[68] *Japan Chemical Annual, 1989*.
[69] "Competition Intensifies as Japanese Lift R&D Effort," *European Chemical News*, Apr. 1, 1991, p. 18.
[70] PMA submission, p. 30.
[71] Ibid.; "Japan: the Pharmaceutical Market Here is the World's 2nd Largest," *Medical Marketing*, August, 1990, pp. 22-34. It was noted by Dr. Masao Uchibayashi, Managing Director of Takeda Chemical Co., in a speech delivered at the Second Annual U.S.-Japan Health Care Symposium in Atlanta GA., Oct. 11, 1990, that no Japanese companies were listed in the top 50 list in 1989 of pharmaceutical firms operating in the United States.

of the foreign firms operating in Japan have R&D facilities in Japan. One company did the majority of the development work on its new product in Japan in preparation for launching it on a global basis.[72] This increase in foreign competition in Japan's large domestic market, created primarily by reduced government trade restrictions, has been one of the main market forces stimulating Japan's developing competitiveness.

Trade

Japan's trade deficit in pharmaceuticals increased from $1.1 billion in 1986 to $1.9 billion in 1989 (see Figure 4-3).[73] Imports increased from $1.9 billion to $2.8 billion during 1986-89, while exports decreased from $732 million to $862 million during this period. The principal sources for Japanese imports during 1989 by percent of total value were Germany (24 percent), the United States (24 percent), Switzerland (12 percent), and the United Kingdom (9 percent).[74]

Figure 4-3
Japan's trade balance for pharmaceutical products



Source: Official U.N. Statistics.

Compared with the export sales performance of United States and Western European firms, Japanese export of pharmaceuticals is small, averaging about 5 percent of annual sales.[75] In 1989, the principal markets for Japanese exports were the United States (25 percent), Germany (9 percent), Korea (7 percent), France (6 percent), Taiwan (6 percent), and Belgium (5 percent).[76] Because Japanese producers serve the second-largest market for pharmaceuticals in the world, the industry has not yet developed an export-oriented attitude. However, industry analysts state that this attitude is being replaced by a growing interest in globalization.[77]

[72] Ibid.
[73] *Data Book 1990*, p. 28.
[74] *Data Book 1990*, p. 30.
[75] *Data Book 1990*, p. 32.

Characteristics of the Industry

Japan's pharmaceutical companies have been, for the most part, family owned and operated. With a market protected until the early 1980s, management style has not changed.[78] However, Japan's innovative firms are now in a transitional management period. Changes in the market brought about by recent trade negotiations[79] and the influence of government cost-containment measures imposed in reaction to rapidly increasing health insurance costs have slowed the growth of Japanese drug firms, and forced a shift in management philosophy to emphasize profitability by increasing R&D efforts and product portfolios.[80] Limited utilization of professional management and excessive emphasis on the home market over other large world markets is cited as a competitive weakness of the Japanese pharmaceutical industry.[81]

Historically, antibiotics have been the major class of pharmaceuticals consumed domestically, but because of changing demographics, there is more diversification by producers and importers who increasingly focus on cardiovascular agents and central nervous system (CNS), digestive system and anticancer drugs. Japan's elderly population is increasing at the fastest rate worldwide. This fact has driven the country's pharmaceutical industry to shift production toward medicaments consumed principally by elderly patients.[82]

Most ethical drugs are sold by manufacturers to primary wholesalers (about 97 percent),[83] who then sell to users (about 93 percent) or secondary or tertiary wholesalers (about 5 percent). The principal consumers of ethical drugs are large hospitals of over 200 beds (35 percent), medium- and small-size hospitals of between 20 and 200 beds (22 percent), clinics of less than 20 beds (41 percent), and independent pharmacies (2 percent). OTC drugs are distributed to end users through pharmacies and primary wholesalers, although, secondary wholesalers and household distribution sales are also available. However, most exclusive manufacturers of OTC products sell their products in their own shops eliminating wholesalers.

Japan's wholesale pharmaceutical distribution system is complex, as foreign drug firms have found, but does not constitute an insurmountable barrier to becoming a successfully competitor in the Japanese

[76] *Data Book 1990*, p. 30.
[77] "Syndromes and Strategies for Japanese Firms in International Markets," *SCRIP*, Mar. 23, 1988, p. 24.
[78] *Competing in Japan*, p. 60.
[79] The Market Oriented-Sector Specific (MOSS) and United States-Japan Structural Impediments Initiatives (SII) talks.
[80] Ibid., pp. 60-61.
[81] Ibid.
[82] "Japan's Ailing Health Care System," *Tokyo Business Today*, February 1988, pp. 12-17.
[83] In comparison, sales of pharmaceuticals by wholesalers in the U.S. market represented 67.3 percent of manufacturers' sales in 1985. See P. Reed Maurer, *Competing in Japan*, pp. 128-129.

market.[84] As noted above, virtually all manufacturer sales of ethical pharmaceuticals in Japan are to wholesalers, who market these products to physicians, hospitals, clinics, and pharmacies.[85] Based on data provided by the Japan Pharmaceutical Wholesalers' Association (JPWA), which represents about 95 percent of such firms, an industry source estimates that 2000 drug wholesalers distribute products at the present time.[86]

Traditionally, Japanese physicians have both prescribed and dispensed medications, gaining income from the difference between their dispensing price and the official reimbursement price.[87] To reach these 180,000 physicians, foreign pharmaceutical firms must supplement their own sales forces with wholesalers' detailmen. An industry source states that successful competitors in the Japanese market provide intensive training to both the firm's sales personnel and wholesaler's sales staff. Personnel costs account for 60 percent of all expenses and overall market growth is slow because of government-directed price decreases. Wholesalers have found it thus necessary to decrease sales forces.[88] This attrition in market coverage may be partially offset by an increase in manufacturers' detailmen.

Recent trade negotiations between the United States and Japan resulted in the proposal by the Japan Fair Trade Commission of new guidelines to be implemented for fair sales activities by manufacturers in order to promote free and fairer competition and to protect consumer's interests. Supplemental guidelines concerning the pharmaceutical industry of Japan were drafted by the Committee for Modernization of the Distribution of Drugs, sponsored by the Ministry of Health and Welfare, and published on July 25, 1990 as the *Ryukinkyo Report.*[89] The report recommends changes in the method used by Koseisho to calculate prices using a weighted-average method in lieu of the present bulk-line process measures which would strengthen wholesalers' position in the market. Furthermore, the report proposes steps to be taken to increase price transparency, establish model contracts, oversee detailmen activities, and improve management in medical institutions.

According to representatives of foreign firms operating in Japan, proposed reform of the drug distribution system could have a significantly adverse impact on future earnings, and, hence on their competitiveness in the Japanese market.[90] As a result of general discussions held under the recent round of SII, the Japanese Government, through the Secretariat of the Fair Trade Commission (FTC), has announced Anti-Monopoly Act changes which will cover the drug distribution system, as well as other distribution systems currently in operation. The *Draft Anti-monopoly Act Guidelines Concerning Distribution Systems and Business Practices,* released on January 17, 1991, by the FTC and scheduled for strict implementation beginning around April, 1991, would reform the pricing system, the method of price reduction compensation, the activities of producers' detailmen, and the system of rebates by manufacturers to wholesalers of pharmaceuticals. The principal concern of U.S.-based, and other foreign firms now doing business in Japan is the transfer of price negotiations with consumers from producers to the wholesalers. Ex-wholesaler prices, which are the basis upon which the Koseisho calculates drug price cuts, will be determined by wholesalers who will be negotiating prices and competing freely for the first time. Given the wide range of ex-wholesaler prices for any given product under the existing system, end users may find that under the new system, their purchase price could either increase or decrease, depending on whether their existing price is below or above the weighted average manufacturer's suggested retail price. Considering the relative strength of end users, and the inexperience of wholesalers to negotiate drug prices, many producers believe that over time, prices will seek the lowest level.

As wholesalers offer prices below manufacturer suggested retail prices, price differences (official price minus ex-wholesaler prices) will expand, leading to steeper price cuts in the future. In particular, the firms interviewed by the Commission staff expect accelerated deterioration in prices of intensely competitive antibiotics and senile dementia drugs, which have been under considerable pressure even under the existing system of manufacturer-controlled ex-wholesaler prices.[91]

Small- and medium-sized drug manufacturers, and small local wholesalers are likely to suffer most under the reformed system. Since most foreign-owned Japanese firms are small- or medium-sized with only one or two major products, they can be expected to be adversely affected as wholesalers are likely to focus on strengthening relationships with larger firms that have several major drugs and many promising products in the R&D pipeline. Long term, however, foreign penetration of the market may be facilitated because of the strong R&D bases of these multinational firms and by the existence of a rational, transparent distribution system.

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[84] USITC, Phase II: Japan's Distribution System and Options for Improving U.S. Access, USITC Publication 2327, Oct. 1990, p. 2-11.

[85] *Competing in Japan,* p. 128.

[86] Ibid.

[87] "Prospects for 'Bungyo' in Japan," *SCRIP,* Apr. 27, 1990, p. 26. The article indicates that bungyo (or the separation of prescribing and dispensing functions in japan) is likely to play a part in a national effort to "foster the rational use of drugs and to curb excess prescribing."

[88] *Competing in Japan,* p. 132.

[89] "Ryukinkyo—A New Word for Our English Vocabulary," *Pharma Japan,* Oct. 8, 1990, pp. 14-15.

[90] USITC field interviews in Japan with representatives of U.S.-based multinational firms and representatives of industry associations during April, 1991.

[91] USITC field interviews in Japan with representatives of U.S.-based multinational firms and representatives of industry associations during April, 1991.

Japan, even with one of the largest domestic markets in the world, is a relatively new global competitor. Nevertheless, Japan is approaching foreign markets on numerous fronts. In Europe for example, Joseph Harford, director and general manager of Yamanouchi, Ireland, noted in a recent interview, "If you are a growing Japanese company, what you seek most is to pursue a knowledgeable infrastructure in the European markets through establishing licensing agreements, building a sales force, then establishing joint ventures. The final step in establishing a strong presence is to purchase the outstanding portion of the joint venture."[92] Although the Japanese do not yet have an extensive product line of new innovative drugs, the diverse presence of the Japanese pharmaceutical industry in Europe is indicated by the following tabulation:

Company	*Country*	*Investment*
Yamanouchi Pharmaceutical	Ireland	Wholly owned subsidiary
Fujisawa Pharmaceutical	Germany	Majority share of King Pharma, Gmbh
Takeda Chemical Industries	France	Joint venture with Roussel-Uclaf
	Germany	Pharmaceutical development center
Eisai Co.	Germany	Joint venture with Sandoz AG
	England	Product development and sales subsidiary
Tanabe Seiyako	France	Joint Venture with Rhone-Poulenc

Several reasons for their lack of international competitiveness to date have been identified, including: (1) an expanding domestic market; (2) the relatively small size of the Japanese companies, as compared to those in the United States and Western Europe; (3) the development of relatively few innovative products by Japanese companies; and (4) the lack of an international marketing infrastructure. They have reportedly participated in a number of joint ventures, licensed out a number of products to U.S. companies and have acquired a number of small research laboratories in the Northeast, but they have not yet established a significant presence in either the United States or Western Europe.[93] According to the 1989 annual edition of the *Japan Chemical Weekly*, the number of Japanese-capital foreign affiliates (i.e., Japanese held assets of 50 percent or greater) numbered 65 in 1987. Fifteen of those affiliates were in the United States while there were 14 in Taiwan, 7 in Germany, and 5 each in Indonesia and Thailand.[94] The following tabulation gives some examples of recent activity by Japanese firms:[95]

- **Takeda**: established a joint venture in the United States with Abbott Laboratories to develop and market ethical drugs; also has ties with firms in Germany, France, and Italy, and funds research at Harvard and Tulane Universities.[96]
- **Fujisawa**: acquired a U.S. firm, LyphoMed, from SmithKline Beecham and owns 74 percent of the assets of the German firm, Klinge Pharma;
- **Chugai**: purchased a U.S. firm, Gen-Probe; also has a small share in British Bio-technology; does joint drug development in West Europe with the French firm, Rhone-Poulenc. Chugai has a marketing joint venture agreement with the U.S. firm, Upjohn for the drug, EPO, which is used to treat anemia resulting from kidney failure, and sell its anti-ulcer drug, Carafate, through an agreement with another U.S. firm, Marion Laboratories;
- **Yamanouchi**: owns the U.S. firm, Shaklee, a vitamins producer, but, in addition, has a facility in Ireland, Yamanouchi Pharmaceuticals, to produce its anti-ulcer drug, Gaster; and
- **Eisai**: owns the Eisai Research Institute of Boston, a recently completed facility used for drug development.

The evolution to the present structure of the pharmaceutical industry in Japan can be traced by a number of publicly available statistics. Since the 1970s Japanese drug manufacturers have doubled their R&D budgets to 10 percent of sales, which is now comparable to U.S. companies. In so doing, they have invested in new research facilities and greatly expanded the number of employees engaged in research. Since 1980, Japanese drugs have won more than 3100 new patents, making Japan the leading source of foreign patents in the United States. In the mid-1970s, Japan paid to foreigners for drug technology three times what it earned in royalties from abroad. Since 1986, it has become a net exporter of such technology.

In addition, the strategic alliances entered into by the Japanese firms allow them access to registration and development systems in the United States and Western Europe and to better understand distribution

[92] Catherine Brady, "Japan's Drug Firms Look Westward," *Chemical Week*, May 10, 1989, p.19.

[93] Nancy Mattison, "Pharmaceutical Innovation and Generic Drug Competition in the USA: Effects of the Drug Price Competition and Patent Term Restoration Act of 1984," *Pharmaceutical Medicine*, 1986, p. 184.

[94] *Japan Chemical Annual, 1989*, p. 78.

[95] "Japan's Drug Firms Look Westward," *Chemical Week*, May 10, 1989, p. 19. Other firms with international connections are Eisai in a joint venture with Sandoz, AG in Germany, and Tanabe Seiyako involved in a joint venture with France's Rhône-Poulenc.

[96] "Japan's Next Battleground: the Medicine Chest," *Business Week*, Mar. 12, 1990, p. 68.

systems in effect in the two market areas. Almost all of the industry representatives contacted expect the Japanese to enter the U.S. and Western European pharmaceutical markets within the next 5-10 years, particularly in the area of biotechnology. The creation of the single market in the EC is expected to make it easier for Japanese firms to enter the EC market. Many believe, however, that they will not be able to enter these markets as strongly as they have several other market sectors because of the lateness of their entry. Sources maintain that they believe that Japanese companies will not be able to purchase major innovative pharmaceutical companies in the United States and Western Europe anymore because they cost too much.[97]

Consolidation in the Global Pharmaceutical Industry

During the past decade, the pharmaceutical industry has undergone increasing consolidation (see Figure 4-4 for a partial listing). Domestic and international mergers, joint ventures, and strategic alliances proliferated in the global pharmaceutical industry in the 1980s. According to one source, approximately 131 pharmaceutical firms announced acquisitions or strategic alliances in the first six months of 1990, compared with a total of 51 in 1989 and 56 in 1988.[98] The trend is expected to continue. Industry sources believe that currently well known companies will disappear; new major players will appear. These sources report, however, that there now is ample room for mergers. The pharmaceutical industry has such a low concentration ratio that a substantial amount of consolidation can occur before any anticompetitive problems are likely.

Several reasons are given by industry sources for the ongoing rationalization and consolidation in the pharmaceuticals industry. First, the reason cited most often is the increase in R&D costs in recent years. Scientists are needed to develop new pharmaceutical products. The scarcity of quality scientists pushes up the price of pharmaceutical research because all major companies are bidding for a limited number of top-notch scientists.[99] Second, manufacturer's profits are squeezed by increasing pressure from National Governments to contain health costs (even though expenditures on pharmaceuticals worldwide at retail prices amount to between only 10 and 20 percent of

[97] One source stated that Japanese firms themselves have stated that they do not have the capital available to buy a major innovative firm.

[98] *Medical Advertising Newsletter*, Sept. 15, 1990, pp. 4-5.

[99] USITC field interviews in the United States with representatives of European-based and U.S.-based multinational pharmaceutical firms and other sources during January-February, 1991.

Figure 4-4
Examples of consolidation in the global pharmaceutical industry during 1983-91

Year	*Companies involved*	
1983	Merck	Banyu
1985	Schering Plough	Key Pharmaceuticals
	Monsanto	Searle
	Rorer	USV/Armour
1986	Boots	Flint
	DuPont	American Critical Care
1988	Fisons	Pennwalt
	American Home Products	A.H. Robins
	Kodak	Sterling
1989	Beecham	SmithKline
	Merrell Dow	Marion
	Bristol-Myers	Squibb
	Novo	Nordisk
	Yamanouchi	Shaklee
	Fujisawa	Lyphomed
	Chugai	GenProb
	Institut Merieux	Connaught
1990	Sankyo	Lultpold-Werk
	Rhone-Poulenc	Rorer
	Roche	Genentech
1991	Sterling	Sanofi

Source: Compiled from data provided by Eli Lilly & Co.

health care costs). Third, it takes longer to get new drugs approved since the industry is now trying to treat chronic aliments like circulatory problems, heart disease, arthritis, or cancer. The testing for these conditions is time consuming as a detailed understanding of the mechanism involved is required if adequate forms of treatment are to be developed. Fourth, national regulators of pharmaceuticals are more demanding. For example, in the early 1960s, it took ICI 31 months to get approval for Inderal, a heart pharmaceutical. In the late 1970s-early 1980s, it took 108 months for ICI to win approval for the pharmaceutical product Tenormin, which is chemically related to Inderal.[100]

Strategic Alliances

Strategic alliances, originally agreements to obtain financing pending the launch of a new product, are more recently entered into to achieve scale economies in the regulatory process and marketing and to broaden geographical reach.[101] Marketing agreements are most popular.[102] Other types include spreading the risks of R&D by agreement to share the products of research in specified areas—e.g., SmithKline/Byk Gulden, and Takeda/Abbott. Smaller companies (e.g., Fisons, Astra) with innovative research accomplishments may prefer to license out or co-develop rather than carry the full development costs, especially for products requiring long-term chemical trials.[103]

One example of an early strategic alliance was the 1983 copromotion agreement between Glaxo and Hoffman-LaRoche. Under the agreement, which was considered fairly unusual at the time, Hoffmann-LaRoche marketed Glaxo's antiulcer product Zantac® in the United States under the Glaxo trade name, rather than its own, for a percentage of the sales revenue generated.[104] The result was beneficial to both companies, with Glaxo establishing name recognition in the United States and Hoffman-LaRoche generating an extra source of revenue that could be used to develop products still in the pipeline to compensate for the 1985 expiration of its patent on Valium®.[105] Hoffmann-LaRoche's sales had mushroomed in the 1970s on the sales of its antianxiety drugs Valium® and Librium®. By the early 1980s, however, there was a temporary gap in Hoffmann-LaRoche's new-product development and sales declined. Hoffmann-LaRoche followed this up with similar deals on other drugs.[106]

The German market, dominated by domestic German and Swiss marketing companies, lends itself especially well to alliances between a domestic company and an overseas company with a new product. France is also dominated by domestic marketing companies, and, with the involvement of the government in pricing approval, many overseas companies forge alliances with French companies. Italy's market is slightly less nationalistic than the previous two, but the need to develop a close relationship with governmental agencies to obtain more timely approval and attractive pricing makes marketing alliances with domestic companies attractive. As in Germany, five of the top 10 drugs are co-marketed. The United Kingdom limits government control to a ceiling on the return on capital employed and a promotional spending limit. Co-marketing alliances are reportedly less common in the UK than in the other EC countries.

Two strategic alliances cited often by industry sources are Merck's recent agreements with DuPont and Johnson & Johnson. Merck's joint venture with DuPont is notable in that it is a research and marketing collaboration. Each company has contributed the following:[107]

DuPont — its entire drug division, with a research staff of about 1,500

Merck — R&D expertise, marketing rights to several of its prescription products, and cash and development funding.

"Significant commercial results," according to one source, are not expected from the venture until the end of this decade.[108]

Under Merck's joint venture agreement with Johnson & Johnson, the two companies will develop and market nonprescription OTC drugs.[109] Merck initiated an agreement with Sigma Tau (Italy) in 1982 to comarket a number of products in Italy.[110] Merck and Sigma Tau have also entered into a research joint venture.[111]

In 1988, the research-oriented Syntex and market-specialist Procter & Gamble created Procter-Syntex Health Products, a joint-venture to develop and market an OTC form of naproxen.[112] The

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[100] "World Pharma Market Near $200 Bill in 1993; IMS," *Marketletter*, June 5, 1989, p. 15; and, "European Drug Makers Face Major Shake-Out," *Chemical Marketing Reporter*, Mar. 19, 1990, pp. SR 34 and SR35.

[101] Burrill and Lee, *Biotech91: A Changing Environment*, 1990, p. 40.

[102] Merck entered into a number of agreements for final products during 1983-89, including a cross-licensing agreement with ICI in 1986, under which ICI co-marketed Merck's antihypertensive product in return for giving Merck co-marketing rights on ICI's experimental anti-diabetic drug. ICI's product was subsequently withdrawn from the FDA approval process.

[103] Shearson, Lehman, Hutton Securities, *Pharmaceutical Profiles*, Feb. 1990, pp. 12, 32, and *The Economist*, Jan. 19, 1991, p. 60.

[104] "The New World of Drugs," *The Economist*, Feb. 4, 1989, p. 63; "SmithKline's Ulcer Medicine 'Holy War'," *Fortune*, Sept. 19, 1983, pp. 129-36.

[105] "SmithKline's Ulcer Medicine 'Holy War'."

[106] "Glaxo Results Buoyant," *European Chemical News*, Oct. 1, 1990.

[107] "Prescription for Cost Containment"; Merck & Co., Inc., *Merck Annual Report 1989*, p. 4.

[108] "Prescription for Cost Containment"

[109] McGraw-Hill, *Business Week*, October 23, 1989, p. 62; Merck & Co., Inc., *Merck Annual Report 1989*, p. 4.

[110] Ibid.

[111] Merck & Co., *1990 First Quarter Report*, p. 20.

[112] "Why Generics May Not Give Syntex a Migraine," *Business Week*, October 10, 1988, p. 76; Syntex Press Release, dated September 19, 1988, entitled "Syntex/Proctor & Gamble Announce Signing of Definitive Agreement."

joint venture is expected to market other products and services produced by both companies.[113] The OTC form of naproxen, besides opening new market possibilities, will also help to offset losses incurred by the expiration of the patent on naproxen. Industry sources expect the trend to continue towards licensing products and establishing strategic alliances earlier in the development process.[114]

Mergers and Internationalism

Mergers and acquisitions provide one way to achieve the multinational status necessary to be a major player. European companies have been somewhat slow in following the United States' example where, for about 20 years, acquisitions have been a popular vehicle for expansion and diversification. The pace among European firms has rapidly increased in anticipation of national barriers coming down in 1992. A number of Western European companies are also enlarging their role in the United States through acquisitions.

The SmithKline Beecham merger is a good example of an objective-oriented marriage of diverse firms. Talks between SmithKline and Beecham began in late 1988, prompted, in large part, by Beecham's concern that if it could not strengthen its drug pipeline, it might be vulnerable to a takeover. SmithKline was reportedly receptive to the idea because of losses in the anti-ulcer market and generic drug competition with another of its major products. The merger created one of the largest ethical drug companies in the world. Its research budget should exceed $500 million per year—among the top five worldwide—and it should be able to deploy 2,800 salespeople in Europe, 1,900 in the United States, and 500 in Japan. SmithKline now is not expected to need a partner to market its prospective OTC version of Tagamet®. The gains from the synergy of the merger are said to be augmenting SmithKline Beecham's R&D pipeline.[115] A source at SmithKline estimated in 1989 that the majority of the savings accrued from the merger, or about 60 percent, would come from the larger combined sales force and the copromotion of a number of products.[116] Bristol-Myers Squibb is another example of a "mega-merger." Bristol-Myers brought "superb marketing and financial prowess" to the match, while Squibb brought its "R&D creativity."[117]

In Europe, the traditional focus of the French industry on its domestic market is slowly changing, as several French firms seek to strengthen their position in foreign markets. The merger between Rhone-Poulenc and Rorer and the strategic alliance between Sanofi (owned by Elf Aquitaine) and Sterling (part of Eastman Kodak) are examples of this trend.

Rhone-Poulenc has been one of the most active European pharmaceutical firms in making acquisitions abroad, seeking alliances, and establishing joint ventures. Over the past few years it has acquired Natermann of Germany, Upjohn Brazil, the bulk analgesics business of Monsanto (US), the U.K. generics company Approved Prescriptions Service, and, through a subsidiary, Connaught BioSciences of Canada. In early 1990 it took a 68 percent share of Rorer Group Inc. to give it an opening into the U.S. drug market.[118]

The alliance between Sanofi and Sterling gives the two firms access to each other's distribution network and creates a combined R&D operation worth $500 million annually. The agreement is considered to be "experimental" in nature: no cash was exchanged, thereby allowing both companies to concentrate their cash on developing new products; and the two companies will share on a 50-50 basis the profits from the three joint ventures that were created.[119] The alliance, which is called an "attractive way" to overcome financial issues that are usually the result of more conventional mergers and which is expected to create additional "critical mass" needed to successfully market new products, is not without perceived potential difficulties. One such difficulty would be future disagreements between the companies in regard to strategic issues such as company operations or possible acquisitions.[120]

Europe has attracted a growing share of Japanese foreign direct investment. This share rose from 10 percent in the early 1980s to 17 percent by the end of the decade. Additional ventures with EC partners are expected in the 1990s, though small- to medium-sized Japanese companies will continue to rely on licensing as an entry strategy.[121]

It had been thought that some of the former East German drug companies would be acquired by West German firms, but such has not been the case (as of May 1991). The two largest, Arzneimittelwerk Dresden and Berlin Chemie, have been negotiating plans to privatize within the next year or two, as is the remainder of the East German pharmaceuticals industry.[122]

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[113] *Journal of Commerce*, Sept. 21, 1988, p. 98; Syntex Press Release, dated September 19, 1988, entitled "Syntex/Proctor & Gamble Announce Signing of Definitive Agreement."

[114] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[115] "Prescription for Cost Containment," p. SR4. The article states that the merger was prompted by a declining market share for its blockbuster product, Tagamet.

[116] "Pharmaceuticals," p. 58.

[117] Ibid.

[118] "European Drug Makers Face Major Shake-Out," *Chemical Marketing Reporter*, March 19, 1990, pp. SR 34-35.

[119] "Pharmaceuticals '91," p. SR10; *The Economist*, Jan. 19, 1991, p. 60.

[120] Ibid.

[121] *European Chemical News*, Apr. 22, 1991, p. 32.

[122] "E German Pharma Industry on Road to Privatisation," *European Chemical News*, May 6, 1991, p. 6.

