Pricing of Prescription Drugs

Investigation No. 332-419
Publication 3333
December 2000

U.S. International Trade Commission

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PREFACE

On June 29, 2000, the U.S. International Trade Commission (Commission) received a letter from the Committee on Ways and Means requesting that the Commission conduct an investigation under section 332 (g) of the Tariff Act of 1930 for the purpose of determining the effect of the utilization of price controls on innovative medicines by the other G-8 countries or other countries that are signatories to the NAFTA on pricing for such drugs abroad and in the United States. The Commission was requested to provide the study within 90 days of receipt of the letter, or by September 29, 2000.

In the letter, the Commission was asked to provide the following information for each of the countries under consideration:

(1) the process by which prescription drug prices are established;
(2) the role of compulsory licensing in setting prices;
(3) a description of the costs associated with the development of prescription drugs, and a comparison of the authorized prices in the specified countries; and
(4) whether and to what extent price control systems utilized by such countries impact pricing for comparable drugs in the United States.

Through subsequent communications with the Committee,[1] the deadline for the Commission's report was extended until December 1, 2000, and the scope of the Committee's original request was modified to address only items 1 and 2 above for each of the countries under consideration; as well as limiting item 3 to a description of the costs associated with the development of prescription drugs in each country. The remaining information sought in the original request–a comparison of authorized prices in the specified countries and whether and to what extent U.S. prices are impacted by foreign price-control systems–is addressed in the form of a general discussion of conditions of competition in the pharmaceutical market, a brief review of the literature that addresses the dynamics of the pharmaceutical market and international price comparisons, and a presentation of the analytical framework that could be used should additional analysis be undertaken at the request of the Committee to assess the impact of price-control systems in the specific countries on comparable U.S. prices. Public notice of this investigation was posted in the Office of the Secretary, U.S. International Trade Commission, Washington, DC 20436, and published in the *Federal Register* (65 F.R. 45998) of July 26, 2000.

The information and analysis in this report are for the purpose of this report only. Nothing in this report should be construed as indicating how the Commission would find in an investigation conducted under other statutory authority.

[1] Chairman Koplan letter of July 21, 2000, and Chairman Archer letter of August 9, 2000.

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Executive Summary

On June 29, 2000, the U.S. International Trade Commission (Commission) received a letter from the House Committee on Ways and Means (Committee) requesting that the Commission conduct an investigation under section 332 (g) of the Tariff Act of 1930 for the purpose of determining the effect of the utilization of price controls on innovative medicines by the other G-8 countries, or other countries that are signatories to the NAFTA, on pricing for such drugs abroad and in the United States. The Commission was requested to provide the study within 90 days of receipt of the letter, or by September 29, 2000.

Through subsequent communications with the Committee, it was agreed that the deadline for the Commission's report would be extended until December 1, 2000, and that the report would provide information on the following for each of the countries under consideration:[1]

(1) the process by which prescription drug prices are established;
(2) the role of compulsory licensing in setting prices;
(3) a description of the costs associated with the development of prescription drugs; and
(4) a general discussion of conditions of competition in the pharmaceutical market, a brief review of the literature that addresses the dynamics of the pharmaceutical market and international price comparisons, and a presentation of the analytical framework that could be used should additional analysis be undertaken at the request of the Committee to assess the impact of price-control systems in the specific countries on comparable U.S. prices.

Innovative medicines, the products of interest to the Committee, are generally patented prescription products in dosage form. Patented prescription pharmaceutical products are used, either alone or in conjunction with other healthcare system components, to prevent, diagnose, alleviate, treat, or cure disease. Pharmaceuticals are generally produced in two major manufacturing stages: (1) the production of pure pharmacologically active chemicals (also called "active ingredients") in bulk form, either by conventional methods or through use of bioengineering procedures, and (2) the formulation of these concentrated, pharmacologically active components into dosage-form products (e.g., pills, capsules, and tablets).

A comparison of selected information regarding the pharmaceutical industries and markets in the countries under consideration is provided in the table at the end of this Executive Summary. Highlights of the investigation are presented below:

Global Trends

- The global pharmaceutical industry is multinational, highly regulated, capital intensive, and driven by large research and development (R&D) expenditures. In 1998, the top 10 pharmaceutical companies worldwide invested almost $18 billion in R&D, or almost 50 percent of global pharmaceutical R&D expenditures; in the United States alone, companies reinvested an estimated 21 percent of their 1999 revenues. Ten of the top

[1] The countries under consideration are Canada, France, Germany, Italy, Japan, Mexico, Russia, and the United Kingdom.

20 firms in the global industry in 1998-99, as ranked by sales, were based in the United States. Of the remainder, 8 were based in Europe, and 2 in Japan.

❑ The world pharmaceutical industry underwent significant consolidation during 1985-2000. Reasons for consolidation included continuing increases in the cost of R&D and shorter product life cycles; increased developmental testing for products intended to treat chronic ailments; increased marketing costs; efforts to increase access to global markets; and increased "cost-containment pressures" worldwide. Given this environment, consolidation allows firms to share the risks and costs of bringing new products to market and to fill in any gaps that might exist in their product development pipeline.

❑ According to IMS HEALTH,[2] the world market for pharmaceuticals was valued at about $337 billion in 1999. The following markets, ranked by size, were the top 10 markets in 1999 and accounted for about 80 percent of the total: the United States, Japan, Germany, France, Italy, the United Kingdom (UK), Spain, Brazil, China, and Canada.

The Process by Which Prescription Drug Prices Are Established

Pricing

❑ The large variety of pharmaceutical products, different medical practices and patterns of pharmaceutical use among countries, and different classes of purchasers within countries make international price comparisons difficult. Factors that make such comparisons difficult include, among other things:

- consumption patterns;
- dosages, concentrations, strengths, pack sizes, and units of measurement;
- courses of therapy;
- nature of distribution chains;
- taxes and subsidies;
- the availability of many products in patented and generic versions; and
- the use of exchange rates or purchasing power parity for currency conversion.

