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Review of Global Competitiveness in the Pharmaceutical Industry

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EXECUTIVE SUMMARY

In 1991, the U.S. International Trade Commission (the Commission) conducted a study on the pharmaceutical industry, *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals*,¹ as part of a series on global competitiveness of U.S. advanced-technology manufacturing industries requested by the Senate Committee on Finance. Many of the findings of that study are still valid today, although significant changes have occurred in the industry. The purpose of this report is to describe the principal factors currently affecting the competitiveness of the U.S. pharmaceutical industry, particularly in relation to the industries of Western Europe and Japan.

The pharmaceutical industry is complex, dynamic, and highly globalized; moreover, the industry is characterized by high research and development (R&D) expenditures and extensive regulation of its products compared with other manufacturing sectors. The industry has also been affected by a high number of mergers and acquisitions (M&As), which have increased globalization and, arguably, heightened efficiency. In the Commission's 1991 study, the major factors of competitiveness were found to be those that affect a company's ability to develop and deliver new pharmaceutical products or new chemical entities (NCEs), particularly those NCEs successful on a global basis.² In the United States, changes in U.S. Food and Drug Administration (FDA) policies have led to faster approval times for NCEs, which result in extended periods during which companies can exclusively market their pharmaceutical products. As noted in the Commission's 1991 competitiveness study, longer periods of market exclusivity for pharmaceuticals increase sales revenues, and increased sales revenues in turn lead to greater profits and potentially more funding for R&D.

The Commission's 1991 competitiveness study also indicated that changes in Government policies affect the competitiveness of pharmaceutical firms. Sweeping changes in barriers to trade worldwide, from tariffs to intellectual property rights and patent issues, have occurred since 1991. An initiative on pharmaceuticals, established during the Uruguay Round, was implemented on January 1, 1995, providing duty-free treatment for about 7,000 pharmaceutical products and pharmaceutical intermediates; another 496 products and intermediates became duty-free on April 1, 1997, and negotiations are currently underway to make further additions. There is greater participation of member countries of the World Trade Organization (WTO), formed in 1995, including those of the European Union (EU),³ in agreements relating to intellectual property and patents. In the Western hemisphere, the North American Free Trade Agreement (NAFTA) has resulted in low or no tariff barriers and greater protection of patents and intellectual property rights among Canada, Mexico, and the United States.

¹ *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals* (USITC Publication 2437, September 1991). A copy of this publication can be obtained by contacting the U.S. International Trade Commission, Office of the Secretary (202/205-1809).

² A new chemical entity, also called a new molecular entity (NME), is defined by the U.S. Food and Drug Administration as a drug for which the active ingredient has not been previously marketed (or approved) for use as a drug product in the United States. A global NCE is generally defined as a product that is eventually marketed in at least seven industrialized countries.

³ The EU comprises Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

Overall, the U.S. pharmaceutical industry seems to enjoy a domestic environment conducive to researching and developing drugs, protecting its intellectual property, and obtaining regulatory approval to market its products. There is also a strong trend in the United States to invest those profits in new R&D. Recent improvements to the patent systems and Government regulatory policies in Western Europe and Japan are likely to benefit the U.S. industry as well. Because of the strong international component to this industry, that which benefits the industry in any one of these three areas will likely work to the benefit of the others. Since aging populations will only bring a rise in the demand for drug products, the U.S. pharmaceutical industry, along with the industries of Western Europe and Japan, can expect growing markets for their products.

CHAPTER 1

Introduction

Purpose and Scope

In 1991, the U.S. International Trade Commission (the Commission) conducted a study on the pharmaceutical industry, *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals*,¹ as part of a series on global competitiveness of U.S. advanced-technology manufacturing industries requested by the Senate Committee on Finance. In the Commission's 1991 study, the major factors of competitiveness were found to be those that affect a company's ability to develop and deliver new pharmaceutical products or new chemical entities (NCEs), particularly those NCEs successful on a global basis.² While the ability to put innovative products on the market is still considered the key to success in the pharmaceutical industry, pharmaceutical companies are currently affected by several changes, such as lower tariff and nontariff barriers, improved protection of intellectual property rights, and global consolidation. The purpose of this report is to describe the principal factors currently affecting the competitiveness of the U.S. pharmaceutical industry, particularly in relation to the industries of Western Europe and Japan.

The original study found that a pharmaceutical company's research and development (R&D) infrastructure is a major contributing factor to its competitiveness. R&D, which by its nature is capital intensive, is necessary to create new, innovative treatments for the market. Sales revenues generate company profits, allowing for more research, which in turn might lead to another successful novel product. A cycle is initiated whereby profits from existing drug sales fund the development and marketing of future drugs. The cycle may potentially be repeated for each new drug developed and marketed.

The Commission's 1991 competitiveness study also indicated that Government policies affect the competitiveness of pharmaceutical firms. Sweeping changes in barriers to trade worldwide, from tariffs to intellectual property rights and patent issues, have occurred since 1991. There is greater participation of member countries of the World Trade Organization (WTO), formed in 1995, including those of the European Union (EU),³ in agreements relating to intellectual property and patents. In the Western hemisphere, the North American Free Trade Agreement (NAFTA) has resulted in low or no tariff barriers and greater protection of patents and intellectual property rights among Canada, Mexico, and the United States. In the

¹ *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals* (USITC Publication 2437, September 1991). A copy of this publication can be obtained by contacting the U.S. International Trade Commission, Office of the Secretary (202/205-1809).

² A new chemical entity, also called a new molecular entity (NME), is defined by the U.S. Food and Drug Administration as a drug for which the active ingredient has not been previously marketed (or approved) for use as a drug product in the United States. A global NCE is generally defined as a product that is eventually marketed in at least seven industrialized countries.

³ The EU comprises Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

United States, changes in Government policies have also led to faster approval times for NCEs by the U.S. Food and Drug Administration (FDA). As noted in the Commission's 1991 competitiveness study, Government policies that lead to longer periods of market exclusivity increase the amount of sales revenues; increased sales revenues lead to greater profits and potentially more funding for R&D.

Another Government policy examined in this report is the initiative on pharmaceuticals established during the Uruguay Round (see chapter 4). The agreement was implemented on January 1, 1995, providing duty-free treatment for about 7,000 pharmaceutical products and pharmaceutical intermediates; another 496 products and intermediates became duty-free on April 1, 1997, and negotiations are currently underway to make further additions. The cumulative effect of this initiative has not yet been ascertained.⁴

The Commission's 1991 competitiveness study examined conditions of competitiveness in world markets. Now, as then, the pharmaceutical industry continues to be global in scope and any distinct delineation between a domestic and foreign firm is further blurred by continued consolidation. In the Commission's 1991 competitiveness study, country and regional data were aggregated based on geographical location of facilities rather than the location of corporate headquarters.⁵ The same practice will be used in this report, unless otherwise specified. Overviews of the U.S., Western European,⁶ and Japanese industries, similar though less extensive than in the Commission's 1991 report, are provided for assessment of relative competitiveness.

Importance of Pharmaceuticals

Pharmaceuticals are important in all aspects of health care and have been shown to be the most cost-effective means of treating some diseases when compared with surgical procedures.⁷ In the United States, emergence of health maintenance organizations (HMOs), coupled with rising private medical care costs and Government management of Medicare and Medicaid health programs, has contributed to a trend toward finding the most cost-effective way of treating illnesses. As a result of these trends, consumption of both ethical⁸ and over-the-counter (OTC) pharmaceuticals increased during 1993-97. Increases in Western European and Japanese consumption of pharmaceuticals also occurred during the period covered.

⁴ "The Uruguay Round Agreement on Pharmaceuticals: Developments in the Two Years After Implementation," *International Trade and Technology Review*, USITC Pub. 3071, October 1997, available at <http://www.usitc.gov/ittr.htm>. See also the USITC annual report *Shifts in Merchandise Trade*, available at <http://www.usitc.gov/332s/332index.htm>. Deficits also occurred in 1996, 1997, and 1998.

⁵ *Global Competitiveness*, pp. 1-2, 1-3. In this way, data for a Japanese firm operating in the United States would be counted in the U.S. industry data, although the firm would still be identified as Japanese.

⁶ For the purpose of this study, Western Europe includes the EU-15 plus Switzerland and Norway.

⁷ *Opportunities and Challenges for Pharmaceutical Innovation: Industry Profile 1996*, Pharmaceutical Research and Manufacturers of America (PhRMA), p. 1; also see *The New England Journal of Medicine*, 325(5):293-302 (1991); and Showstack, J., et al., *The New England Journal of Medicine*, 321(16), 1989.

⁸ In this paper, "ethical" pharmaceuticals refer to those available only by prescription.

Data Sources and Methodology

In the discussion of the U.S. industry, data on employment, R&D expenditures, imports, exports, and domestic production are presented. Employment data used were compiled by the Bureau of Labor Statistics, while most data related to R&D were collected by the Pharmaceutical Research and Manufacturers of America (PhRMA), a U.S. pharmaceutical trade association. The U.S. Department of Commerce published the trade and production data referenced in this report. The European Commission was the primary source of EU data used, including exchange rate data for the euro. Data presented for the Western European industry were published by the European Federation of Pharmaceutical Industries' Associations (EFPIA), while European price index data were compiled by the Organization for Economic Cooperation and Development (OECD). The Japanese Pharmaceutical Manufacturers Association (JPMA) published the data on the Japan pharmaceutical industry that are included in this report, and the exchange rates were based on data provided by the U.S. Department of Commerce.⁹

The methodology used in this paper consists of an analysis of new information that supplements the information in the Commission's 1991 competitiveness study, as well as an analysis of historical trends in trade, Government policies, and international developments from 1991 to the present. The combined effects of these trends on the current and future competitiveness of the pharmaceutical industry are presented.

Organization

Chapter 2 provides a brief overview of the pharmaceutical products covered by this study, with a special focus on new drug approvals. Chapter 3 discusses the U.S., Western European, and Japanese pharmaceutical industries, including (where available) employment, R&D expenditures, the state of the biotechnology sector, and Government policies that affect each industry. These data are helpful in updating the information presented in the Commission's 1991 competitiveness study and in providing an understanding of the factors underlying the trends in trade, pricing, and innovation. Where data are not available, a qualitative and comparative analysis may be provided.

Chapter 4 includes descriptions and analysis of recent developments in international agreements, such as the Uruguay Round Agreements¹⁰ (URA) and NAFTA, and their impacts on the ability of U.S.-based firms to compete in the domestic and world markets. These agreements have had a significant effect on the U.S. pharmaceutical industry, mainly by removing tariff barriers. In the case of the URA, it also provided the global framework for

⁹ Dollar-yen exchange rate data are located online at <http://www.ita.doc.gov/region/japan/exchange.html>.

¹⁰ The legislation that implemented the URA in the United States is known as the Uruguay Round Agreements Act (URAA).

increased patent protection and intellectual property rights, which has encouraged U.S. companies to market their products in countries that did not previously offer these securities. Lastly, Chapter 5 presents conclusions drawn from the data and other information presented elsewhere in the report.

CHAPTER 2

Definition of Pharmaceutical Products

Product Classes

For the purposes of this study, the pharmaceutical industry includes those companies that produce therapeutic products, including antibiotics, hormones, botanical products, in vitro and in vivo diagnostic substances, and other similar substances, used in the treatment of human and veterinary diseases. Pharmaceutical products include those items classified within the Standard Industrial Classification (SIC)¹ code 283 (NAICS 32541) “Drugs.” The two major categories of industry within 283 are industry 2833 (NAICS 325411), “Medicinal chemicals and botanical products,” and 2834 (NAICS 325412, partial), “Pharmaceutical preparations.” Other industry groupings include SIC 2835 (NAICS 325412, partial, and 325413), “In vitro and in vivo diagnostics,” and 2836 (NAICS 325414), “Biological products except diagnostics.”

SIC 2833 covers most active bulk ingredients, whereas the products classified in SIC 2834 consist of pharmaceutical preparations, including OTC products and ethical preparations. OTC preparations include many familiar items such as antihistamine preparations and cold, cough, and fever remedies. Ethical preparations, medications prescribed or administered by a physician, include the products mentioned above as well as intravenous solutions, antibiotics, and general anesthetics. In both the OTC and ethical categories, products can be either brandname or generic.

International Nonproprietary Names

In addition to chemical nomenclature and naming conventions commonly used in the pharmaceutical and chemical industries, the World Health Organization (WHO) established the International Nonproprietary Names (INN) system for pharmaceuticals. The system for designating INNs creates similar names in English, French, Spanish, and Russian, as well as a “universal” INN in Latin. For example, *Abamectin* is an English INN for a product used as an antibiotic; the French INN is *Abamectine*, while the Spanish INN is *Abamectina*, and

¹ The Standard Industrial Classification system was replaced by the North American Industry Classification System (NAICS) effective reference year 1997. Since the data used in this report were still presented by SIC codes, the SIC system seems more relevant to the discussion. For reference purposes, the applicable NAICS codes are provided in parentheses.

the “Universal” name is *Abamectinum*.² The WHO also has a nomenclature system for chemically modified INN products known as INNMs.³

New Chemical Entities

NCEs⁴ are defined by the FDA as those drugs whose active ingredients have not been previously approved in the United States for use as a pharmaceutical. The term “global NCE” refers to an NCE that has been approved or marketed in at least seven industrialized countries. NCEs do not include either biological drugs or diagnostic drugs. According to FDA data, 197 NCEs were approved in the United States between the years 1993 and 1998.⁵

As shown in figure 2-1, the number of new products decreased from 25 in 1993 to 22 in 1994, before increasing to 53 in 1996. This represents an increase of 112 percent during 1993-96. The types of NCEs approved in 1998 represented a wide variety of specific therapeutic categories, including antiviral agents (three for AIDS-related disease), respiratory drugs, and erectile dysfunction treatments. A major factor that has resulted in the large increase seen for AIDS drugs, as well as for all drugs, is the more expeditious FDA approval process for new drug applications (NDAs).⁶ This increase in the approval process is largely the result of increased company involvement through programs such as the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Modernization Act of 1997 (FDAMA), which will be discussed further in Chapter 3.

On a regional basis, Western European companies have developed a large share of the newly marketed drugs. Data available for drugs developed during 1985-89 indicate that the European firms developed 129 NCEs compared with 77 for the United States and 70 for Japan. During 1990-94, however, the most recent period of record, European drug development slowed to a total of 94 while the United States had a total of 84, and Japan developed 77 NCEs.⁷

The comparison of NCE development data is shown in table 2-1. During the 5-year periods for which data are available, European companies as a group recorded the largest number of NCEs. The total of all reported NCEs increased only by about 5 percent over the 20-year period, although the number recorded for Europe dropped by about 37 percent from 149 to 94. The United States, however, gradually increased from 66 to 84 during the same 20

² *International Nonproprietary Names (INN) for Pharmaceutical Substances*, World Health Organization (WHO), Geneva, Switzerland, 1992, p. 1.

³ INNMs consist of an INN with a modifier or “radical,” representing a salt, ester, complex, or other derivative of the basic INN. These modifiers may exist as common chemical prefixes or suffixes, such as “sulfate,” “chloride,” or they may represent more complex chemical derivative names.

⁴ Also called “new molecular entity” (NME).

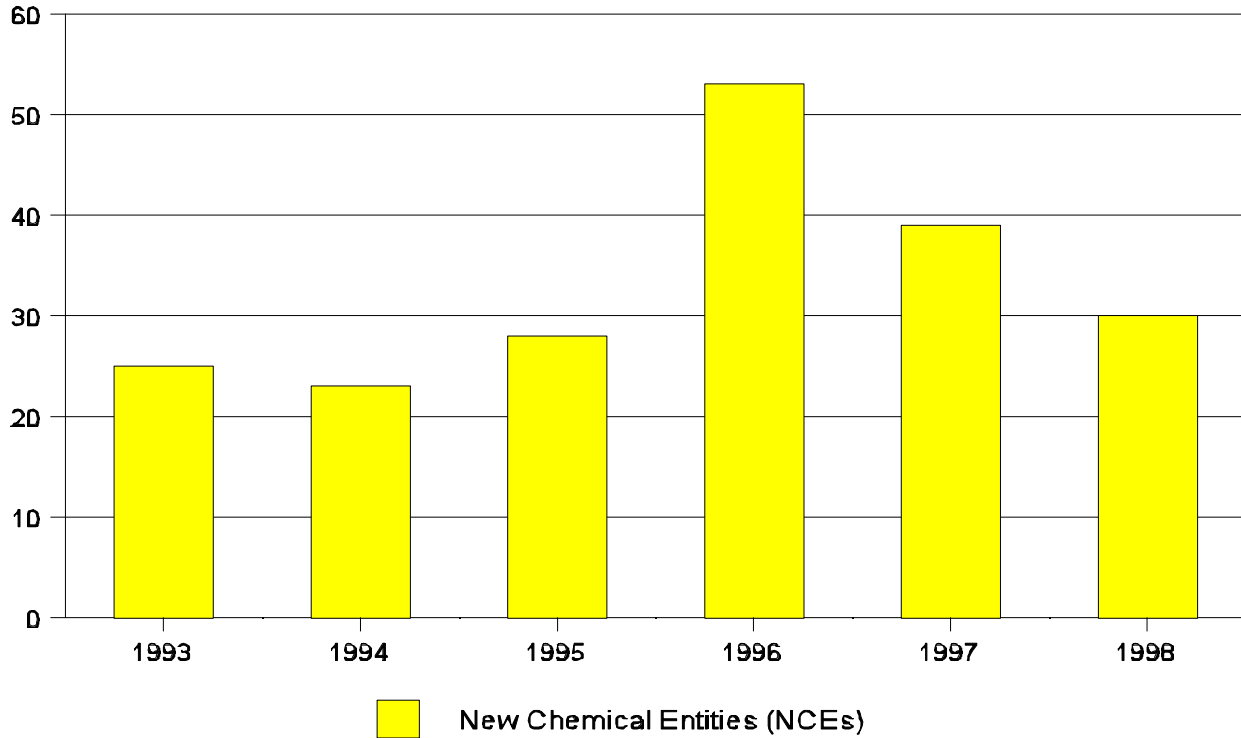
⁵ PhRMA, *New Drugs Approvals in 1998*, p. 1.

⁶ PhRMA, *New Drugs Approvals in 1998*, p. 1.

⁷ EFPIA, *The Pharmaceutical Industry in Figures, 1997*, pp. 22-23.

years, an increase of 27 percent. Japan increased the most in terms of percent growth, from 28 during 1975-79 to 77 during 1990-94.⁸

Figure 2-1
NCEs approved in the United States, 1993-98



Source: Official statistics of the FDA.

Table 2-1
Total number of NCEs developed, by major country or group, by period groupings, 1975-94

Country	Total NCEs developed			
	1975-79	1980-84	1985-89	1990-94
Western Europe	149	126	129	94
Japan	28	57	70	77
United States	66	63	77	84
Other countries	4	2	1	4
Total	247	248	277	259

Source: EFPIA, *The Pharmaceutical Industry in Figures*, 1997, p. 22.

⁸ *Ibid.*

A more “research-friendly” environment is considered to have helped the United States in the relatively robust growth in the number of NCEs approved over the past 20 years, and it could explain why the United States has an increasingly larger share of the total NCEs approved. In the most recent period, the United States introduced more than 32 percent of total NCEs approved in the survey. By contrast, European pharmaceutical firms have been responsible for a decreasing portion of the approved items. It has been argued that European firms have not been able to keep pace with development of new drugs because of diminishing R&D investment.⁹

It is evident from the NCE data presented above that the United States, Western Europe, and Japan are the primary developers of innovative pharmaceutical products. The following chapters explain the factors that have affected the success and competitiveness of the industries in these countries, particularly the United States.

⁹ *Ibid.*

CHAPTER 3

Description of the Pharmaceutical Industries in Selected Countries

Industry Overview

The pharmaceutical industry is complex, dynamic, and highly globalized, with many pharmaceutical companies operating in multiple countries.¹ Adding to the international nature of the industry, there is a continued trend toward outsourcing² various stages of the development and production of a single pharmaceutical product, including intermediate and active ingredient process development; as a result, a single finished product may be the result of materials manufactured in more than one country. In addition to its global aspect, the pharmaceutical industry continues to be characterized by high R&D expenditures and extensive regulation of its products compared with other manufacturing sectors.

The most established pharmaceutical industries are located in the United States, Western Europe, and Japan. The top 10 pharmaceutical companies based on worldwide sales in 1997 (table 3-1) are headquartered in either the United States or Western Europe. While no Japanese firms are among the top 10 companies, several firms fall in the next tier of top worldwide pharmaceutical sales.

Demand for pharmaceutical products is highest in the United States, Western Europe, and Japan. The United States accounted for approximately 33 percent of the total world market for ethical (prescription) pharmaceuticals in 1996, while Europe's share amounted to about 29 percent; Japan's share was nearly 18 percent.³

Based on reports of growth rates of over 10 percent for 1997, and estimates of similar growth for 1998, the pharmaceutical industry appears to be performing well.⁴ A recent review of the major pharmaceutical companies reveals several factors contributing to the

¹ As noted in Chapter 1, this report defines the nationality of a pharmaceutical company by the geographic location of its headquarters, although country data are generally reported for the activities of all companies operating within a nation.