Between 1979 to 1990, four Japanese ethical pharmaceutical manufacturers were acquired:[123]

Mergers of Ethical Pharmaceutical Manufacturers in Japan

Year	Acquiring Company	Acquired Company
1982	Merck	Torii
1983	Merck	Banyu
1985	Merrell Dow	Funai
1986	Boehringer Ingelheim	San-a

Source: *Yano Report, January 1991*, International Pharma Consulting, Ltd., Tokyo, Japan.

According to the Yano Report providing this information, the dominant philosophy in Japan still remains that only as the final measure of survival will a company agree to a merger arrangement, and this philosophy is expected to continue in the conservative ethical pharmaceuticals business.[124]

While more mega-mergers are possible in the future, industry sources believe that it is likely that European firms will seek to merge with medium-sized U.S. companies.[125] Many industry representatives expressed expectations that companies will follow the lead of Merck by entering into strategic alliances.[126] It has been suggested that as profit margins decline in the generic industry 5-7 years hence, more generic firms will ally themselves with brandname companies, such as the arrangement between Rugby and SmithKline Beecham. Under such an alliance, the generic firm would get access to a company's product pipeline, allowing it to reach the market first with new products.[127]

Licensing and Cross-licensing

As is the case in the other sectors of the chemical industry, a company almost always finds that licensing the process and reaction expertise and patent rights for a new pharmaceutical is much less expensive than utilization of the company's own R&D to develop a new product (see Chapter 5 for a discussion of the relationship between products under development and global market share). The practice of licensing has been used in the pharmaceutical industry for a number of years to allow firms to extend their geographic reach, to fill-in gaps in a product line, and to access new technologies.[128] Licensing is most prevalent with the more costly drugs and those with product spin-off potential.

In general, a company may be able to license a drug for sale in a country where the licensor does not have an adequate sales force to compete in that market itself or in a market sector in which it does not have much experience. Swapping licenses with other companies for different drugs in or different types of markets is an example of cross-licensing. With R&D becoming ever more expensive, cross-licensing is certain to increase.

Of the world's top 34 drug companies in 1988, only two had managed to more than double their sales in a five-year period—Glaxo and Marion Laboratories (United States). Marion's increased sales reportedly resulted from licensing an antiangina product, Cardizem, from a Japanese company.[129] In a measurement in 1989 of productivity and payoff of drug research, comparing dollar earnings from new products to ten-year constant-dollar expenditures on R&D, Merck had spent about $1 billion on R&D, and seemed likely to earn 103 percent of what it spent. Marion, on the other hand, appeared likely to earn $7 billion on only $1.2 billion for R&D. More important, perhaps, Marion's profitability in 1988, measured as return on assets, was the highest of all the top 34 top companies.[130] The difference was the product it licensed, which almost certainly cost far less to license than develop.[131]

Another motivation for cross-licensing is the desire to find an appropriate "fit." One company, for example, may believe that it has a special "area of comfort" or expertise with certain types of drugs. When the company develops a new drug that is outside of this comfort area, it seeks another company familiar with that type of drug and attempts to swap its new candidate for a potential new drug of a type with which it is more familiar.[132] In addition, protracted battles between two companies involving patent rights for the same or almost-the-same drugs have, in some cases, been settled by agreement to cross-license, so that each company can produce it by whatever technology it wants.

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[123] *Yano Report -the Japan Pharmaceutical Industry Quarterly - January, 1991*, edited by Yoshio Yano, International Pharma Consulting, Ltd., Tokyo, Japan, pp. 36-37.

[124] Ibid.

[125] USITC staff field interviews in the United States with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[126] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during January-April 1991.

[127] "Side Effects Linger," *Chemical Marketing Reporter - Pharmaceuticals '91*, Mar. 11, 1991, p. SR26.

[128] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[129] "Pharmaceuticals," pp. 68, 70-71, 76-77.

[130] Profitability comparisons in this case are not perfect, because most companies have large interests in other industry segments in addition to pharmaceuticals, and their reported earnings apply to the entire firm. However, Marion, with sales that were more than 90 percent pharmaceuticals, did exceed the profitability of the other nearly-all-pharmaceuticals companies—Merck, Glaxo, and Astra (Sweden).

[131] "Pharmaceuticals," pp. 68, 70-71, 76-77.

[132] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

Commercialization of Products

Today, the United States and other global pharmaceutical industries continue to face a number of challenges that, cumulatively, have a significant impact on their current and future competitiveness. Cost-containment efforts enacted around the world, price controls, export policies, IPR protection, and the continuously increasing costs of R&D all affect the future level and location of R&D performed by innovative firms. The continued impact of these issues on the industry will be discussed in more depth in following sections of this chapter.

Market entry

Entry into the pharmaceutical industry is difficult. A potential entrant must obtain finance for research, endure the years of clinical testing for regulatory approvals, and establish a large and efficient sales force. Exceptions in recent years have been chemical companies with retained earnings or other funds and motivation to diversify into pharmaceuticals.[133] Even the largest and richest chemical or other companies thinking of diversification into pharmaceuticals, judging from recent U.S. experience, are likely to find their attempted penetration of the drug market disappointing unless they take over one of the top pharmaceutical companies.[134]

A number of industry representatives, both in Europe and the United States, believe the day is soon coming when only a handful of companies will be involved in large-scale R&D on innovative pharmaceuticals, primarily because of the rapidly rising costs and risks of R&D and the decreasing time companies have to recoup R&D investment. Today's industry is a research business that primarily depends on new and improved drugs to generate enough profit for continued growth and research. The industry finances the majority of its R&D itself by reinvesting its revenues. PMA member firms, including those based outside the United States, reinvested almost 17 percent of their revenues, $8.2 billion, in R&D in 1990.[135] Since the odds are long on any one prospective new product's success, a company must have enough researchers to be working on a number of prospects over a period of years and provide a minimum R&D budget of about $100 to $200 million per year.[136] Assuming these hurdles are surmounted, a potentially successful new drug candidate probably has less than 10 years to pay off, before its patents expire and the generic manufacturers take over, or a "me-too" drug is created by a competitor.

A sizeable sales force also is needed to exploit a new product quickly during its probable short life. In spite of new tactics such as video press releases, teleconferencing, or "peer-influence groups," the basic sales input consists of legions of detail men meeting one-on-one with doctors.[137] For example, two large U.S. drug companies each have European sales forces that include more than 1,000 field representatives, while world-leader Merck has more than 2,000 in Europe alone. The large European companies, of course, have many more.

An alternative and promising route into the pharmaceutical market is through biotechnology. Many small new companies exploiting discoveries in biotechnology have begun to produce new pharmaceutical products.[138] This proliferation, however, has been concentrated mainly in the United States during the 1980s. It was the result of the creation of a new technology—genetically engineered products; the ability of individual scientists to both discover and produce new products using this technology; and readily available U.S.-based venture capital looking for promising investment possibilities.[139] Now that venture capital is less obtainable in the United States, firms from other countries, particularly Japan, are entering through strategic alliances with U.S. producers.

Intellectual Property Rights

Given the increasingly long product development time, including the longer time needed to obtain FDA approval to market a product, IPR protection has a significant impact on the development and commercialization of new pharmaceutical products. An industry source has estimated that IPR infringement in 1986 cost the U.S. industry approximately $6 billion, possibly reducing R&D investment by $720-900 million.[140]

One study (Mansfield, 1986) is cited as indicating that patents are more important for the pharmaceutical industry than they are for a number of other industries (see Fig. 4-5). According to this study, a number of pharmaceutical products would not have been introduced and/or developed during 1981-83 if patent

[133] "Pharmaceuticals," pp. 61, 62, 77, 78.

[134] "Pharmaceuticals," pp. 58, 68.

[135] OMA, *Annual Survey Report: 1988-90*, 1990, p. 31.

[136] Money, however, is not considered by a number of industry sources to be a guarantee of success as smaller firms can, in some instances, better focus their research productivity than larger firms. The bureaucracies inherent to some large firms can potentially reduce the innovativeness of the firm. Merck, however, is considered to be an exception to this statement. Merck reportedly not only has a strong pharmaceutical R&D program of its own, but also does well in both licensing and in strategic alliances.

[137] A contrary opinion was expressed by a vice president of Hoechst-Roussel in a speech (to a U.S. audience) in 1990. He said that the focus of the marketing effort is quickly moving away from the individual physician. The physician has already been almost halfway replaced by committees, formularies, hospital groups, purchasing agents, and other representatives of HMO's, PPO's, Medicaid, home health care groups, nursing homes, and clinics.

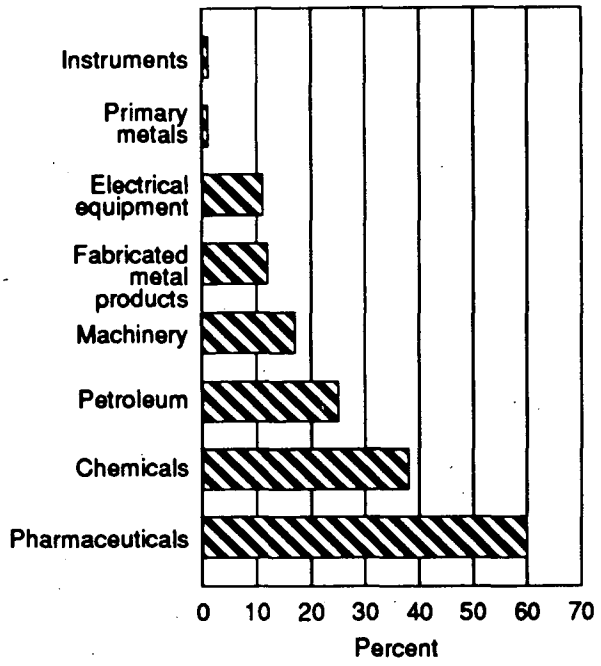
[138] Office of Technology Assessment, *New Developments in Biotechnology 4: U.S. Investment in Biotechnology*, 1988.

[139] Unpublished USITC staff working paper on biotechnology, 1990.

[140] "Health Care Innovation," p. 21.

protection had been absent. Patents are said to be a "core policy instrument in determining the returns to innovative efforts in a core-group of industries and particularly for pharmaceutical drugs" in industrialized countries.[141]

Figure 4-5
Estimation of products not developed in the absence of IPR protection, by sector (1981-83)

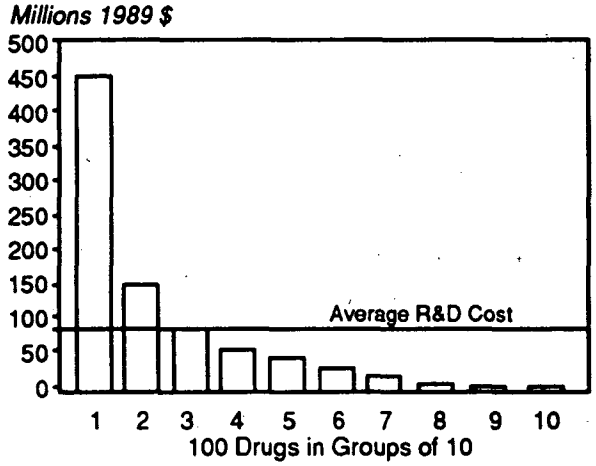


Source: "Patents and Pharmaceutical Drugs".

A recent study of 100 NCEs introduced in the United States during 1970-79 indicated that only 30 of these products earned a return that was as high or higher than the average R&D cost (see Figure 4-6). The returns on the remaining products, although contributing in many cases to firms' profits, were lower than the average.[142] According to the study, if a firm wishes to cover the high fixed costs of product development, it must develop a "blockbuster product," or one that whose present value is comparable to that of the top 20-30 products.[143] Although questions have arisen in the post-World War II period as to what level of return on a pharmaceutical product is appropriate and what period of time is needed to recover this level of return,[144] one source has estimated that the average NCE recovers its R&D investment in 19 years.[145] Another source has stated that one-third of thepresent value of products launched during the 1970s was accrued during years 12-15 of the product's lifetime.[146]

The effective patent terms on individual products have generally decreased since the late 1970s in the United States, Western Europe, and Japan such that the average effective patent life is now about 7-11 years.[147] In the United States, for example, the average length of the effective patent life of a pharmaceutical has declined to 10 years and 10 months, compared with 15 years in the early 1960s, primarily as a result of the average development time increasing to about 10.6 years.[148]

Figure 4-6
Earnings performance of 100 drugs vs R&D cost: After-tax present value



Source: H. Grabowski, Ph.D., 1980-89.

Development of New Products

New Chemical Entities (NCEs)

In order to continue successful competition, innovative companies must develop new products. The development time for these new products, whether discovered in-house or licensed from other companies, can take as long as twenty years from discovery to

[141] "Patents and Pharmaceutical Drugs," *Journal of World Trade*, Vol. 24, No. 6, December 1990, p. 87. The industries examined were: pharmaceuticals; chemicals; petroleum; machinery; fabricated metal products; primary metals; electrical equipment; instruments; office equipment; motor vehicles; rubber; and textiles.

[142] Grabowski and Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science*, Vol. 36, No. 7, July 1990, p. 816.

[143] Ibid.

[144] "The Political Economy of the Pharmaceutical Industry," p. 1180.

[145] *Pharmaceutical Patents: The Stimulus to Medicines Research*, the Centre for Medicines Research, p. 27.

[146] "The Changing Economics of Pharmaceutical Research and Development," p. 35-52.

[147] *Pharmaceutical Patents*, pp. 22-26. It should be noted that the effective patent life of products in these countries has eroded in absolute terms since the early 1960s. Following the downturn in the 1970s, effective patent terms started to increase during the 1980s, but did not return to the levels of the 1960s.

[148] European Federation of Pharmaceutical Industries' Associations, *Memorandum on the Need of the European Pharmaceutical Industry for Restoration of Effective Patent Term for Pharmaceuticals*, p. 7; USITC field interviews in the EC with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during Jan. 8-19, 1990.

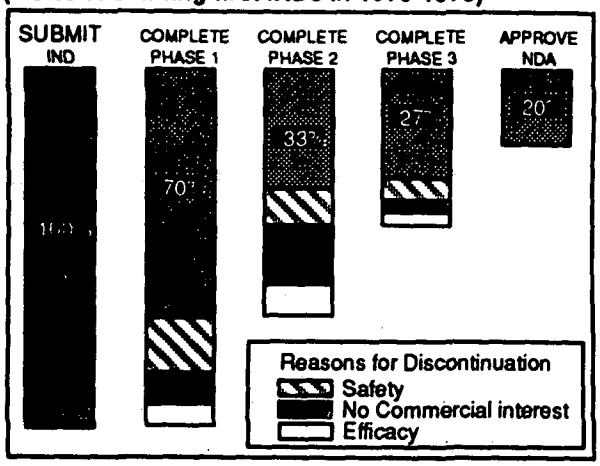
marketing. A number of factors are taken into consideration when a company decides to concentrate research in certain therapeutic areas, including the current level of technical knowledge about a given therapeutic area. Given the often rapid diffusion of discoveries across the scientific community, a number of firms might start discovery efforts in the same therapeutic area(s) at the same time. The first product to be marketed, however, whether or not a blockbuster, generally earns a significant degree of market recognition. Products that follow thereafter, often misleadingly called "me-too's," must differentiate themselves from the first product in order to gather market share.[149] According to industry sources, however, studies have shown that products that are launched later generally do better because they are based on more recent scientific discoveries.[150]

Development accounts for the largest portion of the R&D cost.[151] Once the laboratory and animal studies are completed successfully, a company files for approval of the pharmaceutical product as an IND. At this stage, the company begins clinical studies on the drug (see Figure 3-2).

According to one source, only one out of every 4,000 compounds discovered is marketed commercially;[152] others estimate one in 5,000, or even one in 10,000.[153] Products drop out at various stages of the development process. One example cited is product development in Germany during 1972-81. Of the 280,000 compounds examined by German innovative companies, 2,356 were developed; 47 of these were launched on the market.[154] Figure 4-7 shows the stages of the development of a "successful NCE" and an estimate of the number of products that complete each phase of the process.

The increasing length of time and rising cost needed to develop new products is attributable to the nature of the products being developed. Newer areas of research are focusing more on products used to treat chronic diseases, which need more extensive development and testing and longer clinical trials because a detailed understanding of the mechanism involved is required if adequate forms of treatment are to be developed.[155] Industry sources also cite FDA

Figure 4-7
Success of clinical research
(NCEs submitting first INDs in 1976-1978)



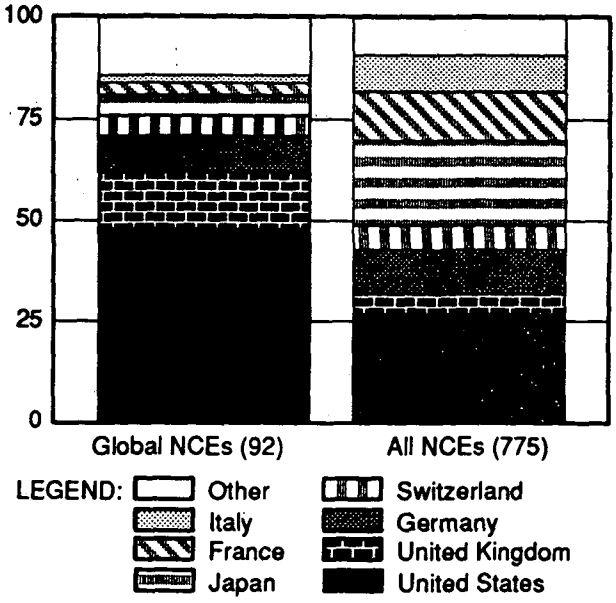
Source: Reproduced with permission from the U.S. Food and Drug Administration.

requests for more safety data, thereby requiring larger trial populations.[156]

During 1975-89, the United States was cited as the world leader in introducing globally successful NCEs (see Figure 4-8).[157] About 775 NCEs were discovered

Figure 4-8
International comparison of research results during 1975-89

Percent



Source: P. Etienne Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World.*

[149] A "me-too" is generally a product which has been developed by modifying the structure of an existing product. In some cases, however, research paths converge, and similar products are introduced into the market within short periods of each other.

[150] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[151] *1992 and the Regulation of the Pharmaceutical Industry*, p. 16; "Pharmaceuticals," p. 61.

[152] Chemical Marketing Reporter, *Pharmaceuticals '89*, Mar. 20, 1989, p. SR8.

[153] *1992 and the Regulation of the Pharmaceutical Industry*, p. 14.

[154] Ibid.

[155] Steven N. Wiggins, *The Cost of Developing a New Drug*, 1987, p. iv; "European Drug Makers Face Major Shake-Out," *Chemical Marketing Reporter*, Mar. 19, 1990, pp. SR34 and SR35.

[156] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[157] P. Etienne Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World (1975-1989)*, August 1990, p. 34.

during this time period, of which 69 percent were discovered in the United States, Japan, the United Kingdom, Germany, and Switzerland (see Chapter 5 for an analysis of the origination and marketing of innovative products in the leading pharmaceutical markets). Of the 775 NCEs, 97, or about 13 percent, were marketed on a global basis.[158] The United States accounted for about 48 percent of the global NCEs, compared with 14 percent for the United Kingdom and about 3-10 percent, on an individual basis, for Switzerland, France, Germany, and Japan. Industry sources cite a number of reasons for the U.S. industry's continued strength, including "an unencumbered U.S. economy" in terms of pricing and cost-containment, good scientists, and the fact that the United States has been the center of industry R&D. The U.S. industry's strength in innovation, however, is perceived to be eroding as a result of factors such as the increasing time required to obtain FDA approval. Concern also exists as to the continued quality of the education system in the United States.[159]

The long-term product pipelines of European companies are reportedly expanding. These products are expected to become important commercial products in about 10 years, as it takes about a decade for pharmaceuticals to move from the R&D stage to being marketed as commercially viable products.[160] Industry sources report that European Governments reportedly foster their local pharmaceutical industries since the products of this industry help to maintain the national health care industry. One example cited is that of faster product approval within Western Europe, within 12 months in some countries, allowing products to be launched on the market earlier in Europe than in the United States. Product liability, another example cited, is perceived to be less of a burden in Europe than it is in the United States since some European countries, such as Denmark, do not allow product liability suits. U.S. pharmaceutical firms usually overlabel products overseas (as compared to European label requirements) to limit potential suits by foreigners based on U.S. liability standards. Industry sources report that overlabeling can have a negative effect on U.S. sales overseas.[161]

[158] A "global" NCE is defined as one that is marketed in seven countries.

[159] Industry sources believe that the United States is not getting the most out of its educational system. Western Europe's and Japan's secondary educational system (i.e., thru high school) are reportedly producing better graduates than that in the United States. The university system to the United States, however, is perceived to be superior to that of Japan.

[160] USITC staff field interviews in the United States with representatives of European-based and U.S.-based multinational pharmaceutical firms and other sources during January-April, 1991.

[161] USITC staff field interviews in the United States and Western Europe with representatives of European-based and U.S.-based multinational pharmaceutical firms and other sources during January-April, 1991.

Whereas it is the consensus of industry sources that the U.S. industry is "the leader" in developing a new product, the British industry is considered to excel within the EC in innovative drug research.[162] Although the UK industry accounted for less than 5 percent of all NCEs discovered during 1975-86, 18 percent of the global NCEs originated in the United Kingdom. In 1990, the UK industry developed 13 of the top 50 pharmaceutical products marketed worldwide.[163] Industry sources attribute the strength of the UK industry to the high quality of education its scientists receive at universities such as Oxford and Cambridge, the sharing of a common language with the United States, and "good conditions" (such as sufficient investment in the industry, as realized through the PPRS system, and relatively high profit levels).

Although France, Germany, and Japan together accounted for about 45 percent, or about 275, of total NCEs developed during 1975-86, they only accounted for about 25 percent, or 16, of the global NCEs. The percentages for France and Japan reflect, to some extent, the traditional focus of these industries on their domestic markets.

The French industry, once very vital, has decreased in strength since 1975, reportedly as a result of French Government controls on the pricing and promotion of pharmaceuticals. As such, France accounted for a relatively low share of the global NCEs marketed during 1975-86 and again during 1990. The French industry is still relatively large, however, because of the large domestic market for pharmaceuticals and, according to at least one industry source, because of the French Government's protectionist policies towards the industry.[164]

Germany's low share, in spite of that country's free-pricing policies and the strength of its industry, is attributed primarily to the structure of its industry. The German pharmaceutical manufacturers are, in many cases, subsidiaries or components of larger chemical firms. As such, it is suggested that perhaps the pharmaceutical sector has not been strongly emphasized. In addition, the implementation of the HRA decreases innovation in the German industry in that it reduces revenues that can be reinvested in R&D. Industry sources also question the quality of the German higher education system.[165]

[162] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during January-April 1991.

[163] "Pharmaceuticals '91," p. SR45.

[164] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991; *Medicines in The Marketplace*, p. 16.

[165] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

Substitute Products

As soon as a successful new drug appears on the market, its producer can be certain that competing companies are likely to soon have 15 or more similar products in the testing phase. Therapeutic categories tend to get crowded the minute there is any movement in the laboratory. "Everybody reads the same papers, so most people can determine market potential and clinical feasibility," said one industry source. "Most can then come up with a rank order of attractiveness and go on from there." The result is that similar chemical entities appear in many research pipelines. As of 1989, these included anti-inflammatory leukotriene antagonists, proton pumps against ulcers, cholesterol-reducing reductase inhibitors and dozens of chemicals that react with cellular receptors. Nearly every sizeable company was pursuing cardiovascular drugs, producing tremendous crowding in older products such as beta blockers and calcium-channel blockers, and considerable jostling in newer classes like cholesterol-reducing agents, or clot busters.[166] Even a less effective me-too drug can do well in the market, depending on the way it's promoted and marketed. Of the 23 NCEs approved in the United States in 1990, 7 were considered to represent "important therapeutic gain," 5 presented "modest therapeutic gain," and 11 showed "little or no therapeutic gain."[167]

The lead time between the appearance of a pioneering drug and a competing product has dwindled to as little as 3 years, compared with 5 to 7 years a decade ago.[168] Tagamet®, SmithKline Beecham's antiulcer drug which quickly grew to $1 billion in sales, was succeeded by a follow-on product, Glaxo's Zantac®, years before its 1993 patent expiration date. Glaxo, then far smaller than SmithKline, elected to compete against Tagamet® in Italy, where it has historical strength rather than going against SmithKline's strength in the United States. Massing its resources by forging a marketing agreement with an Italian drug company, Glaxo assigned a mass of sales representatives to the task. Since then, however, both companies have faced competition from imitators developed by Lilly and Merck. Squibb's innovative billion-dollar antihypertensive blockbuster Capoten®, the first of the angiotensin converting enzyme (ACE) inhibitors,[169] has been confronted with Vasotec® from Merck and two other drugs—with a number more on the way—years before its patent expires.[170]

[166] "Pharmaceuticals," p. 61, 73.

[167] According to information presented by Mr. Gerald Meyer, Deputy Director, Center for Drug Evaluation and Research, FDA.

[168] *Forbes*, Apr. 15, 1991, p. 48.

[169] ACE is responsible for creating a substance that causes hypertension. As such, an ACE inhibitor is an agent that inhibits the action of the enzyme in the body.

[170] "Pharmaceuticals." pp. 61, 73.

New Product Areas

Although most industry R&D is devoted to new products, considerable testing is being done to find new uses for older drugs. Companies are increasingly shifting their R&D emphasis from infection-fighters such as antibiotics to diseases such as cancer, emphysema, diabetes, and inflammation, as well as age-associated diseases such as Alzheimer's. "Most of the early trends in pharmaceuticals were directed toward acute disease," said an industry source. "But now we're focusing more on chronic diseases, which take more time and money to study." The gambles are great because so many companies are working on the same thing.[171] In early 1991, industry opinion, both in the United States and in Europe, was that the near-future areas of major research activity will include CNS drugs, oncology, immunology, viral diseases, geriatric drugs (e.g., for Alzheimer's and Parkinson's diseases), anti-arthritics, cardiovascular drugs, anti-cancer drugs, and drugs for AIDS.[172]

Research Consortia

Because the competitive position of a pharmaceutical company depends overwhelmingly on invention and patent protection of a target medicinal, there have been relatively few joint R&D ventures directed toward new drug discovery. One recent notable venture is a research and marketing collaboration between Merck and DuPont. Industry sources expect that the trend towards licensing products and establishing strategic alliances earlier in the development process will continue.

Some European countries permit and even encourage joint venture consortia[173] (which ordinarily would not be consistent with U.S. antitrust laws.) In Germany, the Federal Ministry of Science and Technology (BMFT) administers support programs for promotion of biotechnology, including basic and applied research, and government funds were set aside (about $20 million in 1982) for specific projects involving cooperative industry research.[174]

The U.S. subsidiary of Immuno AG, in a collaborative R&D agreement with the National Cancer Institute and the National Institute for Allergy and Infectious Diseases, has had its candidate AIDS vaccine approved for human clinical trials by the FDA.[175]

Computer-Aided Molecular Design

Computers are increasingly being used to supplement more sophisticated methods of identifying the substances that form the body's natural defenses,

[171] "Pharmaceuticals," pp. 72-74.