❑ All measurements of overall drug prices, including those surveyed for this report, require choices about relevant samples and means of weighting prices, among other things. Such choices depend on the judgment of researchers in the context of specific analyses, and significantly affect the findings. A single, definitive, and unbiased measure of comprehensive price differences does not exist.

❑ Studies reviewed in this report indicate that U.S. prices for prescription products generally tend to be higher than those in most of the countries under consideration, though the magnitude of the gap is difficult to measure. The GAO found that prices at the ex-manufacturer level for an aggregate market basket of 121 drugs were 32 percent higher in the United States than in Canada. The U.S. House of Representatives Minority Staff Internal Report concluded that average retail prices in Maine averaged 72 percent higher

[2] According to information available on their website, IMS HEALTH supplies "market research, business analysis, forecasting and sales management services to the global pharmaceutical industry." "About Us," found at http://www.ims-global.com/about/about.htm and retrieved on Nov. 22, 2000.

than those in Canada and 102 percent higher than those in Mexico. The Public Citizen Health Research Group found that average acquisition prices to pharmacists for antidepressant and antipsychotic drugs were 1.7 to 2.9 times higher than prices in Canada, Mexico, and European countries. Danzon and Kim, and Danzon and Chao examined prices at the manufacturers' level in the United States, Canada, and Europe and generally found smaller price differences. (For more information regarding the various types of prices used in individual studies, see chapter 2.)

- ❑ Several factors are involved in the pricing of pharmaceutical products, including, among other things, costs of production, costs of regulation, profit, and perceived therapeutic value. Promotional spending, especially in the United States, also plays a role in pricing decisions.

- ❑ The price paid by any one type of consumer (e.g., patients, hospitals, large health plans) within a country varies, depending on factors such as the provisions of individual private insurance plans; the provisions of national healthcare providers; pricing negotiations undertaken by the larger insurers and prescription benefit plans; and national price controls or cost-containment programs implemented in a given country.

  The large variety of purchasers in a given market allows that market to be segmented such that consumers are grouped by specific criteria with different prices charged in different segments. Such price segmentation, whether across a given domestic market or across multiple world markets, allows producers to cover their costs but also allows consumers in various market segments access to products that they might not be able to afford if uniform pricing across the entire market was the rule.

- ❑ There are, however, market factors which diminish total market segmentation, including the occurrence of parallel trade in pharmaceuticals, international reference pricing, or uniform pricing strategies by drug companies in response to the threat of parallel trade or reference pricing.[3]

National Patent Systems and Compulsory Licensing

- ❑ Patents confer upon the innovator companies a period of market exclusivity for pharmaceutical products, generally extending the period before price competition from generic products can occur. This period of market exclusivity allows innovative firms an opportunity to recoup some of their R&D expenditures, some of which, in turn, can then be used in the development of other innovative products. The duration of national patent terms appears to be converging, perhaps as a result of various multilateral agreements implemented in the last two decades. The usual term of such patents in the United States and in each foreign country under consideration is 20 years. However, the UK allows for the possibility of a different term, and for patents issued before October 1, 1989, Canada sets a term of 17 years from the filing date of the application for patent (see chapter 3 for information regarding a World Trade Organization dispute settlement case).

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[3] Parallel trade is the importation of products from countries with low cost by countries with higher costs. Reference pricing is defined as "a system for determining the maximum reimbursement amount for approved categories of pharmaceutical products prescribed by physicians."

- During the 1980s, the effective patent terms for individual products (i.e., the patent term remaining after the product is granted national marketing approval) became considerably shorter in many counties, given increases in the time needed to bring new products to market. Patent restoration programs enacted in the United States and Japan (and the intellectual property principle of the Supplementary Protection Certificate implemented in the European Union (EU)) have helped offset this erosion in the period of market exclusivity. Except for Canada and Russia, all of the countries under consideration allow for either the extension or restoration of a patent term or the issuance of supplementary protection certificates.

- The Committee also asked about the relationship between compulsory licensing and prices. Canada's experience may provide some insights in this regard. Canada is the only country under consideration that has actually applied compulsory licensing to pharmaceuticals. Canada commenced compulsory licensing of patented pharmaceuticals in 1923 and extended the requirement to imported patent pharmaceuticals in 1969. However, in 1987, Canada began the process of phasing out compulsory licensing. Legislation in 1992 completed the process with additional amendments to the Patent Act, in conjunction with the intellectual property rights provisions of NAFTA. Although there remain qualified circumstances in which compulsory licensing may be applied by the Canadian Government, no such instance has yet occurred.

  Industry sources in Canada have stated that the Patented Medicines Price Review Board was responsible for setting prices while compulsory licensing was in effect and that the system had no direct effect on prices. They state, however, that compulsory licensing requirements had a significant negative impact on investment levels in the Canadian pharmaceutical industry, particularly investment by research-based companies; subsequent increases in investment levels coincided with the progressive removal of compulsory licensing beginning in 1987.

Price Controls and Cost-Containment Programs

- A variety of public and private health plans are offered in each country, with many of the countries offering increasing amounts of national healthcare to their citizens, including coverage of prescription drugs. Many of the national plans increasingly call for patient copayments as a way to offset some of the costs.

- Countries use a variety of programs and regulations to control public expenditure on drugs, and, sometimes, to promote macroeconomic policy goals, such as employment and growth. The programs implemented vary by country but include, among many other things, direct and indirect price controls, profit controls, reference pricing, physician budget constraints, and copayment schemes. Although pharmaceuticals are considered by many to be cost-effective in that, at times, they may be used instead of more costly healthcare options such as hospitalization, the number of countries which have implemented price controls or cost-containment programs, or both, has increased in recent years, largely in response to increased national expenditures on pharmaceuticals.

- The amount of pharmaceutical expenditures generally increased during 1992-97 in the countries under consideration. In addition to increases in the prices of many of the pharmaceutical products, especially the newer ones, other reasons for the increased

expenditures included (depending on the country) increased prescribing of medications for growing national populations and the increasing number of senior citizens therein (senior citizens are more likely to develop and need treatment for chronic ailments as they age); new generations of medications, many of which are more expensive than older products, and are entering the market at a faster rate; and, in the United States, increased budgets for advertising products directly to consumers.