² Because of rising R&D costs, it is increasingly important for pharmaceutical companies to maximize the period of time that products are marketed under patent exclusivity. To get products to market quickly, a company must expedite every aspect of product development; because many of the chemicals and processes involved in the pharmaceutical industry are highly specialized, more drug companies are focusing their time and resources on R&D while outsourcing the production of complex intermediates and active ingredients to other firms.

³ *PhRMA Industry Profile, 1998*, p. 70. These data are presented in the following regional/country breakout: Africa, Australasia, Canada, Europe, Japan, Latin America, Middle East, Southeast Asia & China, and the United States.

⁴ Feliza Mirasol, "Pharma Industry is Poised for Double-Digit Growth," *Chemical Market Reporter*, April 13, 1998, p. 15.

Table 3-1
The top 10 pharmaceutical companies, worldwide sales in 1997, and location of corporate headquarters

Company	Sales (billions of dollars)	Location of corporate headquarters
Merck	11.3	United States
Glaxo-Wellcome	10.9	United Kingdom
Novartis	10.5	Switzerland
Bristol-Myers Squibb	9.1	United States
Johnson & Johnson	8.6	United States
Pfizer	8.3	United States
American Home Products	8.1	United States
SmithKline Beecham	7.2	United Kingdom
Hoechst Marion Roussel	6.9	Germany
Lilly	6.4	United States

Source: "Much Promised, but Little Delivered in '98," *European Chemical News*, Nov. 30, 1998, p. 23.

success of the industry on a worldwide basis.⁵ Improved R&D productivity has brought recent opportunities for growth, and many contend that consolidation and restructuring have also been beneficial for pharmaceutical companies.⁶

Several large, high-profile pharmaceutical companies have recently sought to improve their competitive posture and overall company performance by developing promising product lines through licensing, engaging in joint ventures, divesting (or "spinning off") unprofitable business segments, and negotiating mergers and acquisitions (M&As).⁷ M&As, which result in industry consolidation, arguably have the most significant effect on the pharmaceutical industry as a whole.

The motivating factor behind M&As has evolved since the 1960s and 1970s, when the primary impetus was diversification of products. The incentive changed in the 1980s, when companies merged and acquired other firms to increase international presence and infrastructure. Currently, most M&As are intended to maximize the benefits of economies of scale.⁸ By combining the resources of two organizations, administrative staff can be cut and inefficient factories closed, resulting in cost savings; additionally, specialized sales forces and R&D capabilities of each company can complement one another, strengthening overall performance in these areas for the newly formed enterprise.⁹ Table 3-2 outlines some of the more significant pharmaceutical industry M&As in recent years.

⁵ "The Pressure is Still On," *Medical Advertising News*, Sept. 1996, p. 3.

⁶ *Ibid.*

⁷ "Business: The Mother of All Mergers," *The Economist*, Feb. 7, 1998, p. 63.

⁸ Wayne Koberstein, "Pharma Mergers — Point/Counterpoint: A Conversation with Frederick Frank of Lehman Brothers," *Pharmaceutical Executive*, June 1998, p. 78.

⁹ "Business: The Mother of All Mergers," p. 63.

Table 3-2
M&As in the pharmaceutical industry, 1989-97

Year	Companies	Result
1997	Roche and Boehringer Mannheim	Roche
1996	Elan and Athena Neurosciences	Elan
1996	Ciba-Geigy and Sandoz	Novartis
1995	Schwarz Pharma and Reed & Carnrick	Schwarz Pharma
1995	Rhone-Poulenc Rorer and Fisons	Rhone-Poulenc Rorer
1995	Pharmacia and Upjohn	Pharmacia & Upjohn
1995	Hoechst-Roussel and Marion Merrell Dow	Hoechst Marion Roussel
1995	Gynopharma and Ortho-McNeil	Gynopharma
1995	Glaxo and Burroughs Wellcome	Glaxo-Wellcome Plc.
1995	Knoll and Boots	Knoll
1994	SmithKline Beecham and Sterling	SmithKline Beecham
1994	Sanofi and Sterling	Sanofi
1994	Pharmacia and Ergamont	Pharmacia
1994	Hoffmann-LaRoche and Syntex	Roche Holding Ltd.
1994	American Home Products and American Cyanamid	American Home Products
1990	Boots and Flint	Boots
1990	Pharmacia and Kabi	Pharmacia
1990	Rhone-Poulenc and Rorer	Rhone-Poulenc Rorer
1989	American Home Products and A.H. Robins	American Home Products
1989	Bristol-Myers and Squibb	Bristol-Myers Squibb
1989	Merrell Dow and Marion	Marion Merrell Dow
1989	SmithKline and Beecham	SmithKline Beecham

Source: Compiled from information presented by PhRMA in *Industry Profile, 1997*, p. 41, Ann M. Thayer, "Pharmaceuticals: Redesigning R&D," *Chemical and Engineering News*, Feb. 23, 1998, p. 26, and information from the SmithKline Beecham home page (www.sb.com/company/hist_01.htm) obtained on Nov. 12, 1998.

Analysts have noted one negative result of these M&As. Reportedly, a new product must be capable of generating significant sales revenues to attract the resources of a very large pharmaceutical company, primarily because the firm's overall revenues are too high to be affected noticeably by small increases. Products with lower sales value may be overlooked by these large merged pharmaceutical companies, even though the vast majority of pharmaceutical sales do not involve the top selling drugs.¹⁰ However, this trend can work to the advantage of medium-sized pharmaceutical companies. In focusing their business on the development of potential products discovered by other firms (to avoid costly research expenditures), middle tier companies are often able to attract product development from larger firms who may only be willing to devote marketing resources to blockbuster drugs. Also, medium-sized companies are typically more flexible in making deals than larger firms, as reflected in how deals are structured and the timeliness with which the deals are closed.¹¹ In this way, the effect of M&As on the pharmaceutical industry seems to be somewhat balanced, even though it is evolving.

Because of the importance of the United States, Western Europe, and Japan as both suppliers and consumers of pharmaceuticals, the remainder of this chapter focuses on the pharmaceutical industries in these three geographic areas. The following sections provide, to the extent possible, an overview of the industry of each country/country group. There is a review of employment trends for each area. R&D expenditures are also evaluated as a strong indicator of the competitiveness of each industry.¹² The state of the biotechnology industry, widely considered one of the most rapidly developing research areas within the pharmaceutical sector, is assessed as evidence of an industry's ability to invest in risky R&D activities and successfully commercialize the scientific findings. Additionally, relevant Government policies are examined as another critical factor for competitiveness, particularly those policies that affect the rate of drug approval, the extent of patent protection, or the pricing and prescribing behavior in the market. As discussed in the Commission's 1991 competitiveness study, factors that affect a firm's profitability have a significant effect on that firm's ability to invest in the R&D necessary to develop innovative products.

United States

Industry

The pharmaceutical industry in the United States, composed of approximately 700 companies that develop, manufacture, and market ethical pharmaceutical products, including both proprietary (brandname) and generic medicines, appears competitive. Reflecting a 10-percent rise over 1996, the value of U.S. shipments of pharmaceutical products in 1997 was estimated at nearly \$83 billion.¹³ This increase can be attributed to the recent success of new products

¹⁰ Kevin Gopal, "Megamergers — Boon or Bust?" *Pharmaceutical Executive*, Nov. 1996, pp. 34-36.

¹¹ Klaus Veitinger, "Midsized Player — A Model for the 21st Century," *Pharmaceutical Executive*, Oct. 1998, pp. 86-94.

¹² Chapter 2 of the Commission's 1991 competitiveness study addresses the importance of R&D as a factor affecting a company's ability to develop innovative ethical drugs.

¹³ Official statistics of the U.S. Dept. of Commerce; estimate by USITC staff.

and product line extensions as opposed to increases in price or sales volume of existing products.¹⁴ Reportedly, 61 new pharmaceutical products were introduced to the market in 1997, compared with 53 items in 1996.¹⁵

The domestic market for OTC medications, although significant, is smaller than the market for prescription medications. In 1997, there were an estimated 100,000 OTC products on the market, in a variety of sizes and dosage forms, with sales reaching an estimated \$16.6 billion. The extremely competitive market for OTC medications has resulted in an average cost of about \$5.00 per package, compared with an average price of an ethical drug of about \$22.00.¹⁶

In table 3-3, the top 10 companies that have operations in the United States are listed, based on sales from their U.S.-based operations only. It should be noted that not all of the companies on the following list are headquartered in the United States, which indicates the strong multinational presence that is common among drug companies. Because firms may have extensive operations outside of the United States, the ranking order at the world level (table 3-1) is sometimes different from its rank among domestic producers.

Table 3-3
The top 10 pharmaceutical companies in the United States, by U.S. pharmaceutical sales, 1997

Rank	Company	U.S. pharmaceutical sales (in billion dollars)
1	Bristol-Myers Squibb (US)	5.70
2	Johnson & Johnson (US)	5.66
3	Merck & Co. (US)	5.65
4	Glaxo-Wellcome (UK)	5.54
5	American Home Products (US)	5.33
6	Pfizer (US)	4.95
7	Lilly (US)	4.39
8	SmithKline Beecham (UK)	4.02
9	Novartis (Swiss)	3.99
10	Schering-Plough (US)	3.81

Source: "Pharmaceutical Rankings Change as New Products Enter the Scene," *Chemical Market Reporter* (New York), Mar. 9, 1998, p. 35.

¹⁴ "Pharmaceutical Rankings Change as New Products Enter the Scene," *Chemical Market Reporter*, Mar. 9, 1998, p. 35.

¹⁵ *Ibid.* Introducing a product to market is distinct from gaining approval for an NCE (compare with figure 2-1).

¹⁶ Information obtained from the Nonprescription Drug Manufacturers Association (NDMA) website (www.ndmainfo.org/facts) on July 21, 1998.

The U.S. pharmaceutical industry, particularly the research-based companies, has played a significant role in the increased use of outsourcing within the sector. The world market for outsourced services in the patented and brandname pharmaceutical industry is estimated to have been \$4 billion for 1997; of this total, the U.S. pharmaceutical industry demand for outsourcing accounted for about 60 percent. However, U.S. capacity for outsourced services to support the pharmaceutical industry was about 20 percent of the total world capacity and equaled only one-third of European outsourcing production capacity.¹⁷ Reportedly, U.S. chemical companies are discouraged from establishing themselves in the pharmaceutical outsourcing market at least in part because of the disparity in FDA inspection standards for domestic versus overseas facilities.¹⁸ As a result, there is a shortage of U.S. fine chemical facilities that have FDA approval and can also perform the highly specialized processes that are required for the complex chemicals used by drug companies.¹⁹

The outsourcing market for generics is slightly different than for brandname products. Although many producers of bulk active ingredients are located in Europe, import competition also comes from low-cost sources, such as Asia. Also, the recent ruling on patent laws in the EU has made it illegal for companies in member states to sell active ingredients for products that are still under patent anywhere in the world.²⁰ In many countries, including the United States, it is legal to sell patented active ingredients for the development and clinical trials of generic products, even though the generics may not be sold on the market until the expiration of the patent. As a result, U.S. generics manufacturers who had been traditionally supplied by European producers must find alternative sources of patented active ingredients in order to begin marketing a product immediately after patent protection ends for the brandname product.²¹ Although imports from Europe are still strong and shipments from India and China are increasing, the domestic pharmaceutical industry is optimistic that this advantage over the Europeans will encourage the U.S. fine chemicals industry to develop its outsourcing services for bulk active ingredients.²²

Employment

Employment during 1993-97 is shown by 3-digit and 4-digit SIC codes in table 3-4. In 1997, total employment in the pharmaceutical industry (SIC 283) reached the highest recorded levels for the period with 267,200 employees, following a gradual decline in employment during 1993-95. The decrease has largely been attributed to the rationalization of the industry, by which mergers and buyouts resulted in the elimination of many redundant

¹⁷ Bruce Gain, "U.S. Lags Europe in Outsourcing Capacity," *Chemical Week*, Sept. 10, 1997, p. 44.

¹⁸ Andrea Foster, "FDA Foreign Inspections Faulted," *Chemical Week*, May 13, 1998, p. 54. In a March 29, 1999 discussion with an FDA official, he stated that both foreign and domestic inspections of facilities for an NDA are identical; however, limited resources result in less frequent routine "follow-up" inspections of overseas facilities as compared with inspections of facilities located in the United States.

¹⁹ *Ibid.*

²⁰ Sean Milmo, "EU Court Ruling Deals a Setback to Generics Arm," *Chemical Market Reporter*, Aug. 4, 1997, p. 7.

²¹ Matthew Lerner, "Bulk Pharma Taking Root in Americas," *Chemical Marketing Reporter*, May 20, 1996, p. 5.

²² Bill Macdonald, "Asian Plants Relish in Custom Synthesis," *Asia-Pacific Chemicals*, May 1998, p. 31.

structures. After a period low of 259,800 employees in 1995, employment for SIC 283 increased during 1996-97.²³ The upward trend is likely a result of the new products and product line extensions that encouraged growth in the industry.

Table 3-4
Employment in the U.S. pharmaceutical industry, by SIC code, 1993-97

SIC	Description	1993	1994	1995	1996	1997
283	Medicinal Chemicals (Drugs)	264,400	263,000	259,800	260,600	267,200
2834	Pharmaceutical Preparations	215,800	213,300	209,500	207,900	211,100

Source: Bureau of Labor Statistics

Employment for SIC 2834 (pharmaceutical preparations), the largest group, consisting of finished ethical and OTC generic and brandname preparations, decreased from 215,800 to 207,900 employees during 1993-96. Although employment in SIC 2834 did not return to its peak of 1993, the 1997 total of 211,100 employees reflected the first increase in employment levels over the five-year period.²⁴ As in SIC 283, it is likely that employment in SIC 2834 is growing in conjunction with the increasing number of new products and expanded product lines introduced by the pharmaceutical industry.

Research and Development Expenditures

A long-standing measure and determinant of competitiveness in the pharmaceutical industry is the amount spent on R&D.²⁵ Other factors, such as pricing, profit rates, and marketing expenditures have been put forth as measures of competitiveness, but R&D expenditures are associated with the development of newer, proprietary drugs. R&D affords companies the opportunity to develop a drug with unique therapeutic value rather than having to compete on a price basis with OTC, generic, or so-called "me too"²⁶ preparations; innovative drugs bring higher profits, allowing more investment in R&D.

Trends in R&D spending for 1993-97 are shown in figure 3-1. With an increase in the costs to develop NCEs, the amount spent on R&D also increased. It is estimated that in 1997 companies spent \$15.5 billion domestically on R&D to develop ethical pharmaceuticals, compared with \$13.6 billion in 1996. An additional \$3.5 billion was spent by U.S. companies on R&D overseas in 1997. Domestic R&D expenditures for 1998 are expected to reach \$17.2 billion, a rise that further reflects the increasing costs of drug development.²⁷

²³ Based on data reported by the Bureau of Labor Statistics.

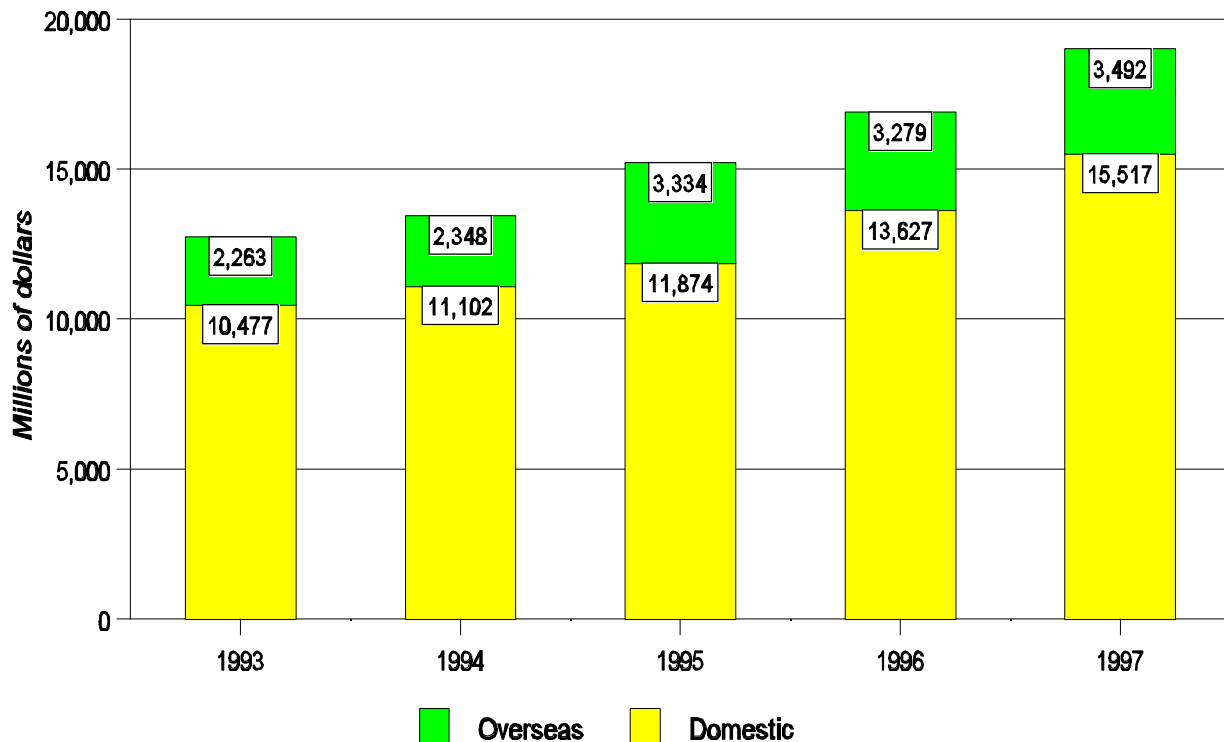
²⁴ *Ibid.*

²⁵ Commission's 1991 *Competitiveness Study*, p. 2-1.

²⁶ A "me-too" preparation, broadly defined, is one that is similar, either therapeutically or chemically, to an existing pharmaceutical product.

²⁷ *PhRMA Industry Profile, 1998*, p. 90.

Figure 3-1
Domestic and overseas R&D expenditures by U.S. companies, 1993-97



Note.—Data for 1997 are estimated.
 Source: *PhRMA Industry Profile, 1998*, p. 90.

Surveys by PhRMA show that the percentage of sales reinvested in R&D during 1993-97 was fairly consistent, ranging from a low of 19.4 percent in 1995 to a high of 20.4 percent in 1994. The estimated ratio of R&D to sales for 1997 is 20.3 percent (table 3-5).

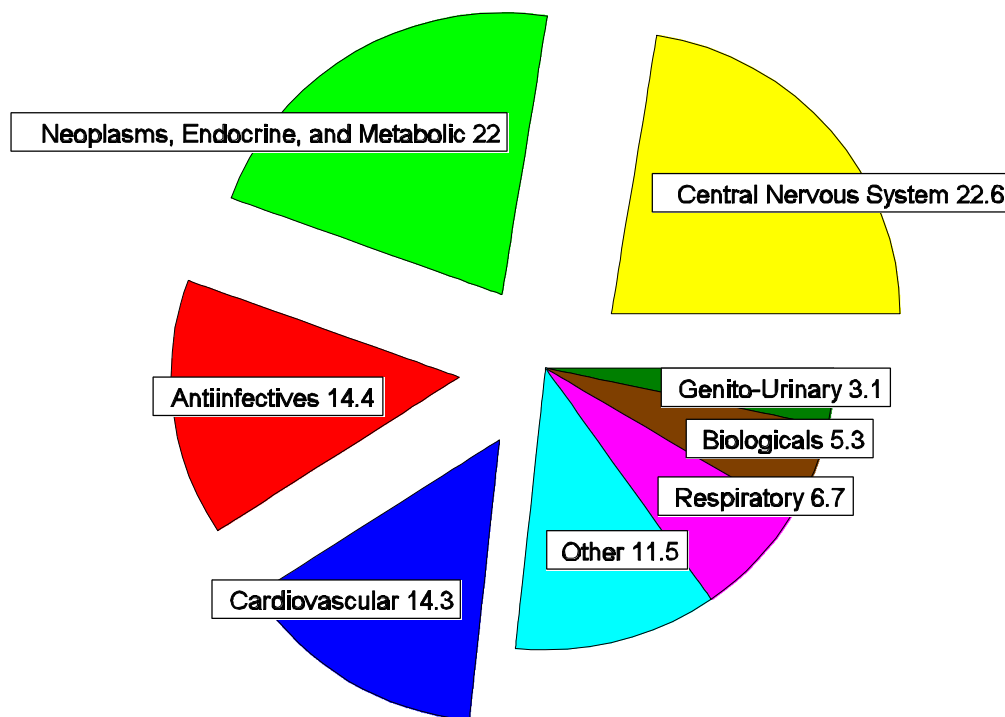
Table 3-5
R&D spending by the U.S. pharmaceutical industry, U.S. sales (including foreign sales), and ratio of R&D to sales, in millions of dollars, 1993-97

Year	Domestic U.S. R&D expenses	U.S. sales, including foreign sales	Ratio of R&D to sales
1993	10,473	52,573	19.9%
1994	11,101	54,346	20.4%
1995	11,834	61,138	19.4%
1996	13,576	68,536	19.8%
1997 ¹	15,422	75,788	20.3%

¹ Data estimated for 1997.
 Source: *PhRMA Industry Profile, 1998*, p. 91.