[172] USITC staff field interviews in the United States and Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during February-March 1991.

[173] Ibid.

[174] Ibid., p.79.

[175] "AIDS Vaccine Is Candidate for Clinicals," *Chemical Marketing Reporter*, Dec. 3, 1990, pp. 9, 23.

isolating disease-causing genes and seeing how they work. Computer models of molecular structure and recombinant DNA techniques focus research on a specific target.[176] Drugs ("ligands") affect specific receptors within the body which are the "switches" that trigger key biochemical reactions in cells. They couple with the receptor in a way that sets off a biological effect on the body, such as stopping swelling, slowing the onset of a disease, or cleaning out arteries. The computer, by doing a myriad of calculations and drawing pictures of its results, shows the researcher parallel images of a new drug and its supposed receptor site. The chemist then can rotate, invert, truncate, or augment the drug image to make it a better fit.[177]

Computer-aided procedures are evolving very rapidly following significant increases in hardware performance. In particular, high-performance RISC-based (reduced instruction-set cpu) UNIX workstations have largely supplanted timesharing minicomputer and graphics terminals combinations to give unprecedented computational and "visualization" power to the individual computational chemist. Many pharmaceutical and chemical companies are turning to supercomputers to solve computational chemistry problems which, it is hoped, will shorten the drug discovery process.

The most important contribution is to tailor-make drugs to correct a condition. Drug research is no longer restricted to looking for a disease that a newly synthesized chemical can cure or screening thousands of products to find one that exhibits therapeutic properties. It now includes the deliberate design of molecules for a specific cure.

Linkages of Pharmaceutical Products and Technology to Other Sectors of the Economy

During the past decade, the costs associated with health care worldwide have increased steadily. In 1989, health-care costs in the United States represented approximately 12 percent of domestic gross national product (GNP), increasing from about 7 percent in 1968.[178] Per capita health expenditures in the United States in 1989 totaled almost $2,000, compared with approximately $1,600 in 1984 and $349 in 1970. On an international basis, in 1984, Canada incurred the next-largest per capita expenditures, reaching almost $1,300, followed closely by France ($1,200) and Germany ($1,100).[179] Per capita expenditures of the United Kingdom, Italy, and Japan were $800 or less.[180]

The increases in health care costs have generated increasing concern about health-care expenditures, prompting countries to consider methods to reduce such expenditures. In many cases, the response has been to implement price controls, cost-containment programs, or both. Thus, the rise in total costs for health care has resulted in government actions that affect the competitiveness of one industry in the field of health care — the pharmaceutical industry.

Price increases for existing drugs and ever higher prices for new drugs in the United States have caused their average price to rise at a faster rate than the Consumer Price Index.[181] However, the portion of total health care costs represented by pharmaceutical products, at least in the United States, has decreased from over 11 percent in 1983 to about 7 percent in 1989.[182] The cost effectiveness of substituting certain pharmaceutical products for a hospital stay has been well documented in recent years, even being presented as part of a company's application for domestic marketing rights.[183] Pharmaceutical products "help to reduce the cost of alternative, more expensive forms of medical care."[184] A recent study has found that over the next 25 years, the estimated savings in health care expenditures from the use of pharmaceuticals will be valued at almost $500 billion.[185] For instance:

> Outpatient prescription drug treatment of coronary heart disease for 1 year costs about $1,032; the cost of coronary bypass surgery is approximately $30,430;
>
> During 1976-86, it is estimated that a single antiulcer drug reduced the costs of the disease by $5.8 billion worldwide and by $4 billion in the United States alone.[186]

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[176] "Pharmaceuticals," pp. 59-60; *A Competitive Analysis of the U.S. Pharmaceutical Industry*, pp. 70-71.

[177] Ibid., and *The Washington Post*, Mar. 22, 1991, p. B3.

[178] "The Economic and Social Impact of Drug Innovation on the Delivery of Health Care: Recent Trends," *Private Practice*, November 1988.

[179] Germany was heretofore referred to as West Germany.

[180] *PMA Statistical Fact Book—Facts at a Glance*, 1989, p. 28.

[181] Nearly all drug categories have shown annual price increases in recent years. Based on Bureau of Labor Statistics data, prescription drug producer price indexes for selected categories in September 1990 showed the following annual increase: Cancer therapy products, 7.0 percent; Cardiovascular therapy, 8.8 percent; Psychotherapeutics, 16.3 percent.

[182] "The Economic and Social Impact of Drug Innovation on the Delivery of Health Care," November 1988.

[183] Some industry sources believe that proponents of cost-containment proposals in the United States look only at drug prices and not at the companies' costs of developing and marketing the products, or at the offsets that pharmaceuticals provide in other areas of health care, such as reduced hospital stays.

[184] PMA submission, p.9.

[185] "The Value of Pharmaceuticals: An Assessment of Future Costs for Selected Conditions," Battelle study, February 1991. The study examines five categories of disease. Given that each was studied independently, the results of the five are not considered to be additive. The number presented in the text, however, gives an idea of the magnitude of estimated savings over the 25 year period (including direct and indirect savings).

[186] "The Economic and Social Impact of Drug Innovation on the Delivery of Health Care," November 1988; "Health Care Cost Containment and Pharmaceutical Innovation," *Pharmaceuticals for the Elderly: New Research and New Concerns*, 1986, p. 26, *PMA Statistical Fact Book: Facts at a Glance*, 1989, p. 24.

New drug products, including those produced via biotechnology, can prolong life and relieve symptoms enough to reduce sick leave, increase productivity, and improve the quality of life. In the last ten years, a number of important new pharmaceuticals have been produced using biotechnology (i.e., biopharmaceuticals) and many more are expected to be developed in the future. The technology developed in this new sector of the pharmaceutical industry should find application in many other areas of research.

Biotechnology

Introduction

Biotechnology is a rapidly growing, research-intensive, multidisciplinary range of technologies, which uses living organisms for a variety of pharmaceutical, agricultural, energy, waste management, and chemical purposes.[187] Although frequently called an "industry," biotechnology encompasses a range of multidisciplinary technologies that can be applied in a wide variety of industries.[188] Because of this diversity, several definitions of biotechnology exist. For example, the term generally refers to the application of scientific and engineering procedures to process substances using biological agents to provide goods and services. This definition is used mainly to describe the recent advances in genetically engineered products; however, it also has been used to include "old" biotechnology processes, such as fermentation, in which the biological activity of microorganisms plays an important role.[189]

By June 1991, there were 12 biotherapeutic products on the market, 22 products submitted for FDA approval, 171 products in clinical trial, and 542 products in preclinical stages. However, the rapid and continuing evolution of biotechnology makes it difficult to quantify the effect of biotechnology on the pharmaceutical industry. It is also difficult to quantify the commercial benefits of the general increase in scientific knowledge that has developed from biotechnology in the last 30 years. As one biotechnology spokesman noted "just as few could have predicted the impact of biotechnology 20 years ago, it is just as unlikely that few can predict the impact of biotechnology 20 years hence."[190]

Because many biopharmaceutical products have been discovered by small entrepreneurial companies, often with close university affiliations, biotechnology has been viewed as a new high technology industry (reminiscent of Silicon Valley) that is competing with the more traditional pharmaceutical companies. While similarities do exist between Silicon Valley and the "new biotechnology companies," representatives of biopharmaceutical companies emphasize the diverse applications of biotechnology to many industries and the use of biotechnology by large firms in both in the United States and around the world. They further note that by the end of the 20th Century, biotechnology will be much more prevalent in larger pharmaceutical company research labs. In the 1990 edition of the Pharma Projects (Scrip), approximately 90 percent of the world's top 80 pharmaceutical companies (defined in terms of sales) indicated some commercial interest in biotechnology. Furthermore, many of these larger companies indicated some research collaboration with a university or a research hospital[191].

This section will focus primarily on the firms developing biopharmaceuticals — referring to them as the biopharmaceutical industry. Recently many of these biopharmaceutical companies have passed from small entrepreneurial research organizations to commercially viable companies. Therefore, these companies must now face production, marketing, regulatory, and litigation problems similar to those of the more established pharmaceutical industry.

History of the U.S. Biotechnology Industry

As brief as the history of the biotechnology industry may be, it has progressed rapidly in a series of short waves. In the 1950s, most of biotechnology focused on basic research carried out in the major universities with little concern for the commercial potential of the new science. During the 1960s and the early 1970s, as basic research continued, it also began to identify promising commercial products. Small biotechnology companies funded by early venture capital appeared during this time. By the late 1970s and early 1980s, these new companies were bringing their first products to clinical trial. By the mid 1980s, the first biotechnology products were on the market, bringing with them regulatory and patent issues. By the late 1980s, marketing, and production issues emerged as the "industry" came into being.

It is generally accepted that the early preeminence of the small, entrepreneurial U.S. company in the world biotechnology industry was fostered by the domestic cultural and economic environment. Three important factors in this environment were (1) Federally funded basic research, (2) entrepreneurial success, and (3) the availability of capital. The basic research that produced the first biotechnology products was not developed by the large pharmaceutical companies; rather, it was nurtured throughout the U.S. university system by academic entrepreneurs and funded by state and Federal institutions such as the

[187] The five market segments most often identified with biotechnology are (1) human diagnostics, (2) human therapeutics, (3) agbiotechnology (plant genetics, crop protection), (4) suppliers to the industry, and (5) other segments such as environment, energy, and animal health.

[188] Industrial Biotechnology Association, "Biotechnology at Work," 1989.

[189] An unpublished Commission working paper on biotechnology.

[190] USITC staff field interviews with representatives of the biotechnology firms in March 1990.

[191] PJB Publications, Pharma Projects, 1990, Surrey, England.

National Institutes of Health (NIH) and the National Science Foundation (NSF).[192] In 1991, Federal support for biotechnology was $3.8 billion, approximately 80 percent of which was funded through NIH. The 1992 Federal budget proposal for biotechnology is $4.1 billion, an increase of $319 million over the 1991 budget.[193]

NIH funded research can be divided into two areas: (a) basic research devoted directly to biotechnology including recombinant DNA techniques and gene mapping; and (b) broad-based research underlying biotechnology, including studies of genetics, biochemistry, etc. In 1990, NIH provided approximately $1.2 billion to basic biotechnology research and approximately $1.6 billion to the basic sciences underlying biotechnology. NIH research is conducted both intramurally at NIH and extramurally through outside contracts. Approximately 80 percent of NIH funded research is conducted extramurally.

To obtain extramural research funds, prospective contractors submit research proposals to NIH that are, in turn, reviewed and graded by their peers within the scientific community (not necessarily at NIH). Research funds are then granted to those proposals with the highest grades. Approximately 39,500 separate training awards, grants, and research contracts, were awarded in 1991. Dr. William Raub, (acting) Director of the National Biotechnology Policy Board noted that while some critics of the Government's role in research have charged that it has not exerted strong enough leadership, "the role of the Federal Government is not to manage commercial innovation but to create conditions for such innovation."[194]

The second factor that reportedly fostered the early development of a biotechnology industry was the presence of an entrepreneurial environment in the United States. While difficult to quantify, the constant mention of entrepreneurial activity from numerous industry sources and analysts lends credence to its importance. Examples of anecdotal information are numerous. One source noted that in contrast to U.S. practice, the tenure system in European and Japanese school systems limits the independence of younger academics. In Japan, in particular, "there are many reasons for this, including the maintenance of the traditional 'koza' (chair professor) system, a paucity of basic research funding and the lack of postdoctoral positions."[195] Analysts noted another aspect of entrepreneurship is society's acceptance of failure which they believe is more prevalent in the United States than in Europe or Japan; and that furthermore, the United States has a legal structure more capable of accommodating business failure. For example, it was noted that Europe has no close counterpart to the Chapter 11 bankruptcy proceedings found in the United States.[196]

The third factor reported to foster the development of U.S. biotechnology is the availability of capital (particularly start-up and venture capital) in the United States. During the 1970s and early 1980s funding for biotechnology development was readily available. The funding options available to the industry are early-stage venture capital, private equity placement, public equity markets, strategic alliances, debt, and consolidation.

Although all new industries must obtain financing while subject to uncertainties in the market, biotechnology companies are also subject to a regulatory process that can take years and offer no guarantee of product approval. This not only lengthens the time needed to get a new product to market, it also adds substantially to costs, and hence the continued need for capital. As these companies grew, many found it difficult to continually raise cash without having a product on the market. In addition, public and private sources of funding have become scarce in recent years and the new companies have had to increasingly turn to joint ventures, and strategic alliances in order to obtain their needed financing.[197] The importance of funding to the industry has prompted one analyst to note that while "the biotechnology industry is driven by science, biotechnology businesses are driven by their financial strategies. At each stage of a company's development, the financing demands and opportunities shape the priorities."[198]

The basis for seed financing is the venture capital market. Once the seed capital is obtained, a typical progression for financing business development is for a private investment to carry the company up to the time it makes its first sales. At that time, a company may consider going to public equity markets with an initial public offering (IPO) or think of forming a strategic alliance. Although the progression of funding appears straightforward, an Ernst & Young publication noted as companies "take a product through clinical trials, bring it to the FDA in a scientifically sound and well-presented filing, get an approval and become a commercial success, . . ., their ability to finance is sustained. When companies get thrown off track their financing dries up."[199]

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[192] The relationship between the new biotech companies and universities is so close that many believe that any definition of a biotechnology industry must include the U.S. university system. Herbert Boyer, a founder of Genentech was a professor at University of California, San Francisco, while Ronald Glazer, a founder of Genentech, was a Nobel Laureate at the University of California, Berkeley. Similarly, the Genetics Institute in Cambridge was established by Harvard scientists.

[193] The Budget For Fiscal Year 1992, Part Two, p.72. (The President's Fiscal Budget Proposal for 1992).

[194] Department of Health and Human Services, Public Health Service, National INstitutes of Health, National Biotechnology Policy Board, 'Minutes of Meeting' October 29, 1990, p.4.

[195] Mark Dibner, "Japan's Biotechnology Industry: Focus on Pharmaceuticals," *Drug News and Perspectives* 3 (2), p.86.

[196] USITC staff field interviews with representatives of biotechnology firms in March 1990.

[197] "Biotech Companies Turn Toward Tokyo."

[198] G. Steven Burrill and Kenneth B. Lee, *Biotech 91: A Changing Environment*, Ernst & Young, San Francisco California, p 61.

[199] Ernst & Young, *Biotech 91: A Changing Environment*, p.63.

Compounding the problem of limited funds for "financially limited" biotech companies, is the inevitable cyclical nature of capital markets. The October, 1987 stock market crash was particularly difficult for the biotechnology stocks. While the Standard and Poor's stock index showed an average price decline of 22 percent for the stocks it covers, the price of biotechnology stocks declined more than 50 percent. Within the biotechnology industry, the smaller companies were particularly hard pressed. The long-term effect of the crash appears to have made the markets more selective. However, the capital market has rebounded; and despite the difficulties inherent in financing, the U.S. capital markets have fostered the growth of small U.S. biotechnology companies. In the first four months of 1991, biotechnology has been able to raise over $1 billion[200] in the U.S. capital markets.

Major Producers

United States

In 1990, there were some 1,100 companies with a primary emphasis in some biotechnology endeavor, of which approximately 63 percent were concerned with biopharmaceuticals. Ernst & Young and the North Carolina Biotechnology Center (NCBC) have conducted surveys analyzing the U.S. biotechnology industry. Looking at the total industry (biopharmaceuticals, agriculture, energy, etc.), and ranking companies in the industry by the number of employees, Ernst & Young was able to show the preponderance of small companies in the industry (see Figure 4-9). The definitions of size are as follows:

Firm size	*Number of employees*
Small	1-50
Mid-sized	51-135
Large	136-299
Top tier	300 or more

Then looking at the entire industry by market segment, Ernst & Young demonstrated that the preponderance of companies in biotechnology were in the human diagnostics and therapeutics sectors (see Figure 4-9).

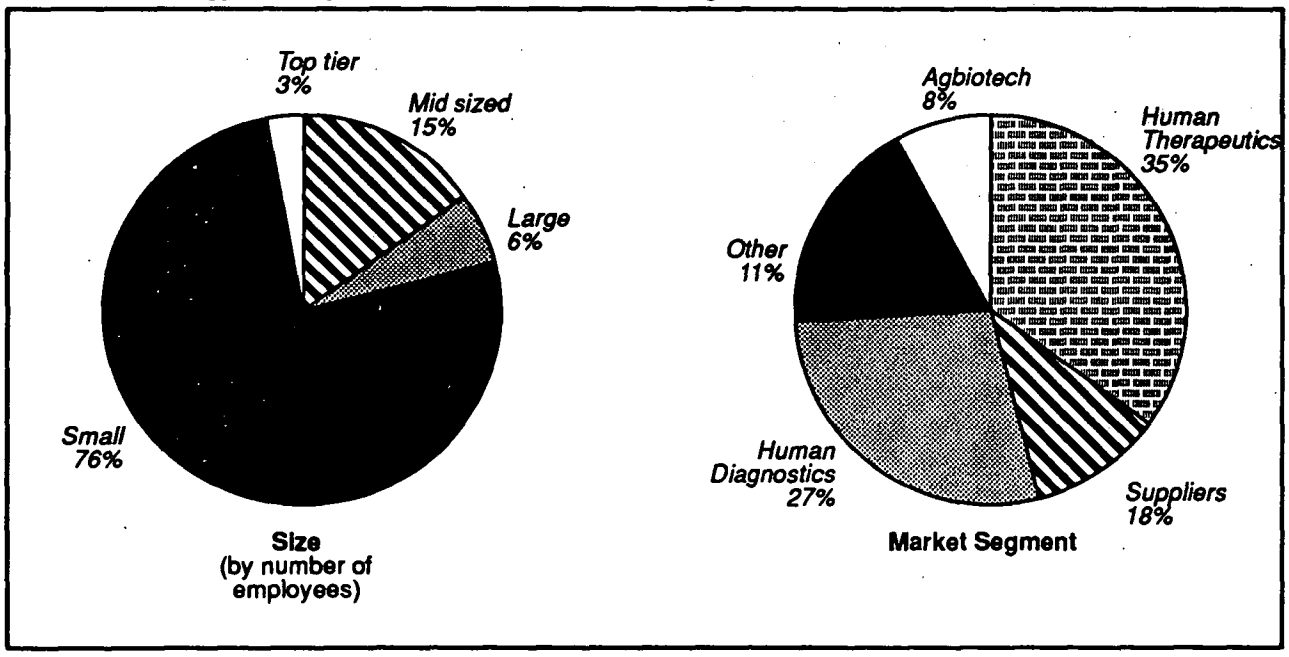
In terms of geographic distribution of companies in the United States, the Ernst and Young analysis found that biotechnology companies are found in the greatest numbers on the West and East Coasts, particularly in the San Francisco Bay Area and the New England area. While these areas have remained centers for biotechnology companies, the industry is, in fact, spread throughout the United States.

When the industry is stratified by value of sales, the most successful companies dominate the industry commercially in a number of measures. Sixty-five percent of "top-tier" companies are profitable, while 21 percent of the industry as a whole is profitable.[201] Eighty-five percent of top-tier

[200] Chemical Marketing Reporter, April 8, 1991, p. 9. Other years in which funding was particularly plentiful were 1983 and 1986.

[201] In *Biotech91: A Changing Environment*, Ernst & Young defines "top-tier" companies as being those with 300 or more employees.

Figure 4-9
U.S. biotechnology industry, 1989: Firm size and market segment



Source: Ernst & Young and North Carolina Biotechnology Center Survey.

companies increased their total assets, compared with 58 percent over all. In 1989, 9 out of 10 top-tier companies out performed the S&P 500, while only 4 out of 10 second-tier companies outperformed the S&P 500. Also, in that year 90 percent of public equity capital raised was for companies in the top-tier.

Top-tier companies have become the major marketers for the second tiercompanies. Significant to this stratification is the fact that different tiers are facing different competitive issues and are affected differently by international factors (see the section below, entitled "Competitive Issues for the U.S. Biotechnology Industry").

Japan

In the early 1980s, Japan caught "biotechnology fever," and since then, some in the trade press and in the industry believe that the Japanese industry, in conjunction with the government, is making a concerted effort to the become world leader by 2000. While Japanese biotechnology companies may, in fact, become the major U.S. competitor by the turn of the century, the early stage of development does not appear to be following the traditional pattern of Japanese industrial expansion in that they are outgrowths of larger firms. Furthermore, the development of the industry in Japan appears quite different from development in the United States, focusing more on commercial development than on basic research.

In Japan, there are very few small new biotechnology companies, because there is very little venture capital and entrepreneurial activity. The rigid labor market, characterized by the life-long employment system in industry and the strict tenure system practiced in the universities, is reported to discourage entrepreneurial activity and spin-off companies. In contrast to the U.S. industry, most Japanese biotechnology is conducted by some 250 well-established, large- and mid-sized companies. Information gathered by the NCBC shows that in 1989 the average U.S. biotechnology firm has 90 employees and about $12 million in sales. The Japanese companies working in biotechnology have an average work force of some 6,000 employees and sales of approximately $2.7 billion.[202]

The Japanese companies come from a wide variety of industries including basic chemicals, food and textiles. During 1982-84, the top ten biopharmaceutical patent registrations in Japan included only one from a Japanese pharmaceutical company. Ajinomoto (food) registered 54 biotechnology patents and Toray (textiles) registered 14 biotechnology patents. Furthermore, Toray was the first company to develop the biopharmaceutical, beta interferon using domestic technology.[203] One competitive strength of the Japanese biotechnology industry is their expertise in "traditional biotechnology" based on fermentation and bioreactors (vessels in which commercial biochemical reactions occur).

Another dissimilarity between the United States and Japan is the level of government funding. The 1989 Japanese Government budget in support of biotechnology (as analyzed by the NCBC) was approximately 84 billion yen, and only a small portion, administered by the Koseisho, was directed toward biopharmaceuticals.[204] Based on an exchange rate of 140 yen per dollar, the 84 billion yen equal some $600 million. On the other hand, recent annual U.S. Federal funding for biotechnology has been approximately $3 billion, most of which was directed towards basic research.

Although the Japanese Government spends only a small portion of the amount of money spent by the United States Government on biotechnology, and although most of this money is spent on development rather than basic research, the government does play a role in developing biotechnology. MITI first became directly involved in 1981 by creating programs and research associations to increase the level of understanding in basic applications. MITI oversees the patents for biotechnology and can thereby facilitate the success of the domestic industry. As in many countries, there is considerable delay for biotechnology patent approvals. To expedite the process, MITI in 1986 established a "fast track" patent approval system if certain criteria are met. Other government agencies are also involved in biotechnology. The Ministry of Education, Science, and Culture (MESC) funds basic research in academia, while the Science and Technology Agency supports specific projects jointly carried out by universities and industry. The Koseisho, which has regulatory and approval control over pharmaceuticals, can also influence biotechnology through its approval process and its pricing policy. It has been suggested that the Koseisho has used its reimbursement policy to stimulate the development of innovative products.[205] Companies creating new innovative biotechnology pharmaceuticals will more readily be reimbursed for higher priced products than traditional pharmaceutical products, thereby creating a market incentive for developing new innovative biopharmaceutical products.

The most notable method by which the Japanese have gained expertise in biotechnology has been through strategic alliances.[206] The NCBC found that of some 300 Japanese strategic biotechnology alliances, 63 percent involved U.S. partners, while 18 percent were with Japanese partners. Marketing agreements accounted for almost 50 percent, while

[202] Mark D. Dibner, Drug News and Perspectives 3(2), March 1990, pps. 85-89.

[203] Aki Yoshikawa, *Technology Transfer*, Winter, 1989, pp 32-39.

[204] *Drug News and Perspectives*, p. 86.

[205] Michael R. Reich, 'Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy', *California Management Review*, Winter 1990, pps 124-150 (see in particular pps 135-138). This view was also expressed in USITC staff field interviews with representatives of biotechnology firms in March, 1990.

[206] "Biotech Companies Turn Toward Tokyo."

marketing agreements plus licensing agreements accounted for almost 75 percent of all agreements. Therapeutics accounted for 45 percent of all alliances while vaccines and diagnostics accounted for an additional 17 percent. The NCBC study noted that the distribution of strategic alliances reflected the Japanese lack of strong basic research and the need for products to bring to the market.[207]

Western Europe

Compared with Japan, Western Europe has received relatively little media attention as posing a future threat to U.S. industry leadership, despite conducting a substantial amount of basic biopharmaceutical research. The limited attention might be explained in part by the relatively few start-up companies in Europe, which, in turn, has been attributed to the lack of entrepreneurial activity fostered by the European University system. A second reason might be the relative lack of publicly available commercial or market research information. As the NCBC recently noted "data from Europe are virtually nonexistent. Moreover, definitions of biotechnology varied among the many resources we consulted."[208] Nevertheless, within the U.S. industry, Europe is considered a major competitor and Britain a major player (see section below, entitled "Competitiveness Issues for the U.S. Biotechnology Industry").

The United Kingdom, slow to exploit its rich academic expertise, has recently approached the United States for venture capital, marketing, and entrepreneurial expertise. At least two U.K. companies, British BioTechnology Group PLC and Celltech Ltd., are considered equal to U.S. companies with respect to technical knowledge.[209]

Germany's strength in conventional pharmaceutical research could have made it a leader in biotechnology. However, public pressure, particularly from the Green movement, and debate over the ethics of biotechnology have slowed commercial development. In response to the environmental concern, many German companies have come to the United States to develop their technology. More recently, attitudes have changed, and the German Government established a 1.4 billion DM biotechnology research budget for 1990 through 1994. In October, 1990, Hoechst won approval for a pilot plant operation to make genetically engineered insulin; and in April 1991, BASF received permission to produce a genetically engineered tumor necrosis factor.[210]

[207] Mark Dibner, Strategic Alliances Are Likely to Remain Important in Japan's Biotech Industry, *Venture Japan*, Vol 2(1), pps. 48-52.

[208] North Carolina Biotechnology Center, *Biotechnology in the U.S. Pharmaceutical Industry*, 1990, section 1, p. 6.

[209] For a comprehensive survey of biotechnology in the EC, see *Biotechnology R&D in the EC, Biotechnology Action Plan (BAP) 1985-89*, Vassarotti and Magnien, editors, Written For the Commission of the European Communities.

[210] 'BASF gets go-ahead for genetic engineering', *European Chemical News*, May 6, 1991, p.28.

Competitiveness Issues for the U.S. Biotechnology Industry

Although the U.S. biotechnology industry has evolved quite rapidly in the last two decades and will continue to do so in the near future, one feature of the industry has become quite clear. Biotechnology has come of age. Today, commercial considerations are as important as scientific and entrepreneurial activities[211].