- The impact of the price controls and/or cost-containment programs implemented by each country varies, depending on perspective (i.e., whether that of the implementing government, domestic and foreign producers, or consumers). Such programs can have a significant impact on the industry, particularly in regard to R&D expenditures, because they often result in decreased revenues to the companies. Another reported effect of the cost-containment programs in some countries is the increased likelihood that older, lower cost products would be prescribed rather than newer, more innovative products.

  In comparison to the other countries under study, the U.S. market is considered to be relatively free of government-mandated price controls or cost-containment programs, and patients generally have access to any approved prescription pharmaceutical product on the market, usually within a short time after the product's launch. Although the U.S. pharmaceutical industry can price its products freely in the U.S. market, participation in many Federal and State buying programs is said to require various forms of price controls, including rebates, discounts, price caps, and limits on price increases. Currently, however, such programs are said to account for only 13 percent of the U.S. market. A recent study, which examined such policies in most of the countries under consideration in this report (with the exception of Mexico and Russia) cites Germany, the United States, and the UK as countries with "relatively less" government intervention in the domestic markets and France as a country with "considerable market intervention."

Costs Associated With the Development of Prescription Drugs

- On average, the development of a pharmaceutical product requires R&D expenditures of $500 million or more, depending on the world region; can take 10-20 years to bring to market; and involves a large degree of risk in the form of failed products. The process generally starts with the basic research needed to identify potential products, progresses to extensive clinical trials of promising products, and culminates in national approval by the appropriate approval body. In the United States, sources suggest that only 1 of about 5,000 compounds initially evaluated as potential products is actually approved.

- Whereas the clinical trial segment of R&D is said to occur in almost every country, primary research is concentrated in a few areas of the world–the United States, Europe, and Japan. Industry sources indicate that, of the countries under consideration in this report, the United States accounted for 45 percent of 152 globally-marketed products developed during 1975-94; the UK, 14 percent; Germany, 7 percent; Japan, 7 percent; and France, 3 percent. R&D spending on a national level varies, depending, in part, on the competitiveness of the industry.

Methodology for Further Research

- The request letter asks that the Commission propose a methodology to be used in future studies to further analyze determinants of prescription drug prices and the "question of whether and to what extent price-control systems utilized by other countries impact pricing for comparable drugs in the United States." Currently available research has generally not addressed this question. If the Commission were requested to undertake additional work on the determinants of prescription drug prices and the influence of foreign price controls on U.S. prices, the following issues could potentially be explored, but it is not clear that a precise answer could be found. First, a data-intensive international price comparison study could attempt to provide an updated comparison of drug prices in the United States and abroad, although likely at a significant cost to the Commission. Second, an industry survey could be attempted to provide a more extensive assessment of market segmentation in the pharmaceutical market. In addition, future research could use quantitative and qualitative methods to analyze parallel trade and reference pricing, and may give an indication of whether this breakdown in market segmentation provides a way for foreign price controls to affect U.S. drug prices. Finally, it should be noted that such work, because it involves acquiring a data base, surveying the industry, and preparing econometric models, would take considerable time to complete.

Table ES-1
Pharmaceuticals: Selected information

Country	Domestic market's share of world market, 1998 (percent)	Prescription products' share of total national health spending, 1997 (percent)	Annual R&D outlays, 1998 (millions of dollars)	Length of time for national approval process, 1999[1] (months)	Length of patent term; patent term restoration or SPC? (years)	Compulsory licensing possible?	Price controls/cost-containment systems currently implemented
United States	36	7.3	17,223	About 12[2]	20; Yes	No	In general, pharmaceutical companies operating in the United States can price products freely. However, participation in some Federal and State buying programs requires some controls , including rebates and discounts. Many private-sector programs (e.g., managed-care programs) reportedly negotiate their own price discounts. Although U.S. patients generally have access to any pharmaceutical on the market, some organizations (including the U.S. Department of Defense and the U.S. Department of Veterans Affairs) have reportedly implemented the use of formularies (i.e., listings of medicinal substances and formulas), which can restrict the products patients receive.
Canada	2	10.8	879	18-19.4[3]	17 or 20[4]; No [5]	Yes	Pharmaceutical companies are technically "free" to set their own prices for drugs. However, the suggested prices of patented medicines must be reviewed by the Patented Medicine Prices Review Board.
EU: France	6	13.9	2,718	7-24[6]	20; Yes	Yes	Prices have historically been controlled directly by the Government on a product-by-product basis. Decisions on reimbursement and prices are negotiated between the Comite Economique du Medicament (which includes representatives of economic ministries and outside experts) and the individual companies.
Germany	6	([7])	3,092	7-24[6]	20; Yes	Yes	A reference pricing system is used with the groupings decided by the Federal Association of Physician and Sickness Funds (excluding the industry).The Federal Association of Company-Based Insurance Funds then fixes reference prices after taking expert, including industry, views into account. At least some patented products are excluded from regulations on the basis of this scheme.
Italy	4	([7])	851	7-24[6]	20; Yes	Yes	The licensing, classification, and reimbursement of new medicines is overseen by the Ministry of Health (with the advice of the Drug Commission). Parties are tied to the average of prices in France, Spain, Germany, and the UK, adjusted for purchasing power parity. Italy does not control the prices of pharmaceutical products it does not reimburse. It also does not control the price of OTC drugs, although OTC prices cannot be raised more than once a year.
UK	3	11.2	4,144	7-24[6]	20; Yes	Yes	The pricing of new medicines is free of regulation, subject to a control on profits from sales to the National Health Service embodied in the Pharmaceutical Price Regulation Scheme. Companies can apply for permission to raise prices only if their profits are below a given level.

See footnotes at end of table.