A breakdown of domestic R&D expenditures for the pharmaceutical industry is shown by therapeutic category in figure 3-2. The categories with the greatest amounts of R&D spending in 1996 were drugs affecting the central nervous system, followed by drugs to treat neoplasms, the endocrine system, and metabolic diseases. Antiinfectives and cardiovascular drugs were third and fourth, respectively, with the four categories together accounting for over 73 percent of R&D spending.

Figure 3-2
Domestic R&D expenditures in 1996, by therapeutic category, in percent



Source: PhRMA Industry Profile, 1998, p. 96.

Shipments and Trade Balance

U.S. shipments in the pharmaceutical industry reached a level of approximately \$82.6 billion in 1997, an increase of 41 percent from \$58.4 billion in 1993. As shown in table 3-6, total trade in pharmaceuticals also increased during those years. U.S. imports increased dramatically, from \$6.1 billion in 1993 to \$12.8 billion in 1997, an increase of about 110 percent. U.S. exports did not increase as quickly as imports, rising from about \$7.2 billion to \$9.6 billion (33 percent) over 1993-97. These changes in trade resulted in a deteriorating trade balance for the United States, ranging from a \$1.1 billion surplus in 1993 to a \$3.2

billion deficit in 1997.²⁸ The most significant increase in imports came from Western Europe, the primary source of imported pharmaceutical products for the United States. There are several factors that contributed to the increase in products from Europe, including related party trade, greater capacity for outsourced²⁹ production as compared with the United States, favorable high technology business policies (e.g., tax incentives) in Ireland, and Government health care policies that have reduced local demand in certain European countries.³⁰

Table 3-6
Pharmaceuticals: U.S. shipments, domestic exports, imports for consumption, merchandise trade balance, apparent consumption, exports as a percent of shipments, and imports as a percent of consumption, 1993-97

Year	Shipments	Exports	Imports	Trade balance	Apparent consumption	Exports as a percent of shipments	Imports as a percent of consumption
						(millions of dollars)	
1993	58,428	7,222	6,094	1,128	59,556	12.4	10.2
1994	60,811	7,565	6,966	599	61,410	12.4	11.3
1995	68,473	7,996	8,583	-587	67,886	11.7	12.6
1996	75,047	8,889	11,161	-2,272	72,775	11.8	15.3
1997	¹ 82,550	9,600	12,836	-3,236	79,314	¹ 11.6	16.2

¹ Estimated by USITC staff.
Source: U.S. Department of Commerce.

Biotechnology Products

With advancements in the study of genetically modified organisms and improved recombinant research methods, the field of biotechnology has become increasingly important to the pharmaceutical industry. Biopharmaceutical products with marketable value, such as antiviral compounds used in the treatment or prevention of AIDS and new cancer and cardiovascular disease diagnostics, have changed the medical field by offering innovative, highly effective treatments for serious ailments.³¹

Returns on investment in the U.S. biotechnology industry were not generally realized until 1997, when profits from the successful commercialization of biopharmaceuticals began to

²⁸ Data from the official statistics of the Department of Commerce.

²⁹ The trend in outsourcing various stages of pharmaceutical production is discussed earlier in this chapter.

³⁰ See USITC Pub. 3120, *Shifts in U.S. Merchandise Trade in 1997*, July 1998, pp. 7-6, 7-7. This report is available online at <http://www.usitc.gov/332s/332index.htm>.

³¹ "Finding the Cure," *Chemical Marketing Reporter*, April 14, 1997, p. SR-3.

compensate for high R&D expenditures. Sales for 1997 reached more than \$5.7 billion, reflecting a 15.5 percent increase over 1996.³² Continued sales growth is expected. While there are over 40 biopharmaceuticals and vaccines currently approved by the FDA, 272 biopharmaceutical drugs are in human clinical trials, with countless others in the preliminary stages of development.³³ The top ten biotechnology products, along with their producers, are listed on table 3-7; three of the top firms in the United States are Amgen, Genentech, and Biogen.³⁴

Table 3-7
Top products in the biotechnology industry, the developer, and the marketer, by 1996 sales, in millions of dollars

Product	Developer	Marketer	1996 sales (\$ million)
Epogen	Amgen	Amgen	1,150
Neupogen	Amgen	Amgen	1,017
Procrit	Amgen	Ortho Biotech	995
Humulin	Genentech	Eli Lilly	884
Engerix-B	Genentech	SmithKline Beecham	568
Intron A	Biogen	Schering-Plough	524
Betaseron	Chiron/Berlex	Berlex/Schering AG	353
Epivir	Biochem Pharma/Glaxo Wellcome	Glaxo Wellcome	306
Activase	Genentech	Genentech	284
Humatrope	Genentech/Eli Lilly	Eli Lilly	268
Total			6,349

Source: Feliza Mirasol, "Biopharmaceuticals Shine, Break-Even Point in Sight," *Chemical Market Reporter*, June 22, 1998, p. 16.

There are currently about 350 publicly held biotech companies in the United States,³⁵ which industry analysts have reported to be excessive given the investment dollars available.³⁶ While several of the larger biotech companies are now able to bring their products to market, smaller

³² Joseph Chang, "Biotech Industry Comes of Age: Sales Surged 15 Percent in '97," *Chemical Market Reporter*, June 22, 1998, p.1.

³³ "Biopharmaceutical Manufacturing Moves Into the Custom Arena," *Chemical Market Reporter*, Jan. 19, 1998, p. F22.

³⁴ Feliza Mirasol, "Biopharmaceuticals Shine, Break-Even Point in Sight," *Chemical Market Reporter*, June 22, 1998, p.16.

³⁵ There are a reported 1,287 companies involved in the biotechnology industry in the United States, a number that includes private corporations, firms whose primary activities lie in other (often tangential) fields, and biotech firms that focus on non-pharmaceutical applications in their research.

"Biopharmaceutical Manufacturing," p. F20. For information about the strong links among Government research agencies, universities, and the biotech industry, please refer to the Commission's *1991 Competitiveness Study*.

³⁶ Chang, "Biotech Industry," p. 21.

firms are generally still in need of larger pharmaceutical firms, or another biotech firm, to see their biopharmaceuticals through the final phases of development and marketing.³⁷ As a result, an increased number of future consolidations and strategic partnerships within the industry are anticipated.³⁸ Formal collaborations in the biopharmaceutical field increased from 320 business arrangements in 1989 to 628 in 1997.³⁹

Overall, the United States is widely considered the world leader in the biotech industry. About 65 percent of worldwide patents on biopharmaceutical products are held by U.S. companies, and of the applications for patents on DNA sequences,⁴⁰ about 63 percent of the worldwide total were submitted by U.S. firms. The U.S. success in this field has been attributed to the availability of funds, an environment conducive to an entrepreneurial spirit in scientific areas, and the relatively efficient review processes of the FDA.⁴¹

Government Policies

Historically, the Food, Drug and Cosmetics Act of 1938 (FDCA) has played an important role in maintaining the safety and efficacy of pharmaceuticals and protecting consumer health.⁴² Several changes to these regulations have occurred since the Commission's 1991 competitiveness report was published, the last of which came under the Food and Drug Administration Modernization Act of 1997 (FDAMA). The most significant modifications have resulted in a shorter FDA approval process for new drug applications (NDAs) and a limited scope of legal action that is allowable against a manufacturer of a drug (or device) found to be defective. Some significant regulations on the industry identified in the Commission's 1991 competitiveness study, such as restrictions on biological products and the Orphan Drug Act, which governs approval of drugs for treatment of diseases affecting 200,000 or fewer people, have changed very little since that time.

As reported in the Commission's 1991 competitiveness study, the ability of a company to compete successfully is dependent upon its ability to innovate, or provide new products.⁴³ Because any new drug to be marketed in the United States requires approval from the FDA, the time taken by the approval process reduces the effective patent "life" of the new drug.⁴⁴ This reduced period of exclusivity subsequently reduces the amount of time available to recover funds invested in R&D.

³⁷ "Beyond the Behemoths," *The Economist*, Feb. 21, 1998, p. 16.

³⁸ Chang, "Biotech Industry," p. 21.

³⁹ "Biotech Industry Sees Dealmaking Double over the Past Eight Years," *Chemical Market Reporter*, June 22, 1998, p. 18.

⁴⁰ DNA sequences provide the genetic coding for an organism.

⁴¹ See the Commission's 1991 *Competitiveness Study* and "Regulations are Making Europe a Biotech Dinosaur," *European Chemical News*, March 23-29, 1998, p. 8.

⁴² 21 USC §301 et seq.

⁴³ Commission's 1991 *Competitiveness Study*, p. viii.

⁴⁴ Patents protect a company's right to exclusively market a particular product for a specified length of time; if that product cannot be legally sold because it has not received approval from the FDA, the period of exclusivity is shortened. As a result, the company's profits from monopoly (i.e., patent protected) sales are diminished.

The average length of the drug approval process⁴⁵ during 1990-96 was 14.9 years, increasing from 14.2 years during the 1980s. Using 14.9 years as the base, the approval process consists of an average of 6.0 years for pre-clinical phase testing of the drug, another 6.7 years for the FDA-required clinical trials, and 2.2 years for the final FDA approval phase. The clinical trial phase of drug development increased since the 1980s average of 5.5 years, whereas the other two phases of drug development decreased. The lengthening of the clinical phase has been attributed to both the rising average total of clinical trials performed for each NDA as well as the increasing number of medical procedures that each clinical trial patient undergoes.⁴⁶

During the 1990s, the FDA has embarked on several strategies to speed the approval of new drugs. The first major development was the Prescription Drug User Fee Act of 1992 (PDUFA), which was effective through September 30, 1997. The primary purpose of the PDUFA was to promote efficiency in the approval process in order to make medicines available to patients more quickly. Specifically, the PDUFA helped establish a new framework for accelerated approval times and provided the FDA with additional resources for the FDA Center for Biologics.⁴⁷

The PDUFA established user fees for the drug application and NDA approval process. The experimental fees were based on an upward sliding scale from 1993 to 1997, when sunset provisions terminated the requirement. The fee scale is shown in table 3-8. To provide for situations where a small company may not have been able to meet application fees or other establishment or product fees, the PDUFA provided that a business with fewer than 500 employees was responsible for only one-half of the standard amounts shown when submitting a human drug application. Initial drug application fees were set to total as much as \$385,000 by the end of the user fee program in fiscal year 1997.

The PDUFA also established for the FDA a number of performance goals for the accelerated approval of drugs. These include on-time review performance goals for NDAs as well as Product License Applications (PLAs). Other goals making up the management framework of the PDUFA are all geared towards the elimination of overdue backlogs, building excellence into the review process, and achieving measurable, high performance.⁴⁸ The third report on the PDUFA, completed in 1995, showed that the FDA was more than one year ahead in meeting its goals overall and was performing three years ahead of scheduled

⁴⁵ The approval process includes preclinical testing, 3 phases of clinical trials, and the submission of an NDA. Preclinical testing involves laboratory and animal testing of a chemical to gauge its safety for testing in humans. Phase I of the clinical trials, which is conducted on 20-100 healthy volunteers, is intended to test for potential side effects and a safe but effective dosage range. Phase II involves 100-300 volunteers who are afflicted with the targeted disease; this stage is used to monitor efficacy and side effects. Phase III expands the number of volunteers to a minimum of 1,000-3,000 patients to further determine the safety and efficacy of the drug. If the data from these trials indicate satisfactory performance, the company then submits an NDA to the FDA. *PhRMA Industry Profile, 1997*, pp.18-19.

⁴⁶ *PhRMA Industry Profile, 1998*, pp. 24-25.

⁴⁷ 21 U.S.C.A. §379(g) and §379(h).

⁴⁸ *Fourth Annual Performance Report: Prescription Drug User Fee Act of 1992*, Food and Drug Administration, Dec. 1, 1996, downloaded from www.fda.gov, Nov. 3, 1997.

goals in new drug approvals.⁴⁹ This trend has continued. The 23-month median approval time for NDAs that existed in the early 1990s gradually decreased to a median approval time of 11.7 months in 1998.⁵⁰

Table 3-8
FDA drug application fees, by fee type, fiscal years 1993-97

Fee Type	Fiscal Year—				
	1993	1994	1995	1996	1997
	<i>(thousands of dollars)</i>				
Annual establishment fee	60	88	126	131	138
Annual product fee	6	9	12.5	13	14
Application fee under subsection (a)(1)(A)(I) ¹	100	150	208	217	233
Application fee under subsection (a)(1)(A)(ii) ²	50	75	104	108	116
Total under subsection (a)(1)(A)(I)	166	247	346.5	361	385
Total under subsection (a)(1)(A)(ii)	116	172	242.5	252	268

¹ Application for which clinical data with respect to safety or effectiveness are required for approval.

² Application for which clinical data with respect to safety or effectiveness are not required for approval.

Source: U.S. Food and Drug Administration.

Legislation (eventually known as FDAMA) to significantly amend the FDCA was introduced around the expiration date of PDUFA. When FDAMA became law on November 21, 1997, it changed the FDA's mission;⁵¹ added 6 months of patent exclusivity for drugs requiring further review for pediatric applications; provided a fast track approval process for drugs intended to treat patients with serious illnesses, such as rare forms of cancer, that do not have satisfactory alternative treatments; and established several other important policies and procedures intended to improve regulation of the pharmaceutical industry in the United States.⁵²

The FDA has recently put forth a draft guidance for direct-to-consumer (DTC) advertisement of prescription drugs over radio and television media. Although the final FDA ruling on all types of promotional activities, including print advertisements, has not yet been finalized, the new guidelines have already affected industry investment in advertising. It was projected that the U.S. pharmaceutical industry would spend \$1.8 billion⁵³ on ethical drug DTC promotion in 1998; if this estimate is accurate, spending will have increased by 80 percent over 1997

⁴⁹ *Third Annual Performance Report: Prescription Drug User Fee Act of 1992*, Food and Drug Administration, Dec. 1, 1995, downloaded from www.fda.gov, Apr. 18, 1997.

⁵⁰ PhRMA, *New Drug Approvals in 1998*, p. 22.

⁵¹ In chapter 3 of the *PhRMA Industry Profile, 1998*, obtained from the PhRMA website (www.phrma.org) on July 30, 1998, the mission is summarized: "to promote public health by the timely review of applications for new products and to protect public health by ensuring the regulated products are safe, effective, and properly labeled." A complete version can be found in Public Law 105-115, Section 406.

⁵² Public Law No. 105-115.

⁵³ Industry sources have suggested that a closer estimate may be in the range of \$1-1.5 billion.

levels, the majority of which was spent for respiratory drugs.⁵⁴ Notably, studies indicate that DTC ads are affecting patients' willingness to request products by name.⁵⁵

Under the FDCA, DTC drug advertisements are required to provide a "brief summary" of significant information about the product (i.e., side effects, contraindications) as well as a "major statement" to enumerate the risks linked with usage of the product. While print advertisements are able to meet these requirements fairly easily, broadcast advertisements are hindered by the time constraints of short advertising spots. Most radio or television advertisements prior to the recent draft guidelines only mentioned a product by name, with no medical claims or performance comparisons mentioned. The FDA guidance outlines acceptable methods for drug companies to refer the public to a source of significant information about the drug, in effect fulfilling the "brief summary" requirement of the FDCA, and has therefore made advertising on the radio or television much more cost-effective. Many firms now provide a Web site or toll-free number in their advertisements to allow consumers access to more complete information about the product in question instead of including the lengthy "brief summary" in the advertisement itself. After reviewing the response to these temporary guidelines, the FDA will issue a final guidance that will also address new concerns such as drug advertising on the Internet.⁵⁶

Western Europe

Industry

Western Europe has an internationally competitive pharmaceutical industry, including both research-based firms and bulk active ingredient producers. Many of the world's top pharmaceutical companies, such as those shown in table 3-1, are active as major producers in the Western European market and industry. Like the leading U.S. drug companies, leading Western European companies are mainly large, multi-product, multinational companies that produce a variety of health care equipment and pharmaceuticals. Industry sources indicate that companies headquartered in Western Europe tend to have facilities located in economically advantageous areas, as is the general practice throughout the pharmaceutical industry.

Although the EU has effectively harmonized member country laws and regulations in many areas, creating a single market for pharmaceuticals has proven to be problematic.⁵⁷ Nonetheless, certain progress has been made. In 1992, harmonization in pharmaceuticals was established in four major areas: wholesale distribution of products, classification of medicines as prescription or OTC, labeling and packaging, and advertising.⁵⁸ The means to extend the

⁵⁴ "Pharmaceutical Advertising Goes Directly to the Consumer," *Chemical Market Reporter*, April 6, 1998, p. 11.

⁵⁵ Mark Peyrot, Neil M. Alperstein, Doris Van Doren, and Laurence G. Poli, "Direct-to-Consumer Ads Can Influence Behavior," *Marketing Health Services*, Summer 1998, pp. 26-32.

⁵⁶ FDA press release (P97-26), "FDA to Review Standards for All Direct-to-Consumer Rx Drug Promotion," Aug. 8, 1997. The ruling is expected during 1999.

⁵⁷ "No EC Harmony on Drug Harmonization," *European Chemical News*, May 24, 1993, pp. 29-30.

⁵⁸ *Ibid.* EU Council Directives 92/25/EEC, 92/26/EEC, 92/27/EEC, and 92/28/EEC, all enacted on Mar. 31, 1992; information obtained from the European Union website (europa.eu.int/eur-lex/en/lif/reg/en_register_133015.html) on March 31, 1999.

patent life of pharmaceuticals, which hurt the generic drug producers but was highly beneficial to research-based companies, was also adopted in 1992 by European Council Regulation (EEC) No. 2309/93.⁵⁹ At that time generics were pushed only by Germany, the United Kingdom, and the Netherlands, though these countries were later joined by other member states.⁶⁰ Additionally, the European Agency for the Evaluation of Medicinal Products (EMA) was established in 1995, providing a unified system for the approval of new drugs.⁶¹ This new system is discussed below.

All Western European countries, including the 15 member of the EU, have their own national health care systems as well as their own distinct drug regulatory agencies. In spite of the overarching single market of the EU, disparities in pricing (market pricing is not the norm), reimbursement policies, and prescribing practices among the countries require the pharmaceutical industry to approach each country differently.⁶² Moreover, the industry faces problems such as parallel importing as a result of the combination of national and supranational laws that affect pharmaceuticals.⁶³ Recent efforts to facilitate greater harmonization for the EU pharmaceutical market are detailed in the section on Government Policies.

Outsourcing has become increasingly important to the Western European pharmaceutical industry. As in the United States, many European pharmaceutical companies are channeling internal resources toward R&D and marketing while contracting out the manufacture of intermediates and active ingredients to fine chemical producers, who are often able to produce complex chemicals more quickly and efficiently than drug producers.⁶⁴ After years of limited interaction between drug companies and fine chemical producers, trust and established expertise have led to the development of longterm strategic partnerships, with the chemical manufacturers involved earlier in the process of drug development.⁶⁵

Although Europe has about 60 percent of the global capacity to provide outsourced services to the patented and brandname pharmaceutical industry, demand from European pharmaceutical firms for outsourcing services accounts for only 30 percent of world demand.⁶⁶ With the trend towards establishing relationships between intermediate suppliers and drug producers, the European pharmaceutical industry expects to increase its outsourcing demand in the future.⁶⁷

⁵⁹ "No EC Harmony on Drug Harmonization," pp. 29-30.

⁶⁰ *Ibid.*, and "European Generics Threatened by SPC," *European Chemical News*, Jan. 18, 1993.

⁶¹ Information obtained from the EMA website (www.eudra.org/abouemea.htm) on January 7, 1999.

⁶² Dr. Philip Brown, "Bringing Order to Pharmaceutical Pricing," *Scrip Magazine*, June 1997, p. 3.

⁶³ Parallel importing is a term applied to the importing of products into a country where those goods are relatively low-priced (typically set low artificially), and the subsequent exporting of those goods to a country with a higher priced market for the same products. Because health care is under the auspices of national Governments, EU countries are allowed to set their own pricing terms; however, the free trade of goods is protected by single market regulations, thereby allowing cheaply purchased drugs to be exported for profit to higher priced countries. This practice benefits the importers/exporters, not pharmaceutical companies. ("Commission Set to Tackle Parallel Pricing Policies," *European Chemical News*, Oct. 19-25, 1998, p. 6.)

⁶⁴ Bill Macdonald, "Middle Management," *European Chemical News*, June 9, 1997, pp. 28, 30.

⁶⁵ *Ibid.*

⁶⁶ Gain, "U.S. Lags Europe," p. 34.

⁶⁷ Sean Milmo, "Outsourcing in Europe Adapts," *Chemical Marketing Reporter*, Aug. 5, 1996, p. SR8.

Employment

Employment levels in the Western European pharmaceutical industry have varied in recent years. During 1985-92, many firms expanded their hiring of new employees, which resulted in an increase of about 79,000 workers to total more than 516,700 employees across the sector. However, with the passage of the Maastricht Treaty, which provided countries with strict fiscal goals for economic and monetary union, and the numerous M&As throughout industry in the years following, employment dropped from 523,000 to 509,500 during 1993-94 (table 3-9). Employment increased to 520,600 employees by 1996, likely the result of increased exporting by the industry. EFPIA estimates that 1997 employment, at 520,000, was down slightly from 1996 levels.⁶⁸

Table 3-9
Employment in the Western European pharmaceutical industry, 1993-97

	1993	1994	1995	1996	1997 ¹
No. of employees	523,000	509,500	516,100	520,600	520,000

¹ Estimated by EFPIA.

Source: EFPIA, *The Pharmaceutical Industry in Figures, 1998*, p. 31.