The company-specific competitiveness factors (both national and international) most often noted include regulatory uncertainty and the associated increases in cost and time to gain regulatory approval; availability of capital; disparate intellectual property laws throughout the world; pricing and reimbursement issues; and manufacturing and marketing strategies. The ability of the U.S. industry to meet these challenges has received considerable attention in the press, and industry surveys conducted by the NCBC and Ernst & Young (EY) have sharpened the focus.[212]

In the 1991 Ernst & Young survey, a substantial majority of the respondents (88 percent) believed the U.S. industry currently has a competitive edge in biotechnology and the basis for this lead was primarily the qualified personal and the depth of research. Factors most often mentioned as hindering the U.S. competitiveness were the short-term outlook of the capital markets and regulatory obstacles.[213]

The respondents to the EY survey cited the three most critical issues were the need for strategic partners (31 percent), competition (30 percent), and the cost of capital (22 percent). As might be expected, the smaller companies expressed concern about financing, while the larger (and presumably more established) firms were more concerned about competition. It was believed that competition in the near future will most likely come from Japan, the United Kingdom, Switzerland, France, and Germany. Closely following competition was concern about patents and reimbursement policies established by the Health Care Finance Administration and other third-party payers. Looking to the future, most respondents believed that as the new products come onto the market, the importance of the company-specific competitive issues of marketing, regulation, liability, and reimbursement will increase dramatically.

The two strategic goals mentioned most often in the EY survey in regard to competing successfully in the current environment and in the future were

[211] see above *Biotech 91: A Changing Environment*, various chapters.

[212] The results of the two surveys conducted by the NCBC are published in (a) 'Who's the Competition in Biotech', *BioTechnology* 8(10), October, 1990, pps 920-923 and (b) 'Barriers to Success: Hurdles in the Biotechnology Race', *Biopharm* 4(3), March 1991, pps 16-20. The results of the two latest surveys conducted by Ernst & Young are (a) *Biotech 90: Into the Next Decade* and (b) *Biotech 91: A Changing Environment*. Additional information was gathered from information gathered by the staff on interviews conducted during March 1991 and other sources.

[213] Biotech:91, p.20.

acquiring financing and forming alliances. Again, as might be expected, the smaller companies were concerned with obtaining finance, while the larger companies were most interested in forming strategic alliances. The reasons cited for forming strategic alliances included the ability to obtain capital, to increase marketing capability, to acquire research capability, and to learn new science/technology. The first two reasons were the most often cited. With specific reference to Japan, many companies voiced the need to improve their access to Japanese regulatory authorities.

In a slightly different format, respondents to a survey conducted by the NCBC were asked to rank, from 1 to 5, 22 separate competitive factors (both external factors such as government regulation and funding and internal factors such as management expertise). Within the biopharmaceutical sector as a whole, companies rated FDA procedures as the highest barrier to success. This was followed by the U.S. patent process and obtaining qualified management and scientific personnel.

When the respondents to the NCBC survey were classified by size, the smallest companies rated venture capital as the greatest barrier to success, followed by acquiring management expertise and the U.S. patent process. The larger companies rated the FDA and the patent system as the greatest barriers. Concerns about the patent system focused on two issues. The first was the delay in gaining patent approvals. The second issue focused on foreign infringement on U.S. patents and the many inconsistencies in the various national patent systems.

When viewed in the context of international competitiveness, it was generally agreed by the NCBC respondents that the increased time and costs of dealing with these issues detracted from developing new products. These issues were particularly hard for small companies. If companies could not acquire sufficient funds in the capital markets, they would most likely join in some strategic alliance with a larger company. It was also generally agreed that to the extent these alliances are with foreign companies, technology will travel to foreign companies and the early dominance of the U.S. industry will likely dissipate.[214]

With respect to foreign acquisition, some industry analysts have expressed concern about the differences in U.S. and foreign accounting conventions and their effect on a U.S. company's ability to acquire another company relative to that of a foreign company.[215] One specific issue revolves around accounting for "good will", when one company purchases another.[216] U.S. accounting practices require the acquiring company to charge the good will as a cost on their income statement and to amortize the amount over a period of 40 years or less, with no tax credit for this expense. The effect is to lower the acquiring company's net income which may reduce its financial standing in capital markets. In many European countries, good will is not recorded on the income statement, but is charged against shareholder's equity on the balance sheet. To the extent that capital markets focus on company earnings, the cost of good will could reduce a company's standing in these markets. However, others have noted that analyzing the strength of a company is a sophisticated process, and the foreign treatment of good will may more an indication of foreign companies' willingness take a longer term perspective on investment.

When questioned about immediate sources of competition by NCBC, biopharmaceutical companies perceived the greatest competition as coming from within the industry. In the near future, however, they expect the greatest competition to come from the larger pharmaceutical corporations, particularly those based in Western Europe. In the latter part of the 1990s, Japan is expected to be a strong competitor.

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[214] USITC staff field interviews with representatives of biotechnology firms in March.

[215] The conventions are promulgated by the Financial Accounting Standards Board (FASB), American Institute of Certified Public Accountants.

[216] Good will may be defined as the excess of purchase price over book value of the aqquired company. The topic is discussed in most general accounting books See for example Rossell and Frasure, *Managerial Accounting*, 2nd. edition, 1972, Charles Merrill Publishing Company, Columbus Ohio, pps 209-214.

CHAPTER 5
ANALYSIS OF THE PHARMACEUTICAL INDUSTRY'S PERFORMANCE IN THE WORLD MARKET

Introduction

Innovation, production and distribution in the pharmaceutical industry are carried out primarily by multinational firms. These firms are headquartered in France, Germany, Japan, Switzerland, the United Kingdom, and the United States. The multinational characteristic of the industry poses problems for analysis, especially when trying to assess the global competitiveness of one nation's (or region's) firms relative to another nation's firms.[1] Consequently, it is difficult to isolate the "U.S. pharmaceutical industry" from the "Western European" or "Japanese" pharmaceutical industries.

Given the difficulty identifying a country's "pharmaceutical industry," the approach taken in this chapter is to begin at an aggregate level to lay a foundation upon which to build the analysis. The analysis begins with the world demand for pharmaceutical products.[2] To the extent pharmaceutical firms rely more heavily on their home markets, demand is linked to competitiveness through factors that can change demand. Changes in the demand for pharmaceuticals is important because consumption provides profits from which firms obtain the revenues to fund R&D, which, in turn, results in innovative products. In addition, new product innovations are expected in markets characterized by sufficient demand to support such new products.[3] From the demand analysis, elasticities can be derived to determine the sensitivity of demand to changes in price and income. Also, the analysis examines regional differences in the demand for pharmaceuticals, which after controlling for economic and demographic factors, could be attributed to alternative government policies.

[1] For example, the firm-level analysis in this chapter is based on data that distinguishes firms by parent location. One problem this creates is that there may be important country-specific factors that affect the overall performance of a firm, and classifying the firm by parent location may mask these effects.

[2] In this chapter, the term "pharmaceutical(s)" represents ethical pharmaceutical products only.

[3] These ideas relate directly to international product cycle theory, for instance see R. Vernon, "International Investment and International Trade in the Product Cycle," *Quarterly Journal of Economics*, May 1966; C. Wasson, *Dynamic Competitive Strategy and Product Life Cycles* (St. Charles, Il: Challenge Books, 1974); and R. Grosse and D. Kujawa, *International Business Theory and Managerial Applications* (Homewood, Il: Irwin Publishers, 1988).

The chapter then investigates differences in the origination and marketing of innovative products across the leading pharmaceutical markets in the world. Specifically, several factors are identified that facilitate the development of innovative products in a country and that determine where a new product is first marketed. This is important because factors that affect the location and marketing decisions also play a role in determining the competitiveness of firms in this industry.

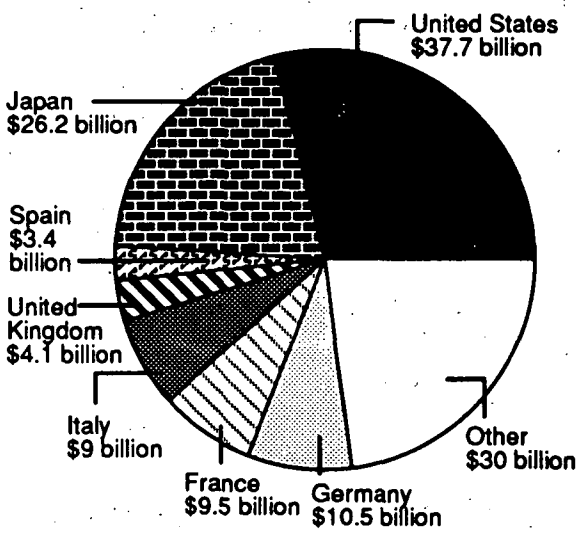
The final part of this chapter focuses on differences among pharmaceutical firms that determine competitiveness. Analysis from this perspective is important because it focuses on firm-specific differences, not easily captured at the country level, that are likely to influence their relative performances. Based on the discussion in chapter 2, competitiveness in this part of the analysis is measured in two ways: (1) global market share, and (2) R&D productivity.

Data

Overview

Examining the pharmaceutical industry in the manner described above requires the construction of two data sets. The first data set contains various annual economic, demographic, and health related measures from 1983-88 for the following seven countries: France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. These countries represent the top 7 pharmaceutical markets in the world, accounting for 77 percent of world pharmaceutical sales in 1989 (see figure 5-1). Moreover, during the 1983-88 period, 23 out of 26 *global* new chemical entities (NCEs) originated from

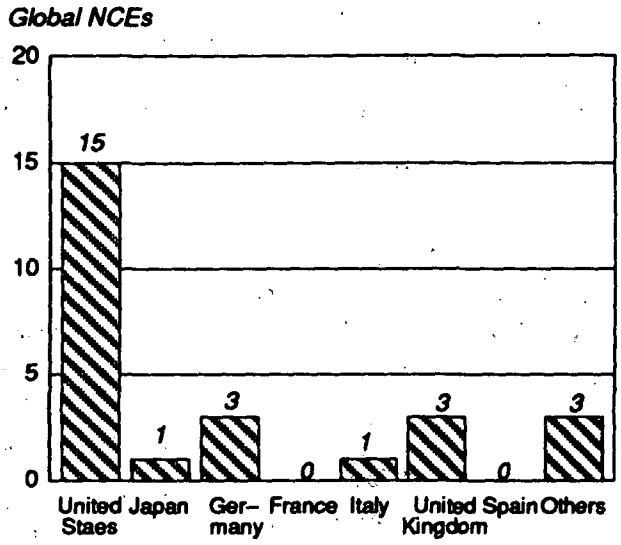
Figure 5-1
Major pharmaceutical markets, 1989



Source: Glaxo Annual Report, 1990

these countries (see figure 5-2).[4] NCEs that are marketed globally are generally recognized as the true innovations in this industry. Figure 5-3 presents an index for the United States, Western Europe,[5] and Japan based on the number of *global* NCEs that have originated from these regions during 1983-88.[6] The index reveals that the United States has generally held the lead in producing *global* NCEs relative to the other two regions during this period.

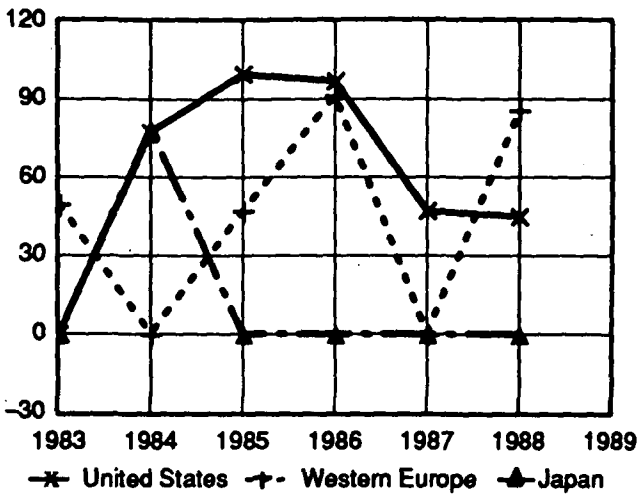
Figure 5-2
Global new chemical entities by country, 1983-88



Source: Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World (1975-1989)*

The second data set comprises various measures for a sample of pharmaceutical firms (11 headquartered in the United States, 9 headquartered in Western Europe, and 9 headquartered in Japan) during 1987-89.[7] These firms accounted for approximately 50 percent of world ethical drug sales (approximately $66.3 billion) in 1989 with global market shares (in ethical sales) ranging from 0.61 percent to 4.21 percent. In 1989, these firms spent $302 million (in real dollars)[8] on pharmaceutical R&D or about $170,000 per R&D employee, on average. The average R&D work force for these firms in 1989 was 2,364 employees. The size of these firms in 1989 averaged approximately 40,500 employees with an average salesforce of about 3,450. In 1989, these firms also had in their R&D pipeline about 43 of their own compounds and 17 licensed compounds, on average.

Figure 5-3
Global NCE index, by country of origination, 1983-88



Source: Estimated by the Staff of the U.S. International Trade Commission.

A Herfindahl-Hirshman Index (HHI) is calculated for the firms in this sample. The HHI measures the extent of market concentration within an industry and provides some indication of the industry's probable economic performance relative to the competitive outcome. The U.S. Department of Justice categorizes industries where the HHI is less than 1,000 as "unconcentrated" for antitrust purposes. The HHI (in terms of world ethical sales) for the top 59 pharmaceutical firms in 1989 is 131 and for this sample of 29 firms is 115. This indicates that thepharmaceutical industry is relatively unconcentrated in the world market.

[4] The NCE data are from P. E. Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World (1975-1989)*, Paris: Foundation Rhone-Poulenc Sante, August 1990. A *global* NCE is defined as a product that is eventually marketed in the following seven major industrialized countries: France, Germany, Japan, Italy, Switzerland, the United Kingdom, and the United States. The country to which the NCE is assigned is the country where the product originated. The originating country may not necessarily develop the discovery. Consequently, products discovered by the foreign subsidiary of a firm are attributed to the country in which the subsidiary is located and not the country where the parent firm is headquartered.

[5] Western Europe consists of France, Germany, Italy, Switzerland and the United Kingdom for these calculations.

[6] To control for differences in the size of the markets, the index values are calculated by dividing the number of *global* NCEs by the region's real gross national product. For ease of exposition the index values are also multiplied by 10,000.

[7] The firms in this sample include for the United States: Abbott, American Home Products, Bristol-Myers (in 1989 this firm becomes Bristol-Myers Squibb), Eli Lilly, Johnson & Johnson, Merck, Pfizer, Shearing-Plough, Squibb (1987 and 1988), Upjohn, Warner-Lambert; for Western Europe: Bayer, Ciba-Geigy, Glaxo, Hoechst, Ingelheim, Rhone-Poulenc, Sandoz, SmithKline Beecham, Roche; and for Japan: Chugia, Daiichi, Eisai, Fujisawa, Sankyo, Shionogi, Takeda, Tanabe, and Yamanouchi. Data constraints limited the sample to these 29 firms.

[8] The base year for the constant dollar data in this chapter is 1985.

However, the HHI for world ethical sales may not be the best structural measure for the pharmaceutical industry because firms typically compete in terms of new innovations, and not on the basis of price. To reflect this dimension of competition, an alternative HHI for this sample of firms is calculated based on the number of R&D compounds in a firm's research pipeline.[9] This measure is intended to reflect the fact that firms compete by creating new innovations, and "potential innovations" is another way to characterize this industry.[10] In this case, the R&D compound HHI for the top 48 pharmaceutical firms in 1989 is 58, and for this sample of 29 firms it is 88. Intuitively, this suggests that no single firm has a large share of the R&D compounds that may eventually get regulatory approval to be sold as new drugs. However, similar values calculated for individual therapeutic classes would likely show varying degrees of concentration, with some being more concentrated than the average for all R&D compounds.

Regional Comparison

Table 5-1 illustrates some of the regional differences evident from this sample of firms during 1987-89. U.S. and Western European headquartered firms have, on average, higher global market shares than Japanese headquartered firms. A comparison of the research pipelines reveals that U.S. and Western European headquartered firms have a larger number of R&D compounds, on average, as compared to Japanese headquartered firms.

A comparison of firm size reveals some striking differences. The Western European-based firms in this sample are by far the largest, followed, in turn, by U.S.-based firms and Japanese-based firms. The discrepancy is caused by the fact that several of the Western European firms are large chemical companies with pharmaceuticals as a subsidiary business. In addition, the small size of the Japanese firms reflects the fact that most Japanese pharmaceutical firms are not multinational and focus primarily on their home market. This is also reflected in the lower average sales force for Japanese firms. Another indication that Japanese firms focus primarily on their home market is their relatively high average ethical sales, given their relatively small average firm size. In Japan, a high portion of consumers' medical expenses, approximately 25 percent, consists of pharmaceutical expenditures.

Analysis of the Pharmaceutical Industry

This section uses statistical analysis to examine factors that may affect the competitiveness of U.S. pharmaceutical firms in the global market.[11] First, it focuses on explaining the apparent differences in the patterns of consumption, origination, and marketing of ethical pharmaceutical products across the seven largest pharmaceutical markets during the period 1983-88. The analysis begins with the demand for pharmaceuticals in these markets and then follows with an analysis of the relationship between the origination and marketing of NCEs and various economic and country-specific factors. Second, it examines the determinants of global market share and R&D productivity at the firm level to assess those factors that affect a pharmaceutical firm's relative economic performance.

[9] R&D compounds include all new chemical entities that have been patented, but have not been approved by regulatory authorities for sale as new drugs.

[10] A controversial issue in economics is whether concentrated industries are more or less likely to promote or retard the rate of new product innovations. See Dennis W. Carlton and Jeffrey M. Perloff, *Modern Industrial Organization* (Glenview, IL: Scott, Foresman and Co.,1990), especially chapter 20. This analysis does not attempt to resolve this debate, but the purpose here is to present an alternative measure, which may be used to describe the distribution of potential innovations across firms.

[11] The methodology used in this chapter is regression analysis. Appendix E presents an explanation of the data, the estimating equations, and the statistical results.

Table 5-1
Regional comparison of 11 U.S.-headquartered, 9 Western European headquartered, and 9 Japanese headquartered pharmaceutical firms, average values for 1987-89

	United States	*Western Europe*	*Japan*
Global market share (percent)	2.23	2.57	1.08
Research and development:			
Own R&D compounds	53	52	28
Licensed compounds	18	16	10
R&D expenditures per R&D employee (thousands)	$145	$134	$235
Total R&D expenditures (millions)	$340	$444	$155
R&D employees	2,627	3,526	784
Size:			
Ethical pharmaceutical sales (millions)	$2,452	$2,855	$1,197
Sales employees	5,023	4,375	1,089
Total employees	36,399	76,347	5,304

Sources: Scrip (various issues), Shearson-Lehman, *Pharma Profiles*, (New York: Shearson-Lehman, February 1990), Japan Pharmaceutical Manufacturers Association *Japan Data Book*, (Tokyo: Japan Pharmaceutical Manufacturers Association, 1990).

Ethical Pharmaceutical Demand

Several factors are likely to affect the quantity of pharmaceutical products demanded in a country. Two fundamental measures affecting demand are price and income. To control for demographic factors, two additional measures included are life expectancy and the number of medical doctors in a country.[12] A measure is also included to distinguish the United States from the other countries in the sample. This is done because pharmaceutical markets outside the United States are more influenced by national health policies (see chapter 3). As an alternative, measures that distinguish Japan and Western Europe from the United States are also used. This particular configuration focuses on differences across the three primary pharmaceutical regions: the United States, Japan, and Western Europe.

As expected, price is inversely related to demand and price elasticities of demand of -1.12 and -1.28 are found, suggesting that if the price (in real terms) of pharmaceutical products decreases by 1 percent, the quantity demanded of those products would increase by 1.12 to 1.28 percent. Although consumers in these countries are unlikely to pay the full retail price for ethical pharmaceutical products because of private and government health insurance in the United States and nationalized health care in Western Europe and Japan, the demand for pharmaceuticals is responsive to changes in relative prices. This result indicates that there is some substitutability between pharmaceuticals and other medical treatments. For example, in the case of ulcers, surgery was often the only treatment option. Today there are several pharmaceutical products that can be used instead of surgery to cure ulcers.

Similarly, income is positively related to demand and an income elasticity of 1.28 is found, suggesting that if income rises by 1 percent in a country, then the quantity demanded for ethical pharmaceutical products would increase by 1.28 percent. Again, this result seems plausible since countries with higher standards of living are likely to purchase more ethical drugs.

The results suggest that differences in a country's life expectancy are important in explaining variation in the demand for pharmaceuticals. Moreover, this relationship is highly elastic. The elasticity estimates found are 5.1 and 11.1, suggesting that a small change in the life expectancy of a country, such as 0.5 percent, will result in a 2.5 to 5.6 percent increase in the quantity demanded for pharmaceuticals.[13]

[12] It is acknowledged that pharmaceutical products, over the long-run, may affect life expectancy as well.

[13] The results from this analysis indicate that differences in the relative number of physicians in a country did not have a statistically significant effect on pharmaceutical demand within this sample of high-income industrialized countries.

The measure distinguishing non-U.S. countries indicates that those countries have a higher overall demand for pharmaceuticals. This may reflect generally lower prices and cultural differences outside of the United States including the possibility of a higher level of access to health care across all income levels. When Japan and Western Europe are distinguished, the same pattern of results are found.

New Chemical Entities

New chemical entities are key to the competitiveness of a country's pharmaceutical industry. The profits that fund the extensive R&D efforts of large innovative firms come primarily from the development of *global* NCEs. Consequently, it is important to focus on those factors that may advance the discovery of *global* NCEs in a particular country.

Origination of global *new chemical entities*

This analysis focuses on the origination of truly innovative NCEs. An innovative NCE is a global product marketed in at least seven major industrialized countries, whereas an NCE marketed in only its home market or limited international markets is unlikely to be an innovative drug.[14] Other researchers have used similar classifications and have found that drugs marketed in a limited number of countries are not the innovative drugs.[15]

The level of research commitment in a country should have an impact on the number of *global* NCEs originating from that country. The measure for research commitment is the level of real pharmaceutical R&D expenditures in a country both by the firms in that country and by government research efforts. The analysis also includes the level of real gross domestic product (GDP) growth for a country. This measure is included because a robust economy should facilitate a productive pharmaceutical industry and potentially lead to more *global* NCEs in a country.[16] A non-U.S. measure, as well as measures distinguishing Western Europe and Japan, are also used to test for differences across regions.

The results of this analysis reveal some important relationships. As expected, countries that have higher levels of R&D expenditures have more *global* NCEs originating in their countries. This probably reflects a number of factors that provide a positive environment for creative R&D. For example, countries with high levels of R&D most likely have national programs that

[14] For a complete discussion of *global* NCEs see Barral, 1990.

[15] For example, see Henry Grabowski, "Innovation and International Competitiveness in Pharmaceuticals," in *The Proceedings of the 2nd International Joseph Schumpeter Society Meetings* (Ann Arbor, MI: University of Michigan Press, 1990), pp. 167-185 and Henry Grabowski, "An Analysis of US International Competitiveness in Pharmaceuticals," *Managerial and Decision Economics*, special issue, 1989, pp. 27-33.

[16] In addition, see the citations in fn. 3.

effect new drug development. In the United States, the National Institutes of Health and the publicly supported university system provide a natural conduit for the creation and dissemination of scientific information. An equally not surprising explanation may be that countries with a larger number of pharmaceutical firms are likely to spend more on R&D, and therefore, it is plausible to see relatively more *global* NCEs originating from those countries. However, one reason that firms locate in a particular country may be its highly developed science and education system.

The analysis indicates that overall economic activity represented by GDP growth does not immediately affect the number of *global* NCEs that originate from a country.[17] However, the results indicate that the mean level of global NCEs is less for the non-U.S. countries used in this analysis. In particular, the results indicate that, on average, fewer *global* NCEs originate in Japan relative to the United States. This is not surprising since the Japanese pharmaceutical industry has traditionally focused on its home market and develops quite a few "me-too" NCEs.

First introduction of new chemical entities[18]

When a drug is developed it is not necessarily introduced first in the country where it was discovered. This is important for competitiveness because countries that attract NCEs are likely to be those countries that have a strong demand for pharmaceuticals, thus providing the firms operating there with the revenue to channel towards their R&D efforts.

This analysis includes several factors beyond regulatory approval constraints that may affect the marketing strategy of an NCE. First, is the level of real drug prices in a country and second, is the overall state of the economy, represented by the real growth rate of GDP. Countries with higher prices and growing economies should attract more NCEs for initial marketing because firms will recognize the strong demand and profit potential in those countries. In addition, countries with consumers who spend a higher proportion of their income on medical expenses should attract more NCEs. This measure is represented by the percent households spend on medical care in a country. Finally, the measures that distinguish the three regions are included to account for potential regional differences.

The results of this analysis indicate that, other things being equal, countries with growing economies and higher prices for pharmaceuticals attract more NCEs to be introduced there. Moreover, countries with higher household expenditures on health care also attract NCEs as a place to begin marketing. The results of this analysis also suggest that, on average, more new products are introduced in markets outside the United States. This is plausible because some countries, for example Japan and France, market many NCEs, but only market them in their home market. Alternatively, since the regulatory approval process is considered to be the strictest (i.e., most costly in terms of time and resources) in the United States, firms may be more likely to market their drugs first in other countries.

Firm Analysis

The analysis below identifies several important factors that affect the competitiveness of firms in this industry. In particular, the analysis examines the determinants of competitiveness as measured by global market share and R&D productivity.[19]

Global Market Share

One measure of a firm's competitiveness is its market share. Since the pharmaceutical industry operates in a global market, the analysis in this section identifies important factors that determine a pharmaceutical firm's global market share. Global market share is defined as the percent of world ethical pharmaceutical sales for a firm.

The level of real pharmaceutical R&D expenditures by the firm is expected to have a positive impact on global market share. To control for differences in the composition of a firm's employees, the analysis includes several labor-force measures. One measure is the number of employees that engage in R&D activities and another measure is the number of sales-force employees. A higher number of employees committed to these activities should result in a higher global market share.[20] For example, a larger R&D staff is likely to develop a larger pool of compounds from which the probability of developing an innovative drug is higher. Similarly, a larger sales force will increase the firm's marketing channels, which is likely to lead to a higher level of sales, given a firm's product mix. However, increases in each factor are potentially subject to diminishing returns. In addition, to control for the differences in overall firm size, the analysis includes a measure for the total number of employees. This measure is likely to capture differences across firms that would not be reflected by the other two measures.

In order to remain competitive and hold or gain global market share, a pharmaceutical firm needs to maintain compounds in its R&D pipeline. Firms add compounds to their pipelines by two methods. They either discover the compounds through their own research efforts or they license compounds from other firms that they believe they can develop into profitable

[17] This result could reflect the fact that GDP growth in one year is not likely to lead to discoveries in the same year. However, due to data constraints it was not possible to test for lagged effects of GDP growth.