Table ES-1 (continued)
Pharmaceuticals: Selected information

Country	Domestic market's share of world market, 1998 (percent)	Prescription products' share of total national health spending, 1997 (percent)	Annual R&D outlays, 1998 (millions of dollars)	Length of time for national approval process, 1999[1] (months)	Length of patent term; patent term restoration or SPC? (years)	Compulsory licensing possible?	Price controls/cost-containment systems
Japan	14	15.3	5,200	30-48	20; Yes	Yes	The Ministry of Health and Welfare fixes the introductory price of every new prescription brand-name drug through negotiation with its manufacturer. Japanese physicians generally dispense the drugs they prescribe. The Government sets the reimbursement price; the dispensing physician or hospital receives reimbursement from the social insurance program. The dispensing physician or hospital can thus profit from any margin between the reimbursement price and the manufacturer's price.
Mexico	([7])	([7])	([8])	6-8	20; Yes	Yes	The Mexican Government is the largest producer of pharmaceuticals in Mexico. The Institute Mexicano de Seguro Social is the largest purchaser of pharmaceuticals, and can impose its prices on drugs sold in the public sector. In the private sector, retail prices are limited by SECOFI's Department of Standards and Acquisition. The Government must approve all final retail prices.
Russia	([7])	([7])	([9])	6	20; No	Yes	A price-control system for certain essential pharmaceuticals was introduced in Russia by decree No. 347, "On Measures for State Control over Pricing on Medicines," effective March 29, 1999. The decree provides Government control over market prices, setting an upper limit to the selling price. Prices are registered at the Federal level, but it is up to local officials to implement the controls.

[1] These data may also include approval times for generic products. Generic products are generally approved on a faster basis than innovative products. The approval time is intended to represent the time taken by the national agency to review and approve new drug applications. This time is not considered to include the time taken to perform clinical trials.

[2] Defined by the U.S. Food and Drug Administration (FDA) as the median approval time. According to an FDA representative, FDA's goals are to act on new drug applications in either 6 months for priority applications or 10-12 months for standard applications. This action could be in the form of either approving the drug, not approving it, or approving it conditionally while seeking more information from the applicant.

[3] According to a representative of Canada's Research-Based Pharmaceutical Companies (Rx&D), the difference in approval times can be attributed to the fact that the data were obtained from different sources using different survey data. Rx&D obtained the estimate of 19.4 months by surveying its members (i.e., innovative companies); the Therapeutic Products Programme of Health Canada 's estimate of 18 months was reportedly obtained from a survey of a broader group of companies.

[4] The term of a patent based on an application filed before October 1, 1989, is 17 years, measured from the date that the patent was issued. The term of a patent based on an application filed on or after October 1, 1989, is 20 years, measured from the filing date of the application.

[5] The term of any individual patent may be extended by an Act of Parliament, but that is rare.

[6] According to a representative of EFPIA, although the EU mandates that member States have 210 days to nationally authorize a drug, the actual times may vary; no data are reportedly available regarding actual times. Commission staff telephone interview with a representative of EFPIA on Oct. 25, 2000.

[7] Not available.

[8] Most R&D is conducted at the Mexican Centre of Pharmaceutical Development & Research (a joint government/industry venture funded by hospitals, universities, and research centers).

[9] Most Russian companies reportedly do not conduct primary research.

Sources: FDA (U.S. approval times); IMS HEALTH (1998 market data); *OECD Health Data, 2000* (prescription products' share of total health spending); and national trade organizations (annual R&D outlays). The various sources for the remaining data are noted in chapters 3 and 4.

CHAPTER I
INTRODUCTION

Purpose and Scope of Study

On June 29, 2000, the Commission received a letter[1] from the Committee on Ways and Means requesting that the Commission conduct an investigation under section 332 (g) of the Tariff Act of 1930 for the purpose of determining the effect of the utilization of price controls on innovative medicines by the other G-8 countries or other countries that are signatories to the NAFTA on pricing for such drugs abroad and in the United States.[2] The Commission was requested to provide the study within 90 days of receipt of the letter, or by September 29, 2000.

In the letter, the Commission was asked to provide the following information for each of the countries under consideration:

(1) the process by which prescription drug prices are established;
(2) the role of compulsory licensing in setting prices;
(3) a description of the costs associated with the development of prescription drugs, and a comparison of the authorized prices in the specified countries; and
(4) whether and to what extent price control systems utilized by such countries impact pricing for comparable drugs in the United States.

Through subsequent communications with the Committee,[3] the deadline for the Commission's report was extended until December 1, 2000, and the scope of the Committee's original request was modified to address only items 1 and 2 above for each of the countries under consideration as well as limiting item 3 to a description of the costs associated with the development of prescription drugs in each country. The remaining information sought in the original request–a comparison of authorized prices in the specified countries and whether and to what extent U.S. prices are impacted by foreign price-control systems–is addressed in the form of a general discussion of conditions of competition in the pharmaceutical market, a brief review of the literature that addresses the dynamics of the pharmaceutical market and international price comparisons, and a presentation of the analytical framework that could be used should additional analysis be undertaken at the request of the Committee.

Public notice of this investigation was posted in the Office of the Secretary, U.S. International Trade Commission, Washington, DC, and published in the *Federal Register* (65 F.R. 45998) of July 26, 2000. Public notice of the extension, and the subsequent extension of the Commission's deadline for written submissions, was posted in the Office of the Secretary, and published in the *Federal Register* (65 F.R. 51327) of August 23, 2000.[4]

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[1] The request from the Committee is reproduced in full in appendix A.

[2] The countries under consideration are Canada, France, Germany, Italy, Japan, Mexico, Russia, and the United Kingdom.

[3] Chairman Koplan letter of July 21, 2000, and Chairman Archer letter of August 9, 2000.

[4] The notice is included in appendix E.