Based on data for pharmaceutical employees in EU member states only, the labor productivity index rose from 111.7 to 131.2 during 1992-94 (table 3-10). Similarly, the unit labor cost index decreased from 100.9 in 1992 to 88.5 in 1994. These data reflect relatively stable output by the pharmaceutical industry in spite of decreasing numbers of employees.⁶⁹ However, it is also noteworthy that European labor productivity in pharmaceuticals for 1997 equaled only 72 percent of U.S. productivity levels.⁷⁰

Table 3-10
Employment and labor productivity indexes for the EU pharmaceutical industry, 1992-96

	1992	1993	1994	1995	1996
Employment (thousands)	429	422	409	¹ 397	¹ 421
Labor Productivity Index ² (1990=100)	111.7	118.7	131.2	(³)	(³)
Unit Labor Cost Index ⁴ (1990=100)	100.9	95.9	88.5	(³)	(³)

¹ Estimate/forecast.

² Index of production/index of employment.

³ Not available.

⁴ Index of labor costs/index of production.

Source: European Commission, *Panorama of EC Industry 1996*, p. 7-35.

⁶⁸ EFPIA, *The Pharmaceutical Industry in Figures, 1998*, p. 31.

⁶⁹ European Commission, *Panorama of EC Industry 1996*, p. 7-35.

⁷⁰ "Pharma Sector Puts Brake on European Performance," *European Chemical News*, Dec. 1-7, 1997, p. 4.

Research and Development Expenditures

For the Western European pharmaceutical industry, R&D expenditures gradually increased during 1993-96, reaching just over \$14.4 billion in 1996 (table 3-11). Between 1993, when expenditures totaled \$11.6 billion, and 1996, R&D expenditures (in dollar value) increased by approximately 25 percent. Although estimated 1997 R&D expenditures in dollar value show a decrease from reported 1996 levels, the estimated euro value indicates a slight rise in R&D funding during 1996-97.⁷¹

Table 3-11
R&D expenditures by the Western European pharmaceutical industry, in millions of dollars, 1993-97

	1993	1994	1995	1996	1997 ¹
R&D expenditures (millions of dollars)	11,559	12,262	13,943	14,424	13,608

¹ Estimated by EFPIA.

Source: EFPIA, *The Pharmaceutical Industry in Figures, 1998*, p. 21.

Among the countries of Western Europe, the pharmaceutical industries of certain countries have particularly high pharmaceutical R&D spending levels compared with the rest of the world. As a percent of 1995 pharmaceutical R&D expenses worldwide, Germany (10 percent), France (9 percent), the United Kingdom (7 percent), and Switzerland (5 percent) ranked third through sixth, respectively, behind the United States (36 percent) and Japan (19 percent).⁷² Germany in particular has been actively promoting itself as an ideal location for conducting research. According to the German pharmaceutical trade association, Verband Forschender Arzneimittelhersteller, its member companies increased R&D spending by nearly 30 percent during 1994-97.⁷³

Shipments and Trade Balance

As shown in table 3-12, Western European pharmaceutical production increased from \$92.1 billion in 1993 to an estimated \$111.1 billion in 1997, or by 21 percent during the period. Western European exports also increased from \$40.5 billion in 1993 to \$62.1 billion in 1996, a change of about 53 percent. Industry sources indicate that large, world-scale plants have been built in certain Western European countries, such as Ireland, that offer low capital costs and access to a low-cost, skilled labor force. Moreover, Western Europe has several large pharmaceutical production facilities that serve as the base for world distribution of specific types of drugs, including cardiovascular and anti-infective agents; this fact is underscored by the rise in the ratio of exports to production from 44.0 percent in 1993 to 52.3 percent in 1996.⁷⁴

⁷¹ EFPIA, *The Pharmaceutical Industry in Figures, 1998*, p. 21.

⁷² Based on information obtained from the PhRMA website (www.phrma.org/facts/phfacts/8_97a.html) on July 30, 1998.

⁷³ Kevin Gopal, "Home-court Advantage," *Pharmaceutical Executive*, July 1998, pp. 34, 36.

⁷⁴ EFPIA, *The Pharmaceutical Industry in Figures, 1998*, pp. 17, 29.

Table 3-12

Pharmaceuticals for human consumption: Western European production, domestic exports, imports for consumption, merchandise trade balance, apparent consumption, ratio of exports to production, and ratio of imports to consumption, 1993-97

Year	Production	Exports ¹	Imports ¹	Trade balance	Apparent Consumption	Ratio of Exports to Production	Ratio of Imports to Consumption
	(millions of dollars)					(percent)	
1993	92,069	40,537	27,523	13,013	79,055	44.0	34.8
1994	99,007	46,712	31,766	14,946	84,061	47.2	37.8
1995	114,038	57,594	39,480	18,115	95,923	50.5	41.2
1996	118,731	62,115	42,711	19,404	99,326	52.3	43.0
1997	² 111,136	(³)	(³)	(³)	(³)	(³)	(³)

¹ Trade data include exports and imports within Europe.

² Estimated by EFPIA.

³ Not available.

Source: EFPIA, *The Pharmaceutical Industry in Figures, 1998*, pp. 17, 29.

Because the trade data presented in table 3-12 include exports and imports within Western Europe, the ratio of exports to imports is lower than if intra-regional trade were not included. Based on the data in table 3-12, the ratio is around 1.5 for 1996; when data on trade exclusively outside of the region are used, the ratio is about 3.1 for the same year. The significant disparity in these ratios reflects the high level of trade in pharmaceuticals within Western Europe.⁷⁵

The Western European market for pharmaceuticals, in terms of value, is the largest in the world.⁷⁶ The value of Western European consumption of pharmaceuticals increased from about \$79.0 billion to \$99.3 billion during 1993-96, and the imports-to-consumption ratio fluctuated between 34.8 and 43.0 percent during 1993-96. Western Europe has a higher population than the United States, and per capita expenditures for health care in Germany and France, two of the most developed European countries, are higher. According to recent data, the United States spends less on pharmaceuticals as a percent of total health care spending than any industrialized EU country.⁷⁷ Western European production and consumption trends observed during 1993-97 are expected to continue in the next few years.⁷⁸

⁷⁵ *Ibid.*, pp. 27, 29.

⁷⁶ Compare apparent consumption, tables 3-6 and 3-12. However, the United States is the leading market for prescription drugs. See pp. 3-3, 3-4.

⁷⁷ *PhRMA Industry Profile, 1997*, p. 48.

⁷⁸ European Commission, *Panorama of EC Industry 1996*, pp. 7-34 - 7-37.

Biotechnology Products

For some years the United States has been a recognized leader in biotechnology, but recently the industry in Europe has begun to emerge as a contender. Industry surveys indicate that the number of European biotechnology companies increased by 25 percent during 1997, with a 35 percent rise in employment.⁷⁹ Moreover, R&D expenditures per biotech employee are comparable in the United States and Europe.⁸⁰ The recent increase in European activity can be attributed to a combination of factors. Most importantly, the various national patent laws of member states were homogenized under EU-wide legislation to permit patents on genetically engineered plants and animals, which met with strong opposition from the so-called “green” movement among others.⁸¹ Also of importance is Germany’s formal commitment to developing its biotech industry, which was underscored by \$1.14 billion in Government and private support for biotech projects in 1995.⁸²

The European biotech industry still faces some significant challenges. In fact, it has been argued that European biotech companies are more involved in the production of equipment and basic chemical and biological building blocks used in the industry than in the development of biopharmaceutical applications.⁸³ There are also assertions that the EU regulatory agency, the EMEA, is a problem for this sector in particular. Compared with the FDA approval process, the European system is said to lack the speed and transparency necessary for a truly competitive biotech industry.⁸⁴

Government Policies

Since the member states of the EU are responsible for determining their own health care policies, and pharmaceutical expenditures are a category of a health care budget, each nation has its own system of pricing drugs. In general, there are several factors that influence a drug pricing system. The Government funding allocated for health care, which is often a reflection of the social policy of a country, puts an overall constraint on how much the Government can budget for drugs. The financial goals established under the Maastricht Treaty provided considerable incentive for Governments to reduce expenses across all sectors, and pharmaceuticals were affected by these cost-cutting measures.⁸⁵ Additionally, the cost of living in a country often affects the perception of what is considered to be a reasonable price for pharmaceutical product. As a result of the differences in budget size, social policies, and wealth among the EU-15, pharmaceutical prices vary widely (table 3-13) from country to country.

⁷⁹ “Europe’s Biotechnology Sector is Booming,” *European Chemical News*, 13-19 April 1998, p. 40.

⁸⁰ “European Entrepreneurial Life Sciences Surge Ahead,” *Chemical Market Reporter*, June 1, 1998, p. 9.

⁸¹ Alex Scott, “Europe Approves Patent Law,” *Chemical Week*, May 20, 1998, p. 19.

⁸² “Shot in the Arm for Biotech R&D,” *The Economist*, Nov. 9, 1996, p. S12B.

⁸³ “International Competition,” *Pharmaceutical Executive*, May 1998, p. 32.

⁸⁴ “Regulations are Making Europe a Biotech Dinosaur,” *European Chemical News*, 23-29 March 1998, p. 8.

⁸⁵ EFPIA, *The Pharmaceutical Industry in Figures, 1998*, p. 10.

Table 3-13
International pharmaceutical price indexes in the EU, 1993

Country	OECD ¹	ABDA ²
Denmark	164	133
Germany	152	105
Netherlands	152	148
Austria	129	NA
Ireland	128	133
Belgium	113	116
United Kingdom	111	123
Luxembourg	110	97
Finland	108	NA
Sweden	108	NA
EU-15 average	100	100
Portugal	77	67
France	76	63
Italy	72	96
Spain	63	94
Greece	51	85

¹ Organization for Economic Cooperation and Development.

² ABDA is the German pharmacists' association.

Source: Ian Senior, "International Medicine Prices — Is a New Index Needed?" *Scrip Magazine*, Sept. 1996, p. 13.

A subcommittee of the EU Council of Ministers, the Internal Market Council (IMC), recently acknowledged that the competitiveness of the EU pharmaceutical industry is negatively affected by the combination of the right to the free trade of goods, protected under EU law, and national pharmaceutical pricing systems. In its report to the European Commission, the IMC suggested ways to reduce price differentials across the Common Market.⁸⁶ The IMC recognized that pharmaceutical pricing is largely a function of national social policy and the size of a country's health budget, making an EU-wide pricing policy impractical; however, the IMC noted that within the pharmaceutical sector there are different product groupings, such as OTC products and generics, that might be reasonable candidates for longterm deregulation plans.⁸⁷ The importance of R&D was also emphasized as a means to minimize health care costs by offering innovative, more efficient treatments.⁸⁸

⁸⁶ Per Wold-Olsen, "Completing the Single Market for Medicines in Europe," *Scrip Magazine*, July/Aug. 1998, pp. 11- 12.

⁸⁷ Kevin Gopal, "In Search of Direction," *Pharmaceutical Executive*, Aug. 1998, pp. 30-34.

⁸⁸ Wold-Olsen, "Completing the Single Market for Medicines," pp. 11- 12.

Notably, the European Commission has been clear that it will not underscore the EU objective of competitiveness to the detriment of the right to free movement of goods, thereby securing the right to continue parallel importing.⁸⁹ In the pharmaceutical market in particular, where each EU country determines its own drug pricing, price differentials are not likely to be diminished through free trade.⁹⁰ Based on the work of the IMC, in November 1998 the European Commission issued a communication on harmonization for the pharmaceutical market. From the perspective of the EFPIA, the European Commission did not present a vision for harmonizing the pharmaceutical market as had been expected, but rather provided a listing of suggested cost-containment measures relating to pharmaceuticals.⁹¹ Recent meetings involving the industry, the 15 member states, and the European Commission to resolve these disputes and design a coherent framework for the single market for pharmaceuticals have only met with moderate success.⁹²

The EMEA began operations in 1995, establishing a new system for the approval of pharmaceutical products in the EU. The EMEA, which is headquartered in London, England, has several important functions. Primarily, it is intended to provide multinational expertise for EU-wide procedures to authorize, monitor, and withdraw pharmaceutical products. The EMEA also advises pharmaceutical companies on research activities and coordinates the efforts of the national agencies that maintain the quality and safety of pharmaceutical products. Additionally, the EMEA is responsible for coordinating information systems across the EU for the purpose of facilitating informed drug use.⁹³

Along with the creation of the EMEA came the introduction of two new drug approval procedures. The first is the centralized procedure, which results in EU-wide authorization. Centralized approval is required for all biotechnology products and certain veterinary pharmaceuticals. Under this process, an application is submitted by a company directly to the EMEA, which then sends the application on to its Committee for Proprietary Medicinal Products (CPMP) for its review. The CPMP evaluation is due for delivery to the European Commission, the member states, and the applicant within 210 days. The European Commission then has 30 days to draft its decision on whether or not to approve the proposed pharmaceutical.⁹⁴

In the decentralized procedure, an application is submitted directly to the national drug regulatory agency of the applicant's choice. The national authorizing agency uses its normal assessment procedure to render an opinion on the application. The agency must supply an exhaustive report for any products it approves, in addition to granting approval to the text of the product label and patient information leaflet. The applicant then has the opportunity to forward that exact application on to the regulatory agencies of other member states, who have 90 days to review the report from the original authorizing agency and render their own

⁸⁹ *Ibid.*, p. 12.

⁹⁰ Dr. Eckhard Kucher, "An International Strategy for Pricing and Profits," *Scrip Magazine*, September 1997, p. 30.

⁹¹ Kevin Gopal, "The State of Europe: An Expanded European Report," *Pharmaceutical Executive*, Jan. 1999, p. 34.

⁹² *Ibid.*, pp. 33-37.

⁹³ Information obtained from the EMEA website (<http://www.eudra.org/abouemea.htm>) on January 7, 1999.

⁹⁴ Stef Eckman, "The Wheels are Finally Starting to Turn at the EMEA," *Medical Marketing and Media*, Jan. 1995, p. 32.

judgements. In the event that any country rejects an approved application, the EMEA is responsible for settling the points of conflict.⁹⁵

The EMEA and CPMP are under the auspices of the EU's Directorate General (DG) III, the directorate in charge of industry affairs. As a result, certain critics have suggested that the EMEA's ability to protect public safety is constrained by its obligation to maintain both the competitiveness of the pharmaceutical industry as well as free trade of pharmaceutical products. Because of these assertions, a separate Scientific Committee on Medicinal Products and Medicinal Devices (SCMPMD) was established under DG XXIV, the directorate for Consumer Policy and Consumer Health Protection, in November 1997. Although both the CPMP and SCMPMD currently seem to have distinct and useful functions, this situation may be complicated if DG V, the directorate for public health, goes forward on proposals to create its own committee to advise on pharmaceuticals.⁹⁶

The national drug approval agencies are still important, even with the existence of the EMEA. National agencies are the primary actors in the EMEA's decentralized procedure, and national authorization procedures are still available for drugs marketed solely in one member state. However, by coordinating and monitoring the activities at the national level, the EMEA is expected to improve the regulatory environment for the European pharmaceutical market by minimizing the fees and the time investments associated with drug approval.⁹⁷

The EU is currently reviewing legislation that would establish orphan drug incentives under the EMEA. Under current policies, the EMEA may waive its fees, which typically total about \$222,000, when processing drugs intended for the treatment of rare diseases. However, the EMEA's limited funding curbs the number of drugs for which fees can be exempted, and the EU affords no particular market protection to orphan drugs.⁹⁸ By comparison, the United States offers orphan drug developers several incentives, including research grants, tax incentives,⁹⁹ and a guarantee of 7 years of market exclusivity. The EU has recognized its need to develop comparable policies if it is to become more competitive in the orphan drug market segment.¹⁰⁰

According to the latest proposals, the new EU orphan drug regulations will likely result in all orphan drugs being processed through the EMEA at no cost to the applicants. There will also be provisions for 10 years of market protection, with certain caveats for drugs initially developed for rare diseases but later found to have more broadly based applications.¹⁰¹ Additionally, patients will be represented on the EMEA committee responsible for determining which drugs qualify as orphan drugs, reflecting an unprecedented level of inclusion of EU patients in drug policy-making. These proposals are expected to be refined and eventually adopted by the 15 EU countries by the end of 2000.¹⁰²

⁹⁵ *Ibid.*, and Martin Harvey, "EMEA Open for Business," *Pharmaceutical Executive*, Mar. 1995, p. 24.

⁹⁶ Dr. John Griffin, "Is Change Needed in the EMEA Drug Approvals Process?" *Scrip Magazine*, September 1998, p. 27.

⁹⁷ Harvey, "EMEA Open for Business," p. 24.

⁹⁸ "EU in Move to Encourage 'Orphan Drug' Development," *European Chemical News*, July 26, 1998, p. 8.

⁹⁹ Because the national Governments of EU member states have control of fiscal policy, EU-mandated incentives such as tax credits are not possible. *Ibid.*

¹⁰⁰ "Business: Safety in Numbers," *The Economist*, May 30, 1998, pp. 64-65.

¹⁰¹ "EU to Encourage 'Orphan Drug' Development," p. 8.

¹⁰² "Business: Safety in Numbers," pp. 64-65.

The EU is considering the elimination of its current ban on DTC advertising. The recent loosening of regulations on DTC advertisements in the United States has significantly increased the amount of information on prescription drugs available via the Internet, thereby giving Europeans access to information posted online in other countries. European pharmaceutical companies, however, are prohibited from disseminating information in this matter, putting them at a disadvantage in the market. It is expected that initial policy changes on this issue will likely involve increased freedom to distribute product information to patients, while a more formal directive on advertisements will probably take several years to finalize.¹⁰³

Japan

Industry

Japan's pharmaceutical market is the third largest in the world behind the United States and Western Europe. In fiscal 1996, the Japanese spent about \$53.5 billion on pharmaceuticals of all types, with nearly \$42.5 billion (about 80 percent) spent on prescription drugs alone.¹⁰⁴ As such a large market, it would seem likely to attract foreign interest. However, the pharmaceutical industry in Japan is decidedly more domestic in nature than the industries of Western Europe and the United States.¹⁰⁵

The top 20 Japanese pharmaceutical firms, based on sales in Japan, are listed in table 3-14. For this market, it is difficult to compare non-Japanese with Japanese companies, because sales data for U.S. and Western European pharmaceutical firms in Japan are likely to include sales of other, non-pharmaceutical products by the companies. Novartis (Switzerland), with the highest total 1996 sales in Japan among non-Japanese pharmaceutical companies, ranks no higher than thirteenth when its total sales (\$1.2 billion) are compared with pharmaceutical-only sales by Japanese companies.¹⁰⁶ By comparison, the U.S. and Western European markets reflect a more globalized pharmaceutical industry, as U.S. and European firms typically sell their products in multiple foreign markets.

Although Japan is open to foreign pharmaceutical firms, according to a report by the Japan External Trade Organization (JETRO), non-Japanese companies seem to encounter significant hindrances to entering the Japanese market. Among the 230 global NCEs¹⁰⁷ introduced since 1985, only 100 have been marketed in Japan.¹⁰⁸ The JETRO 1998 report "Survey on Actual Conditions Regarding Access to Japan" outlines several factors that

¹⁰³ "Update for EU Advertising Rules," *Scrip*, No. 2378, Oct. 14, 1998, p. 4.

¹⁰⁴ "JETRO Identifies Japanese Entry Barriers," *Scrip*, No. 2352, July 15, 1998, p. 17.

¹⁰⁵ Robert Triendl, "Japan's Drug Manufacturers Edge toward Globalization," *Research Technology Management*, Sep./Oct. 1998, p. 8.

¹⁰⁶ Japan Pharmaceutical Manufacturers Association (JPMA), *Data Book 1997/98*, p. 1-10, and Yakugyo Jiho, *Pharmaceutical Handbook '98*, p. 114. As indicated, this ranking is qualified because data for Novartis, which are likely to include non-pharmaceutical products, are compared with data for pharmaceutical-only sales by Japanese companies.

¹⁰⁷ A global NCE is one that has been marketed in at least seven industrialized countries.

¹⁰⁸ "'Drug Lag' a Growing Problem in Japan," *Scrip*, No. 2356, July 28, 1998, p. 18.

Table 3-14**The top 20 Japanese pharmaceutical companies, by Japanese pharmaceutical sales, and total sales, in millions of dollars, fiscal 1996**

Company	Pharmaceutical sales, 1996 (in million dollars)	Total sales, 1996 (in million dollars)
Takeda	4,226	5,858
Sankyo	3,644	4,070
Yamanouchi	2,831	2,872
Eisai	2,157	2,371
Daiichi	2,047	2,106
Taisho Pharmaceutical	1,971	2,185
Fujisawa	1,866	2,065
Shionogi	1,828	2,112
Chugai	1,569	1,569
Tanabe	1,518	1,709
Kyowa Hakko	1,509	3,106
Banyu	1,338	1,341
Ono Pharmaceutical	1,105	1,163
Dainippon	1,013	1,264
Meiji Seika	754	2,351
Yoshitomi	706	992
Santen	674	690
Tsumura	685	851
Mochida	586	668
The Green Cross ¹	575	657

¹ The Green Cross was acquired by Yoshitomo in April 1998. (Robert Triendl, "Japan's Drug Manufacturers Edge toward Globalization," *Research Technology Management*, Sept./Oct. 1998, p. 9.)