[18] This section includes all NCEs, not just *global* NCEs as in earlier sections.

[19] These measures of competitiveness are used because data constraints precluded the use of other firm-level measures such as profitability.

[20] It is acknowledged that causality may run in both directions. However, it is likely that the primary direction is as indicated in the text.

products. To account for these potential differences in a firm's research pipeline, the analysis includes three measures. The first is the total number of drugs in a firm's R&D pipeline. Firms that maintain more compounds in their R&D pipeline are likely to attain higher global market shares because the probability of developing an innovative drug will be higher. However, a firm may achieve a higher market share with fewer R&D compounds in its research pipeline if it is relatively more efficient at selecting those for further development.

It may be more important for a pharmaceutical firm if the compounds are discovered in-house as opposed to licensing compounds from other firms. To test this proposition, the number of a firm's own R&D drugs and the number of R&D drugs that a firm obtains by license are used in the analysis separately instead of the total number of R&D drugs. However, there are no *a priori* expectations for these measures.

Finally, to capture possible differences in countries that may influence a firm's ability to gain or hold market share, a measure that distinguishes non-U.S. headquartered firms from U.S.-headquartered firms is included in the analysis. The differences that this variable may control for include direct or indirect government price or profit controls, which may potentially affect a firm's ability to fund its R&D efforts or may potentially affect its internal allocation of resources.

The results of this analysis reveal several important aspects associated with a competitive pharmaceutical firm. For example, the results indicate that the greater the R&D expenditures and the higher the number of R&D employees, the higher global market share obtained by a firm. The analysis also suggests that the larger a firm's sales force, the higher its global market share. These characteristics are regarded by the industry as critical factors for a pharmaceutical firm to be globally competitive.[21]

The R&D drug measures yield interesting results. These results suggest that firms with higher global market shares have more of their own R&D drugs in their research pipeline. Conversely, firms with more R&D compounds licensed from other firms have lower global market shares. Taken together, these results suggest that successful firms maintain a relatively higher number of potential products in their research pipelines while less successful firms, in term of global market share, use licensed compounds to a greater extent in their research process.

The result from the non-U.S. measure indicates that, on average, this sample of non-U.S. headquartered firms has a higher global market share than this sample of U.S.-headquartered firms. This result may reflect the global nature of this industry. Although a firm may be headquartered in a country that has restrictions on pricing or profits, it may be successful in world markets.

[21] USITC field interviews with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during 1991.

Research and Development Productivity

The second measure used to assess the competitiveness of pharmaceutical firms is R&D productivity. More productive firms are more competitive in world markets. The analysis below identifies important factors that determine a pharmaceutical firm's R&D productivity.

R&D productivity is measured in two ways. The first measure is calculated as the ratio of the number of a firm's own R&D drugs to the number of its R&D employees. This definition follows the standard economic definition for productivity, i.e., output per employee. The second measure of productivity uses the level of a firm's own R&D drugs. Both of these measures use a firm's own R&D compounds and excludes those compounds that they have licensed from other firms.

The analysis using the first definition of R&D productivity includes the ratio of real R&D expenditures per R&D employee. Firms that invest in higher levels of R&D should be more productive. Furthermore, the analysis tests for possible diminishing returns to additional funds allocated to R&D. As firms increase spending per R&D employee, research productivity should rise; however, at some point within the sample, firms may experience diminishing returns to the additional R&D spending. The analysis also investigates whether the effect of changes in R&D expenditures per R&D employee differs by firm size.

The analysis using the second definition of R&D productivity includes the number of R&D employees in a firm to investigate the potential benefits of additional R&D employees and if adding additional R&D employees reaches diminishing returns. The analysis also investigates whether the effect of changes in the number of R&D employees on productivity varies by firm size. One final factor is included in this analysis as well, the level of real R&D expenditures.

To test whether spillovers occur because pharmaceutical research is performed in a country by national research efforts, both analyses include the total level of real pharmaceutical R&D spending in a country. Finally, to control for differences in firm size, both analyses also include the total number of employees in the firm.

The results of this analysis indicate that a higher level of spending per R&D employee results in more R&D compounds per R&D employee. For example, this estimation, evaluated at the mean of the variables in this sample, indicates that an additional $8.8 million in R&D expenditures will result in one R&D compound.[22] Alternatively, at the sample mean, a 10

[22] This figure should not be confused with estimates for the cost of a new drug by DiMasi et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* vol. 10, July 1991, pp. 107-42; Wiggins, *The Cost of Developing a New Drug* (Washington, D.C.: Pharmaceutical Manufacturers Association, 1987); and Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects

percent increase in R&D spending per employee would give an additional 4.5 R&D compounds.

However, the returns to additional R&D spending diminishes at some point. When evaluated at the mean of the variables in the sample, diminishing returns to additional R&D spending per R&D employee is reached at $300,000 per R&D employee. Interestingly, the level of R&D expenditures per R&D employee averaged $170,000 for the 29 firms in this sample. This result suggests that the average firm's current spending is less than the estimated point of diminishing returns.

The results indicate that larger firms produce fewer of their own R&D compounds per R&D employee, for an *additional* dollar spent per R&D employee than small firms produce for the same *additional* dollar spent per R&D employee. This may reflect inefficient bureaucracies of the larger firms that reduce the effectiveness of additional R&D expenditures.

Finally, the results using the first definition of R&D productivity reveal that when R&D expenditures per R&D employee are greater than $110,000, increases in the total employment of the firm will have a positive impact on R&D productivity. Also, using the first definition of R&D productivity, national research efforts in a country did not have a statistically significant effect on this R&D productivity measure.

The results using the second definition of R&D productivity also yield interesting implications. Indeed, the results suggest that the addition of R&D employees is beneficial. However, the results indicate that the returns to additional R&D employees diminishes at some point. In fact, when evaluated at the mean of the variables in the sample, the point at which productivity diminishes for an additional R&D employee is reached at 3,986 R&D employees. The level of R&D employees averaged 2,323 for the 29 firms included here. Once again, this result suggests that the average firm's current R&D staffing level is below the estimated point of diminishing returns.

The results indicate that the incremental effect of increases in R&D employees on a firm's production of its own R&D compounds increases with firm size. One plausible explanation is that larger firms have greater amounts of capital and, as a consequence, when a firm adds an additional R&D employee to its staff, that employee will be more productive.

The analysis also reveals that when the number of R&D employees is greater than 3,000, increases in the total employment of the firm will have a positive impact on R&D productivity. Finally, as expected, higher levels of real R&D expenditures by a firm result in more R&D compounds in the pipeline for the firm. Furthermore, using the second definition of R&D productivity, country R&D spending is found to be positively related to a firm's R&D productivity indicating that there may indeed be spillovers from national research efforts to the level of R&D compounds for a pharmaceutical firm.

Conclusion

The analysis in this chapter yields some insights into factors that determine the competitiveness of pharmaceutical firms. The analysis reveals that global pharmaceutical demand is price and income elastic. Moreover, the results indicate that countries with higher life expectancies demand more pharmaceuticals. Taken together, these results suggest that the major industrialized countries are likely to maintain a strong demand for medicinal products, which in turn, will continue to provide pharmaceutical firms with the necessary revenues to continue to develop innovative products.

After examining the demand for pharmaceuticals, the analysis shifts to investigating factors that explain the pattern of origination and introduction of new chemical entities across countries. NCEs are the output of innovative activity in the pharmaceutical industry, and firms engage in R&D with the goal of developing these products. Furthermore, firms also strive to develop products that will be successful globally. A competitive pharmaceutical industry is likely to be in a country (or region) that fosters innovative activity and attracts new products. One significant but not surprising result of this analysis is that a higher level of R&D commitment in a country is consistent with the origination of more *global* NCEs. The United States, with its pervasive academic research activities that create and disseminate scientific information and its public sector research through the National Institutes of Health, excels at creating *global* NCEs. In fact, the United States originated 15 out of 26 *global* NCEs between 1983 and 1988. Furthermore, the results suggest that countries with higher prices, growing economies, and consumers that spend a relatively higher proportion of their income on medical expenses, attract relatively more new pharmaceutical products.

The final part of the analysis examines differences in competitiveness across firms. The firms in this analysis are assigned to the country where they are headquartered, although they generally have operations all over the world. The analysis focuses on the determinants of two important measures of competitiveness in this industry: global market share and R&D productivity. The analysis finds that higher levels of R&D spending, larger numbers of R&D employees, and a large sales force lead to higher global market shares. In addition, the results suggest that higher global market shares are associated with firms that develop a larger portion of its own R&D compounds. U.S.-based and Western European based firms excel in all of these factors. In particular, these

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22—Continued

of Proposed Regulatory Changes," in *Issues in Pharmaceutical Economics*, ed. by Robert Chien (Lexington, MA: Lexington Books, 1979), pp. 151-191. These researchers attempt to estimate the cost of a new drug from its discovery to marketing (including the opportunity cost of the invested capital), whereas, the figure reported here is only an estimate of the additional cost of increasing the R&D pipeline by one compound.

two regions spend a larger amount on R&D, have larger sales forces, and have more of their own products under development.

After investigating the determinants of global market share, the analysis shifts to examining the factors that explain R&D productivity. R&D productivity is defined in two ways: (1) R&D output per R&D employee; and (2) R&D output. The analysis indicates that increases in expenditures per R&D employee and increases in the number R&D employees lead to greater R&D output. In addition, the analysis finds that when a larger firm adds an additional R&D employee, that employee is more productive than when an additional R&D employee is added to a smaller firm. However, the results also indicate that smaller firms are more productive for an additional dollar spent per R&D employee than larger firms are for an additional dollar spent per R&D employee. Furthermore, increases in firm size result in higher R&D productivity given that the firm has greater than 3,000 R&D employees and spends more than $110,000 per R&D employee. Finally, the productivity analysis suggests that there are positive spillovers to firm level R&D productivity from national research efforts.

From the results of the R&D productivity equations, it is clear that pharmaceutical firms must make a considerable commitment to research and development, both in terms of the size of their R&D budget and R&D staff to remain competitive. Both the U.S. and Western European headquartered firms in this sample have made such a commitment. The U.S.-headquartered firms average nearly $340 million in real R&D expenditures and have an R&D staff that averages approximately 2,600. Similarly, the firms headquartered in Western Europe average nearly $445 million in real R&D expenditures and have an R&D staff that averages approximately 3,500. In addition, most European-based firms have made large R&D investments in the United States, which makes the United States a formidable competitor in this industry. This most likely explains why a disproportionate amount of the truly innovative, i.e. *global*, products originate in the United States. Moreover, it is also likely that U.S.-based research efforts benefit from the research undertaken at the National Institutes of Health.

The results from this analysis have potential policy implications for facilitating a competitive pharmaceutical industry.[23] The analysis points to a growing national economy as an important underlying base for this industry. The elasticity results from the demand analysis suggest that policies that foster a rise in real national income will, in turn, result in a higher demand for pharmaceuticals. Higher demand for pharmaceuticals generates revenues that the firms need to increase their probability of producing innovative products. The analysis also indicates that national research efforts help foster the discovery of innovative NCEs and that relatively higher prices for pharmaceuticals partially explain the larger number of NCEs introduced into a country. In addition, the analysis indicates that higher levels of R&D expenditures and R&D employees are important for global market share and R&D productivity. Consequently, policies that minimize unnecessary restrictions on the production and distribution of pharmaceutical products as well as those which improve the educational system (with a goal towards improving the quality and supply of research scientists) will likely enhance the competitiveness of this industry.

[23] One caveat, however, is that statistical analysis of specific government policies was not directly performed because data are not available to allow such testing in the context described above. On the other hand, the results in this chapter can be used to make broad generalizations regarding the factors that are likely to enhance a competitive pharmaceutical industry.

CHAPTER 6
PRINCIPAL FINDINGS

The global pharmaceutical industry transcends geographical barriers, in that most of the major firms are multinational, with operations in the United States, Western Europe, Japan, and other markets worldwide. The distinctions of geographical boundaries have been further blurred by recent mergers in the industry that have created entities such as the "transnational" SmithKline Beecham. This report generally includes firms of foreign parentage when referring to the industry in a given country or region, except for certain parts of the economic analysis. Discussions in the report on the level of competitiveness of the U.S. industry address issues such as the ability of the United States to retain its large share of the world's production and R&D facilities.

The discussion in this report of the potential effect of U.S. Government policies on the future competitiveness of the U.S. industry is drawn, in large part, from an examination of the impact of current policies enacted in Western Europe and Japan. The effects of current U.S. regulations are discussed, as well as potential effects of proposed legislation. Since the primary purpose of this chapter is to summarize the issues presented in this report, the conclusions, and any inferences, are based on the analysis found in this report.[1]

[1] Many of the quotes and statements presented in this chapter are drawn directly from the report. As such, the cites for these already appear in other chapters of the report.

Summary of Major Competitive Factors and Determinants

The competitive factors examined in this report range from those that are quantifiable to those that are best discussed in anecdotal terms. Nonetheless, all have an impact on the industry, particularly when taken in concert. Table 6-1 lists, by country, a number of the findings presented in this report.[2]

Government Policies

The results of the economic analysis developed in this report suggest that major industrialized countries are likely to maintain their strong demand for medicinal products. This, in turn, will provide pharmaceutical firms with the revenues necessary to continue developing innovative products. Future levels of revenues and innovation, however, are likely to be strongly affected by U.S. and foreign government policies. A number of domestic and foreign government policies are examined in this report, including regulatory policies, product liability, intellectual property rights, taxation, the Drug Export Act, and the implementation of pricing controls and cost-containment programs. Each of these government policies has a significant effect on members of the global industry. However, they do not operate in isolation.

The multinational pharmaceutical industry must confront a combination of many of these policies, which compounds the total impact.

[2] Please note that the time frames presented for the data are not consistent across all fields in the table.

Table 6-1
Some of the factors/determinants of competitiveness considered in this report.

Estimated global market share, 1989 (percent)[1]	40	40	20
Industry R&D expenditures, 1989 ($ billions)	[2]7.3	[3]8.4	[4]3.3
Number of "global" NCEs discovered during 1975-89[5]	47	44	5
Number of "global" NCEs discovered during 1985-89[5]	14	5	0
Percent of GDP spent on healthcare, 1987[6]	12	4-12	7
Percent of healthcare expenditures on pharmaceuticals[6]	7	10-17	22
Pricing policies implemented?	No	Yes[7]	Yes
Cost-containment programs implemented?	[8]	Yes[7]	Yes
National health insurance programs	No	Yes	Yes
National patent restoration programs?	Yes	No[9]	Yes

[1] Derived from the market shares held by the top 80 companies worldwide.
[2] PMA.
[3] Derived from data provided by the European Federation of Pharmaceutical Industries' Associations.
[4] Derived from data provided by Japan Pharmaceutical Manufacturers Association.
[5] P. E. Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World (1975-1988)*
[6] Derived from data compiled by Eli Lilly & Co. (Data for the United States and Japan cited from a 1989 reference.)
[7] In some member states.
[8] Implemented on a limited scale in the United States under the Omnibus Budget Reconciliation Act of 1990.
[9] Legislation to allow for extensions of market exclusivity based on delays in the approval process is pending under the EC92 program.

Regulatory Issues

Optimal regulatory policy for the pharmaceutical industry requires a balance between the time necessary to prove a product safe and efficacious, the time needed by companies to recoup their R&D expenditures, and the time needed to launch new products on the market for patients who need them. Delays in regulatory procedures can shorten a product's effective patent life by a number of years. They also delay a product's entry onto the market. Although regulatory delays generally affect all companies operating in a given geographical area, it is possible to argue that the domestic industry bears a large share of the impact inasmuch as the domestic industry often incurs a major portion of its revenues from its home market.[3]

In 1960, the drug approval process in the United States took about 3 years. After the Kefauver-Harris amendments in 1962 increased the emphasis on safety and efficacy, total testing and FDA review time increased, on the average, to 10 years. The average FDA review time for the 20 new drugs approved in the United States in 1988 was about 31 months, compared with approximately 15 months for those of the 20 that were first approved in foreign markets.[4] Industry sources state that this differential in approval times prompts many companies to seek market approvals overseas first. According to a recent study, the average break-even point for new products in the United States can be reduced by about 3-4 years, if regulatory delays are reduced by about 1 year. In the EC, delays in the registration process under the current system cost the industry an estimated 0.5 to 1.0 percent of EC industry costs.

Delays at the FDA have been attributed to a number of factors, ranging from personnel shortages to the increasing amount of data required to demonstrate the safety of the product under consideration. Suggestions on improving the efficiency of the FDA approval process range from the implementation of user fees on NDAs to the better preparation of applications on the part of industry. Reaction to the idea of user fees is mixed, both in industry and in Congress. User fees are perceived by many to be a tax on innovation. Others question the administration of user fees. Still others believe, however, that users fees could provide needed resources for the FDA, presuming that the fees would go directly to that agency and not to the U.S. Department of the Treasury.[5]

In addition to allowing for the extension of a product's period of market exclusivity based on delays in the regulatory process, the 1984 Waxman-Hatch Act authorized accelerated approval procedures (ANDAs) for generic products in the United States, allowing them to enter the market faster after the patent expires on innovative products. The entry of generic products now results in upwards of a 50-percent loss in market share in two years for the innovative products. Since the recent FDA generic drug problem, however, it is possible that generics will also be required to undergo more testing to prove safety and efficacy, thereby prolonging their approval process. This could increase the prices on many generic products over time, possibly resulting in the closure or sale of a large number of domestic generics manufacturers.

Intellectual Property Rights

IPR have a significant effect on the development of pharmaceuticals; most importantly, they allow firms a period of market exclusivity in which they can partially recoup R&D expenditures. Two basic IPR considerations are (1) the extension of patent terms on pharmaceuticals to allow for regulatory delays and (2) the implementation of adequate patent protection legislation in a number of countries. Companies generally patent products as soon as they show signs of pharmacological activity. Given that patents are applied for fairly early in the development process, however, any delays in regulatory approval can shorten the period of market exclusivity for a given product.

In 1984 and 1988, the United States and Japan, respectively, implemented patent-restoration provisions that were intended to mitigate the impact of delays in the regulatory procedure. Although the two systems vary in terms of actual procedures, the basic effect is to allow a maximum of 5 years additional market exclusivity for pharmaceutical products. The average length of time for all the extensions granted in Japan since enactment in 1988 is 3 years and 11 months. As of April 1990, 85 innovative products had their patents extended in the United States. However, no products were able as yet to take advantage of the full 5-year extension permissible under the Waxman-Hatch Act.

The EC Commission recently has issued a regulation on patent restoration that allows for the creation of a supplementary protection certificate for medicinal products. The certificate is seen by many as a device rather than an extension of the patent term itself.

The implementation of adequate patent protection in a number of countries is a major goal of both the U.S. Government and the PMA. Concern exists about patent systems in a number of developing countries, as well as in developed countries such as Canada. The Canadian patent system is said to be the weakest in any industrialized country and in some developing countries. Canada's compulsory licensing system, according to industry sources, has resulted in the

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[3] For example, according to a representative of PMA, U.S. pharmaceutical sales accounted for 55-57 percent of total pharmaceutical sales of U.S.-based innovative companies in 1989.

[4] It should be noted that comparison of approval times in the United States and overseas can be difficult because time periods vary depending on when in the process the "clock was started" and foreign approval times do not necessarily include the time used for preclinical testing in the United States.

[5] "Should Drugmakers Pay FDA Bills," *Business Week*, Feb. 19, 1990, p. 108.

essential demise of a research-based industry.[6] The Canadian Patent Act was amended in 1987 (via passage of legislation generally referred to as C-22) in an effort to strengthen the Canadian industry. According to one source, the changes were expected to increase the reinvestment of revenue to R&D in Canada to 10 percent by 1996. By 1990, the ratio of R&D investment to sales in Canada had increased to 8.8 percent from 3 percent in 1979. Industry representatives, however, have stated that the Canadian system needs further amendment to sustain this level of reinvestment.

Under the provisions of the 1984 Trade Act, the U.S. Government has been able to negotiate improved patent protection in a number of countries/regions, including Argentina, Chile, Mexico, Korea, and, most recently, Eastern Europe. However, a number of countries are still believed to have inadequate patent systems. It was estimated that worldwide IPR infringement in 1986 cost the U.S. industry approximately $6 billion, possibly reducing R&D investment by $720-900 million.

Cost containment and Price Controls

The enactment of cost-containment programs, price controls, or both, on a national level often results in decreased levels of R&D spending in that these programs reduce revenues that can be reinvested in R&D programs. Several countries that have implemented such programs have seen their pharmaceutical industries weaken or shift outside their borders.

Cost Containment

The United States has historically had a "relatively unencumbered" economy, with, according to industry sources, the most market-oriented pricing system in the world. The Federal Government, until 1989, did not implement pricing or cost-containment programs. Under the Omnibus Budget Reconciliation Act of 1990, however, pharmaceutical companies are required to provide rebates to the Medicaid program to have their prescription drugs reimbursed by the Government. This legislation is perceived by representatives of the pharmaceutical industry as one of the first stages of cost-containment efforts in the United States. The level of rebate directly affects a company's profits. The industry is concerned that (1) such rebates, although currently limited to the Medicaid program, could be adopted by other insurance programs in the United States and (2) additional cost-containment legislation could be implemented.

A number of countries in Western Europe have implemented cost-containment programs for health care expenditures. Among other things, these programs are intended to lower the portion of health-care expenditures accounted for by pharmaceuticals. Germany, for example, one of the countries that has traditionally practiced free pricing, recently enacted the Health Reform Act (HRA). The HRA fixes reimbursement levels for products that are offpatent and have a relatively high volume at a level between the generic price and the original manufacturer's price (reportedly closer to the former than the latter). In addition to reducing revenues of the firms operating in Germany, the HRA has also increased the market share held by generics. Currently, one of the largest pharmaceuticals producers in Germany is a generic manufacturer.

In Japan, domestic companies are now said to be facing pressure to enter foreign markets as a result of national policies to curb expenditures on pharmaceuticals. Japan's pharmaceutical market, second in value only to that of the United States, has traditionally been large enough to generally disincline Japanese pharmaceutical manufacturers from attempting any large scale moves toward internationalization. However, because of cost-containment efforts on the part of the Japanese Government and increased international competition in the Japanese market, Japanese pharmaceutical producers are now seeking to expand on a global basis. As such, they have been increasing their R&D activity and investment so as to to develop more global NCEs and have been formulating strategies to compete with the successful U.S. and Western European multinationals. Japan's globalization strategies for the pharmaceutical industry include merger, acquisition, and licensing activities abroad, and the construction of wholly owned subsidiary plants and research facilities in the United States and Western Europe.

Price Controls

The United States has not yet implemented price controls on pharmaceuticals. In Japan, however, the prices for pharmaceutical products are set by the government and decline on a biennial basis. Pricing controls also have been enacted by almost all of the member states in the EC. The United Kingdom, for example, uses the PPRS, a profit-control system. The voluntary program is intended to maintain price levels that allow for a "reasonable return on capital," to ensure that prices of pharmaceutical products are not raised arbitrarily, and to limit the cost of drugs to the National Health Service (NHS).[7] The majority of the pharmaceuticals consumed in the United Kingdom are provided through the NHS. The PPRS only addresses those brand-name ethical pharmaceutical products that are sold to the Department of Health and does not apply to generic or OTC products. The PPRS also calls for a cap on promotional spending by companies. The latter is said to have more of an impact on small- and medium-sized companies because of the higher ratio of promotional spending to sales generally incurred by these firms, as compared with of larger firms.

[6] The Canadian industry is currently composed primarily of generic producers.

[7] Shearson Lehman Hutton, *A Controversial Vision of the Future: Challenges Posed by Pharmaceutical Deregulation*, February 1989, p. 51.

It is unlikely that, under the EC92 program, a community-wide national price-control and/or cost-containment program will be implemented within the next 20 years. But many in the industry and in the EC Commission are watching the implementation of such programs in individual countries across the EC and weighing their merits. Industry sources have stated that, if it is necessary to have price controls and/or cost-containment programs, the PPRS is probably one of the best, particularly if compared with the reference pricing system implemented under the HRA in Germany.[8] The PPRS is credited with having increased investment in the British pharmaceutical industry.[9] In contrast, the implementation of the HRA, which utilizes the concept of therapeutic clustering, has reportedly resulted in a 25-40 percent decrease in pharmaceutical prices in Germany. This decrease in revenues is expected to have a significant impact on future innovation in Germany. Therapeutic clustering, or the grouping of drug products for similar indications for reimbursement at similar price levels by either health insurance plans or national health systems, regardless of whether the products are patent protected, is expected to exacerbate the impact of cost-containment programs. One industry representative indicated that such efforts also undercut domestic IPR protection in that they decrease or eliminate the market exclusivity conferred by such protection.

The implementation of price controls in the EC has resulted in price differentiation in the individual Western European countries, which has, in turn, resulted in increased parallel trade (particularly from the southern countries), trade barriers, or both. According to EFPIA and PMA, the undercutting in price that results from parallel trade results in a decrease in revenue, which, in turn, could potentially have a negative impact on R&D. Price controls are also believed, in some cases, to favor the domestic industry. France, for example, is said to foster its domestic industry by giving indirect R&D incentives to local firms or foreign-based firms with significant investment levels in France by allowing for better domestic prices, more rapid product approval, and reimbursement for exports. Nonetheless, the implementation of price and promotion controls reportedly weakened the French industry by reducing revenues that could have been reinvested in R&D to develop more global NCEs.

Product Liability

Product liability law, under which an injured consumer can sue the manufacturer of a defective product, is well developed in the United States, particularly in the area of pharmaceuticals. Aspects such as strict liability, contingency fees, jury trials, and extensive discovery have reportedly led to a system in which lawsuits are frequent, awards are high, and insurance is harder to obtain. According to industry sources, product liability has led to a decline in the ability of the U.S. pharmaceutical industry to compete with its overseas counterparts. The threat of extensive litigation and large awards to plaintiffs has stunted the innovation and marketing of needed drugs, especially in the fields of contraceptives and vaccines.

In the European Community, a new product-liability directive is replacing traditional liability that required proof of negligence with a strict liability standard similar to the U.S. model. Switzerland still operates under the older negligence-based system. Product liability law in Japan in not as developed as in the United States, partly because of a preference for the negotiated settlement of disputes rather than litigation. The Japanese government has established a fund, to which pharmaceutical manufacturers and the government contribute, for the relief of persons injured by drug side-effects.

Taxation

In regard to taxation, industry concerns focus on the U.S. tax system. Industry groups identified three actions in the field of taxation that would strengthen the pharmaceutical industry: (1) restructuring the R&E credit and making it permanent; (2) reducing the cost of capital by reducing the tax on capital gains and encouraging long-term savings and investment; (3) resolving issues raised by section 861 by permanently setting a percentage of R&D expenditures for allocation against U.S. income.