Study Approach and Organization

The Commission obtained information from a variety of sources. In addition to conducting a literature search of industry and Government publications, the Commission conducted telephone interviews to obtain firsthand information about the pharmaceutical industry and market in the United States and each of the countries under consideration.[5] These telephone interviews were with representatives of (1) domestic and foreign companies that produce pharmaceuticals; (2) principal trade associations around the world;[6] (3) U.S. and foreign governments; (4) major private and governmental research groups; and (5) representatives of various insurance groups and a coalition of healthcare providers. The Commission also obtained information from submissions from interested parties, as well as from consulting firms and from testimony presented at various congressional hearings. Given the short duration of the study and the number of countries examined, some data were not readily available or were not aggregated at the level of patented prescription drugs only.[7]

The remainder of this chapter presents comparative data for the world pharmaceutical industries and markets covered in this report, as well as a brief discussion of some of the data. Chapter 2 presents a general discussion of conditions of competition in the pharmaceutical market and a brief review of the economic literature that addresses the dynamics of the pharmaceutical market and international price comparisons. The chapter also includes a brief discussion of the analytical framework that could be used should additional analysis be undertaken at the request of the Committee to assess the impact of price-control systems in the specified countries on prices of pharmaceutical products in the United States.

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[5] The data and information presented for each country's industry generally include the operations of foreign-based firms operating in that country. It is not possible to break out information for each country strictly on the basis of the operations of domestic firms.

[6] Information was obtained from the following trade associations representing research-based pharmaceutical companies: Pharmaceutical Research and Manufacturers of America (PhRMA represents pharmaceutical companies operating in the United States); European Federation of Pharmaceutical Industries and Associations (EFPIA represents pharmaceutical companies operating in Europe); Association of International Pharmaceutical Manufacturers (AIPM represents international research-based pharmaceutical and medical equipment companies operating in Russia); Japanese Pharmaceutical Manufacturers Association (JPMA represents companies operating in Japan); and, in Canada, Canada's Research-Based Pharmaceutical Companies (Rx&D) represents the research-based companies operating in that country. The National Chamber of Pharmaceutical Industry (Canifarma) is a nonprofit autonomous organization that represents and protects the interests of pharmaceutical companies operating in Mexico. According to its website, Canifarma cooperates with the Secretariat of Commerce and the System of Information for Mexican Companies within the boundaries established by the laws and regulations of the Mexican Government.

Within the EU, member trade associations of EFPIA that represent research-based companies include France's Syndicat National de l'Industrie Pharmaceutique (SNIP), Germany's Association of Research-Based Pharmaceutical Companies (Verband Forschender Arzneimittelhersteller (VFA)), Italy's Associazione Nazionale dell'Industria Farmaceutica (Farmindustria), and the United Kingdom's Association of the British Pharmaceutical Industry (ABPI). Another German trade association, the Association of the German Pharmaceutical Industry (Bundesverband der Pharmazeutischen Industrie, (BPI)), a "founder member" of EFPIA, notes in its website that it represents research-based companies as well as manufacturers of generic products.

[7] In some cases, especially when official statistics are not available, broadly aggregated data from several sources and, sometimes, several time-frames, are presented for purposes of comparison.

Chapter 3 examines product development in the countries under consideration; in addition, synopses of selected aspects of the national patent laws are presented. Chapter 4 discusses, on a country-by-country basis, national healthcare programs and coverage; the process by which prices for prescription pharmaceuticals are established; and national price-control and cost-containment programs. Although the United States is not one of the specified countries, brief discussions regarding U.S. development of, and pricing practices for, prescription pharmaceuticals are also presented to allow for comparisons in chapters 3 and 4, respectively.

Although focused in terms of several broad topics, these discussions differ on a country-by-country basis because of the wide range of healthcare and pricing practices used by the countries under consideration and, in some cases, the limited amount of information available, either for pharmaceuticals overall or for patented prescription products specifically. Moreover, given the short duration of the study; the high costs associated with obtaining data for national industries; the fact that the national trade associations in many of the countries often represent and provide data regarding the pharmaceutical industry in the given country; and that economic research in this field is concentrated among a few individuals, data sources were of necessity limited and many are cited frequently in the report.

The economic methodology is presented in appendix F. Appendix G contains submissions from interested parties. Additional information regarding the patent system in each of the countries under consideration is presented in appendix H, and appendix I consists of a glossary.

Product Coverage

Pharmaceutical products are one component of a comprehensive healthcare system that also includes other forms of treatment, including hospitals, outpatient facilities, and clinics. Pharmaceutical products are used, either alone or in conjunction with other healthcare components, to prevent, diagnose, alleviate, treat, or cure disease in humans.[8] At times, pharmaceutical products are used instead of costlier options such as hospitalization.

Pharmaceutical products include preparations available by doctor's prescription, whether patented or generic products,[9] and over-the-counter preparations (OTC). Innovative medicines, the products of interest to the Committee, are patented prescription products in dosage form. The development of such products requires large research and development (R&D) expenditures, estimated at $500 million or more[10] on average by various sources,[11] depending on the region of the world, and involves a large degree of risk in the form of failed products. (For more information, see chapter 3.)

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[8] *Stedman's Medical Dictionary*, 23rd edition, 1976, p. 423. Pharmaceuticals may also be used to treat animals; the discussion in this report, however, will concentrate on products used for humans.

[9] Generic products are introduced once the patent on the original innovative product expires.

[10] The $500 million is in terms of 1990 dollars. A higher estimate of $635 million for average R&D costs in the EU is in terms of 1997 dollars.

[11] Numerous economists and organizations have made estimates over the years regarding the cost of developing pharmaceutical products, including, but not limited to: Hansen, 1979 estimate; Wiggins, 1987 estimate; Di Masi et. al., 1991 estimate; Office of Technology Assessment, 1993 estimate; Meyers & Howe, 1997 estimate; and the Office of Health Economics & Lehman Brothers, UK, 1999 estimate.

Pharmaceuticals are generally produced in two major manufacturing stages. The first stage is the production of pure pharmacologically active chemicals (also called "active ingredients") in bulk form, either by conventional methods or through use of bioengineering procedures. The second stage is the formulation of these concentrated, pharmacologically active components into dosage-form products. Dosage-form products, typically the pure active ingredients plus inert substances such as diluents or extenders, are available in several forms, including pills, capsules, tablets, creams, and lotions.

Pharmaceutical products can be grouped in terms of therapeutic use. Major therapeutic groupings include antihistamines, antineoplastic agents (i.e., anticancer drugs), cardiovascular drugs, central nervous system agents, gastrointestinal drugs, analgesics and anti-inflammatory agents, hormones, and vitamins.