Source: JPMA, *Data Book 1997/98*, p. 1-10.

are affecting entry of foreign firms into the Japanese pharmaceutical market. First, companies entering the market must acquire licenses for importing and sales, manufacturing, and wholesaling of pharmaceutical products. Comparatively, entry into the U.S. and European markets is a more streamlined, less bureaucratic process.¹⁰⁹ The Japanese drug approval

¹⁰⁹ "JETRO Identifies Japanese Entry Barriers," p. 18.

process can also be problematic for foreign companies. In the past, the primary obstacle has been the mandatory repeating of costly clinical trials in Japan to establish data for the local population, which the Ministry of Health and Welfare (MHW) argues has critical biological and dietary differences from U.S. and European patients; however, recent policy revisions have mitigated this factor considerably.¹¹⁰ Also, the establishment of “good clinical practices” (GCP) has challenged researchers, who are still adapting to the new requirements.¹¹¹

The Japanese pricing system has also been identified by JETRO as a disincentive for foreign innovative pharmaceutical companies. Although a new system will be in place by the year 2000, the current reimbursement price scheme (described in the Government Policies section) allows the Government to set reimbursement prices that do not always reflect the high R&D costs of innovative drugs. By comparison, “me-too” products reportedly gain disproportionately from the current price system.¹¹²

Lastly, the Japanese pharmaceutical market requires a large sales presence to maintain sufficient contact with physicians. For a foreign company not already established in the market, the added costs of a large staff of sales representatives can be a strong disincentive to market entry, particularly in conjunction with the other factors noted above.¹¹³

Just as foreign firms are not widely represented in the Japanese market, Japanese firms could be considered under-represented in the global pharmaceutical market. For example, the top two Japanese pharmaceutical companies, Takeda and Sankyo, are ranked twentieth and twenty-second behind companies headquartered in the United States or Western Europe (table 3-1).¹¹⁴ However, there are indications that Japanese companies may be growing more global in their outlook. In particular, Takeda has established a wholly owned subsidiary in the United Kingdom (Takeda UK), plus holding companies in other European countries and the United States. Reportedly, other firms have plans to increase foreign operations, including expansions within East Asia.¹¹⁵

Employment

Because company layoffs are an anomaly in the Japanese culture, employment data for a given period are not an effective means of monitoring the overall health of an industry. Nonetheless, table 3-15 shows employment in the Japanese pharmaceutical industry during 1992-96. It should be noted that only 1995 data are inclusive of all Japanese pharmaceutical companies.

¹¹⁰ Information obtained from industry contacts, February 1999.

¹¹¹ “JETRO Identifies Japanese Entry Barriers,” p. 18.

¹¹² *Ibid.*

¹¹³ *Ibid.*

¹¹⁴ “Much Promised, but Little Delivered in ‘98,” *European Chemical News*, Nov. 30, 1998, p. 23.

¹¹⁵ Triendl, “Japan’s Drug Manufacturers Edge toward Globalization,” p. 8.

Table 3-15
Employment in the Japanese pharmaceutical industry, fiscal 1992-96

	1992 ¹	1993 ¹	1994 ¹	1995 ²	1996 ³
Pharmaceutical employees	149,100	159,600	160,300	244,774	152,699

¹ Based on a survey of the top 100 companies; in 1992, only 96 companies responded.

² Data inclusive of all Japanese pharmaceutical companies.

³ Based on a survey of the 86 JPMA firms.

Source: JPMA, *Data Book 1997/98*, p. 1-3.

Research and Development Expenditures

R&D expenditures by the Japanese pharmaceutical industry increased from \$5.1 billion in 1992 to \$6.1 billion in 1996, with a peak of \$6.8 billion in 1995 (table 3-16). However, the ratio of R&D to sales for Japanese companies decreased marginally during 1992-96, from 8.7 percent to 8.1 percent. In 1994 the ratio was at its lowest, 7.8 percent.¹¹⁶

Table 3-16
R&D expenditures by Japanese pharmaceutical companies, and ratio of R&D to sales, in millions of dollars, 1992-96

Year	Japanese R&D expenses (millions of dollars)	Ratio of R&D to sales (percent)
1992	5,080	8.7
1993	5,658	8.2
1994	6,191	7.8
1995	6,828	8.0
1996	6,133	8.1

Source: JPMA, *Data Book 1997/98*, p. 1-32.

Over the five-year period, the total amount spent on pharmaceutical R&D by Japanese companies was considerably lower than expenditures by U.S. firms. Similarly, the ratio of Japanese pharmaceutical companies' R&D expenditures to sales was significantly lower than the same ratio for U.S. companies (table 3-5). These data may support the claims by some industry analysts that conditions in Japan, including regulatory and pricing policies, are less conducive to innovative pharmaceutical research than those of the United States.

¹¹⁶ JPMA, *Data Book 1997/98*, p. 1-32.

Although the Japanese pharmaceutical industry has traditionally been domestically focused, the trend toward globalization is even affecting R&D. Pharmaceutical R&D increasingly involves highly complex research tools (such as genomics and combinatorial chemistry¹¹⁷) that are used extensively by European and U.S. scientists. Because Japanese scientists are generally less experienced with these tools, some Japanese companies have begun to conduct research activities in Western Europe and the United States.¹¹⁸ Furthermore, Japanese companies have not yet adapted fully to GCP, which was established by the MHW in 1997. These guidelines were introduced to make Japanese drug development practices consistent with the standards of the United States and Western Europe. However, the formal incorporation of GCP into the behavior of clinical researchers takes time and training, which has created further incentive for the use of foreign clinical research facilities.¹¹⁹

Shipments and Trade Balance

During 1992-96, Japan was a net importer of pharmaceuticals, with a trade deficit ranging from a low of \$1.9 billion in 1992 to a high of \$3.1 billion in 1995 (table 3-17). Japanese exports rose steadily from \$1.4 billion to \$2.1 billion during the five-year period, whereas imports reached a peak of \$5.0 billion in 1995, declining to \$4.6 billion in 1996.¹²⁰ Japanese shipment data for pharmaceuticals were not available at the time this report was prepared.

Table 3-17

Pharmaceuticals: Japanese domestic exports, imports for consumption, merchandise trade balance, ratio of imports to exports, and exports as a percent of sales, 1992-96

Year	Exports	Imports	Trade balance	Ratio of imports to exports	Exports as a percent of sales ¹
	<i>(millions of dollars)</i>				
1992	1,447	3,396	-1,949	2.35	4.4
1993	1,562	3,972	-2,410	2.54	3.8
1994	1,646	4,251	-2,605	2.58	2.3
1995	1,962	5,014	-3,052	2.56	2.5
1996	2,097	4,591	-2,494	2.19	2.5

¹ Based on JPMA companies only.

Source: JPMA, *Data Book 1997/98*, pp. 1-19, 1-21.

Japanese exports comprise a small percentage of total pharmaceutical sales compared with the United States (table 3-6). During 1992-96, this ratio reached a high of 4.4 percent in

¹¹⁷ Genomics is the study of genes and their functions. Combinatorial chemistry is a research technique involving the systematic combination of molecules and molecular building blocks to develop thousand of new compounds, which are then tested for potential use as pharmaceutical products, in a short period of time.

¹¹⁸ Triendl, "Japan's Drug Manufacturers Edge toward Globalization," p. 8.

¹¹⁹ "Drug Lag' in Japan," p. 18.

¹²⁰ JPMA, *Data Book 1997/98*, p. 1-19.

1992, falling to 2.3 percent in 1994.¹²¹ By comparison, the U.S. industry ratio of exports to shipments was approximately 12 percent throughout the period. These data seem to underscore the domestic orientation of the Japanese industry.

Japan's trading partners in pharmaceuticals are primarily the United States and Western Europe. In 1996, the key pharmaceutical export markets for Japan were the United States (30 percent), Germany (10 percent), and France (9 percent). In the same year, Japan imported pharmaceuticals principally from Germany (20 percent), the United States (20 percent), and the United Kingdom (11 percent).¹²²

Biotechnology Products

The Japanese biotechnology industry has not met the high expectations of the Ministry of International Trade and Industry (MITI), which in 1981 declared it to be one of three high priority industries.¹²³ One weakness is that compared with the United States, Japan has less funding available for the basic research on which biotechnology thrives.¹²⁴ Additionally, biotechnology is a fast-paced field where scientists move around among different laboratories, which is inconsistent with the scientific culture in Japan.¹²⁵ Eighty percent of Japan's demand for all biotechnology products, which is similar in size to the U.S. market, must be supplied by imports; this reflects a significant missed opportunity for the Japanese biotech industry.¹²⁶

Government Policies

When the Japanese health care system was originally established in 1961, it was appropriately designed to serve a young population with greater needs for acute rather than chronic care. As the population aged, and Japan's economic growth slowed, the Japanese Government began to look for ways to reduce health care costs. For example, beginning in September of 1997, patients faced higher insurance copayments, a move the Government hoped would curb demand for medical products and services. However, sufficient change could not be affected through modifications to the established system, and the MHW mandated a reform plan to incorporate several objectives.¹²⁷ A formal health care reform bill is expected in the spring of 1999.¹²⁸

Given the changing demographics of Japan, one intended reform is the establishment of clear delineations in insurance programs for old versus young patients and acute versus chronic conditions. Additionally, fee-for-service insurance policies are to be eliminated in favor of flat-sum reimbursements. However, the most significant revision from the perspective of the

¹²¹ *Ibid.*, p. 1-21.

¹²² *Ibid.*, p. 1-20.

¹²³ "Biotechnology in Japan: Alien Culture," *The Economist*, Nov. 18, 1995, p. 79.

¹²⁴ *Ibid.*

¹²⁵ "Biological Warfare: How the U.S. Triumphed and Japan Beat Itself," *Fortune*, April 1, 1996, p. 40.

Also, for more information see the Commission's *1991 Competitiveness Study*.

¹²⁶ "Biotechnology in Japan," *The Economist*, p. 79.

¹²⁷ P. Reed Maurer, "Understanding Japan's Changing Rules," *Scrip Magazine*, Feb. 1998, p. 37.

¹²⁸ "Japanese Groups Renew Call for Free Pricing," *Scrip*, No. 2365, Aug. 28, 1998, p. 12.

pharmaceutical industry is the planned revamping of the pricing system.¹²⁹ Notably, both foreign and domestic industry groups have been consulted in the development of the new system.¹³⁰

The pharmaceutical pricing system in Japan is based on set reimbursement prices, which are paid to health care providers for products disbursed, and the actual prices charged by wholesalers for those products. The difference between these two prices is a profit for the physician, a system which encourages excessive prescribing and negotiations of discounts from the wholesalers. The Government has undertaken certain measures to mitigate these factors, such as setting the reimbursement price as a percent of the physician's actual price and reducing reimbursement prices when the number of prescriptions exceeds a predetermined limit. Nonetheless, the history of reimbursement pricing has played a significant role in shaping the innovative pharmaceutical industry.¹³¹

Because the Japanese market puts a high premium on new drugs, pharmaceuticals are introduced at a higher price than in the U.S. or Western European market. However, Japanese prices drop off fairly quickly, as the MHW revises the reimbursement prices to reflect the actual costs negotiated by health care providers. In this way, companies have an incentive to introduce new products to maximize price advantages.¹³² However, it has been argued that instead of truly innovative drugs, in some cases reimbursement pricing encouraged the introduction of "me too" drugs.

But industry analysts differ in their views on the value of truly unique, innovative drugs versus newly improved versions of existing products. Some would argue that the disproportionate emphasis on the former neglects the significant impact that small modifications to a pharmaceutical product can have on drug treatment. As "me too" drugs have somewhat fallen into disfavor with the price setting regime, there have been reports of Japanese companies dropping development plans for effective new drugs in clinical trials because those products were not expected to be considered innovative enough for top-level pricing.¹³³

It is anticipated that Japan will replace reimbursement pricing with a reference pricing system.¹³⁴ With reference pricing, a Government sets a ceiling on the amount to be reimbursed for the purchase of a pharmaceutical product, leaving the patient or his insurer responsible for any difference between the actual price and the reference price. In setting these price ceilings, the Government typically classifies products together in groups based on chemical structure or therapeutic application, and all products included in a particular group are assigned the same price. As a result, patented products and generic products may be given the same price value, diminishing the advantage of market exclusivity for a new drug.¹³⁵

The innovative pharmaceutical companies have responded negatively to the proposed reference pricing for patented products, asserting that such a system is essentially an

¹²⁹ Maurer, "Understanding Japan's Changing Rules," p. 37.

¹³⁰ "Japanese Groups Renew Call for Free Pricing," *Scrip*, p. 12.

¹³¹ This summary of the Japanese pricing system is based on discussions with various industry sources; similar information can be found in trade journal articles.

¹³² P. Reed Maurer, "A Watershed for the Industry in Japan," *Scrip Magazine*, April 1996, p. 42.

¹³³ Peter O'Donnell, "Are Japanese Cuts Starting to Bite?" *Pharmaceutical Executive*, Sept. 1996, p. 36.

¹³⁴ "Japanese Groups Renew Call for Free Pricing," *Scrip*, pp. 12-13.

¹³⁵ *PhRMA Industry Profile 1998*, p. 72.

infringement of IPR. The Japanese Government has stated that granting unique pricing status to patented drugs could result in a rise in “me-too” products, already considered by some to be a problem under reimbursement pricing. However, the pharmaceutical companies have rebutted that argument, noting that “me-too” drug development in Japan has slowed, largely as a result of international harmonization policies such as patient consent requirements for clinical trials and improved data reviews.¹³⁶

In addition to the planned reforms to the health care system, the MHW itself has also been the focus of change. In the wake of scandals relating to the pharmaceutical industry, a major reorganization of the MHW went into effect on July 1, 1997. The now-defunct Pharmaceutical Affairs Bureau (PAB), once responsible for both the regulation and the promotion of the pharmaceutical industry, has been replaced by a new entity, the Pharmaceutical and Medical Safety Bureau (PMSB). The PMSB is responsible primarily for safety and efficiency in the approval process and post-market regulation of drugs, cosmetics, and medical devices, while the Health Policy Bureau of MHW has taken on the task of promoting the industry.¹³⁷ Under the former structure one bureau was responsible for regulating and promoting the same industry, often creating an inappropriately close relationship between PAB bureaucrats and Japanese pharmaceutical companies.¹³⁸ The new organizational structure of the MHW is expected to give foreign companies a more level playing field in the drug approval process due to improved transparency; moreover, the approval process itself is expected to be harmonized with U.S. and European processes, which will also benefit foreign companies.¹³⁹ This new bureaucracy has been well-received by the U.S. industry as a move forward for the Japanese market.¹⁴⁰

Based on the terms of the U.S.-Japan Enhanced Initiative on Deregulation and Competition, which was signed at the G8 summit held in May 1998, several modifications to the Japanese drug approval process will be implemented over the next few years. The processing of new drug applications will be expedited, with the goal of reducing review periods to 12 months by April 2000. The agreement also requires the Japanese to accept foreign clinical trial data in accordance with the terms of the International Conference on Harmonization (ICH). More generally, the Japanese Government expressed its commitment to acknowledge the merit of innovative products and to consult with foreign pharmaceutical firms on issues for which the domestic industry is consulted.¹⁴¹

¹³⁶ Now that patient consent is required for clinical trials, some potential trial candidates are hesitant to agree to participate when there is a similar product already on the market. “Japanese Groups Renew Call for Free Pricing,” *Scrip*, pp. 12-13.

¹³⁷ “Japan: New Pharmaceutical Bureau,” *East Asian Executive Reports*, June 15, 1997, p. 6.

¹³⁸ P. Reed Maurer, “Crisis at Koseisho: Japan’s Mega-Agency Finally Faces Change,” *Pharmaceutical Executive*, January 1997, p. 60, and “Cleaning House,” *Pharmaceutical Executive*, January 1997, p. 61.

¹³⁹ Maurer, “Crisis at Koseisho,” pp. 60-61.

¹⁴⁰ “Japan: New Pharmaceutical Bureau,” p. 6.

¹⁴¹ “Japan to Speed Up Product Approvals,” *Scrip*, No. 2338/39, May 27/29, 1998, p. 21, and PhRMA press release, “U.S.-Japan Agreement Will Bring Innovative Medical Products to Japanese Patients Sooner, Says PhRMA,” May 15, 1998, obtained from the PhRMA website (www.phrma.org/news/5-15-98.html) on June 23, 1998.

The Japanese Government has also loosened regulations related to the use of contract research organizations (CROs)¹⁴². Although CROs have played an important role in the pharmaceutical industries of Western Europe and the United States, where their work is held in high esteem, Japan considered data provided by these organizations to be of lower quality than data of the pharmaceutical companies. As of June 1997, there were approximately 700 CROs operating in the United States and Europe, while Japan only had about 13.¹⁴³ However, as the result of a 1996 MHW report, there is a more positive perception of CROs, and allowances have been made to incorporate them fully into the development stage for pharmaceuticals in Japan. By facilitating the final stages of product development, particularly clinical trials, for foreign companies, this could prove to be a significant step toward increased access to the Japanese market.¹⁴⁴

¹⁴² In the pharmaceutical industry, CROs typically run clinical trials for pharmaceutical firms seeking new drug approval. By specializing in this stage of product development, CROs can save companies both time and expense by carefully constructing the trials so that the highest quantity of useful information can be obtained in the fewest number of trials. Furthermore, CROs have experience in presenting clinical trial data clearly and efficiently to regulatory agencies, enhancing the likelihood and speed in receiving approval for a product. (Geoffrey Carr, "Survey: The Pharmaceutical Industry: Trials and Tribulations," *The Economist*, Feb. 21, 1998, p. S13-S15.)

¹⁴³ Stephen Barker, "Reforming the Clinical Trials Process in Japan," *Scrip Magazine*, June 1997, p. 14.

¹⁴⁴ Stephen Bentley, "CROs in Japan — New Tools for Industry," *Pharmaceutical Executive*, Nov. 1997, pp. 80-84.

CHAPTER 4

Current Issues in the Pharmaceutical Industry

Since the Commission's 1991 competitiveness study, two major trade agreements have affected the U.S. economy: the Uruguay Round Agreements¹ (URA) which entered into force on January 1, 1995, and NAFTA, which entered into force on January 1, 1994. Both of these agreements affected the pharmaceutical industry, largely by reducing tariffs and enhancing intellectual property rights (IPR) protection. Stronger IPR protection should particularly benefit the U.S. pharmaceutical industry in its ability to compete, as losses due to unauthorized copying of patented drug products amount to an estimated \$2-5 billion per year.² However, it could be argued that the most significant change came from the URA, under which the United States and 21 other countries³ agreed to eliminate tariffs on pharmaceutical finished products, certain active ingredients, and certain approved chemicals used by the pharmaceutical industry.

The following section describes the duty reductions and enhanced protection of IPR negotiated during the Uruguay Round and NAFTA. The section also includes an analysis of trade data during 1992-97 to assess the effect of duty reductions on trade flows. The last section provides an overview of the significant changes that have occurred in national IPR and patent policies worldwide as a result of international agreements.

Changes in International Agreements

GATT/WTO Agreements

GATT was originally negotiated in 1947. The legal framework of the GATT established basic disciplines in international trade, liberalized markets by reducing tariff and nontariff barriers, and provided a forum for dispute settlement, among other objectives. The agreement rests on the legal pillars of nondiscrimination and national treatment and is accompanied by

¹ The legislation that implemented the URA in the United States is known as the Uruguay Round Agreements Act (URAA).

² Theresa Beeby Lewis, "Patent Protection for Pharmaceuticals: A Survey of the Patent Laws of Various Countries," *Int'l Lawyer*, 30, pp. 835, 845 (winter 1996). The Pharmaceutical Manufacturers Association (now "PhRMA") estimated that patent piracy accounted for \$6.4 billion in yearly losses worldwide for the U.S. drug industry. *Ibid.* at 844-45. These estimates are typically calculated by multiplying the estimated number of pirated copies sold by the price of the item set by the patent holder or licensee. Consequently, these figures are frequently considered to be inflated because they do not take into account that demand for the product drops as the price rises.

³ The EU-15, Canada, Czech Republic, Japan, Norway, Slovak Republic, and Switzerland. However, some of these countries decided to stage tariffs down to zero gradually as opposed to an immediate elimination.

schedules of tariff concessions negotiated by the parties and by subsidiary specialized codes.⁴ The GATT was supervised over the years by a small secretariat body, which conducted regular meetings of the contracting parties and provided general legal and technical support.

Following several rounds of multilateral tariff negotiations and a significant expansion of membership over time, the latest round opened in Uruguay in 1994.⁵ The established basis for the Uruguay Round was that the GATT and its subsidiary agreements were designed to succeed or fail as a unit, and the eventual package was to be adopted by means of a single instrument. Countries would eventually have the choice of remaining as parties to the 1947 GATT, with membership in subsidiary agreements optional, or of joining the new 1994 WTO Agreement with all rights and obligations entailed in the package. The signatories to the WTO Agreement reserved the right to adopt differential treatment toward nonsignatories, with a view toward greater adherence to the broadened obligations, enhanced dispute resolution, and the reduction of "free ridership" on the part of nonmembers.

Uruguay Round Initiative on Pharmaceuticals

During the Uruguay Round negotiations, the United States and several other GATT members sought the reciprocal elimination of duties on all pharmaceutical products, including certain chemical intermediates used in the production of pharmaceuticals. The elimination of duties, it was argued, would serve to increase trade with fewer Government-imposed tariffs.