U.S. Drug Export Act

U.S. firms are increasingly seeking marketing approval overseas prior to or during application for such approval in the United States. The 1986 Drug Export Act allows companies to export unapproved pharmaceuticals to countries with effective drug-approval regimes under certain conditions. The industry is, however, concerned about certain aspects of the law, citing that (1) a number of important markets have been omitted from the law; (2) a company cannot export a product that, although approved for marketing overseas, would not be approved in the United States; and (3) the process to obtain FDA approval to export products under this Act is considered cumbersome. Without this law, it is likely that many firms would have had to relocate current facilities or site future facilities overseas in order to best access foreign markets. Negative aspects of the law, however, are believed to place domestic firms at a disadvantage with firms in foreign industries who do not operate under such laws.

[8] USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

[9] One source argues, however, that despite the fact that the U.K. industry "has a good record of investment and innovation, . . . it is likely that it could have been still more successful if it had not been for the curtailment of profits through the PPRS."

Duty Suspensions in the EC

The primary tariff barrier identified as affecting the U.S. industry is the recent change in the EC's procedure for granting duty suspensions. The new duty suspension guidelines may effectively limit the availability of duty suspensions for pharmaceutical products. The increased difficulty in obtaining duty suspensions in Europe may increase the possibility that U.S. firms will move production facilities to Europe.

The Global Competitors

The competitive stature of an industry depends on the industry's level of commitment to R&D and the productivity of its R&D programs. Thus, it is probably not surprising that the economic analysis developed in this report found that a competitive pharmaceutical industry is likely to be located in a country (or region) that fosters innovative activity and attracts new products. One significant result of this analysis is that a higher level of R&D commitment in a country is consistent with the origination of more global NCEs. The results of the empirical analysis indicate that pharmaceutical firms must make a considerable commitment to research and development, both in terms of the size of their R&D budget and R&D staff to remain competitive.

The economic analysis in this study also examined the determinants of two important measures of competitiveness in the pharmaceutical industry, global market share and R&D productivity, at a firm level. With respect to global market share, the analysis found that higher levels of R&D spending, larger numbers of R&D employees, and a large salesforce are associated with higher market shares. With respect to R&D productivity, the analysis found that increases in expenditures per R&D employee and increases in the number of R&D employees lead to greater R&D output, although the effect of additional R&D spending is subject to diminishing returns. In addition, the results indicate that when a larger firm adds an additional R&D employee, that employee is more productive than when an additional R&D employee is added to a smaller firm. However, the economic analysis indicates that smaller firms are more productive for an additional dollar spent per R&D employee than larger firms are for an additional dollar spent per R&D employee. Finally, the productivity estimations suggest that there are positive spillovers to firm level productivity from national research efforts.

Considering the findings of this analysis, it is not surprising that the U.S. pharmaceutical industry (including all firms operating in the United States) has maintained a high degree of competitiveness during 1980-90, as compared with the industries in Western Europe and Japan. The U.S. industry was a leader in innovation during 1975-89, developing the majority of the globally successful products introduced during this time period. A number of reasons have been cited for the industry's success, including the size of the domestic market; the industry's expansion overseas; the industry's continued high level of R&D expenditures; and, perhaps most important, the "relatively unencumbered" U.S. economy, in that it has not to date implemented price controls on pharmaceuticals and is considered by many to be the country with "the last of the free pricing." Each of these factors has had a significant impact on the development of the U.S. industry.

The U.S. market is the largest of all of the single-country markets considered in this report, valued at about $43 billion in 1989, compared with about $31 billion for the Japanese market. The Western European market was valued at about $44 billion, of which Germany accounted for 23 percent, France for 21 percent, and Italy for 19 percent.

The large size of the U.S. market has provided an incentive for development for both domestically-owned firms and for many subsidiaries of foreign firms. In 1986, total assets of affiliates of European-based companies in the United States were estimated to be approximately $9.7 billion, of which $8.9 billion, or 92 percent, was accounted for by Western European firms. In spite of the relatively recent entry of Japanese firms into the U.S. market on a majority-owned basis, about 18 Japanese companies with equity ownership of more than 50 percent were operating in the United States in 1989.[10]

Concentration on one's home market, however, is often not sufficient to build a strong industry that is able to compete on a global basis, as indicated by the experiences of the industries in France and Japan. The industries in these countries have, until recently, focused primarily on their relatively large home markets. This focus and the implementation of price controls and cost-containment programs in the two countries have delayed their development of R&D and marketing infrastructures that are comparable to those of stronger and more innovative industries such as those in the United States and some Western European countries.[11] Conversely, the strength of the industries in the United States, the United Kingdom, and Switzerland was established fairly early by their expansion beyond domestic borders.

During 1976-90, the cost of developing a pharmaceutical product in the United States increased from $54 million to $231 million.[12] The relatively

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[10] *Data Book 1990*, p. 34. On an individual firm basis, this number of firms represented the largest share of Japanese investment overseas, or 23 percent. Taiwan was the next largest site, with about 16 majority-owned Japanese firms.

[11] It should be noted that the decline in strength of the French industry has been attributed primarily to the implementation of certain Government policies in that country.

[12] This amount includes the direct costs associated with bringing the drug through discovery, clinical testing, development, and marketing approval, as well as the cost of capital. It should be noted that the values for 1976 and 1990 in constant (1982) dollars are $86 million and $197 million, respectively. The value presented for 1990 is in terms of 1987 dollars.

high cost of developing a drug is based on factors such as (1) the uncertainty of success and the number of products that have failed during the development process; (2) the reported delays in receiving marketing approval from the FDA; and (3) the industry-wide trend towards development of products to treat chronic diseases. In 1989, innovative companies invested a record $7.3 billion, an increase of 12.3 percent from 1988.

In the United States, approximately half of the cost is represented by direct, "out-of-pocket" costs, whereas the remainder represents the cost of capital. If the product is developed overseas, PMA estimates that the direct costs would be comparable, but the cost of capital would be considerably less.

The period of market exclusivity for innovative products has become considerably shorter in the United States, Western Europe, and Japan during the past decade, given the increase in the time needed to bring a pharmaceutical product to market. It is estimated that, in the United States, it takes 19 years for the average new chemical entity (NCE) to recover its R&D investment.[13] However, the average length of the effective patent life of a pharmaceutical in the United States has declined to 10 years and 10 months from 15 years in the early 1960s.[14] Innovative products also face competition from the speedier entry of generic products per the provisions of the Waxman-Hatch Act. Patent-restoration programs enacted in the United States and Japan, however, offset the decline in the effective patent life of products to some extent by allowing for an additional period of market exclusivity. The lack of adequate patent protection in many foreign countries can both erode a product's lifetime and cause a company substantial losses in revenue.

The continued increase in the cost of R&D is considered to be one of the driving forces behind the industry's current trend towards consolidation. Consolidation (i.e., mergers/acquisitions, joint ventures, or strategic alliances) allows firms to share the risks and the costs involved with bringing new products to market. It also allows firms, particularly those wishing to enter the U.S. market, to expand their geographical reach and balance product portfolios.

A major focus of criticism of the pharamceutical industry is the role played by rising drug prices in escalating health care costs. During the past decade, the costs associated with health care worldwide have increased steadily. In 1989, health-care costs in the United States represented approximately 12 percent of domestic gross national product (GNP), increasing from about 7 percent in 1968. Price increases for existing drugs and ever higher prices for new drugs in the United States have caused their average price to rise at a faster rate than the Consumer Price Index.[15] However, the portion of total health care costs represented by pharmaceutical products, at least in the United States, has decreased from over 11 percent in 1983 to about 7 percent in 1989.[16] The cost effectiveness of substituting certain pharmaceutical products for a hospital stay has been well documented in recent years, even being presented as part of a company's application for domestic marketing rights.

According to some observers, the Western European industry, traditionally less competitive than the U.S. industry, has slowly been strengthening its position in recent years. The relative strengths of the individual Western European countries vary, as reflected in the number of globally successful innovative products that were developed in each of the Western European countries during 1975-89 (see Fig. 4-9).

The disparities in the strength of different national industries are attributed by industry sources primarily to government policies enacted in the various countries, and to different standards of living. Countries that have traditionally practiced free-pricing for pharmaceutical products and have been the source of higher revenues such as Switzerland, the United Kingdom, and Germany, developed strong research-based industries, whereas the industries in countries such as Italy, Spain, and Greece have generally been weaker. Italy, however, has taken a progressive approach in regard to pricing and patent protection, thereby strengthening its industry.[17]

In Western Europe, as in the United States, the increases in health care costs have generated increasing concern about health-care expenditures, prompting countries to consider methods to reduce such expenditures. The implementation of price controls, cost-containment programs, or both, in individual countries, however, have had significant effects on the industries in a number of Western European countries. For example, the implementation of the HRA could weaken the German industry by reducing or limiting companies' revenues. The PPRS, although credited with increasing investment in the United Kingdom, is viewed by some as limiting the innovativeness of the UK industry. The French industry, once quite strong, has diminished in strength, largely, according to many sources, as a result of the implementation of national price controls. As evidenced by the Rhone-Poulenc

[13] According to sources, only one out of every 4,000-10,000 compounds discovered is marketed commercially.

[14] It should be noted that innovative companies generally patent a product fairly early in the discovery process. Therefore, any delays in bringing the product to market shorten the product's effective patent life.

[15] Nearly all drug categories have shown annual price increases in recent years. Based on Bureau of Labor Statistics data, prescription drug producer price indexes for selected categories in September 1990 showed the following annual increase: Cancer therapy products, 7.0 percent; Cardiovascular therapy, 8.8 percent; Psychotherapeutics, 16.3 percent.

[16] "The Economic and Social Impact of Drug Innovation on the Delivery of Health Care," November 1988.

[17] *The Pharmaceutical Industry*, p. 47; USITC staff field interviews in Western Europe with representatives of EC-based and U.S.-based multinational firms and representatives of industry associations during April 1991.

merger and the strategic alliance between Sanofi and Sterling, however, several French companies are currently seeking to strengthen their position in foreign markets, reportedly in an effort to offset the effects of the price controls in their domestic market.

In general, many Western European drug companies have been preparing to reorganize themselves as national barriers come down in 1992. A number of Western European companies are enlarging their role in the United States, most easily accomplished by acquisitions and strategic alliances.

Information collected by interviews with industry representatives and literature sources indicate that most Japanese pharmaceutical firms probably will not become major competitors in the world innovative pharmaceutical industry over the next 5 to 10 years. They have reportedly participated in a number of joint ventures, licensed out a number of products to U.S. companies, have acquired a number of small research laboratories in the Northeast, and are studying the market closely, but they have not yet established a significant presence in either the United States or Western Europe.[18]

Industry sources have pointed out that Japanese firms do not currently have many new products in their drug development pipelines compared with U.S.-and Western European companies. As seen in table 6-1, Japan's share of "global" NCEs from 1975 to 1989 was only about 5 percent of the total introduced worldwide over this period. However, this does not mean that they will not increase their share of the world pharmaceutical market. The Japanese pharmaceutical industry has made significant strides toward globalization because: (1) the downward pressure on drug prices from government cost-containment measures over the last 10 years, and (2) the changes in investment policies enabling foreign firms to become more competitive in the Japanese market.

Some analysts maintain that most of Japan's recent building expansion, and merger and acquisition activity has been in Western Europe, possibly in anticipation of the growth opportunities that will result from consolidation of the EC market after 1992. Participation in this new market will allow the Japanese to learn to operate under the regulations and guidelines of EC drug regulatory authorities as well as establish the marketing forces necessary to increase their share of sales. In addition, Japanese pharmaceutical firms have been active to a lesser degree in the United States, and have made major investments in academic research institutions at several U.S. universities as well as developing private research centers. These ventures can be construed as an effort to accelerate their R&D productivity, a primary step in the drive to become a major producer of innovative pharmaceuticals in the world market.

Currently, it is only in Japan that the large and very successful U.S.-and West European pharmaceutical manufacturers must truly compete with their Japanese counterparts.[1] Recent changes in Japan's investment laws, and other factors brought about, in part, by United States-Japan trade negotiations resulted in greater access to the market by foreign firms. Most foreign participants now operate independently of Japanese partners and have captured certain segments of the market because of their strong R&D commitments to innovative products and because of their increased access to the distribution system. Industry spokesmen for these foreign operations caution, however, that some of these changes, namely, changes to the Anti-monopoly Act regulating business practices and the wholesale distribution system (see chapter 4), could have a negative effect on their competitiveness in the Japanese market.

Firms engaged in another area of Japan's pharmaceutical industry, namely biopharmaceuticals, are reportedly in a position to become major competitors in the world market. At present, the strength of Japan's biotechnology industry lies in its experience in process refinement. Unlike the small, innovative U.S. biotech companies, Japanese firms engaged in biopharmaceuticals are, for the most part, affiliated with large keiretsus (i.e., conglomerates of Japanese manufacturing firms controlled by a central banking firm), which shield these subsidiaries from the venture capital problems and investor impatience faced by the small U.S. companies. Japan's biotechnology industry is actively seeking to obtain new biopharmaceuticals from innovative world drug firms through joint ventures, cross-licensing, mergers, etc. Once new biopharmaceuticals are obtained, the Japanese firms, with their experience in process refinement, could become a major world competitor in this new sector of the pharmaceutical industry.

[18] Nancy Mattison, "Pharmaceutical Innovation and Generic Drug Competition in the USA: Effects of the Drug Price Competition and Patent Term Restoration Act of 1984," *Pharmaceutical Medicine*, 1986, p. 184.

[19] *Competing in Japan*, p. 54.

APPENDIX A

LETTERS FROM THE COMMITTEE ON FINANCE, UNITED STATES SENATE, REQUESTING THE INVESTIGATION

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510

September 27, 1990

The Honorable
Anne Brunsdale
Acting Chairman
United States International
Trade Commission
500 E Street, S.W.
Washington, D.C. 20436

Dear Madam Chairman:

The Committee on Finance has received the Commission's report identifying U.S. advanced technology manufacturing industries for monitoring and possible comprehensive study. We understand that the Commission proposes to conduct comprehensive studies of the following three industries: communications technology and equipment, pharmaceuticals, and semiconductor manufacturing and testing equipment.

The Committee hereby approves the Commission's recommendations. As indicated in our letter of June 21, 1990, the Commission should complete the study of these three industries within 12 months.

Sincerely,

Lloyd Bentsen

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510-6200

June 21, 1990

The Honorable
Anne Brunsdale
Chairman
United States International
Trade Commission
500 "E" Street, S.W.
Washington, D.C. 20436

Dear Madam Chairman:

As part of its policymaking process, the Senate Committee on Finance anticipates a need for impartial and detailed information on the competitiveness of advanced technology manufacturing industries in the United States. As an independent Federal agency with the authority to investigate the impact of international trade upon domestic industry, it would be a logical extension of the Commission's responsibility to expand and enhance its capacity to provide information on an ongoing basis concerning the relative global competitiveness of American industry.

Accordingly, the Committee hereby requests the Commission to expand its collection of, and ability to analyze, information on the competitiveness of such industries pursuant to sections 332(b), 332(d), and 332(g) of the Tariff Act of 1930.

While the Committee wants the Commission to develop a long-term capacity on a broad range of industries, it recognizes that this expertise must evolve in stages. Thus, the Committee requests initially a two-step investigation. Within three months of the receipt of this letter, the Commission is requested to provide to the Committee a list of industries about which the Commission will develop and maintain up-to-date information. In identifying these industries, the Commission should consider the following criteria, as well as any other criteria it may choose to establish:

-- Those industries producing a product that:

(1) involves use or development of new or advanced technology, involves high value-added, involves research and development expenditures that, as a percentage of sales, are substantially above the national average, and is expected to experience above-average growth of demand in both domestic and international markets; and

(2) benefits in foreign markets from coordinated -- though not necessarily sector-specific -- policies that include, but are not limited to, protection of the home market, tax policies, export promotion policies, antitrust exemptions, regulatory policies, patent and other intellectual property policies, assistance in developing technology and bringing it to market, technical or extension services, performance requirements that mandate either certain levels of investment or exports or transfers of technology in order to gain access to that country's market, and other forms of Government assistance.

At the time the Commission provides this list of industries, the Commission is requested to recommend to the Committee three industries for comprehensive study. In selecting these industries, the Commission should consider, among any other factors it considers relevant, the importance of the industries producing these products to future U.S. global competitiveness; and the extent of foreign government benefits to industries producing competing products.

The Commission's report on these three industries should include, but is not limited to, the following information:

-- Existing or proposed foreign government policies that assist or encourage these industries to remain or to become globally competitive, existing or proposed U.S. Government policies that assist or encourage these industries to remain or become globally competitive, and impediments in the U.S. economy that inhibit increased competitiveness of these U.S. industries.

The Commission should complete the study of these three industries within 12 months of the Committee's approval of the list of recommended industries.

It would be the Committee's intention to review the report carefully in order to determine how to expand, extend, or otherwise modify this request, if necessary, to ensure that future reports continue to yield worthwhile results.

Sincerely,

Lloyd Bentsen
Chairman

APPENDIX B
THE COMMISSION'S NOTICE OF INVESTIGATION

programs for these subspecies held in captivity.

PRT-753821

Applicant: California State University, Haycoard, CA.

The applicant requests a permit to trap, mark, transport, implant with mirco telemetry transitors, and release Santa Cruz long-toed salamanders (*Ambystoma macrodactylum croceum*) in Valencia and Ellicott Ponds of Santa Cruz County, California for population censusing and monitoring of the species.

PRT-752415

Applicant: John M. Rife, Jr., Winter Park, FL.

The applicant requests a permit to import the sport-hunted trophy of one male bontebok (*Damaliscus dorcas dorcas*), culled from the captive herd maintained by M.J. D'Alton, P.O. Box 400, Bredasdorp, 7280 Republic of South Africa, for the purpose of enhancement of survival of the species.

PRT-752791

Applicant: The Planning Center, Newport Beach, CA.

The applicant requests a permit to live-trap and release Stephen's kangaroo-rats (*Dipodomys stephensi*) on the southeast quarter of section 34, T4S, R6W of Lake Mathews Quad (Riverside county), California, for preliminary biological survey purposes.

Documents and other information submitted with these applications are available to the public during normal business hours (7:45 am to 4:15 pm) room 430, 4401 N. Fairfax Dr., Arlington, VA 22203, or by writing to the Director, U.S. Office of Management Authority, 4401 N. Fairfax Drive, room 432, Arlington, VA 22203.

Interested persons may comment on any of these applications within 30 days of the date of this publication by submitting written views, arguments, or data to the Director at the above address. Please refer to the appropriate PRT number when submitting comments.

Dated: November 9, 1990.

Karen Wilson,

Acting Chief, Branch of Permits, U.S. Office of Management Authority.

[FR Doc. 90-26942 Filed 11-14-90; 8:45 am]

BILLING CODE 4310-55-M

INTERNATIONAL TRADE COMMISSION

Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries

In the matter of Investigation No. 332-301, Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Communications Technology and Equipment; Investigation No. 332-302, Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals; Investigation No. 332-303, Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Semiconductor Manufacturing and Testing Equipment.

AGENCY: United States International Trade Commission.

ACTION: Institution of investigations and scheduling of a single public hearing.

EFFECTIVE DATE: November 8, 1990.

FOR FURTHER INFORMATION CONTACT: General inquiries regarding the three names investigations may be directed to Mr. Aaron Chesser, Office of Industries (202-252-1380). Industry-specific information regarding the three investigations may be obtained from the following staff members, also located in the Office of Industries, U.S. International Trade Commission, 500 E Street SW., Washington, DC 20436:

Inv. No. 332-301 (Communications Technology and Equipment), Ms. Sylvia McDonough (202-252-1393);

Inv. No. 332-302 (Pharmaceuticals), Mr. Edmund Cappuccilli (202-252-1368); and

Inv. No. 332-303 (Semiconductor Manufacturing and Testing Equipment), Mr. Nelson Hogge (202-252-1395).

For information on legal aspects of these investigations contact Mr. William Gearhart of the Commission's Office of General Counsel (202-252-1091).

BACKGROUND: On July 20, 1990, at the request of the Senate Committee on Finance, and in accordance with section 332(g) of the Tariff Act of 1930 (19 U.S.C. 1332(g)), the U.S. International Trade Commission instituted investigation No. 332-294, Identification of U.S. Advanced-Technology Manufacturing Industries for Monitoring and Possible Comprehensive Study. The Committee requested the Commission to expand its collection of, and ability to analyze, information on the competitiveness of advanced-technology manufacturing industries in the United States, pursuant to sections 332(b), 332(d), and 332(g) of the Tariff Act of 1930.

Specifically, the Committee requested that the Commission, under a two-stage investigation, (1) within 3 months of receipt of the letter, identify for the purpose of monitoring, using criteria provided by the Committee and any additional criteria of the Commission's choosing, U.S. advanced-technology manufacturing industries, and recommend three of those industries as subjects for comprehensive Commission studies; and (2) within 12 months of the receipt of the Committee's approval (or modification) of the Commission's recommendations, submit its report on three industries the subject of comprehensive studies.

Notice of the Commission's investigation was posted in the Office of the Secretary, U.S. International Trade Commission, Washington, DC, and published in the **Federal Register** (55 FR 30630) of July 26, 2990. All persons were afforded the opportunity to submit written views concerning the industries to be included on the list and that may be the subject of a comprehensive study.

The Commission's report on investigation No. 332-294 (USITC Publication 2319, September 1990) was transmitted to the Senate Committe on Finance on September 21, 1990. In its report, the Commission identified ten advanced-technology industries and recommended the following three for comprehensive study: communications technology and equipment; pharmaceuticals; and semiconductor manufacturing and testing equipment.

By letter of September 27, 1990, the Senate Committee on Finance acknowledged receipt of the Commission's report on investigation No. 332-294 and approved the Commission's recommendation concerning the three industries for comprehensive study; the Committee further indicated its desire that the Commission complete its study of the three industries within 12 months.

In identifying the industries to be monitored, the Committee requested that the Commission consider the following criteria as well as any other criteria it may choose—

(1) Industries producing a product that involves use or development of new or advanced technology, involves high value-added, involves research and development expenditures that, as a percentage of sales, are substantially above the national average, and is expected to experience above-average growth of demand in both domestic and international markets; and

(2) benefits in foreign markets from coordinated—though not necessarily sector specific—policies that include, but are not limited to, protection of the home market, tax policies, export promotion policies, antitrust exemptions, regulatory policies, patent and other intellectual property policies, assistance in developing technology and bringing it to market, technical or extension services, performance requirements that mandate either certain levels of investment or exports or transfers of technology in order to

gain access to that country's market, and other forms of Government assistance.

The Committee requested that the report on the three industries to be selected include at least the following information—

Existing or proposed foreign government policies that assist or encourage these industries to remain or to become globally competitive, existing or proposed U.S. Government policies that assist or encourage these industries to remain or become globally competitive, and impediments in the U.S. economy that inhibit increased competitiveness of these U.S. industries.

As requested by the Committee, the Commission will attempt to include the aforementioned information in its reports.

PUBLIC HEARING: A consolidated public hearing in connection with the three investigations will be held in the Commission Hearing Room, 500 E Street SW., Washington, DC 20436, beginning at 9:30 a.m. on January 17, 1991, and continuing as required on January 18, 1991. All persons shall have the right to appear by counsel or in person, to present information, and to be heard. Persons wishing to appear at the public hearing should file requests to appear and should file prehearing briefs (original and 14 copies) with the Secretary, United States International Trade Commission, 500 E St., SW., Washington, DC 20436, not later than the close of business on January 3, 1991. Posthearing briefs must be filed by January 31, 1991.

WRITTEN SUBMISSIONS: In lieu of or in addition to appearances at the public hearing, interested persons are invited to submit written statements concerning the investigations. Written statements are encouraged early in the investigative process, but should be received no later than the close of business on June 7, 1991. Commercial or financial information which a submitter desires the Commission to treat as confidential must be submitted on separate sheets of paper, each clearly marked "Confidential Business Infromation" at the top. All submissions requesting confidential treatment must conform with the requirements of § 201.6 of the Commission's *Rules of Practice and Procedure* (19 CFR 201.6). All written submissions, except for confidential business information, will be made available for inspection by interested persons. All submissions should be addressed to the Office of the Secretary of the Commission in Washington, DC.

Hearing-impaired individuals are advised that information on this matter can be obtained by contacting the Commisison's TDD terminal on (202) 252-1810.

By order of the Commission.

Issued: November 8, 1990.

Kenneth R. Mason,

Secretary.

[FR Doc. 90-26928 Filed 11-14-90; 8:45 am]

BILLING CODE 7020-02-M

[Inv. No. 337-TA-311]

Certain Air Impact Wrenches; Commission Decision Not to Review an Initial Determination Designating the Investigation More Complicated

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined not to review an initial determination (ID) issued by the presiding administrative law judge (ALJ) designating the above-captioned investigation more complicated and extending the administrative deadline for filing the final ID by three months. The Commission has also extended the deadline for completion of the investigation by three months, *i.e.*, until August 5, 1991.

ADDRESSES: Copies of the ID and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street, SW., Washington, DC 20436, telephone 202-252-1092.

Hearing-impaired individuals are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-252-1810.

SUPPLEMENTARY INFORMATION: On October 3, 1990, the presiding ALJ issued an ID designating the investigation more complicated and extending the administrative deadline for filing the ALJ's final ID by three months. No petitions for review or agency comments were received. The investigation was designated more complicated because of the serious illness of the president of respondent Astro Pneumatic Tool Co. (Astro) that temporarily jeopardizes the ability of Astro and respondent Kuan-I Gear Co. to defend themselves in the investigation.

Authority for the Commission action is found in section 337(b)(1) of the Tariff Act of 1930 (19 U.S.C. 1337(b)(1)) and in Commission interim rule 210.59 (19 CFR 210.59).

By order of the Commission.

Issued: November 7, 1990.

Kenneth R. Mason,

Secretary.

[FR Doc. 90-26926 Filed 11-14-90; 8:45 am]

BILLING CODE 7020-02-M

[Investigation No. 731-TA-456 (Final)]

Certain Laser Light-Scattering Instruments and Parts Thereof From Japan

Determination

On the basis of the record [1] developed in the subject investigation, the Commission determines,[2] pursuant to section 735(b) of the Tariff Act of 1930 (19 U.S.C. 1673d(b)) (the act), that an industry in the United States is threatened with material injury [3] by reason of imports from Japan of certain laser light-scattering instruments (LLSIs) and parts thereof,[4] provided for in subheadings 9027.30.40 and 9027.90.40 of the Harmonized Tariff Schedule of the United States, that have been found by the Department of Commerce to be sold in the United States at less than their fair value (LTFV).