Global Industry and Markets

The global pharmaceutical industry is multinational, highly regulated, capital intensive, and driven by large R&D expenditures.[12] Ten of the top 20 firms in the global industry in 1998-99, as ranked by sales, were based in the United States.[13] Of the remainder, 8 were based in Europe, and 2 in Japan. R&D expenditures by country are presented in table 1-1.[14]

In 1998, the top 10 pharmaceutical companies worldwide invested almost $18 billion in R&D, or almost 50 percent of global pharmaceutical R&D expenditures.[15] These R&D expenditures represented a reinvestment of almost 20 percent of their sales revenue. In the United States alone, the industry reinvested an estimated 21 percent of company revenues in 1999 and an estimated 20 percent in 2000.[16]

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[12] Company R&D costs also include certain fixed costs (e.g., salaries and benefits of permanent employees; rent; equipment; utilities; taxes; and depreciation) and management/administrative costs (e.g., services provided by non-R&D personnel). Bert Spilker, *Multinational Drug Companies: Issues in Drug Discovery and Development*, Raven Press, New York, 1989, pp. 486-487.

[13] EFPIA, *The Pharmaceutical Industry in Figures*, 2000 ed., Brussels, p. 13. The U.S. firms cited as among the top 20 in 1998-99 were Merck & Co., Bristol-Myers Squibb; Pfizer; American Home Products; Eli Lilly; Johnson & Johnson; Schering-Plough; Pharmacia-Upjohn; Abbott; and Warner-Lambert.

[14] There are potential comparability problems for the various types of data presented in table 1-1, given the multiple sources, product definitions, and, in some cases, years, of the individual data sets. As noted by IndustryCanada, for example, in regard to its presentation of data for the U.S. and Canadian pharmaceutical industries on their website, comparison of data across countries is difficult because one is comparing: (1) different economies of scale between countries; (2) a different product mix produced in each country; (3) differing industry cost structures; and (4) differing locations and levels of processing and R&D performed in the subsidiary country, which, in turn, are often determined by the parentage of the company. "Chapter 1-Definition and Inter-industry comparisons," *Pharmaceutical and Medicine Industry–(SIC 3741)*, June 23, 2000, found at http://strategis.ic.gc.ca/SSG/io37412e.html, retrieved Aug. 3, 2000.

[15] EFPIA, *The Pharmaceutical Industry in Figures*, p. 15. The worldwide R&D expenditures cited are defined by EFPIA as the total of R&D expenditures in the United States, Europe, and Japan.

[16] PhRMA, *Pharmaceutical Industry Profile 2000: Research for the Millennium*," Washington, DC, p. 21.

Table 1-1
Pharmaceuticals:[1] Certain industry statistics for the United States and the eight countries under consideration, 1998

Country	Number of companies[2]	Production	Imports	Exports	Apparent consumption[3]	Domestic market[3]	Imports-to-consumption	Exports-to-production	R&D as a percent of sales	R&D expenditures
		Million dollars					*Percent*			*Million dollars*
United States	42	107,692	17,847	11,944	113,595	[4]111,146	16	11	21.2	17,223
Canada	60	3,370	2,801	1,006	5,165	[4]4,961	54	30	15.5	879
France	300	23,885	5,077	7,925	21,037	[4]17,709	24	33	16.2	[5]2,718
Germany	341	19,833	8,377	14,218	13,992	[4]18,378	60	72	16.7	3,092
Italy	285	13,955	5,812	5,275	14,492	[4]10,963	40	38	7.9	851
Japan	82	44,600	3,737	1,909	46,428	[4]43,558	8	4	8.0	5,200
Mexico	[6]149	([7])	[8]5,360	[8]3,738	([7])	([7])	([7])	([7])	([9])	([9])
Russia	[10]50	[11]1,000	[11]766	[11]40	1,726	[11]1,800	44	4	([12])	([12])
United Kingdom	375	18,556	5,667	9,715	14,508	[4]10,245	39	52	33.4	4,144

[1] The scope of data provided for most countries is broader than patented prescription products and may include generic and OTC preparations.

[2] The 1998 data for Germany, Canada, and Japan are the number of companies that belong to the individual national pharmaceutical trade associations in that year. Most of the companies operating in the countries under consideration are multinational. In comparison, Japan and Russia reportedly have fewer multinationals operating in their domestic markets.

[3] Apparent consumption data are derived from production and trade data (production plus imports minus exports). According to a recent report, the value of "out-of-hospital" sales of patented prescription and generic products in each of the countries in 1999 was as follows: the United States: total prescription sales of $112 billion, of which generic products accounted for approximately $7.7 billion; Canada: total prescription sales of $5.6 billion, of which generic products accounted for approximately $541 million (on an ex-factory sales basis); France: total prescription sales of $19.6 billion (including OTC products), of which generic products accounted for approximately $400 million to $600 million; Germany: total prescription sales of $24.6 billion (including OTC products), of which generic products accounted for approximately $7.9 billion; Italy: total prescription sales of $14.1 billion, of which generic products accounted for approximately$141 million; Japan: total prescription sales of $44.7 billion, of which generic products accounted for approximately$3.6 billion; and the UK: total prescription sales of $9.8 billion, of which generic products accounted for approximately $2.3 billion. Elaine Last and Neil Turner, Ed., *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, 2000, Cambridge, UK, various pages.

[4] Data provided to the Commission by IMS HEALTH via e-mail dated Oct. 6, 2000. According to information found on the IMS HEALTH website regarding similar data for 1999, such data were obtained by collecting data from a sample of representative companies (e.g., retail pharmacies and drug stores) and then using the data to project an overall total for the country. They state, however, that products mainly used in hospitals or clinics may not be included in their entirety. "World-wide Pharmaceutical Market, 1999," found at http://www.ims-global.com/insight/world_in_brief/review99/year.htm and retrieved on Sept. 26, 2000.

[5] 1997 data.

[6] Includes research-based and generic firms.

[7] Not available.