As a result of the negotiations, the United States and 21 trading partners agreed to the elimination of duties on nearly 7,000 pharmaceutical products. These products included approved INNs from WHO Lists 1-69, certain other active ingredients for which INNs had not been established, and certain chemical intermediates used in the production of pharmaceutical products. The initiative also listed certain chemical prefixes and suffixes that may be combined with any of the approved INNs to produce INNMs. As a result, the derivatives of INNs, such as salts and esters, are also granted duty-free entry. In the United States, the results of this agreement were incorporated into the HTS as the Pharmaceutical Appendix, effective January 1, 1995.

Because of continued development of new chemical intermediates and downstream pharmaceutical products, many new items have been proposed for incorporation into the list since its initial formulation. However, it was noted by many WTO members that certain products, although having an approved INN designation, had a predominating industrial use outside of pharmaceutical applications and therefore should be excluded from this initiative. As a result of further negotiations, subsequent modifications to the original WTO list were made in 1996 and adopted by the United States and other major WTO member countries on April 1, 1997.⁶ WHO Lists 70-73 were included in this first review.

⁴ The schedules largely consist of commitments known as "bindings" to maintain normal-trade-relations (NTR, formerly most-favored-nation) tariff rates at no higher than the stated level. The schedules also indicate how concession rates will be reduced following negotiations.

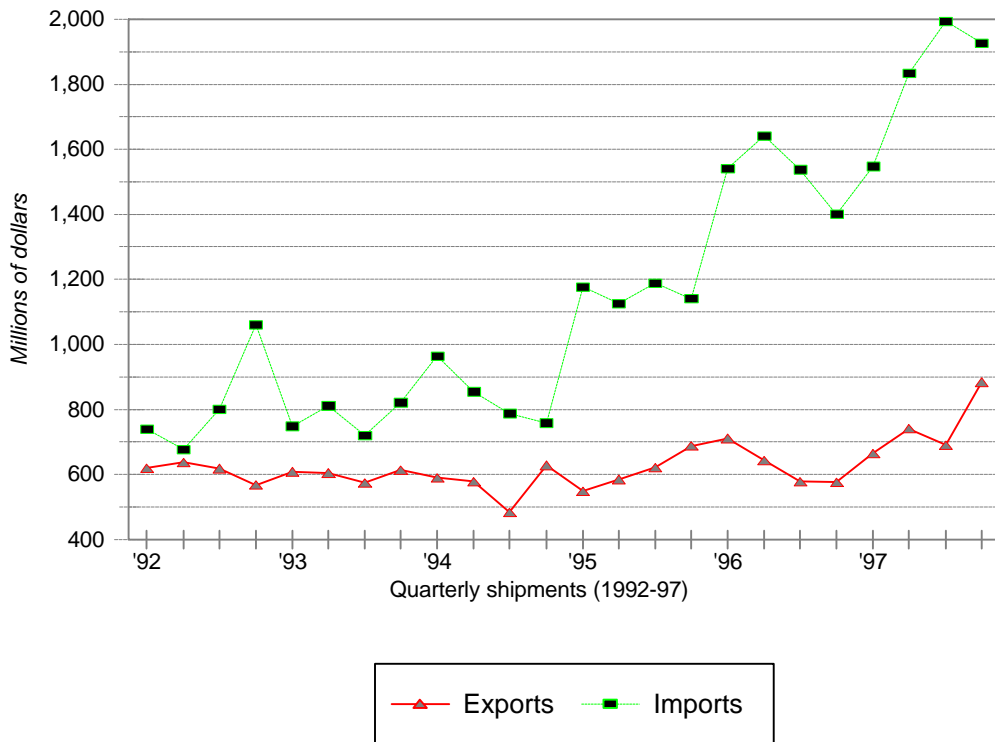
⁵ Significant among these codes, which GATT 1947 members were not and are not obliged to ratify, are those negotiated during the Tokyo Round concerning customs valuation, antidumping and countervailing duty measures, trade in civil aircraft, Government procurement, and other nontariff barriers to trade.

⁶ *Federal Register*, Vol. 62, No. 64, April 3, 1997, pp. 16039-16048.

A second review to amend the approved list of duty-free items is currently underway. Included in the discussions are WHO Lists 74-78 of INNs, as well as approximately 370 chemical prefixes and suffixes and chemical intermediates used in the production of drugs. It is anticipated that the additions to the list will be officially incorporated into tariff schedules in mid-1999.

Figures 4-1 and 4-2 show the rise in trade that has occurred since the 1995 elimination of tariffs.⁷ In particular, there has been a significant increase in U.S. exports and imports of bulk pharmaceutical products. As the bulk pharmaceutical market is more price sensitive than the market for finished drug products, it is not surprising that the elimination of tariffs would have a more noticeable effect on SIC 2833. Although there are other factors that also affected trade during this period,⁸ the zero-for-zero negotiations seem to have had a positive influence on international trade in this sector.

Figure 4-1
Bulk medicinal chemicals and botanical products (SIC 2833): U.S. domestic exports and imports for consumption, quarterly shipments in millions of dollars, 1992-97

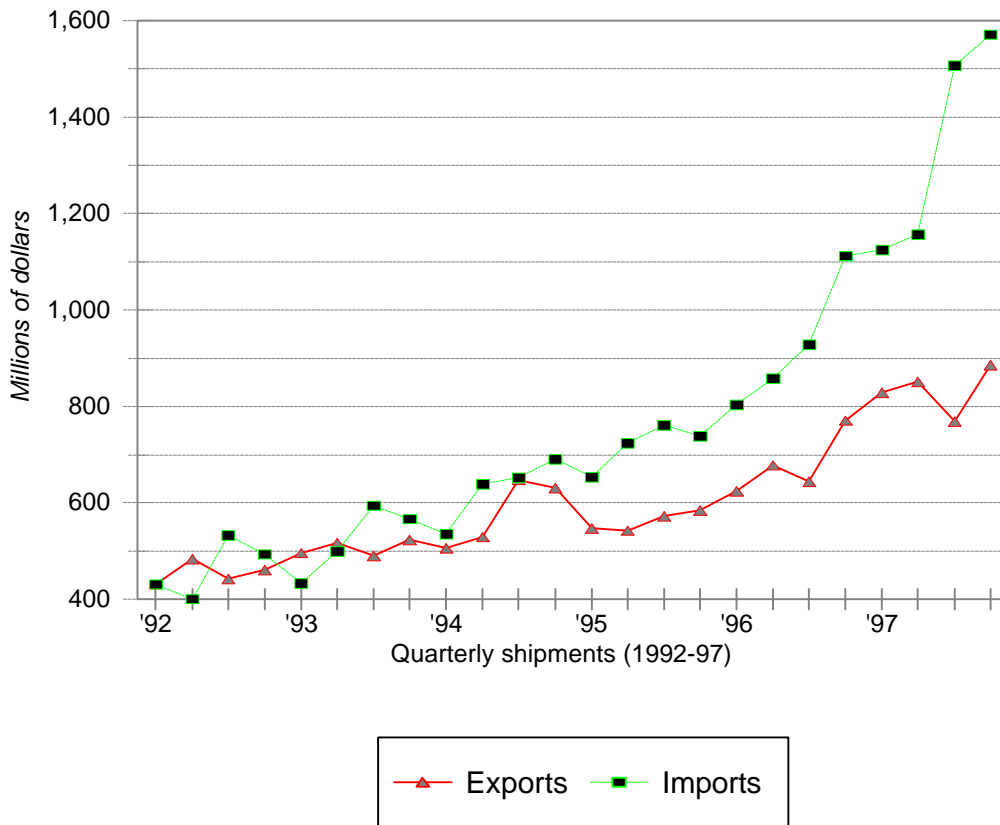


Source: Official statistics of the U.S. Dept. of Commerce.

⁷ Data tables for 1992-97 U.S. trade in pharmaceuticals with its primary trading partners can be found in appendix A of this report.

⁸ For more information on the effect that this initiative and other factors have had on trade, please refer to: "The Uruguay Round Elimination of Duties on Pharmaceuticals: Developments in the 2 Years Since Implementation," *Industry Trade and Technology Review*, USITC Pub. 3071, October 1997, pp. 1-12. This report is available online at <http://www.usitc.gov/ittr.htm>.

Figure 4-2
Pharmaceutical preparations (SIC 2834): U.S. domestic exports and imports for consumption, quarterly shipments in millions of dollars, 1992-97



Source: Official statistics of the U.S. Dept. of Commerce.

IPR Initiatives

The United States set forth a number of objectives regarding intellectual property when it entered into the Uruguay Round of multilateral trade negotiations. The objectives included: (1) in all member nations, the enactment and effective enforcement of laws that adequately protect intellectual property; (2) the establishment within GATT of effective standards for the protection of intellectual property standards, procedures to enforce such standards both within member nations and at their borders, and improved dispute settlement procedures within the GATT; (3) assurances that the standards and procedures within GATT would not prejudice other complementary initiatives in other international organizations; and (4) supplementation and strengthening of intellectual property protection in existing intellectual conventions

administered by other international organizations.⁹ Pharmaceuticals was one industry sector that the United States specifically addressed in the areas of patents and IPR.

The agreement that resulted from these negotiations is called “Trade-Related Aspects of Intellectual Property Rights” (TRIPs).¹⁰ TRIPs is administered by the WTO with the special assistance of the Council on Trade-Related Aspects of Intellectual Property.¹¹ TRIPs relationship to the WTO makes it distinct from many other multilateral agreements on intellectual property, such as the Paris and Berne Conventions, which are administered by the World Intellectual Property Organization (WIPO), a specialized agency of the United Nations. According to one analyst, the United States sought to shift intellectual property protection from WIPO to the WTO due to the perceived weakness of WIPO’s enforcement procedures and the historically greater influence of the United States in GATT, the predecessor to the WTO.¹² The TRIPs Agreement contains wide-reaching obligations on normal trade relations (NTR, formerly most-favored-nation) and national treatment, and it confers rights on nationals of the member countries with respect to covered intellectual property matters.¹³

Of particular importance to the pharmaceutical industry are the provisions on patents. Each WTO country is required to make patents available with respect to inventions in all fields of technology, with a few narrowly stated exceptions. Pharmaceuticals, micro-organisms, and non-biological and microbiological processes can all be patented, though members can deny patents to plants and protect them by other means.

In addition, special provisions have been made for countries with less established patent regimes. Each such country must immediately provide an interim system that permits patent applications for these products to be filed. When the application is examined, novelty is determined as of the date of that filing. If a product is the subject of an application under this interim system, the country in question must provide exclusive marketing rights for a period of five years after the product receives marketing approval, or until a patent is granted or rejected, whichever period is shorter. To qualify for market exclusivity, the product must also be patented in another WTO member country and approved for marketing there.¹⁴

As a result of the agreement, the U.S. patent laws required changes in several respects. The most significant impact of TRIPs is that the term for a U.S. patent has been changed from 17 years from the date the patent issued to 20 years from the date the patent application was filed.¹⁵ As a result of this amendment, the U.S. Patent and Trademark Office (PTO) and some industry representatives believe that many U.S. patents will now have terms longer than under previous law because most patents are issued less than two years after the application was

⁹ Omnibus Trade and Competitiveness Act of 1988, Pub. L. No. 100-418, § 1101(b)(10), 102 Stat. 1107, 1123-24 (statement of principal negotiating objectives of the United States regarding intellectual property) (1988).

¹⁰ The agreements resulting from Uruguay Round, which include TRIPs, were signed by the leaders of the member nations on April 15, 1994.

¹¹ *TRIPs*, art. 68.

¹² Monique L. Cordray, “GATT v. WIPO,” *Journal of the Patent and Trademark Office Society (JPTOS)*, 76, pp. 121, 122-24, 131-32 (February 1994).

¹³ *Ibid.*, p. 313.

¹⁴ *Statement of Admin. Action*, p. 317.

¹⁵ 35 U.S.C. § 154(a)(2) (1997 supplement), as amended by the Uruguay Round Agreements Act (URAA), P.L. 103-465, § 532(a)(2) (December 8, 1994).

filed.¹⁶ Also, the patent term may be extended by up to five years to compensate for court appeals, interference actions, and certain other delays.¹⁷ This latter provision may help alleviate some of the concerns regarding pharmaceutical and biotechnology patents, which are routinely subject to extended delays.¹⁸ Inventive activity in any WTO member country can now be counted to support the claimed date of invention, patent terms are longer, "infringing activities" are defined as the term relates to patents,¹⁹ and access is made available to courts as well as to the Board of Patent Appeals or Interferences. Various other changes were made regarding the patent application system, including establishment of a provisional patent application structure.²⁰

North American Free Trade Agreement

NAFTA entered into force on January 1, 1994, following the adoption of necessary domestic measures by the three parties, Canada, Mexico, and the United States.²¹ Under the NAFTA, tariffs on goods originating in the NAFTA region and barriers to trade in goods among the three parties are being eliminated as provided in the countries' schedules of concessions and other legal instruments. In addition, NAFTA obligates its signatories to nondiscriminating between domestic and NAFTA goods, along with many other legal requirements, which applies to the parties' state and local Government entities as well as to federal organizations, except as explicitly provided for, or "grandfathered," by schedules of existing subfederal exempted measures. In that respect, NAFTA differs from the GATT/WTO, with the latter generally applicable to national-level units and only in limited cases to subnational ones. The NAFTA contains specific statements of legal obligations that already appear in the GATT, because in many instances the NAFTA dispute resolution mechanism supplants that of the WTO in terms of jurisdiction in matters affecting the parties, and because of the subfederal application of many such obligations.

Tariff Reductions/Eliminations

NAFTA did not establish a common external tariff for Canada, Mexico, and the United States, or eliminate disparities in rates on particular goods among the parties during the staging period. Many goods were immediately assessed a "free" rate of duty, but some goods will still be dutiable for up to 15 years because of the agreed duty rate staging. Tariff

¹⁶ Karen Tripp and Linda Stokley, "Changes in U.S. Patent Law Effected by the Uruguay Round Agreements Act -- The GATT Implementation Legislation," *Intellectual Property Journal*, 28 3, 5 n.14 (1996). In FY 1996, the average time for prosecuting a patent application was 20.8 months. This represents an increase of 1.2 months over the preceding year, due to a surge in applications, shortages of personnel, and budget cutbacks. USPTO FY 1996 Annual Report.

¹⁷ 35 U.S.C. § 154(b), added by the URAA § 532(a)(4).

¹⁸ See Kenneth Burchfiel, *U.S. GATT Legislation Changes*, JPTOS 77 222, 223-24 (March 1995). Prosecution refers to the process of getting a patent to issue from an application.

¹⁹ Article 28.1 requires that product patents allow owners the right to stop anyone from making, using, offering for sale, selling, or importing the patented product; article 28.2 holds that process patents must give owners the right to stop anyone from using the protected process, and from using, offering for sale, selling, or importing a product obtained directly therefrom. *Statement of Admin. Action*, p. 335.

²⁰ *Ibid.*, p. 322.

²¹ In the United States, the U.S. Congress enacted the North American Free Trade Agreement Implementation Act.

reductions on originating goods²² under the NAFTA were negotiated in various categories: those duty rates that were to be immediately eliminated, those reduced in five or ten equal annual cuts, and those on import-sensitive goods taking effect over fifteen years. For a very few goods, different schedules (such as seven or twelve years) were adopted. Because the NAFTA replaced the United States-Canada Free Trade Agreement ("CFTA") between those two parties, with an ongoing schedule running from 1989 through 1998, rates of duty on goods traded between the United States and Canada were lower when NAFTA became effective than rates on goods traded between Mexico and either of the other parties. The rates applicable to goods of Mexico have independent staging commitments.

In the case of pharmaceutical products, both parties' CFTA schedules of concessions for goods of chapter 30 (i.e., finished, dosage-form products) of the Harmonized Commodity Description and Coding System ("HS") either accorded 10-year staging (with duties eliminated as of January 1, 1998) or continued existing duty-free treatment. Pharmaceuticals and pharmaceutical intermediates falling elsewhere in the HS were generally accorded 5-year staging by both parties (with duty-free entry effective on January 1, 1993) or were the subject of commitments to continue existing duty-free entry. These commitments were incorporated by reference into the NAFTA.

In the U.S. schedule of concessions to the NAFTA, some Mexican products classified in chapter 30 were accorded 10-year staging (to be free of duty on January 1, 2004) while others continued to receive existing duty-free treatment or were accorded immediate duty-free status. Many Mexican pharmaceutical goods falling outside chapter 30 were given 10-year staging and others 5-year staging; the remainder continued to enter free of duty.²³

Canada's concessions on goods of Mexico were generally similar in terms of staging periods to those of the United States, though not identical with respect to specific goods. Mexico's schedule of concessions contains two columns, one with rates applicable to goods of Canada and the other to goods of the United States; for goods covered by this report, the rates are essentially identical. The overall duty staging for pharmaceutical products of chapter 30 binds existing free rates and uses 10-year staging for other goods. Dutiable goods falling outside chapter 30 seem to have been given predominantly 10-year staging.

Because the three countries do not maintain common NTR rates of duty or have identical NAFTA staging schedules, it is necessary during the transition period to have rules to determine the appropriate preferential rate of duty for each originating good. These rules, known as the "marking rules," are applied only when it has already been determined that a good originates in one or more NAFTA countries.²⁴ In July 1996, the Commission published

²² The term "originating goods" refers to products determined to have originated within Canada, the United States, or Mexico. Specific rules set out in the Harmonized Tariff Schedules of the United States are used to determine the origin of the product before the NAFTA (or other) rate of duty may be applied.

²³ In the case of the United States, commitments were made in both the CFTA and the NAFTA to give mandatory duty-free entry to goods covered by existing or recently expired duty suspension legislation. In addition, the United States agreed to bind duty-free access for goods of Mexico that had been entering free of duty under the Generalized System of Preferences.

²⁴ In the case of the HTS, the rules of origin for the NAFTA are set forth in general note 12, primarily in subdivision 12(t). (See also Annex 302.2 to the NAFTA at paragraphs 12 and 13.) The change-of-tariff-classification rules in that subdivision apply to goods that contain non-NAFTA inputs; these foreign inputs must be classified for tariff purposes when they enter the NAFTA region, and then undergo sufficient processing in one or more NAFTA countries to change classification into a finished good, in a combination

its report on Investigation No. 332-366,²⁵ which, at the request of the Committee on Ways and Means of the U.S. House of Representatives, included sections focusing on the impact and application of such rules with respect to pharmaceutical products. The report covered all country-of-origin marking rules and rulings, whether applicable to NTR trade²⁶ or to preferential-program shipments. It also included discussions of rules applied by the FDA as the primary domestic regulatory body. For this sector, the standards used and the type of information generally required by the FDA and the U.S. Customs Service (Customs) for imported goods are not identical. While many companies reportedly have not considered any additional wording desired by Customs as significant,²⁷ others saw the lack of harmonization between Customs and FDA as having an adverse effect on this industry and were hopeful that the Agreement on Rules of Origin under the auspices of the WTO could lead to harmonized global rules.²⁸

Intellectual Property

With respect to intellectual property in general, and particularly patents, the NAFTA represents considerable progress, but concerns about certain parallel imports (e.g., imports not authorized by the domestic patent holder that are intended to be relabeled as "domestic" in an effort to undercut domestic sales by the patent holder) nonetheless remain.²⁹ The pharmaceutical industry, with its heavy R&D costs and multinational production, places special emphasis on obtaining additional protections and enforcing existing ones to recoup the investments made to develop new drugs.

The IPR provisions under NAFTA are based on the principles of nondiscriminatory or national treatment and of open access to enforcement mechanisms. For the first time at the international level, NAFTA requires the parties to make patent protection available for pharmaceutical products, upon request, for at least the same length of time as is remaining on the patent if any one of the parties has already issued a patent on such a product and it is being marketed in either of the other parties for the first time. This commitment is referred to as "pipeline protection." (Government agencies are also forbidden from disclosing test data submitted to them for regulatory approval.) In addition, however, NAFTA allows the parties

of tariff categories prescribed by the note, before being shipped to another NAFTA party. The objective of these rules is to ensure that tariff preferences or other special treatment are accorded only to goods that are "products of" the NAFTA region, and to make the nonpreferential substantial transformation standard more objective by representing it in the form of particular changes of tariff classification. However, it should be noted that the NAFTA origin rules, linked as they are to granting a duty preference, do not set forth every possible tariff-linked representation of substantial transformation--only those where the parties agreed to give a duty preference. Goods that do not meet the rules of origin of general note 12 will continue to be dutiable even after the staging period, including those that might be deemed "substantially transformed" in Mexico or Canada for nonpreferential purposes.

²⁵ *Country-of-Origin Marking: Review of Laws, Regulations, and Practices*, USITC Publication No. 2975.

²⁶ The pertinent provision of statute is 19 U.S.C. 1304, as amended, which requires that all imported goods be marked as to their origin, unless they are incapable of being marked or would not reach their "ultimate consumer" in the United States in that form because of processing that results in their substantial transformation.

²⁷ See p. 6-22 of above-cited report.

²⁸ See table F-3 of above-cited report.

²⁹ Noah, Lars, "NAFTA's Impact on the Trade in Pharmaceuticals," *Houston Law Review*, 33 (1997), pp. 1293-1326.