Background

The Commission instituted this investigation effective July 6, 1990, following a preliminary determination by the Department of Commerce that imports of LLSIs and parts thereof from Japan were being sold at LTFV within the meaning of section 733(a) of the act (19 U.S.C. 1673b(a)). Notice of the institution of the Commission's investigation and of a public hearing to be held in connection therewith was

[1] The record is defined in sec. 207.2(h) of the Commission's Rules of Practice and Procedure (19 CFR 207.2(h)).

[2] Acting Chairman Brunsdale and Commissioner Lodwick dissenting.

[3] Commissioners Rohr and Newquist further determine that, pursuant to section 735(b)(4)(B), they would not have found material injury by reason of the imports subject to the investigation but for the suspensions of liquidation of the entries of the subject merchandise.

[4] The products covered by this investigation are laser light-scattering instruments and parts thereof from Japan that have classical measurement capabilities, whether or not also capable of dynamic measurements. The following parts are included in the scope of the investigation when they are manufactured according to specifications and operational requirements for use only in such an LLSI: Scanning photomultiplier assemblies, immersion baths, sample-containing structures, electronic signal-processing boards, molecular characterization software, preamplifier/discriminator circuitry, and optical benches.

APPENDIX C
CALENDAR OF WITNESSES APPEARING AT THE PUBLIC HEARING

As of 1/11/91

TENTATIVE CALENDAR OF PUBLIC HEARING

Those listed below are scheduled to appear as witnesses at the United States International Trade Commission's hearing:

Subject	:	GLOBAL COMPETITIVENESS OF U.S. ADVANCED TECHNOLOGY MANUFACTURING INDUSTRIES: COMMUNICATIONS TECHNOLOGY AND EQUIPMENT; PHARMACEUTICALS; AND SEMICONDUCTOR MANUFACTURING AND TESTING EQUIPMENT
Inv. Nos.	:	332-301 through 303
Date and Time:	:	January 17 (& 18), 1991

Sessions will be held in connection with the investigation in the Main Hearing Room 101, United States International Trade Commission, 500 E Street, S.W., in Washington, D.C.

Government Witnesses:

Robert Scace, National Institute of Standards and Technology, U.S. Department of Commerce (332-303)

WITNESS AND ORGANIZATION:	INV. NO.	TIME CONSTRAINTS
Pharmaceutical Manufacturers Association Washington, D.C. Gerald J. Mossinghoff, President	332-302	10 Minutes
Industrial Biotechnology Association Washington, D.C. Lisa Raines, Director of Government Relations	332-302	10 Minutes
North American Telecommunications Association, Washington, D.C. Edwin B. Spievack, President	332-301	10 Minutes

- more -

WITNESS AND ORGANIZATION:	INV. NO.	TIME CONSTRAIN
United States Advanced Ceramics Association Washington, D.C. Steven B. Hellem, Executive Director	332-303	10 Minute
Semi/Sematech Austin, Texas Peggy Haggerty, Vice Presdient of Public Policy (representing over 130 U.S. Semiconductor Equipment and Materials Suppliers)	332-303	10 Minute
Lithography Systems, Inc. Wilton, Connecticut Vahe Sarkissian, President	332-303	10 Minute
Semiconductor Equipment and Materials International (SEMI) Washington, D.C. Joel Elftmann, Chairman, SEMI Board of Directors and Chairman, FSI International, Inc. Michael Ciesinski, Director, North American Operations Victoria Hadfield, Manager, Government Relations	332-303	10 Minute

- end -

APPENDIX D
INTERNATIONAL COMPETITIVENESS IN THE PHARMACEUTICAL INDUSTRY

In considering the international "competitiveness" of the U.S. pharmaceutical industry in the world market, a brief discussion of various definitions of international competitiveness is provided to assist the reader. This appendix provides such a discussion, as well as an overall survey of recent papers on international competitiveness. In addition, two attempts made to measure this economic concept will be reviewed.

Defining International Competitiveness

The competitiveness of the U.S. economy in the global market became a growing concern during the 1980s, due to sustained deterioration in the U.S. trade deficit despite a significant decline in the value of the dollar against other major currencies.[1] This suggested that there were other factors within the economy causing this persistent trade imbalance. Further, the loss of market share in products such as microelectronics, an industry many thought invulnerable to foreign competition, began to raise questions regarding the overall international competitiveness of the U.S. economy. Consequently, the debate on the competitiveness issue has become one of the central preoccupations of government and industry in the United States and other nations.

National competitiveness matters because it determines the extent that productive resources, particularly labor and capital, are put to productive and remunerative uses which increase national income and raise the standard of living. The study by President Reagan's Commission on Industrial Competitiveness, in fact, defined competitiveness in terms of its effect on a nation's standard of living:

Competitiveness is the degree to which a nation can, under free and fair market conditions, produce goods and services that meet the test of international markets while simultaneously maintaining or expanding the real incomes of its citizens.[2]

Competitiveness at the national level is sometimes defined as involving not only standards of living, but also the expansion of employment opportunities and the nation's ability to maintain its international obligations.

Although it is appropriate to consider international competitiveness at the national level, it has a different meaning when applied at the industry or individual firm level. For example, at the sectoral level, competitiveness may be defined as the ability of an industry or firm to sustain and/or expand its market position profitably in a competitive environment as products and production processes evolve. This definition considers an industry's or firm's long–run profit performance relative to its rivals, and highlights the fact that competitiveness requires dynamic responsiveness to a changing technological and market environment.

Competitiveness at the national sectoral levels are intertwined, however, since the former depends on the competitive strength of firms and/or industries to generate productivity levels needed to support high wages and hence higher standards of living in the economy. Similarly, sector competitiveness depends upon appropriate policy at the national level that, for example, provides a framework for the promotion of high levels of skill through education and maintenance and/or development of infrastructure. Nevertheless, the policies appropriate for promoting competitiveness of particular industries and those relevant for a country as a whole may be quite different. Consequently, policymaking will depend on whether competitiveness is being promoted at the national, industry, or firm level.

The studies reviewed below focus primarily on competitiveness at the national level. An assessment of the international competitiveness at the industry level, specifically for the pharmaceuticals industry, is presented in chapter 2.

Review of Literature

There is a general consensus in the literature that national competitiveness depends on much more than the cost of production and prices of products. These factors are partial determinants of output levels as well as an industry's ability to sell in domestic and international markets. Increasingly, other factors, such as product quality, service, and product innovations, are seen as instrumental for an industry's competitive success. Due to the rapid pace of technical

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[1] L. Tyson, "Managed Trade: Making the Best of Second Best" in Lawrence, R. and C. Shultze, eds., *An American Trade Strategy: Options for the 1990's*, Brookings, 1990.

[2] U.S. President's Commission on Industrial Competitiveness, *Global Competition: The New Reality*, 1985. Reagan Administration, Blue-Ribbon Panel Competitiveness Report. John Young (Hewlett-Packard CEO), chair.

change, particularly in high–technology industries, R&D and innovation efforts on a continuous basis are critical to maintaining improvements in the manufacturing process and product design. Consequently, industry must make efforts to upgrade worker and managerial skills as well as improve the manufacturing process. The resulting higher productivity implies higher average incomes, contributing in turn to higher national standards of living.

There is, thus, agreement in the literature that in order to enhance its international competitiveness, the United States needs to improve: (a) the ability of its firms to develop and use technology; (b) the ability of its firms to mobilize capital resources; and (c) all aspects of human resource use throughout the economy, both within firms and in the educational system. There is, however, disagreement in the literature as to the role of the U.S. government and industry in achieving these goals. There are three major policy recommendations offered in the literature as a whole: the activist industrial policy perspective; the neomercantilist or managed trade perspective; and the neoclassical and/or liberal economics perspective. The recommendations made by the latter are perhaps the most accepted view in economic literature for enhancing U.S. economy's competitiveness. These recommendations are discussed below after a brief presentation of the activist industrial policy and managed trade perspectives. A short description follows of two attempts that have been made to measure competitiveness at the national level. Finally, this section presents a concise summary of the findings associated with the literature survey.

The first two perspectives essentially recommend an active government role in shaping a nation's trade policy. They use the performance of the Japanese economy as the basis for recommendations on formulating a strategic U.S. trade policy. The difference between the proponents of the activist industrial policies and those of managed trade lies in the selection of industries targeted for government assistance. The former recommends government assistance for all industries, whereas the latter emphasizes high–technology industries.

Activist Industrial Policies Perspective

The advocates of industrial policies in the early 1980s recommended an active government role to enable all industries within an advanced economy to shift production towards higher value–added and more competitive outputs.[3] These advocates categorized industries into three types: standardized businesses with low–skilled employees, declining in the face of strong competition from newly industrialized countries; cyclical businesses with high fixed costs in plant, equipment, and labor; and emerging businesses with high–skilled employees, characterized by rapid technological change.

In the case of declining industries, proponents of activist industrial policies recommend that agreements between the United States and governments of other advanced nations should be worked out to ease adjustment of less competitive firms by granting subsidies as well as protection from imports for a limited period, as needed. In addition, government should fund worker retraining. In the case of cyclical businesses, the United States should: continue to discourage foreign export subsidies and below–cost pricing; provide long–term financing to prevent unemployment and promote investment in new equipment; and subsidize upgrading of worker skills. Finally, in the case of emerging businesses characterized by high value–added products, the U.S. government should provide subsidies, loan guarantees, and tax benefits to lure them to locate at home rather than abroad. Such an incentive package is recommended because emerging businesses are expected to be associated with large externalities or spillovers into other areas of the economy which would translate into improved national welfare. A more recent study,[4] advocated an activist set of employment and technology policies involving large federal and state labor force training programs and expenditures and technological extension services for small businesses. It also suggested providing extensive federal research

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[3] M. Wachter and S. Wachter, eds., *Toward a new U.S. Industrial Policy*, University of Pennsylvania, 1982; I. Magaziner and R. Reich, *Minding America's Business*, HBJ, 1982; F. Adams and L. Klein eds., *Industrial Policies for Growth and Competitiveness: An Economic Perspective*, D.C. Heath, 1982; R. Reich, "Beyond Free Trade", *Foreign Affairs*, 61:4, 1983; C. Shultz, "Industrial Policy: A dissent," *The Brookings Review*, Fall 1983; and C. Johnson, eds., *The Industrial Policy Debate*, Institute for Contemporary Studies, 1984.

[4] U.S Congress, Office of Technology Assessment, *Making Things Better: Competing in Manufacturing*, OTA-ITE-443, U.S. Government Printing Office, February 1990.

support for certain selected industries, believed by the authors to be particularly important for future international competitiveness of the United States.

Neomercantilist or Managed Trade Perspective

The neomercantilists or proponents of managed trade[5] consider the reality of international trade to be managed trade rather than free trade, since most governments, including the U.S. government, actively intervene in trade. These interventions include export subsidies and import restrictions as well as agreements covering voluntary export restraints (VERs) and voluntary import expansion (VIEs). Managed trade can be broadly defined as trade that is controlled, directed, or administered by government policies and conducted by either bilateral or multilateral agreements. Multilateral agreements are recommended since they involve a larger number of participants, resulting in less discriminatory outcomes.

The neomercantalists recommend some form of managed trade in high–technology industries since they believe these industries are strategic for the economy as a whole, because they have the potential to generate important externalities, implying economic benefits for the economy. Hence, they suggest that the fate of these industries cannot be left solely to market forces, particularly in the presence of activist government intervention abroad. Also, high–technology products account for a significant and growing share of U.S. trade — approximately 38 percent of nonagricultural merchandise exports and 25 percent of non–petroleum merchandise imports in 1988.[6] Furthermore, according to managed trade proponents, trade arrangements that would result in increased exports and reduced imports of such products would require a smaller decline in the dollar's value to help adjust the U.S. trade imbalance, consequently resulting in a lower loss in real income.

Thus, they argue, managed trade could be "result–oriented," with quantitative trade targets negotiated with appropriate trading partners utilizing VERs and/or VIEs. The managed trade proponents consider that VERs and VIEs increase competition and trade flows, unlike free traders who consider their use to be restrictive. As mentioned earlier, both activist industrial policy and managed trade proponents use Japanese trade performance to support their views since they consider Japan's success as a case study of how a country can realize its trade–related goals through extensive, but carefully planned protectionism.

Neoclassical and/or Liberal Economics Perspective

The proponents of the neoclassical/liberal economics perspective[7] reject the activist industrial and managed trade policy recommendations for enhancing the U.S. economy's international competitiveness. They argue that pursuing such a strategic trade policy would require vast, unknown amounts of information about the economy and externalities associated with interventionist policy. Also, most economists believe that such policies could result in raised costs for other sectors within the economy and in trade wars.

The neoclassical/liberal economics perspective is perhaps the most accepted view in the economics literature of promoting the U.S. economy's international competitiveness and increase the standard of living. According to the neoclassical proponents, these dual goals are achieved by allowing private markets to function competitively while the government pursues

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[5] R. Reich, "Beyond Free Trade," *Foreign Affairs* 61:4, 1983; J. Goldstein and S. Krasner, "Unfair Trade Practices: The Case for a Differential Response," *American Economic Review* 74:2, May 1984; L. Tyson, "Managed Trade: Making the Best of Second Best," in Lawrence, R. and C. Shultze, eds., *An American Trade Strategy: Options for the 1990's*, Brookings, 1990; R. Dornbusch, "Policy Options for Freer Trade: the Case for Bilateralism," in R. Lawrence and C. Schultz, eds., *An American Trade Strategy: Options for the 1990's*, Brookings, 1990.

[6] L. Tyson, "Managed Trade: Making the Best of Second Best" in Lawrence, R. and C. Shultze, eds., *An American Trade Strategy: Options for the 1990's*, Brookings, 1990.

[7] U.S. President's Commission on Industrial Competitiveness, *Global Competition: The New Reality*, 1985; A. Dixit, "Trade Policy: An Agenda for Research," in P. Krugman, ed., *Strategic Trade Policy and the New International Economics*, MIT 1986; G. Hatsopoulos, P. Krugman, and L. Summers, "U.S. Competitiveness: Beyond the Trade Deficit," *Science*, July 15, 1988; M. Dertouzos, K. Lester, and R. Solow, *Made in America: Regaining the Competitive Edge*, MIT, 1989; M. Porter, *The Competitive Advantage of Nations*, Free Press 1990; R. Landau, "Capital Investment: Key to Competitiveness and Growth," *The Brookings Review*, Summer 1990.

policies to create a stable economic environment. They believe such an economic environment can best be promoted by the U.S. government by maintaining an advanced economic infrastructure, correcting market failures in technology, encouraging research and development, promoting human resource development (such as providing a good education throughout the national school system), and striving continuously for liberal trade policies worldwide. They would particularly encourage the United States to pursue macroeconomic policies to stimulate savings and reduce the federal budget deficit, which would stimulate investment and productivity growth.

There is a divergence in opinion among the proponents of liberal economic policies as to the extent to which government and firms are responsible for enhancing the nation's international competitiveness. This divergence of opinion is presented in three major studies; recommendations made by these studies are summarized below.

The report by the President's Commission on Industrial Competitiveness[8] focused primarily on government initiatives in four areas: (a) provision of incentives towards technological advances, for example, by enhancing tax credits for private sector R&D; (b) enhancement of the availability of capital at lower cost by reducing the federal budget deficit and restructuring the tax system to encourage higher savings and investment; (c) enhancement of human resources by improving the educational system at all levels; and (d) assignment of high priority to trade matters. The commission had limited recommendations on how firms should improve their competitiveness. There is mention, however, that firms should improve manufacturing capabilities, de-emphasize simple short-term financial measures, and establish a cooperative relationship between labor and management. There are no recommendations provided on how firms are expected to achieve these goals.

The MIT study on industrial productivity,[9] on the other hand, emphasizes what firms should do to improve competitiveness in the international market. The role of the U.S. government is recognized to the extent it could reduce the federal budget deficit and restructure the tax system to provide incentives for achieving a higher savings rate. The study highlights the weaknesses associated with industrial production in the U.S. economy. Some of these limitations include: reliance on outdated marketing strategies; technological weakness in product development and production; neglect of human resources due to limited formal and extensive on-the-job training; managing production in a short-sighted manner; and failures in labor-management corporation. The study reported that firms that competed successfully were characterized by the following: simultaneous improvement in quality, cost, and delivery; close relationships with consumers and suppliers; technology integrated with planning, manufacturing, marketing, and human resources; and innovative human resource policies. Consequently, the study's recommendations reflect the activities of those firms that were successful in being competitive.

Finally, the Porter study recommends a role for firms as well as the U.S. Government. Porter states that the national standard of living depends on the productivity of capital and labor resources, and that productivity is the root of competitiveness and prosperity. Porter argues that the nation's competitive advantage depends on four key, interrelated dynamic features of an economy: factor conditions (i.e., human, physical, and capital resources; educational resources; and infrastructure), demand conditions, related and supporting industries, and firm strategy and rivalry. The stronger its advantages in each of these four features, the stronger an economy is. To achieve this strength, Porter's recommends government initiatives to: maintain a strong antitrust policy to foster domestic competition; maintain an open trade policy and avoid devaluation to boost exports; create incentives for higher savings and allow interest rates to fall to encourage investment and longer time horizons on R&D projects; and fund university research centers to rejuvenate national R&D.

Porter's recommendations for firms involve dedication to relentless upgrading, improvement, and innovation at all levels of the value chain, that is, from R&D to after-sales service. Porter suggests that firms should: sell to more sophisticated and demanding customers in order to feel pressure to innovate; treat employees as permanent in order to enhance their skill level;

[8] U.S. President's Commission on Industrial Competitiveness, *Global Competition: The New Reality*, 1985.

[9] Dertouzos et al., *Made in America: Regaining the Competitive Edge*, MIT, 1989.

and be willing to help upgrade local suppliers, in order to reap the rewards of informal collaboration with them. Porter's study is one of the few studies in the literature which emphasizes the service sector as well as the manufacturing sector.

Measuring National Competitiveness

None of the studies surveyed so far measure national competitiveness, nor do they, except for Porter's study, explicitly recommend any possible indicators of international competitiveness. Porter uses standard measures, such as share of world exports, export and import levels, and growth of total U.S. exports. Two studies, however, have attempted to measure international competitiveness. The Council on Competitiveness publishes an annual "Competitiveness Report Card and Index."[10] The index is actually four indices covering investment (industry expenditure on plant and equipment as a share of GDP), productivity (real GDP per manufacturing employee), trade (merchandise exports), and the standard of living (real GDP per capita). In each case the index measures U.S. performance relative to the other G–7 countries (Canada, France, Great Britain, Italy, Japan, and West Germany). These indices do not reflect however, the impact of regulations, innovation, and R&D expenditures on the output levels of the firms in the economy.

Another international competitiveness indicator is provided by IMD/World Economic Forum (IMD).[1] This index is constructed by considering 326 variables chosen to reflect a nation's suitability as a base for competitive firms. These variables include GDP measures, inflation rates, firms' price/earnings ratios, bank size, and R&D expenditures by sector. The index also attempts to include firms' perceptions about infrastructure adequacy and executives' expectations of the growth in long term employment. This data was obtained by country from a Business Confidence Survey of executives. The index was then computed by associating weights with each variable. The IMD study concluded that overall, the United States' ranks second in the G–7, behind Japan, and third out of all countries surveyed. While the IMDs index contains interesting details on social, economic, and political indicators for the countries surveyed, the weighting scheme used to has been criticized in the literature as ad hoc in nature.

Summary of Findings

On the basis of the studies surveyed above, it appears that the mid– 1980s represented a turning point in the national debate about competitiveness. Though opinions diverge with respect to how competitiveness can be achieved, there is a consensus in the economic literature regarding the following issues: competitiveness is more than a transitory exchange–rate problem which involves macroeconomic variables such as savings and the budget deficit and that more variables than problems in human resource management, capital mobilization, and technology have resulted in lower productivity in U.S. firms. Furthermore, there is a need to understand competitiveness broadly in terms of the national standard of living, and therefore, a variety of measures should be used in conjunction with each other toward that end.

Finally, as was mentioned above, the literature, except for Porter and the MIT study, has focused primarily on competitiveness at the national level, while factors that determine competitiveness at the industry or firm level have received limited discussion. This report was an attempt to analyze the international competitiveness of the pharmaceuticals industry and to suggest several measures of competitiveness applicable to this industry and factors that determined these measures.

[10] Council on Competitiveness, *Competitiveness Index*, 1990, Washington D.C.

[11] IMD/World Economic Forum, *The World Competitiveness Report*, 1990, Geneva.

APPENDIX E
METHODOLOGY, DATA SOURCES, AND ESTIMATION RESULTS

APPENDIX E METHODOLOGY, DATA SOURCES, AND ESTIMATION RESULTS

Methodology

The methodology used in chapter 5 is regression analysis. Both sets of equations, country and firm, are estimated as pooled cross-section time- series models. The country models use annual data covering the period 1983-88 for the seven largest pharmaceutical markets: France, Germany, Japan, Italy, Spain, the United Kingdom, and the United States. The firm models also use annual data covering the period 1987-89 for the following firms headquartered in the United States: Abbott, American Home Products, Bristol-Myers (in 1989 this firm becomes Bristol-Myers Squibb), Eli Lilly, Johnson & Johnson, Merck, Pfizer, Shearing-Plough, Squibb (1987 and 1988), Upjohn, Warner-Lambert; for the following firms headquartered in Western Europe: Bayer, Ciba-Geigy, Glaxo, Hoechst, Ingelheim, Rhone-Poulenc, Sandoz, SmithKline Beecham, Roche; and for the following firms headquartered in Japan: Chugia, Daiichi, Eisai, Fujisawa, Sankyo, Shionogi, Takeda, Tanabe, and Yamanouchi. Data constraints limited the sample to these 29 firms.

The models in chapter 5 are estimated using ordinary least squares based on the covariance model for pooled data.[1] Accordingly, the models include time dummy variables to allow the intercept term in the models to vary over time, and thus, control for other factors that are not included in the model. In addition, the first set of estimations (ethical pharmaceutical demand across countries) uses a two-step procedure. In the first stage, price is estimated as a function of the exogenous variables in the demand equation and a productivity variable, which is endogenous to the supply of pharmaceuticals, to compute its predicted value. In the second stage, the demand function is estimated using the predicted value for the price measure instead of the actual price measure.

[1] See Pindyck and Rubinfeld, *Econometric Models and Economic Forecasts*, 2nd ed. (New York: MaGraw Hill Book Co., 1981), pp. 252-61.

Equation Specifications

Country Models

Demand

These estimations examine the demand for ethical pharmaceutical products. The quantity of pharmaceutical products demanded is derived from pharmaceutical sales data that are reported for each country over the time period 1983-88. The sales data for a given year are divided by an average pharmaceutical price for that country to obtain an estimate of the quantity purchased (QUANTITY).[2] This measure is expressed on a per capita basis to control for the different sizes of countries included in the sample.

Several factors are likely to affect the quantity of pharmaceutical products demanded in a country. One is price, which is expected to be inversely related to quantity demanded. Price is measured as the real (inflation adjusted) price of a common basket of pharmaceutical products (PRICE). Since price is likely to be endogenous, the demand equation is estimated using the two-stage estimation procedure described above. A second factor affecting quantity demanded is income. Countries with higher levels of income are likely to demand more pharmaceutical products, all other factors equal, and therefore, the demand for pharmaceuticals is expected to be directly related to income (INCOME). Income is measured as real gross domestic product (GDP) per capita.

To control for demographic factors, two additional explanatory variables are included in the demand estimation. The first measure is the life expectancy in a country (LIFE). Countries with higher life expectancies are expected to demand more pharmaceuticals products.[3] The second measure is the population per physician (DOCTORS). Countries with a relatively lower population per physician are likely to have a higher demand for pharmaceuticals, since the countries in this sample require a prescription to

[2] Other researchers have used this technique. For example, see Sam Peltzman, "The Health Effects of Manditory Prescriptions," *Journal of Law and Economics* vol. 30, October 1987, pp. 207-38.

[3] It is acknowledged that pharmaceutical products, over the long-run, may affect life expectancy as well.

purchase ethical drugs and a physician is required to obtain these products.[4]

Finally, a dummy variable (NONUS) is included to distinguish the United States from the other countries in the sample. This is done because in pharmaceutical markets outside the United States some sort of government intervention (direct and indirect) exists. Since many countries have control over their pharmaceutical markets, which sometimes results in lower prices, the demand for drugs in these markets is expected to be higher, and thus, the sign on this variable to be positive. As an alternative, some specifications include a Japan dummy variable (JAPAN) and a Western European dummy variable (EUROPE). This particular configuration focuses on differences across the three regions: the United States, Japan, and Western Europe.[5] Furthermore, this distinction across regions may more accurately reflect the differences than are captured in the U.S./non-U.S. configuration.[6] The demand equations are specified as:[7]

$$\text{QUANTITY} = \beta_0 + \beta_1\text{PRICE} + \beta_2\text{INCOME} + \beta_3\text{DOCTORS} + \beta_4\text{LIFE} + \beta_5\text{NONUS} + \beta_6\text{D88} + \beta_7\text{D87} + \beta_8\text{D86} + \beta_9\text{D85} + \beta_{10}\text{D84} + \varepsilon_0$$

$$\text{QUANTITY} = \beta_0 + \beta_1\text{PRICE} + \beta_2\text{INCOME} + \beta_3\text{DOCTORS} + \beta_4\text{LIFE} + \beta_5\text{EUROPE} + \beta_6\text{JAPAN} + \beta_7\text{D88} + \beta_8\text{D87} + \beta_9\text{D86} + \beta_{10}\text{D85} + \beta_{11}\text{D84} + \varepsilon_0$$

[4] It should be noted, however, that in some countries it is possible to purchase over-the-counter drugs that are considered prescription drugs in other countries.

[5] As an extension to the analysis, a demand equation is estimated with dummy variables for each non-U.S. country. However, the results reveal that individual country differences do not matter when other factors affecting demand are accounted for in the estimation. This not surprising since the estimation uses such a broad measure to capture the effects of government policies in the individual countries.

[6] The dummy variables in all the estimations need to be interpreted with care. Although this specification does capture possible differences in government policies, it is unable to distinguish between specific policies. Moreover, it controls for other differences among the countries that are not explicitly accounted for in this estimation.

[7] These equations are also estimated in logarithmic form so that the estimated coefficients represent elasticities.

The results of these estimations are presented in table E-3 below.[8]

New Chemical Entities

The next set of estimations examines the origination and marketing of new chemical entities (NCEs), i.e., new ethical drugs. The first set of equations models the origination *global* NCEs. *Global* NCEs are those products that are marketed in at least seven major pharmaceutical markets including France, Germany, Japan, Italy, Switzerland, the United Kingdom, and the United States. The *global* NCEs originating in a country (GLOBALNCE) are represented by the ratio of *global* NCEs from a particular country to the total number of *global* NCEs for a given year.[9] The level of research commitment in a country should have an impact on the number of *global* NCEs originating from that country. The measure for research commitment is the level of real pharmaceutical R&D expenditures (R&DEXP) in a country both by the firms in that country and government research efforts. This research is expected to have a positive effect on the number of *global* NCEs.