[8] "The Pharmaceutical and Pharmochemical Industries in Mexico and the Federal District," Sept. 24, 1999, found at www.un.org.mx/cepal, retrieved Aug. 4, 2000.

[9] For domestic companies, R&D is conducted largely at the Mexican Centre of Pharmaceutical Development and Research which is a joint government/industry venture funded by hospitals, universities and research centers.

[10] 1999 data. Represents the number of AIPM members in 1999, including companies that produce medical devices. However, according to the Russian Ministry of Health, as of August 10, 2000, the Ministry had registered prices on 5,699 pharmaceuticals from 343 manufacturers. Of these, 162 were domestic producers.

[11] Pyrabelisk, "Russian Drug Market," company located in London, contact at http://www.pyrabelisk.com.

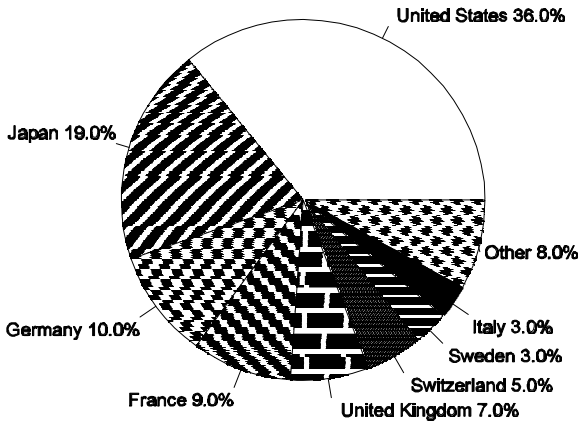
[12] Most Russian companies reportedly do not conduct primary research.

Sources: EFPIA (French, German, Italian, and UK production, trade, and research expenditures); PhRMA (U.S. member companies and U.S. research expenditures); IMS HEALTH (domestic sales for all countries except Mexico and Russia); AIPM (Russian member companies); Pyrabelisk (Russian production, trade, and sales statistics as reported in their report "Russian Drug Market"); Rx&D (Canadian research expenditures and percent of sales); IndustryCanada (Canadian production and trade statistics); JPMA (Japanese member companies and Japanese production, trade, and sales statistics and research expenditures); official statistics of the U.S. Department of Commerce (U.S. pharmaceutical production and trade statistics); the Commerce and Industrial Development Secretariat ((SECOFI) the number of pharmaceutical firms in Mexico); and Commission estimates.

The R&D process generally starts with the basic research needed to identify potential products, progresses to extensive clinical trials, and culminates in national approval by the appropriate approval body. Whereas the clinical trial segment of R&D is said to occur in almost every

country, primary research is concentrated in a few areas of the world.[17] In 1997, the majority of company-financed R&D was conducted in the United States, Europe, and Japan (see figure 1-1).[18] Of the countries under consideration in this report, the United States accounted for 45 percent of 152 globally-marketed products developed during 1975-94; the UK, 14 percent; Germany, 7 percent; Japan, 7 percent; and France, 3 percent.[19] The U.S. industry was also considered by industry sources to be more successful than the European or Japanese industries in marketing new products on a global basis.[20] During 1984-98, 22 percent of new products developed by the U.S. industry were launched globally (i.e., in the United States, Europe, and Japan), compared with 13 percent of those developed by European companies, and 6 percent of those developed by Japanese companies.

Figure 1-1
Company-financed pharmaceutical R&D, as a share of world total, by country, 1997



Source: Obtained from PhRMA (*Pharmaceutical Industry Profile 2000*, p. 89) and used with their permission. The original source was *Centre for Medicines Research, U.K., 1999*. Graphic presentation rearranged by the Commission.

Another characteristic of the world pharmaceutical industry has been its ongoing consolidation during 1985-2000, generally in the form of mergers or strategic alliances between firms of all sizes, including some of the largest firms in the global industry (figure 1-2 and table 1-2).This consolidation is attributable to several factors, including–

[17] Commission staff telephone interview with an industry representative, July 26, 2000.

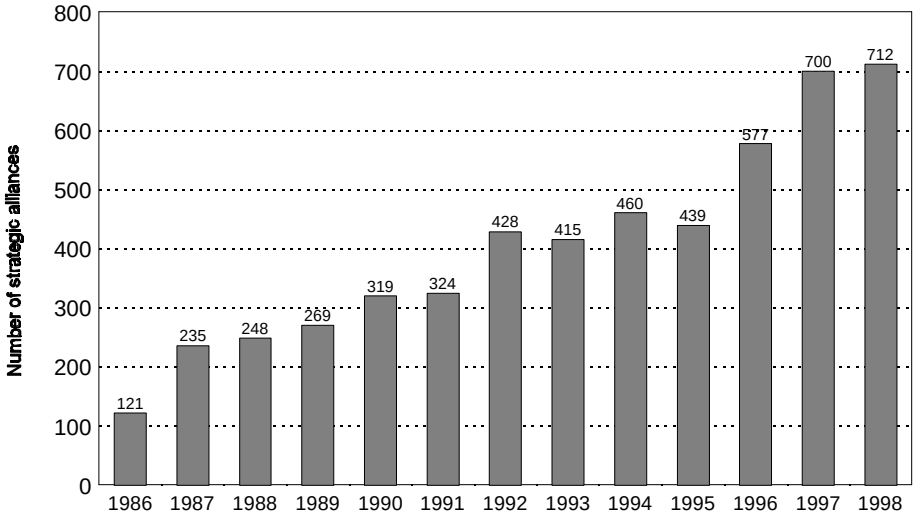
[18] PhRMA reports that several overseas companies are moving their research operations into the United States. Commission staff interview with representatives of PhRMA on July 13, 2000.

[19] PhRMA, *Pharmaceutical Industry Profile 2000*, p. 88.

[20] Ibid., and EFPIA, *The Pharmaceutical Industry in Figures*, p. 23. A global drug is generally defined as one marketed in the United States, Japan, France, Germany, the UK, Italy, and Switzerland.