"to exclude certain limited subject matter from patentability, including some plants and animals that are patentable under U.S. law."³⁰ NAFTA imposes specific limits or conditions on other aspects of patent-related legal procedures, allows an inventor to count creative work in Canada or Mexico in establishing the date of an invention, and does not create a right to engage in "parallel imports" and in some circumstances puts the burden of proof as to alleged infringements of process patents on the defendant.³¹ Last, the provision "limits the extent to which NAFTA Governments may grant 'compulsory licenses,' that is, permit use of a patented product or other subject matter without the patent owner's permission."³² However, because of other domestic legal limitations, this protection is largely inapplicable to the pharmaceutical sector.³³

NAFTA resulted in significant changes in some provisions of the domestic law of the parties,³⁴ and for the first time brought about protection in Canada for patents on pharmaceutical products. Under its prior law, Canadian firms could pay minimal royalties to patent holders and then sell generic copies of drugs patented in other countries even while the patent terms continued.³⁵ In 1987, Canada modified this scheme to give exclusivity to the foreign patent holder, but only during the first seven years of the patent term. This compulsory licensing system had the effect of depressing domestic prices in Canada, which interfered with drug companies' ability to recoup R&D costs. While the CFTA did not alter this situation, in 1993 Canada passed legislation (retroactively effective from December 20, 1991) that extended patent life to 20 years and largely ended the licensing system. This status is now bound under NAFTA obligations.³⁶ The changes in patent laws during 1987-1993 did not occur without substantial opposition and bitter fighting in the Canadian Parliament.³⁷

Similarly as a result of the NAFTA accord, Mexico was required to make substantial changes in what had been viewed as a very weak IPR system. Until the agreement, the Government had failed to recognize product patents for pharmaceutical products and had little enforcement power. With the NAFTA negotiations beginning, Mexico enacted the Industrial Property Law³⁸ in 1991 and began the modernization of its patent laws. During 1993-1994, with NAFTA about to be implemented, Mexico amended the 1991 act and began to recognize product patents. Mexico also acted to limit loopholes concerning the protection of process patents.³⁹ The 1994 amendments also established the Mexican Institute for Industrial Property and gave it authority to administer all patent-related laws. Moreover, the NAFTA requires Mexico to provide access to injunctive relief in appropriate circumstances to enforce

³⁰ *Statement of Administrative Action*, Ch. 17: A.5., p. 186.

³¹ *Ibid.*, p. 189.

³² *Ibid.*, p. 192.

³³ *Ibid.*

³⁴ The changes required in U.S. law were (1) the extension of protection to holders of patents issued by Mexico and Canada where no U.S. patent existed (as noted above) and (2) the recognition of inventive work done in the other 2 parties when application for U.S. patents are filed.

³⁵ See Noah article at p. 1299 *et seq.*

³⁶ *An Act to Amend the Patent Act*, 1993 S.C., ch. 2, sec. 3 (Can.); Noah, p. 1300.

³⁷ See Weissman, Robert, "A Long, Strange TRIPs: The Pharmaceutical Industry Drive to Harmonize Global Intellectual Property Rules, and the Remaining WTO Legal Alternatives Available to Third World Countries," *U.Pa.J. of Int'l. Econ. L.*, 17 (1996), p. 1069, at 1080-1082.

³⁸ *Ley de Fomento y Proteccion de la Propiedad Industrial (Law for Development and Protection of Industrial Property)*, 453 D.O. 4, June 27, 1991.

³⁹ Noah, p. 1302.

patent rights⁴⁰ and elevates all of the IPR protections to the level of treaty obligations. Along with NAFTA, Mexico also joined major international organizations that have treaty-related authority over IPR matters, so that those instruments' rights and obligations likewise influenced domestic law.

NAFTA does not, however, regulate parallel imports. In the United States, firms rely primarily on FDCA,⁴¹ as enforced by the FDA, to control such parallel imports. The FDCA requires manufacturers and sellers of drugs to register with the FDA and comply with FDA rules; it applies also to firms that relabel drugs and covers imports as well as domestically made drugs. U.S. law also prohibits counterfeit drugs from being marketed in the United States, and this also would apply to parallel imports.⁴² Another statute, the Prescription Drug Marketing Act of 1987,⁴³ bars the reimportation of prescription drugs made in the United States by any person other than the original manufacturer. Its provisions restrict, if not bar, imports of relabeled drugs, and imposes recordkeeping burdens on wholesale distributors concerning sales of prescription drugs to establish a chain of title.

Nontariff Measures

NAFTA's provisions on the elimination of nontariff barriers to trade contain an exception for standards adopted for health and safety purposes.⁴⁴ Few changes in Canadian law were required by NAFTA, and Mexico is now accepting FDA documentation as proof of drug safety and effectiveness and is phasing out local production requirements.⁴⁵ However, the more complex and rigorous U.S. laws--though largely preserved under NAFTA based on FDA's involvement in the negotiations--might at some point be challenged as nontariff barriers not required for or linked to public health. One such provision is the regulatory requirement that only FDA personnel conduct site inspections, even in foreign facilities.⁴⁶ Other U.S. regulations linked to the goal of reducing usage of environmentally hazardous or ozone-depleting substances might be challenged as falling outside the public health exception as well.

Changes in Nations' Patent Laws

Patents in the Pharmaceutical Sector

Until the TRIPs agreement's obligations are completely implemented in 2006, the pharmaceutical sector continues to face widely varying patent and IPR systems worldwide. The U.S. patent regime, for example, has allowed patent holders to use or license covered

⁴⁰ *Ibid.*

⁴¹ Pub. L. 75-717, ch. 675, 52 Stat. 1040 (1938), as amended and codified at 21 U.S.C. secs. 321-393; Noah, p. 1304.

⁴² Pub. L. 89-74, sec. 9, 79 Stat. 226, 234-35 (1965).

⁴³ Pub. L. 100-293, 102 Stat. 95 (1988).

⁴⁴ See NAFTA, arts. 309, 712, and 904.

⁴⁵ Noah, pp. 1317 *et seq.*

⁴⁶ 21 CFR 207.40.

goods or processes or to allow the patent to lie idle over its entire life.⁴⁷ At the same time, there are countries that have given no patents, including Argentina, with respect to pharmaceuticals.⁴⁸ In such countries, firms could legally produce and sell any drug, even if the drug were patented in another country. Other countries have varying degrees of patent protection. Some have issued patents on products but not on processes. Conversely, India issues patents on processes but not products, allowing other producers to make the same drug by other processes.⁴⁹ In some other countries, another provision of concern to patent holders includes "work the patent" requirements. These requirements state that firms must do some production (not just selling) in those countries or lose patent protection there.

In light of these variations, many pharmaceutical companies in the United States, Japan, and the EU have tried to get countries that have little or no patent protection to remake their patent laws and accord at least some of the patent protections contained in U.S. law. Through vigorous lobbying, U.S. pharmaceutical trade associations and firms have had high-profile roles in influencing Congress and USTR in developing U.S. policy, seeking to enforce their rights through mechanisms such as section 301 and the "special 301" section of the Trade Act of 1974 (19 U.S.C. 2411).⁵⁰ Pharmaceutical firms and associations generally support the GATT Uruguay Round effort to require other WTO signatories to strengthen their laws.

The patent scheme options available to developing countries are generally more conservative under the TRIPs agreement. Many features tend to mirror the extent of protection afforded in the United States. Developing countries can use certain nondiscriminatory taxes and price controls, and even highly regulated compulsory licensing, provided that particular measures fall under the "public health" or "environmental protection" exceptions.⁵¹ Countries can deny patents on any drug, or produce or obtain them non-commercially, and distribute them through public health authorities or non-profit entities, provided that the restriction can be shown to be "necessary" (i.e., the "least-trade-restrictive measure"). To be acceptable under TRIPs, countries' approaches must be balanced and take into account the legitimate interests of third persons, and avoid unreasonably or excessively restricting patent-holders' rights.

Moreover, countries can adopt special measures to encourage trade in pharmaceuticals used as orphan drugs and similar limited-impact goods. They can also employ measures that allow certain uses if the patent holder is contacted but does not reply within a reasonable time, circumstances surrounding the license grant later change, or a license is improperly restricted.

⁴⁷ Weissman, Robert, "A Long, Strange TRIPs: The Pharmaceutical Industry Drive to Harmonize Global Intellectual Property Rules, and the Remaining WTO Legal Alternatives to Third World Countries," U.Pa. *J. of Int'l. Econ. L.*, 17 (1996), p. 1069 *et seq.*, at 1072.

⁴⁸ *Ibid.*

⁴⁹ *Ibid.*, p. 1073. See also "Prospects and Limits of the Patent Provision in the TRIPs Agreement: The Case of India," Adelman, Martin J. and Sonta Baldia, *Vanderbilt J. of Transnat. L.* (1996), p. 507 *et seq.* This article states that India was a "free rider" on other countries' technological developments until changes were mandated by the TRIPs agreement. The article also describes the agreement's effort to regulate compulsory licensing systems in signatory countries. These changes are said to be of great future importance, once phased in, given India's position as a major producer and net exporter of many bulk drugs. Under India's patent laws, which must be changed to comply with TRIPs by 2006, firms could obtain new drugs, re-engineer their production processes, and sell them domestically; the sector had price controls and high tariffs to protect them from imports, plus lower capital costs. The authors comment, however, that Indian drug producers have focused on making drugs for export, rather than on making drugs for conditions such as malaria and leprosy that affect the Indian people.

⁵⁰ *Ibid.*, p. 1077.

⁵¹ *Ibid.*, pp. 1098-1099.

Because patent holders may not wish to grant every licensing request, the issue of what constitutes appropriate remuneration might become a subject of dispute.⁵²

Inadequate patent systems in developing countries can also affect companies' development of new products based on plants and plant extracts. Many new developments in pharmaceuticals have been or likely will be prompted by discoveries of, or based upon, naturally occurring substances or plants, and much of the discovery work occurs in developing countries. However, most of these discoveries are the result of efforts by the large, multinational firms, rather than the small domestic firms in those countries. While the natural substances cannot be patented, processes to synthesize naturally occurring drugs, or more effective derivatives, can be patented in many cases. One analysis noted:

The image of the adventurous pharmaceutical company explorer-genetic prospector superficially suggested by the corporate effort to survey Third World genetic resources is inaccurate. Company representatives do not wander into the rain forest jungle to collect samples. Instead, corporate botanists and anthropologists rely on Third World farmers and herbalists, especially from indigenous communities that make their home in or live off of the rain forest, to direct them to plants that they use in local medicines. Over centuries, these farmers and herbalists have identified, cultivated, bred, and protected the plant varieties. These informal innovations are not patentable, however, because they are not "new." More obviously, a Kayapo farmer in Brazil and a Sakai herbalist in Indonesia have no practical means to patent their innovations. . .

Recognition of this reality undermines the pharmaceutical companies' moral claim to strict patent rules in every country. Furthermore, calling attention to the Third World's unacknowledged contribution to the development of pharmaceuticals also raises the possibility of alternative approaches to patent policy.⁵³

On the issue of public domain and the scope of patents, the comment continues:

What is defined as public and what is defined as private is thus an ultimate issue of patent law. It is in the pharmaceutical companies' interest to define the biological resources of the Third World as "the common heritage of mankind." That makes the resources public, and thus unpatentable. If the biological resources are not patentable, then Third World countries are basically unable to capture any of the wealth-producing benefits of their industrial development.⁵⁴

One possible driving force to encourage developing countries to adopt restrictions on patents for plant-derived drugs might be that the granting of pharmaceutical patents may still not promote domestic investment. Drug companies frequently wish to produce particular drugs in only one or a handful of locations worldwide. Thus, as noted by one source, granting patents may serve only to limit competition in the developing country's own market, to restrict growth, and to raise consumer prices.⁵⁵

⁵² *Ibid.*, pp. 1114-1115.

⁵³ *Ibid.*, pp. 1090-1091, citing other authors.

⁵⁴ *Ibid.*, p. 1092.

⁵⁵ *Ibid.*, p. 1092.

Issues Arising Under TRIPs

As the TRIPs transition period continues, several matters of concern to the United States have been under discussion with other WTO members. One such matter involves India's alleged violation of TRIPs patent provisions. The country has been described as “. . . a ‘haven’ for bulk pharmaceutical manufacturers who ‘pirate’ the intellectual property of the world's pharmaceutical industry.”⁵⁶ An investigation under section 301 of the Trade Act of 1974, as amended, was opened on July 8, 1996, based on a complaint to USTR by PhRMA that India has no "mailbox" designated for filing applications for patents, and that legislation to correct patent-related problems had not been adopted after initial U.S. inquiries. The United States also called for the formation of a WTO investigative panel concerning pharmaceuticals and agricultural chemicals when 22 months of bilateral consultations failed to resolve outstanding issues. India agreed to the formation of such a panel.⁵⁷ The EU reserved the right to participate as a third party.

Another concern of the pharmaceutical industry has involved Argentina, which was charged under section 301 with failure to protect trade secrets relating to pharmaceuticals. After finding a March 1996 confidentiality law unacceptable, the United States threatened to invoke trade sanctions if an acceptable confidentiality law was not enacted by December 20, 1996. The United States had already acted to bar access to certain Argentine products and opted not to honor commitments to buy Argentine beef and peanuts. Argentina responded that the U.S. demand for protection of all industrial and trade information (including that already obtained) exceeded the obligation under TRIPs for prospective coverage as to new products only.⁵⁸ Foreign pharmaceutical laboratories located in Argentina had alleged that local firms trying to get drugs approved for sale were obtaining technical information from Argentine Government files. New legislation passed the Lower House of the Argentine legislature on December 12, 1996, and received Senate approval on December 18. However, USTR continued to review a possible revocation of certain benefits under the Generalized System of Preferences (GSP) valued at \$30-40 million annually, based upon concerns about how the new law's language would be interpreted and applied.⁵⁹ Subsequently, the President proclaimed the removal of GSP benefits for a wide range of Argentine products, effective as of May 17, 1997.⁶⁰

United States

The United States has made a number of important amendments to its patent laws as a result of TRIPs and, to a lesser extent, NAFTA. Select changes are summarized below.⁶¹

⁵⁶ *World Intellectual Property Report* ["WIPR"], **10** (Sept. 1996), p. 283.

⁵⁷ *WIPR*, vol. 11 (Jan. 97), p. 22.

⁵⁸ *WIPR*, vol. 10 (June 1996), p. 167; vol. 11 (Jan. 1997).

⁵⁹ *WIPR*, vol. 12 (Feb. 1997).

⁶⁰ Pres. Proclamation 6988 of April 11, 1997, *62 Fed. Reg.* 19017 (Apr. 17, 1997). The action affects goods in several sectors and HTS sections.

⁶¹ Not discussed here are the recent changes to section 337 of the Tariff Act of 1930, 19 U.S.C. § 1337, which is administered by the U.S. International Trade Commission.

Transition, Extension, and the Waxman-Hatch Act

To accommodate the transition from a 17-year to a 20-year patent term, measured from the date of filing and not issuance, the Uruguay Round Agreements Act (URAA) provides that any patent that was either in force on or resulted from an application filed prior to June 8, 1995 (the effective date of the change in the patent term) will have a term that is 17 years from the year of issuance or 20 years from the date of filing, whichever is longer.⁶² A conflict arose as to how this transition was to be applied to pharmaceutical patents that were entitled to patent term restoration under the Waxman-Hatch Act.⁶³ The Waxman-Hatch Act entitles the holder of a pharmaceutical patent to extend the term of patent protection by up to five years in order to compensate for delays caused by the FDA's premarket approval process.⁶⁴ Patent term extension was given to the patent holders in exchange for a provision authorizing generic producers to rely on safety and efficacy testing submitted earlier by the original patent holder, thus expediting the marketing of lower cost generic drugs by eliminating the need for generic producers to submit their own test data to the FDA.⁶⁵

The PTO and the FDA, supported by generic drug producers, took the position that for pharmaceutical patents issued prior to June 8, 1995, the term of the patent would be the longer of: (a) 17 years from the date of filing plus the Waxman-Hatch extension; or (b) 20 years from the issuance.⁶⁶ Brandname pharmaceutical manufacturers, on the other hand, argued that the Waxman-Hatch extension should be added to either a 17-year from issuance or a 20-year term from filing, whichever was longer. This controversy resulted in litigation that went before the U.S. Court of Appeals for the Federal Circuit in the case *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543 (Fed. Cir. 1996). After reviewing the statutory provisions in the URAA and the Waxman-Hatch Act, the Federal Circuit agreed with the pharmaceutical industry that pharmaceutical patents in force as of June 8, 1995, were entitled to have a restoration extension added to the longer of a 17-year term from the date of issuance or a 20-year term from the date of filing.⁶⁷

Pending Patent Legislation

Congress is presently considering legislation to further amend U.S. patent laws, partly as a result of two bilateral patent accords recently negotiated between the United States and Japan, as discussed below. On April 23, 1997, the House of Representatives passed H.R. 400, the "21st Century Patent System Improvement Act." On May 22, 1997, the Senate

⁶² 35 U.S.C. § 154(c), as amended by the URAA, P.L. 103-465, § 532(a)(4).

⁶³ Formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417, the Waxman-Hatch Act is codified at 35 U.S.C. § 156.

⁶⁴ 35 U.S.C. § 156(g)(6)(B). Only one extension may be obtained, and the effective patent term may not exceed 14 years following FDA approval of the new drug. *Ibid.* § 156(c)(3).

⁶⁵ 21 U.S.C. § 355(j)(7)(B).

⁶⁶ There was no dispute that a patent issued after June 8, 1995, on a transition application filed before that date was entitled to add the Waxman-Hatch extension to either the 17-year or the 20-year term, whichever was longer.

⁶⁷ *Merck*, 80 F.3d 1543. According to the court, the only exception is for pharmaceutical patents that were in force on June 8, 1995 solely because of a previous Waxman-Hatch extension; such patents are not entitled to apply an extension to a 20-year term. *Ibid.*

Judiciary Committee reported out a similar bill, S. 507, the “United States Patent and Trademark Organization Act of 1997.” Final passage of the legislation is pending.⁶⁸

Both bills would make the PTO, currently under the Department of Commerce, an independent agency and ensure that fees collected by the PTO were used only to support the PTO and its mission. In addition, both bills would guarantee that the term for a patent would be at least 17 years from the date of issue by extending the patent term for up to 10 years to compensate for delays caused by judicial appeals, and up to three years to compensate for “unusual delays” during the PTO’s processing of an application.⁶⁹

More controversial is the section that would require the PTO to publish patent applications within 18 months of filing, rather than keeping them secret until the patent has issued, as required by current law.⁷⁰ However, applicants would be entitled to receive a “reasonable royalty” from any person who makes, uses, sells, or imports the claimed invention during the period between the date of publication and the date the patent is issued.⁷¹ Supporters of publication, which include the PTO, major industry associations, and certain intellectual property bar associations, argue that early publication would allow U.S. inventors to utilize technological advances more quickly, including advances disclosed in applications from which patents never issued, and would thus lead to more efficient use of research resources. Critics argue that early publication would weaken the ability of inventors to protect their innovations and facilitate exploitation of U.S.-developed technology by other countries.⁷²

Western Europe

In response to rising development costs and regulatory delays required to bring new pharmaceutical products to market, the European Community (now the EU) approved a new regulation (Regulation (EEC) 1768/92) that permits member nations to extend the patent term for medical products by up to five years through the issuance of Supplementary Protection Certificates (SPCs). This regulation is intended to make European-based pharmaceutical companies more competitive with companies in the United States and Japan, where patent term extensions are already available.⁷³

SPCs are available for any patented “medicinal product,” which is defined as any substance or combination of substances for treating or preventing disease in humans or animals, or

⁶⁸ As of March 28, 1999, the last action on H.R. 400 was a March 23, 1998 report to the Senate from the Committee on Judiciary; on S. 507, the last action was the introduction of the Leahy Amendment No. 3174 on July 16, 1998 (<http://thomas.loc.gov/bss/d105query.html>).

⁶⁹ H.R. 400, § 208; S. 507, § 301 (amending 35 U.S.C. § 154(b)).

⁷⁰ H.R. 400, § 202; S. 507, § 202 (amending 35 U.S.C. § 122). The House bill would exempt from publication applications filed by small entities, individual inventors, and institutions of higher education. The Senate bill contains no such exemption. Most other countries, including Canada, Mexico, and Japan, publish patent applications 18 months after they have been filed with the national patent office.

⁷¹ H.R. 400, § 204; S. § 204 (amending 35 U.S.C. § 154).

⁷² Bob Gravely, *Patent Bill Gets Committee Nod*, Congressional Quarterly, March 15, 1997, at 590.