As an economic factor, the analysis also includes the level of real GDP growth (GROWTH) for a country to control for general economic activity. A robust economy represented by real GDP growth should facilitate a growing pharmaceutical industry spurring firms to engage in more R&D, and thus, lead to more NCEs.

To account for differences in public policies across countries, the same non-U.S. dummy (NONUS) is included as before. Dummy variables for Western Europe (EUROPE) and Japan (JAPAN) are also included to test for diffe-

[8] Some of the variables in this specification may be collinear, e.g., LIFE and DOCTORS. The results of statistical tests performed on these variables indicated that the degree of multicollinearity between these variables is not severe enough to seriously effect the estimations.

[9] The year the NCE is first marketed is the reference year although it may have taken 3 to 5 years for an NCE to qualify as a global NCE.

rences across regions. The origination of *global* NCE equations are specified as:

$$\text{GLOBALNCE} = \beta_0 + \beta_1 \text{R\&DEXP} + \beta_2 \text{GROWTH} + \beta_3 \text{NONUS} + \beta_4 \text{D88} + \beta_5 \text{D87} + \beta_6 \text{D86} + \beta_7 \text{D85} + \beta_8 \text{D84} + \varepsilon_0$$

$$\text{GLOBALNCE} = \beta_0 + \beta_1 \text{R\&DEXP} + \beta_2 \text{GROWTH} + \beta_3 \text{EUROPE} + \beta_4 \text{JAPAN} + \beta_5 \text{D88} + \beta_6 \text{D87} + \beta_7 \text{D86} + \beta_8 \text{D85} + \beta_9 \text{D84} + \varepsilon_0$$

The results of these estimations are presented in table E-4 below.

This set of equations examines the location where all NCEs (including *global*) are first marketed. The measure used in this analysis is the ratio of the number of NCEs first marketed in a country to the total number of NCEs first marketed in a particular year (NCE). This estimation includes two economic factors that may affect the marketing strategy of an NCE. First is the level of real drug prices in a country (PRICE) and second is the overall state of the economy, represented by the real growth rate of GDP (GROWTH). Countries with higher prices and growing economies should attract more NCEs for introduction because firms will recognize the strong demand and profit potential in those countries.

As a demographic measure, countries with consumers who spend a higher proportion of their income on medical expenses should attract more NCEs. This measure (MEDICAL) is represented by the percent households spend on medical care in a country. Finally, NONUS and the regional dummies (EUROPE and JAPAN) are included to capture potential government influence in the market and regional differences. The first marketing NCE equations are specified as:

$$\text{NCE} = \beta_0 + \beta_1 \text{PRICE} + \beta_2 \text{GROWTH} + \beta_3 \text{MEDICAL} + \beta_4 \text{NONUS} + \beta_5 \text{D88} + \beta_6 \text{D87} + \beta_7 \text{D86} + \beta_8 \text{D85} + \beta_9 \text{D84} + \varepsilon_0$$

$$\text{NCE} = \beta_0 + \beta_1 \text{PRICE} + \beta_2 \text{GROWTH} + \beta_3 \text{MEDICAL} + \beta_4 \text{EUROPE} + \beta_5 \text{JAPAN} + \beta_6 \text{D88} + \beta_7 \text{D87} + \beta_8 \text{D86} + \beta_9 \text{D85} + \beta_{10} \text{D84} + \varepsilon_0$$

The results of these estimations are presented in table E-5 below.

Table E-1 provides the relative magnitudes of the variables used in the above country specifications. The statistics reported include the minimum, maximum, and mean values.

Firm Models

The firm level estimations examine the determinants of global market share and R&D productivity for ethical pharmaceuticals across a sample of 29 firms. See the text of chapter 5 for the discussion of the reasons and expected impact of the various explanatory variables used in the global market share and R&D productivity estimations.

Table E-1
Summary statistics for the country estimations

Variable	*Minimum*	*Maximum*	*Mean*
Dependent variables:			
QUANTITY	523.76	4,212.02	1,715.38
GLOBALNCE	0.00	4.00	0.55
NCE	0.00	23.00	5.33
Explanatory variables:			
PRICE (1985 dollars)	1.27	26.73	5.80
INCOME (thousands of 1985 dollars)	4.26	22.87	11.58
DOCTORS (population per physician)	230.00	780.00	514.76
LIFE (years)	74.00	78.00	76.10
R&DEXP (millions of 1985 dollars)	64.00	5,948.13	1,447.28
GROWTH (percent)	0.80	4.30	2.67
MEDICAL (percent)	7.00	14.00	10.71

Source: See below.

The first set of equations model global market share (MKTSHARE) as a function of R&D expenditures (R&DEXP), R&D employees (R&DEMP), sales force employees (SALESEMP), total employees (TOTALEMP), the number of compounds in R&D (R&DDRUGS) or alternatively, the number of the firm's own R&D compounds (OWNDRUGS) and the number of compounds that the firm has licensed from other firms (LICDRUGS), the non-U.S. dummy variable, and the time dummy variables. The market share equations are specified as:

$$\begin{aligned}\text{MKTSHARE} = {} & \beta_0 + \beta_1 \text{R\&DEXP} + \\ & \beta_2 \text{R\&DEMP} + \beta_3 \text{SALE} \\ & \text{SEMP} + \beta_4 \text{TOTALEMP} + \\ & \beta_5 \text{R\&DDRUGS} + \beta_6 \text{NONUS} \\ & + \beta_7 \text{D89} + \beta_8 \text{D88} + \varepsilon_0\end{aligned}$$

$$\begin{aligned}\text{MKTSHARE} = {} & \beta_0 + \beta_1 \text{R\&DEXP} + \\ & \beta_2 \text{R\&DEMP} + \beta_3 \text{SALES-} \\ & \text{EMP} + \beta_4 \text{TOTALEMP} + \\ & \beta_5 \text{OWNDRUGS} + \beta_6 \text{LIC-} \\ & \text{DRUGS} + \beta_7 \text{NONUS} + \\ & \beta_8 \text{D89} + \beta_9 \text{D88} + \varepsilon_0\end{aligned}$$

The results of these estimations are presented in table E-6 below.

The second set of estimations examines the determinants of a pharmaceutical firm's R&D productivity. R&D productivity is measured in two ways. In the first estimation it is measured as the R&D output per R&D employee (OUTPUTEMP), and in the second estimation it is measured as the R&D output of the firm (OUTPUT). R&D productivity is modeled in the first estimation as a function of R&D expenditures per R&D employee (R&DEXPEMP), R&DEXPEMP^2 (to test for diminishing returns), the total number of employees in the firm (TOTALEMP), an interaction term between R&DEXPEMP and TOTALEMP,[10] the level of pharmaceutical R&D performed in the firm's country (COUNTRYR&D), and the time dummy variables. R&D productivity is modeled in the second estimation as a function of R&D employees (R&DEMP), R&DEMP^2 (to test for diminishing returns), R&D expenditures (R&DEXP), the total number of employees in the firm (TOTALEMP), an interaction term between R&DEMP and TOTALEMP, the level of pharmaceutical R&D performed in the firm's country (COUNTRYR&D), and the time dummy variables. The productivity equations are specified as:

$$\begin{aligned}\text{OUTPUTEMP} = {} & \beta_0 + \beta_1 \text{R\&DEXPEMP} + \\ & \beta_2 \text{R\&DEXPEMP}^2 + \beta_3 \text{EMP} \\ & \text{TOTAL1} + \\ & \beta_4 \text{TOTALEMP} + \beta_5 \text{COUN-} \\ & \text{TRYR\&D} + \beta_6 \text{D89} + \\ & \beta_7 \text{D88} + \varepsilon_0\end{aligned}$$

$$\begin{aligned}\text{OUTPUT} = {} & \beta_0 + \beta_1 \text{R\&DEMP} + \\ & \beta_2 \text{R\&DEMP}^2 + \beta_3 \text{R\&DEXP} \\ & + \beta_4 \text{EMPTOTAL2} + \\ & \beta_5 \text{TOTALEMP} + \beta_6 \text{COUN-} \\ & \text{TRYR\&D} + \beta_7 \text{D89} + \\ & \beta_8 \text{D88} + \varepsilon_0\end{aligned}$$

The results of these estimations are presented in table E-7 below.

Table E-2 provides the relative magnitudes of the variables used in the above firm specifications. The statistics reported include the minimum, maximum, and mean values.

Variable Definitions and Sources

Country Data

This section provides the definitions and sources for the variables used in the country estimations.

Dependent Variables

QUANTITY: This measure is computed by dividing the ethical pharmaceutical sales data reported for each country by the average nominal pharmaceutical price calculated for each country (discussed below). The sales data were found in Glaxo's annual reports (various years) and were reported in millions of British pounds. These data were converted to U.S. dollars using the exchange rates reported in the 1990 *Economic Report of the President.*

GLOBALNCE: This measure is the number of NCEs that are marketed in at least seven major pharmaceutical markets including France, Germany, Japan, Italy, Switzerland, the United Kingdom, and the United States divided by the total number of *global* NCEs originated in that year. These data are from P.E. Barral, *Fifteen Years of Pharmaceutical Research Results Throughout the World (1975-1988).*

[10] An interaction variable is created by multiplying explanatory variables in an estimating equation. Interaction terms are often included when one does not believe that the explanatory variables have the same effect on the dependent variable given the values of the other explanatory variables.

Table E-2
Summary statistics for the firm estimations

Variable	*Minimum*	*Maximum*	*Mean*
Dependent variables:			
MKTSHARE (percent)	0.61	4.78	1.94
OUTPUTEMP	0.00	0.06	0.03
OUTPUT	14.00	87.00	44.78
Explanatory variables:			
R&DEXP (millions of 1982-84 dollars)	80.08	745.49	314.53
R&DEMP	300.00	5,100.00	2,323.32
R&DEXPEMP (thousands of 1982-84 dollars)	50.96	431.70	170.19
SALESEMP	800.00	8,000.00	3,556.02
TOTALEMP	3,164.00	167,781.00	39,178.49
R&DDRUGS	21.00	110.00	61.22
OWNDRUGS	14.00	87.00	44.78
LICDRUGS	4.00	36.00	16.44
COUNTRYR&D (millions of 1982-84 dollars)	914.79	6,259.68	3,508.89

Source: See below.

NCE: This measure is the number of NCEs that were first marketed in a given country in a given year divided by the total number of NCEs first introduced in that year. These data were taken from the *Scrip Yearbook* (various years) for the years 1985 to 1988; the 1984 data were taken from Scrip No. 959, December 19, 1984; and the 1983 were taken from Scrip No.'s 857 & 858, December 21 & 26, 1983. The important difference between GLOBALNCE and NCE is that the former are reported by country of origination while the latter are reported by country where the NCE was first marketed.

Explanatory variables

PRICE: This measure is constructed in the following manner. First, Scrip No. 1329, July 27 1988 reports an average pharmaceutical price for each country for 1986. These data were expressed in U.S. dollars, which were then converted into each country's currency using the exchange rates discussed above. Second, an index of pharmaceutical prices or health-care costs for a country was used to obtain estimates for the other years included in the sample. For the United States, the Medical Care Commodities CPI (1990 *Economic Report of the President*) was used; for Japan, the CPI-All Items (*OECD, Main Economic Indicators Historical Statistics*) was used; for Germany, the German Pharmaceutical Price Index (1989 *Scrip Yearbook*) was used; for France, an average of the French Pharmaceutical Price Index for reimbursed ethical and over-the-counter (OTC) products (1990 *Scrip Yearbook*) was used; for Italy, the CPI-All Items (*OECD, Main Economic Indicators Historical Statistics*) was used; for the United Kingdom, the Manufacturers' Price Index for Pharmaceutical Preps (1990 *Scrip Yearbook*) was used; and for Spain, the CPI-All Items (*OECD, Main Economic Indicators Historical Statistics*) was used. Third, these price data were then converted back into U.S. dollars using the aforementioned exchange rates to yield an average pharmaceutical price series for each country. And fourth, these price data were converted into real terms using various indices reported in the *OECD, Main Economic Indicators Historical Statistics*. For the United States, Japan, France, Italy, and Spain, the respective CPI-All Items was used; and for Germany and the United Kingdom, the respective CPI-All Items (excluding seasonal items) was used.

INCOME: This measure is GDP (expressed in millions of U.S. dollars) for each country divided by the country's CPI discussed above. The real values were then expressed in per capita terms using the total population (expressed in millions) for each country. The GDP data and population data were taken from the *World Development Report* (various issues) published by the United Nations; and the CPI data were the same as discussed for PRICE.

DOCTORS: This measure is the population per physician in a country. These data are taken from the *World Development Report* (various issues). Since these data are not reported for

each year, 1984 data were used for 1988 and 1987; 1981 data were used for 1986, 1985, and 1984; and 1980 data were used for 1983. This potentially understates the actual number doctors in a country for any given year. However, the variation among the countries across time appears reasonable.

LIFE: This variable is the life expectancy for the population expressed in years. These were found in the *World Development Report* (various issues).

R&DEXP: This variable is the value of R&D expenditures by the pharmaceutical industry for each country, expressed in each country's currency. These data were converted into U.S. dollars using the exchange rates discussed for PRICE. These data were then deflated using the CPI data for each country that were also discussed for PRICE. These data for R&D were found in the 1989 and 1990 *Japan Data Book* published by the Japanese Pharmaceutical manufacturers Association.

GROWTH: This measure is simply the percentage change in Gross Domestic Product for a given year relative to 1980 for the years 1985 to 1988, and relative to 1973 for the years 1983 and 1984. These data were taken from the *World Development Report* (various issues).

MEDICAL: This is the percentage of total household consumption spent on medical care. Since these data were reported for only one year, the same data were used in all years of the sample. This, however, may be reasonable since the percentage for a given country is not likely to significantly change over this short time period. These data were taken from the 1990 *World Development Report.*

NONUS: This variable is a binary measure that has the value of 1 for the non-U.S. countries in the sample, and a value of 0 for the United States.

EUROPE and JAPAN: These variables are binary measures that have the value of 1 for Western European countries or Japan , and 0 otherwise.

Di, i=1984 to 1988: These variables are binary measures that have the value of 1 for year i, and 0 otherwise.

PRODUCTIVITY: This measure is used as a cost shifter in the first stage estimation of the demand function. The rationale is that the two-stage estimation procedure requires a parameter that is likely to shift the supply function, but not the demand function, and this is a plausible measure. This measure is an output-per-man-hour index for manufacturing reported by the U.S. Bureau of Labor Statistics for all countries except Spain. The index for Spain was constructed in the following manner. Since the aforementioned index is based in 1982, a value of 100 was assumed for Spain in 1982. The next step was to use the data for the percentage change in labor productivity in manufacturing (*OECD Economic Surveys, Spain*) to construct the value of the index in latter years.

Firm Data

This section provides the definitions and sources for the variables used in the firm estimations.

Dependent Variables

MKTSHARE: This variable is the global market share for the firm in ethical pharmaceuticals. For 1989, the global sales of ethical drugs are from *Pharma Profiles*, published by Shearson-Lehman. The data on ethical sales for 1987 and 1988 were derived in the following manner using these figures. The ratio of ethical sales to ethical and OTC sales for 1989 was multiplied by the amount of ethical and OTC sales (from the 1990 *Japan Data Book*) for 1987 and 1988 to calculate an approximation for ethical sales of the sample firms. The ethical sales data for each of the years is then divided by the amount of global ethical drug sales in each of the three years. The global ethical sales data are from Glaxo's annual reports.

OUTPUTEMP: This variable is the number of R&D compounds per R&D employee in a firm. These data are from *Scrip Yearbook* (various years).

OUTPUT: This variable is the number of R&D compounds developed by the firm. It does not include compounds that the firm has licensed from other firms. These data are from *Scrip Yearbook* (various years).

Explanatory Variables

R&DEXP: This variable measures the level of pharmaceutical R&D expenditures by the firm in constant 1985 dollars. The nominal R&D data for 1989 are from *Pharma Profiles* and the nominal data for 1987 and 1988 are

from the 1990 *Japan Data Book*. To calculate the real level of R&D expenditures, these data were divided by the CPI for the country in which the firm is headquartered.

R&DEMP: This variable represents the number of R&D employees for each firm. The 1989 data are from *Pharma Profiles*. The 1987 data are from the 1990 *Scrip Yearbook*. Since data from 1988 were unavailable, 1989 data are used as a proxy for 1988 assuming that there is little year-to-year change in the number of R&D employees.

R&DEXPEMP: This variable measures the amount of R&D expenditures per R&D employee and is calculated as a ratio of the above two variables.

SALESEMP: This variable measures the size of the salesforce for each firm. The 1989 data are from *Pharma Profiles*. The 1989 data are used as a proxy for the 1987 and 1988 sales force levels based on the assumption that there is unlikely to be a significant change in the size of a firm's sales force in such a short period of time.

TOTALEMP: This variable is the total number of employees for the firms in this sample. The 1987 and 1988 data are from the *Japan Data Book* (various years). The level of employment for 1989 is calculated by scaling the 1988 figures by the growth rate of a firm's employment between 1987 and 1988.

R&DDRUGS, OWNDRUGS and LICDRUGS: these variables represent the number of R&D drugs that a firm has in its pipeline in a given year. R&DDRUGS is the total number of drugs in research. OWNDRUGS are those compounds developed by the firm and LICDRUGS are those compounds that are licensed from other firms. These data are from *Scrip Yearbook* (various years).

COUNTRYR&D: This variable represents the total amount of pharmaceutical R&D carried out in a country in a given year by both firms in that country and national research efforts. The 1987 and 1988 data are from the *Japan Data Book* (various years). The level of country pharmaceutical R&D for 1989 is calculated by scaling the 1988 figures by the growth rate of a country's R&D expenditures between 1987 and 1988.

NONUS: This variable is a binary measure that has the value of 1 for those firms that are headquartered outside the United States, and a value of 0 for U.S.-headquartered firms.

Di, i=1988 to 1989: These variables are binary measures that have the value of 1 for year i, and 0 otherwise.

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APPENDIX G
GLOSSARY

Glossary of Terms and Acronyms

AI—Active ingredient. The specific chemical in a formulated drug that exhibits the desired medical result.

ABC—Association of Biotechnology Companies. A U.S. trade association representing the biotechnology industry.

ANDA—Abbreviated New Drug Application. A simplified submission permitted for a duplicate of an already approved drug.

Biologics—Defined in 21 CFR 600.3, as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man.

Biopharmaceuticals—Pharmaceutical products produced by the application of biotechnology.

"Blockbuster drugs"—A term for drugs that have attained worldwide acceptance and initial world wide sales in the tens of millions of dollars.

Brandname—The name given to a drug by an individual company used to associate the drug with the company.

CPMP—Committee on Proprietary Medicinal Products. A committee established during 1975-87 by the European Commission to examine matters relating to the extent, suspension, or revocation of marketing authorities.

Chuikyo—Central Social Insurance Medical Council (Japan).

DEAA—See below, U.S. Drug Exports Amendments Act of 1986.

Detailing—Calls made by a company's sales force on physicians to describe a product's efficacy and the benefits to the patient that would accrue through use of the product.

Drug Pipeline—The progress of new drugs through the discovery, development, and marketing phases. A drug may fail at any stage in the pipeline and be eliminated from the firm's portfolio of potential new products. Several drugs can be in the pipeline simultaneously.

Drug Price Competition and Patent Reform Term Restoration Act (Waxman Hatch Act)—Legislation enacted in 1984 that contained provisions to allow partial restoration of an innovative drug's patent term up to five years, depending on the amount of time lost during regulatory review. It also amended the FDCA to provide for ANDAs for generic versions of previously approved drugs.

EFPIA—European Federation of Pharmaceutical Industry Associations. The federation of the national pharmaceutical industry associations in 16 European countries.

EUREKA—European Research Cooperation Agency. A 19-member organization including the countries of the EC, EFTA, and Turkey formed in 1985 to stimulate cross-border cooperation in industrial research in order to heighten Europe's productivity and competitiveness in the world market.

Ethical drug— A drug available only through a prescription issued by a physician.

FDCA—Federal Food, Drug and Cosmetic Act (21 USC 301 et seq.).

Formulary—A book containing a list of medicinal substances and formulas.

Generic products—Generic products are non-patented products.

Generic name—The common name for a specific drug irrespective of the producer.

HMO—Health Maintenance Organization. The generic name for a U.S. private health plan.

HRA—Health Reform Act. Legislation enacted in 1989 in Germany that fixes reimbursement levels for products that are off patent and that have a relatively high volume of sales.

IBA—Industrial Biotechnology Association. A trade association for the U.S. biotechnology industry.

IND—Investigational New Drug Application. An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans.

IPR—Intellectual Property Rights. The term for issues dealing with patent rights.

Innovative firm—A drug manufacturer which invents, develops, and, in most cases, markets a new product. Such firms dedicate a significant share of sales to primary research and development activities.

JETRO—Japanese Economic and Trade Research Organization. A Japanese Governmental agency dealing with Japanese international trade issues.

JPWA—Japan Pharmaceutical Wholesalers Association. A Japanese trade organization for the Japanese pharmaceutical industry.

Koseisho—Ministry of Health and Welfare. A Japanese Government agency.

MOSS—Market Oriented Sector Specific. Intergovernmental talks between the United States and Japan concerning a variety of trade issues that transpired during the 1980s.

MHW—Ministry of Health and Welfare (Koseisho). A Japanese Government agency.

Medicament—Any medical substance used in therapy.

Me-too Products—Defined broadly as a product that is therapeutically similar to an existing pharmaceutical product. Some "me-too's" are also chemically similar to the existing product.

MITI—Ministry of International Trade and Industry. A Japanese Government agency.

NCBC—North Carolina Biotechnology Center.

NSF—National Science Foundation. A U.S. governmental agency concerned with domestic and international science issues.

NCE—New Chemical Entity. The generic name for a chemical that is being tested or marketed as a potential drug. The compound can be at any stage in the development process from discovery to initial marketing.

NDA—New Drug Application. An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from clinical studies needed for FDA review.

NHS—National Health Service. The name of the United Kingdom's national health program.

NIH—National Institutes of Health. The U.S. agency responsible for coordinating federal research activities.

ODA—See below, Orphan Drug Act of 1983.

OTC—Over-the-counter. See "proprietary products" below.

Orphan Drug Act of 1983—Legislation that provides technical and economic assistance and economic incentives to pharmaceutical companies to develop and market products for the treatment of rare diseases.

PMA—Pharmaceutical Manufacturers Association. A U.S. trade organization for the U.S. pharmaceutical industry.

Parallel imports—A European phenomenon referring to the importing of products from countries with low costs

Pharmacokinetics—The chemical kinetics (e.g. chemical reaction mechanisms) of pharmaceuticals.

Pharmacopeia—A publication issued by an officially recognized authority describing drugs, chemicals, and medicinal preparations (e.g., the United States Pharmacopeia (U.S.P.).

Pharmacovigilance—Term used by the Commission of the European Communities, which includes all information on adverse drug reactions, the scientific evaluation of these adverse drug reactions, and the regulatory decisions resulting from such evaluations.

Physicochemical—process pertaining to both physics and chemistry.

Proprietary products—Proprietary products are non-prescription, over-the-counter drugs.

PPRS—Pharmaceutical Price Regulation Scheme. The name, since 1978, of the United KIngdom's national system to maintain price levels that allow for a "a reasonable return on capital". See VPRS below.

Recombinant DNA technology—The techniques used to insert portions of deoxyribonucleic acid (DNA) from the same or dissimilar species into a selected strand of DNA.

Review clock—Time frame of 180 days allowed FDA to review NDAs.

SII—Structural Impediments Initiatives. The acronym given to the United States-Japan trade negotiations relating to non-tariff barriers to U.S. trade with Japan.

Strategic alliances—Specific arrangements between two companies to develop a product allowing both sides to benefit, but does not involve a merger.

Teratogen—An agent or influence that causes physical defects in the developing embryo.

Therapeutic clustering—A term applied to the administrative practice of the German Govemment of grouping together drug products for similar indications at similar price levels for reimbursement by either health insurance organizations or the national health system.

U.S. Drug Exports Amendments Act of 1986—Legislation that allows U.S. pharmaceutical producers to export products, under certain conditions, to any of 21 countries enumerated in the legislation.

VPRS—Voluntary Price Regulation Scheme—The name from 1957 to 1978 for the United Kingdom's national system to maintain price levels that allow for a "reasonable return on capital." See PPRS above.

APPENDIX H
INDIVIDUALS, COMPANIES, AND ORGANIZATIONS VISITED AND/OR CONTACTED IN THE COURSE OF THIS STUDY

Organizations and Individuals Interviewed or Contacted

In Japan

Bristol-Myers Squibb K.K.
Eisai Co., LTD.
Embassy of the United States
Goldman Sachs (Japan) Corp.
Japan Pharmaceutical Manufacturers Association
Japan Upjohn Limited
KMB Japan
Lederle (Japan), LTD.
Ministry of Health and Welfare
Ministry of International Trade and Industry
Pfizer Pharmaceuticals Inc.
Pharmaceutical Manufacturers Association (Japan)
Sankyo Company LTD.
SmithKline Beecham Seiyaku
Takeda Chemical Industries, LTD.
Yamanouchi Pharmaceutical Co., LTD.

In the United States

Amgen
Booz-Allen & Hamilton
Bristol-Myers Squibb
Burroughs Wellcome
Center For The Study Of Drug Development, Tufts University
Cetus
Chiron
Ciba Geigy
Cyanamid International, Lederle Division
Duke Universitiy, Department of Economics
Embassy of Japan
Ernst & Young, High Technology Industry Services
Financial World
Genentech
Generic Pharmaceutical Industry Association
Glaxo
Johnson and Johnson
Hoechst-Roussel
Industrial Biotechnology Association
Marion Merrell Dow
Merck
North Carolina Biotechnology Center
Oxford Pharmaceutical Services, Inc.
Pfizer
Pharmaceutical Manufacturers Association
Sandoz
Schering Plough
Shearson Lehman Hutton
SmithKline Beecham
Syntex
Upjohn
U.S. Food and Drug Administration

In Western Europe

The Association of the British Pharmaceutical Industry
European Federation of Pharmaceutical Industries' Associations (EFPIA)
Glaxo Holdings p.l.c.
Guerbet, S.A.
Dr. Heinz Redwood
The Institute of Economic Affairs
Lehman Brothers International
Lilly Research Centre
A. Menarini Chemical and Pharmaceutical Laboratories
Merrell Dow France
Merck Sharp & Dohme (Europe)
Pfizer International
Pharmaceutical Manufacturers Association
Rhone-Poulenc
Schering-Plough Ltd.
Sigma Tau
SmithKline Beecham
Syndicat National de l'Industrie Pharmaceutique
University of London
Dr. Stuart Walker