⁷³ Herwig von Morze & Peter Hanna, “Critical and Practical Observations Regarding Pharmaceutical Patent Term Restoration in the European Communities” (Part I), *JPTOS* 479, 77, 479-80 (June 1995). France and Italy enacted their own laws on pharmaceutical patent term restoration in January 1993. *Ibid.* Creation of a uniform system of patent term restoration in Europe was intended in part to avoid the development of disparate national laws. *Ibid.*

administered for making a medical diagnosis or restoring, correcting, or modifying physiological functions in humans or animals.⁷⁴ To qualify for an SPC, four conditions must be met: (a) the product in question must be protected by a patent in force in an EU member country; (b) the product must be subject to a valid authorization to market the product as a medicinal product; (c) such marketing authorization must be the first to place the product on the market as a medicinal product; and (d) the product must not already be the subject of an SPC.⁷⁵

To apply for an SPC, an application must be filed within six months from the date the marketing authorization was granted or from the date the patent issued, whichever is later.⁷⁶ The application is filed with the member state that granted the patent or on whose behalf it was granted and in which the marketing authorization was obtained.⁷⁷ If the application and product meet the conditions laid down in the regulation, the member state is to grant the SPC.⁷⁸

The SPC extends the patent term by a period, not to exceed five years, that is equal to the period that elapsed between the date the patent application was filed and the date the first marketing authorization was approved, less five years.⁷⁹ This provision puts a premium on completing the development of a medicinal product and obtaining marketing approval within 10 years of the date the patent was filed because any period after that date will not be matched by a further patent extension.⁸⁰ Because this term is based on the date the *first* marketing authorization was approved, an effective strategy to maximize the effectiveness of the patent term should focus on obtaining the earliest approvals in the largest number of major markets, rather than obtaining market approval first in the smaller markets.⁸¹ Finally, it is important to note that the SPC does not extend the scope of the patent as a whole, but only with respect to the product and uses covered by the marketing authorization.⁸² SPCs are presently available throughout the EU.⁸³

⁷⁴ Regulation 1768/92, art. 1(a) (definitions).

⁷⁵ *Ibid.*, art. 3.

⁷⁶ *Ibid.*, art. 7.

⁷⁷ *Ibid.*, art. 9.

⁷⁸ *Ibid.*, art. 10.

⁷⁹ *Ibid.*, art. 13. One commentator summarizes the patent term extension by the formula: extension = date of authorization - (date of filing patent application + 5 years) < 5 years. For example, if the marketing authorization were granted 9 years after the patent application had been filed, then the patent term would be extended by 9 - (0 + 5) = 4 years. However, if the marketing authorization were issued 11 years after the patent application had been filed, then the formula would yield 11 - (0 + 5) = 6 years, but the patent term extension would be capped at 5 years. George Metaxas-Maranghidis, "The European Dimension," *Intellectual Property Laws of Europe* (John H. Wiley & Sons, Inc., 1995; George Metaxas-Maranghidis, ed.) at 22-23.

⁸⁰ Herwig von Morze and Peter Hanna, "Critical and Practical Observations Regarding Pharmaceutical Patent Restoration in the European Communities" (Part II), *JPTOS*, 77, 505, 517 (July 1995).

⁸¹ *Ibid.* at 517-18.

⁸² Regulation 1768/92, art. 4. Article 4 is somewhat ambiguous, for it is unclear whether the SPC covers only uses of the product authorized up to the time the SPC was granted or whether its scope may be "expanded" to include uses authorized after the SPC is granted but before it expires. von Morze and Hanna (Part I), *supra* note 118, at 495-97. The authors believe the former interpretation is the better view. *Ibid.* at 496-97.

⁸³ Von Morze and Hanna (Part II), *supra* note 125, at 523-24, 526 (table). SPCs were not immediately made available in Spain, Greece, and Portugal because these countries did not provide patent protection for pharmaceutical products *per se* until 1992. Pursuant to the terms of the Regulation, SPCs became available in these countries five years after the Regulation entered into force, *i.e.*, January 1998. See Regulation

Japan

Since 1991, representatives of the United States and their counterparts in Japan have entered into two agreements to initiate reforms to their respective patent laws and procedures in order to resolve long-standing disputes. The first agreement, the Japan-U.S. Mutual Understanding on Patents, was signed by the heads of the U.S. PTO and the Japanese Patent Office (JPO) on January 20, 1994.⁸⁴ The second agreement, the New Patent Accord, was signed by the U.S. Secretary of Commerce and the Japanese ambassador on August 16, 1994.⁸⁵ The Japanese Diet has already passed legislation to implement both these agreements,⁸⁶ while the U.S. Congress is still considering such legislation.⁸⁷

Under the Japan-U.S. agreement, the JPO agreed to: (1) permit foreign nationals to file patent applications in English, with a Japanese translation to follow within two months; (2) permit the correction of translation errors from the original English document; and (3) permit the JPO to charge reasonable fees for these procedures. These changes are significant because under previous Japanese law, a translation error could not be corrected if the correction would change the essence of the invention. In one well-publicized case, for example, a U.S. chemical company lost an infringement case in Japan because “boron” had been mistranslated as “bromine,” an error that rendered the patent worthless.⁸⁸ These changes would also make Japanese patent law more similar to that of the United States, which already permits applications to be filed in a foreign language, provided an English version is filed within two months.⁸⁹ In exchange, the PTO agreed to propose legislation to change the term of U.S. patents from 17 years from the date of issue to 20 years from the date of filing, a change already anticipated by TRIPs.⁹⁰

The New Patent Accord is an extension of the Japan-U.S. agreement. The U.S. Department of Commerce agreed to propose legislation: (1) to make patent applications public 18 months after filing; (2) to expand the grounds for reexamining a patent and to allow third parties an opportunity to comment in such proceedings; and (3) to prevent the PTO from granting compulsory licenses, a practice rarely followed by the PTO anyway. In exchange, the JPO agreed to make or pursue three changes in its patent procedures. First, the JPO agreed to end its current practice of allowing third parties to oppose a competitor’s patent before it is granted, a practice that has been criticized as cumbersome and as resulting in lengthy delays in the issuance of Japanese patents.⁹¹ Secondly, the JPO agreed to accelerate the patent

1768/92, art. 21.

⁸⁴ “Japan-U.S. Mutual Understanding on Patents,” Jan. 20, 1994, *I.L.M.* 33, 313 (1994).

⁸⁵ “Japan-United States: Exchange of Letters Containing Patent Systems Agreement, August 16, 1994,” *I.L.M.*, 34 121 (1995). These agreements were the result of discussions conducted under the U.S.-Japan Framework for a New Economic Partnership, signed by President Clinton and then-Prime Minister Hosakawa on July 10, 1993. *Ibid.*

⁸⁶ Office of the United States Trade Representative, *1997 National Trade Estimate Report on Foreign Trade Barriers*, pp. 183, 201.

⁸⁷ See subsection on pending legislation under the United States section, *supra*.

⁸⁸ Lesavich, *supra* note 62, at 173-74.

⁸⁹ 35 U.S.C. §§ 119, 135.

⁹⁰ Lesavich, *supra* note 62, at 157.

⁹¹ *Ibid.* at 174-75. Some U.S. companies also argue that the pre-grant opposition system is discriminatory because Japanese companies have collaborated to block the issuance of patents, primarily to foreign applicants. *Ibid.* Elimination of pre-grant opposition is expected to give foreign inventors better protection for their inventions in Japan. *Ibid.*

examination process to enable applicants to obtain disposition of their patent applications within 36 months. This will have the effect of lengthening the effective term of a patent, which is measured from the date of filing.⁹² Finally, the JPO agreed to end the practice of issuing compulsory licenses to Japanese competitors. Under previous procedures, the JPO could issue a compulsory license when the patented invention had not been “worked” (defined as “used in manufacture”) for more than three years or when a strong need existed to exploit the patent in furtherance of the public interest. Although Japanese companies rarely sought compulsory licenses, the threat of such licenses alone and the fear of costly and protracted patent prosecution in the face of a competitor’s opposition led many foreign companies to enter into voluntary cross-license agreements with Japanese competitors. With the threat of compulsory licenses removed, U.S. companies may be less willing to transfer valuable technology to Japanese competitors.⁹³

Despite Japan’s implementation of these two agreements, USTR has raised complaints with other aspects of Japan’s patent system, particularly with respect to the narrow claiming encouraged by the JPO and Japanese courts. In the United States and many other countries, patent claims cover not only what it literally described in the claims and specification, but also embodiments that deviate in only insubstantial ways from the patent (the so-called “doctrine of equivalents”). While Japanese courts have not expressly disavowed the doctrine of equivalents, the doctrine is rarely applied.⁹⁴ Thus, a Japanese patent must literally cover an accused device in order for the device to be found infringing. Similarly, the JPO limits claims only to what is literally set forth in the application and examples that have actually been produced (“reduced to practice”). This is problematic, especially in the chemicals area, where a compound may have thousands of variations and it is impractical to list each example after reducing it to practice. These narrow claiming practices have encouraged “patent flooding,” in which companies flood the JPO with applications that deviate only marginally from an original application, thus contributing to the backlog at the JPO and creating uncertainties regarding the scope of patent rights.⁹⁵

The JPO alleviated these concerns somewhat in 1995 by issuing revised guidelines to its patent examiners. These guidelines directed examiners to grant patent rights that go beyond actual examples set forth in the application if the applicant has shown how one skilled in the relevant technological art can make variations on these examples and such variations are not otherwise known to the public. These guidelines, which will be applied retroactively to pending as well as new applications, will bring JPO procedures more closely in line with procedures in the United States and other countries.⁹⁶

Some commentators are of the view that these problems are more the result of the failure of U.S. business to understand and adapt to Japan’s unique patent system than to weakness in the system itself. For example, foreign patent applications are often subject to delays in

⁹² *Ibid.* at 175-76. Decreasing the processing period for a patent will also shorten the time competitors have to review a pending application, which is published after 18 months, before patent protection is finally issued. *Ibid.* at 176.

⁹³ *Ibid.* at 177-79.

⁹⁴ Thorson and Fortkort, *supra* note 62, at 306-09.

⁹⁵ *Fact Sheets: “Special 301” on Intellectual Property Rights and 1996 Title VII Decisions*, Office of the U.S. Trade Representative, pp. 3, 4 (June 13, 1997); and *1997 National Trade Estimate Report on Foreign Trade Barriers*, pp. 200-201.

⁹⁶ *Ibid.*

prosecution due to failure to comply with Japanese legal requirements; failure to use proper Japanese technical terminology; or poor translations.⁹⁷ U.S. companies are also advised to emulate their Japanese competitors by regularly reviewing patent applications to learn the latest technology and by filing multiple claims to cover numerous variations of an invention in order to compensate for the absence of a doctrine of equivalents.⁹⁸ Other observers, however, have recounted the numerous difficulties encountered in enforcing patent rights in Japan.⁹⁹

⁹⁷ Thorson and Fortkort, *supra* note 62, at 293-94.

⁹⁸ *Ibid.* at 298, 301-06.

⁹⁹ William C. Revelos, "Patent Enforcement Difficulties in Japan: Are There Any Satisfactory Solutions for the United States?," 29 *Geo. Washington Journal of Law and Economics* 503 (1995).

CHAPTER 5

Conclusions

As we enter the twenty-first century, the U.S. pharmaceutical industry appears to be in a strong competitive position. Over half of the top 10 pharmaceutical companies of 1997 (table 3-1) are headquartered in the United States, which indicates that U.S. firms are highly competitive with foreign companies. Additionally, NCE approvals are on the rise in the United States (figure 2-1, table 2-1), pointing to a regulatory environment that is particularly conducive to innovation.

In assessing the competitiveness of the pharmaceutical industry, starting with the premise that the ability to develop and market NCEs is the best indicator of success,¹ two aspects of the industry must be separated: the R&D aspect and the regulatory and marketing aspect. Research in the pharmaceutical industry is complex, time-consuming, and expensive, all of which necessitate top quality employees and facilities. On this basis, it seems that the United States, Japan, and Western Europe are similarly equipped to produce high quality R&D.

However, the biotechnology industry, a particularly innovative and high-tech field, has demonstrated certain strengths of the U.S. industry. Specifically, entrepreneurial initiative and inventiveness are encouraged in the United States, much more so than in Japan. These qualities have led to the development of many small, cutting-edge firms in the United States, in part because the U.S. scientific community generally accepts mobility of scientists among firms and the barriers to enter the market are low. Although these firms typically require the support of a large pharmaceutical firm to assist in bringing products to market, there are significant scientific benefits to conducting research at the level of a small firm (e.g., flexibility). Overall, the success of the U.S. biotech industry appears to be a strong indicator of an outstanding technical environment for pharmaceutical R&D in the United States.

The U.S. patent system also seems to be effective in protecting the interests of innovative pharmaceutical companies. Japan and the EU also offer reasonable protection for patented items, especially since the implementation of several new policies. The Japanese patent system is becoming more usable for foreigners, and the EU now allows for the issuance of patents on biotechnology products. Although each of the three systems is distinct, the general trend is toward harmonization, which would be extremely beneficial to pharmaceutical companies.

Just as sufficient patent protection is important to allow companies to recoup their investment in R&D, it is equally important for Government regulatory agencies to complete the new drug approval process in time for drugs to be marketed under patent protection. If the approval process becomes excessively time consuming, the drug developers may face significantly abbreviated protection. The disparity in approval processes across Western Europe has at times proven to be a hindrance to companies, but the establishment of the EMEA is intended

¹ See the Commission's *1991 Competitiveness Study*.

to facilitate drug approvals in a timely, more economical manner. Japan's newly established regulatory agency structure should be a great benefit to foreign companies, particularly U.S. firms, who were often at a disadvantage under the old system. Moreover, the U.S. system has been overhauled, and the FDA performance, especially its rate of drug approvals, has dramatically improved as a result. While these national agencies regulate all companies, foreign and domestic, and do not serve to discourage the U.S. industry in particular, the overall health of the pharmaceutical industry is adversely affected by impediments to drug approval in any of these three significant markets.

From the point of view of industry, the next step in recouping R&D costs, and thereby providing the profits for future R&D, comes through a company's ability to set a reasonable price for its product. As a result of various Government drug pricing policies across Western Europe, there can be a negative effect on profitability. If prices are set too low, or other less expensive drugs are deemed equivalent to an innovative new product, companies can be discouraged from R&D-intensive activities.² Companies doing business in the EU also face the controversial issue of parallel importing, which decreases profits and diminishes the incentive for investment in R&D. Japan has also moved to more regulated price controls for pharmaceutical products, which is not a positive change for the industry.

Globally, the pharmaceutical industry benefited from the tariff eliminations negotiated during the Uruguay Round. Lowering the costs of production is a boon at the company level, although country-specific data may indicate diminishing competitiveness. It is clear from the level of investment in R&D by U.S. firms that scientific and technical development is still being conducted locally, even though some production has moved to countries with lower labor costs.

One area that may prove to hinder the U.S. pharmaceutical industry is the inadequate number of domestic FDA-approved fine chemical facilities that are capable of producing the intermediates and other complex chemicals used to make drugs. There are significant benefits to outsourcing these tasks to local operations, where a synergy between the drug company and fine chemical firm can be cultivated from the early stages of product development. The Western Europeans presently have an advantage in this area, although the U.S. chemical industry is technically capable of developing outsourcing services for the pharmaceutical industry.

Overall, the U.S. pharmaceutical industry seems to enjoy a domestic environment conducive to researching and developing drugs, protecting their intellectual property, and obtaining regulatory approval to market these products. There is also a strong trend in the United States to invest those profits in new R&D. Recent improvements to the patent systems and Government regulatory policies in Western Europe and Japan are likely to benefit the U.S. industry as well. Because of the strong international component to this industry, benefits to the industry in any one of these three areas will likely work to the benefit of the others. Since aging populations will only bring a rise in the demand for drug products, the U.S. pharmaceutical industry, along with the industries of Western Europe and Japan, can expect growing markets for their products.

² *PhRMA Industry Profile, 1998*, pp. 69-70.

APPENDIX A
TABLE TABLES

Table A-1
Bulk medicinal chemicals and botanical products (SIC 2833): U.S. domestic exports, in
thousand dollars, 1992-97

Major trading partners	1992	1993	1994	1995	1996	1997	Percent of total 1997 trade
	<i>(Thousand dollars)</i>						
EU-15	1,354,622	1,249,056	1,194,080	1,243,464	1,245,141	1,490,525	50.7
Netherlands	168,379	155,404	164,526	231,720	272,680	446,393	15.2
France	227,429	234,246	270,514	226,788	173,874	254,901	8.7
United Kingdom	149,880	129,547	134,888	226,588	216,458	195,824	6.7
Germany	184,493	128,292	145,058	114,804	153,744	169,794	5.8
Belgium	149,029	152,822	170,181	193,143	159,869	162,247	5.5
Italy	233,621	219,911	150,391	148,778	143,717	135,198	4.6
Ireland	141,700	128,246	52,811	31,666	45,183	46,962	1.6
Other EU	100,091	100,588	105,711	69,977	79,616	79,206	2.7
Japan	331,331	345,008	274,772	346,780	313,872	416,292	14.1
Canada	99,402	139,144	151,045	170,838	186,406	230,621	7.8
Brazil	60,108	82,233	87,554	96,979	124,815	105,376	3.6
Mexico	79,323	84,591	81,252	69,092	84,110	93,471	3.2
All others	518,808	500,919	492,658	517,774	557,076	605,991	20.6
Total	2,443,594	2,400,951	2,281,361	2,444,927	2,511,420	2,942,276	100.0

Source: Official statistics of the U.S. Department of Commerce.

Table A-2
Bulk medicinal chemicals and botanical products (SIC 2833): U.S. imports for consumption, in
thousand dollars, 1992-97

Major trading partners	1992	1993	1994	1995	1996	1997	Percent of total 1997 trade
	<i>(Thousand dollars)</i>						
EU-15	1,591,678	1,615,461	1,931,055	2,883,905	3,959,589	4,798,700	65.8
Ireland	172,312	229,952	257,367	443,578	995,691	1,528,945	21.0
United Kingdom	339,984	572,718	655,225	775,358	900,568	1,070,002	14.7
Germany	650,825	319,031	377,151	686,629	886,654	885,785	12.1
Italy	178,602	220,600	225,700	406,985	440,405	413,068	5.7
France	58,917	87,752	190,977	265,154	259,328	303,355	4.2
Belgium	25,742	13,576	23,562	63,199	128,242	210,112	2.9
Other EU	165,296	171,832	201,073	243,003	348,700	387,433	5.3
Switzerland	311,283	374,564	372,339	528,344	612,412	741,071	10.2
Japan	538,737	485,959	526,282	589,448	739,408	672,836	9.2
Singapore	21,832	28,993	50,348	37,794	172,587	313,282	4.3
China	89,405	114,028	118,950	159,112	200,462	211,241	2.9
Mexico	151,433	58,203	58,777	60,557	58,785	121,702	1.7
All others	572,346	424,018	308,175	372,996	377,556	439,133	6.0
Total	3,276,714	3,101,226	3,365,926	4,632,156	6,120,799	7,297,965	100.0

Source: Official statistics of the U.S. Department of Commerce.

Table A-3
Pharmaceutical preparations (SIC 2834): U.S. domestic exports, in thousand dollars, 1992-97

Major trading partners	1992	1993	1994	1995	1996	1997	Percent of total 1997 trade
	<i>(Thousand dollars)</i>						
EU-15	567,565	558,922	696,120	683,278	997,768	1,375,745	41.3
United Kingdom	63,306	112,328	190,109	150,777	280,567	389,661	11.7
Netherlands	74,999	53,410	83,244	76,180	132,717	358,594	10.8
Italy	77,763	69,008	46,447	93,961	169,840	238,445	7.2
Germany	92,258	94,721	109,046	111,713	128,966	123,010	3.7
France	118,112	89,279	79,303	101,469	120,417	76,176	2.3
Ireland	26,702	24,176	59,564	20,050	32,617	64,970	1.9
Belgium	26,974	31,273	35,419	58,024	57,413	56,573	1.7
Other EU	87,451	84,727	92,988	71,104	75,231	68,316	2.0
Canada	487,710	574,259	590,484	639,508	752,804	861,008	25.8
Japan	237,876	272,685	259,804	284,843	245,896	193,530	5.8
Brazil	20,848	27,126	34,402	46,186	76,658	125,428	3.8
Australia	51,124	68,765	61,024	53,279	61,601	88,863	2.7
Switzerland	52,982	74,414	241,564	68,938	60,441	61,456	1.8
All other	400,362	451,102	431,479	471,108	523,183	628,672	18.9
Total	1,818,467	2,027,273	2,314,877	2,247,140	2,718,351	3,334,702	100.0

Source: Official statistics of the U.S. Department of Commerce.

Table A-4
Pharmaceutical preparations (SIC 2834): U.S. imports for consumption, in thousand dollars, 1992-97

Major trading partners	1992	1993	1994	1995	1996	1997	Percent of total 1997 trade
	<i>(Thousand dollars)</i>						
EU-15	1,191,434	1,452,968	1,682,796	1,898,157	2,443,790	3,717,223	69.4
Germany	105,672	183,031	269,678	434,548	367,293	1,343,960	25.1
United Kingdom	494,963	576,995	720,805	747,634	1,114,185	1,287,589	24.0
Italy	80,934	160,170	155,584	120,928	203,015	271,566	5.1
Ireland	110,282	120,942	104,901	74,613	165,536	157,203	2.9
France	102,678	113,240	71,150	80,785	116,941	156,359	2.9
Belgium	68,044	80,908	82,677	84,073	81,165	108,962	2.0
Netherlands	12,473	27,403	21,809	22,074	17,858	49,491	0.9
Other EU	216,388	190,279	256,192	333,502	377,797	342,093	6.4
Canada	82,455	103,556	201,503	245,044	323,573	521,790	9.7
Switzerland	415,766	324,800	359,952	430,704	433,609	454,947	8.5
Japan	121,513	125,071	129,579	210,380	297,221	387,085	7.2
Israel	17,833	60,328	108,354	53,697	138,354	204,227	3.8
All others	30,445	29,243	35,161	39,303	65,680	72,895	1.4
Total	1,859,446	2,095,966	2,517,345	2,877,285	3,702,227	5,358,167	100.0

Source: Official statistics of the U.S. Department of Commerce.