- ❏ continuing increases in the cost of R&D and shorter product lifecycles;
- ❏ efforts to maintain continued productivity and uniform flow in product pipelines;[21]
- ❏ efforts to obtain increased access to global markets;
- ❏ increased "cost-containment pressures" worldwide;[22]
- ❏ increased developmental testing for products to treat chronic ailments,[23] particularly those intended for the growing senior citizen populations worldwide,[24] so as to fully understand the mechanism of these conditions;[25] and
- ❏ increased marketing costs, including promotional spending, particularly for products that may become "megabrands."[26]

Figure 1-2
Increasing frequency of strategic alliances, 1986-98



Note.--Strategic alliances range from marketing agreements to agreements to share the products of research in specified areas; individual companies may enter into multiple strategic alliances. PhRMA has stated that "these alliances are diverse in nature and may involve domestic and foreign pharmaceutical companies, biotech firms, university research centers, contract research organizations, or other parties."

Source: Graphic obtained from PhRMA and used with their permission. The original source cited for the data was *Windhover's Pharmaceutical Strategic Alliances, 2000*.

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[21] A "product pipeline"is a term used to refer to the progress of new drugs through the discovery, development, and marketing phases. A drug may fail at any stage in the pipeline and be eliminated from the firm's portfolio of potential new products. Several drugs can be in the pipeline simultaneously.

[22] PhRMA, *Pharmaceutical Industry Profile 2000*, p. 70.

[23] Chronic ailments include circulatory problems, heart disease, arthritis, and cancer.

[24] "Outpatient Pharmaceuticals and the Elderly: Policies in Seven Nations," *Health Affairs*, May/June 2000, p. 259. According to the article, "Although the nations [Australia, Canada, Germany, Japan, New Zealand, the UK, and the United States] vary greatly in the percentages of their populations over age sixty-five, all are rapidly aging."

[25] USITC, *Global Competitiveness*, publication 2437, pp. 1-4, 1-5, and 4-13.

[26] Lehman Brothers International (Europe), *The Trend Towards Pharmaceutical Megabrands*, Nov. 15, 1999, p. 1. As stated in the article, AstraZeneca's definition of a megabrand is: (1) the product has reached $1 billion in annual sales by the second year after launch and will likely earn several billion dollars in its lifetime; (2) it is introduced and marketed in as many as 60 countries during the first 2 years after launch; and (3) significant marketing expenditures are required. AstraZeneca reportedly estimates that marketing expenditures amounting to $450 million to $1 billion will be incurred just in the first 2 years after launch with about 25 percent of that commitment needed before product introduction. The article states that these marketing expenditures are most likely in addition to development expenditures.

Table 1-2
Mergers and acquisitions in the pharmaceutical industry, 1985-99

Year	Companies
1999	Monsanto and Pharmacia & Upjohn
1999	AHP/Warner-Lambert and Pfizer/Warner Lambert (pending)
1999	Roche and Genentech
1999	Warner-Lambert and Agouron
1998	Hoechst AG and Rhone-Poulenc Rorer
1998	Sanofi SI and Synthelabo
1998	Zeneca and Astra
1997	Hoffmann-La Roche and Boehringer Mannheim
1997	Nycomed and Amersham
1996	CibaGeigy and Sandoz
1996	Elan and Athena Neurosciences
1995	Knoll and Boots
1995	Glaxo and Burroughs Wellcome
1995	Gynopharma and Ortho-McNeil
1995	Hoechst-Roussel and Marion Merrell Dow
1995	Pharmacia and Upjohn
1995	Rhone-Poulenc Rorer and Fisons
1995	Schwarz Pharma and Reed & Carnrick
1994	American Home and American Cyanamid
1994	Hoffmann-La Roche and Syntex
1994	Pharmacia and Erbamont
1994	Sanofi and Sterling (prescription drug operation)
1994	SmithKline Beecham and Sterling (over-the-counter pharmaceutical unit)
1991	SmithKline and Beecham
1990	Boots and Flint
1990	Pharmacia and Kabi
1990	Rhone-Poulenc and Rorer
1989	American Home and A.H. Robins
1989	Bristol-Myers and Squibb
1989	Dow and Marion
1988	Kodak and Sterling
1986	Schering-Plough and Key
1985	Monsanto and Searle
1985	Rorer and USV/Armour

Source: Obtained from PhRMA (*Pharmaceutical Industry Profile 2000*, p. 71) and used with their permission. The original source was *Windhover's Health Care Strategist, 2000*.

Consolidation, whether in the form of mergers or acquisitions or strategic alliances,[27] such as joint ventures, allows firms to share the risks and costs of bringing new products to market and to fill any gaps that might exist in their product development pipeline. For example, smaller companies who have identified potential new products may prefer to form strategic alliances by licensing out or codeveloping products rather than carry the full development costs.[28] Consolidation also allows firms, particularly those wishing to enter the U.S. market, to expand their geographical reach and balance their product portfolios.

The world market for pharmaceuticals was valued at about $337 billion in 1999.[29] As shown in the following tabulation, in 1999 the top ten world markets accounted for about 80 percent of the world total (in billions of dollars):[30]

United States	$130	United Kingdom	$ 11
Japan	$ 54	Spain	$ 7
Germany	$ 19	Brazil	$ 6
France	$ 18	China	$ 6
Italy	$ 11	Canada	$ 6

The situation was similar in 1998, when the U.S., European, and Japanese markets accounted for approximately 81 percent of the total. Figure 1-3 shows the relative sizes of the markets in major world regions in 1998.[31]

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), the U.S. market grew faster in 1999 than any other market in the world, increasing by about 17 percent. In comparison, EFPIA states, the European market increased by only 7.2 percent and "between 1990 and 1998, the U.S. market grew twice as fast as the European and Japanese markets in real terms."[32] Reasons cited for this growth, particularly in the latter half of the decade, include: increased numbers of prescriptions dispensed; "record sales" of new

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[27] There are numerous forms of strategic alliances, ranging from marketing agreements to agreements to share the products of research in specified areas. Moreover, individual companies may enter into multiple strategic alliances. USITC, *Global Competitiveness,* publication 2437, p. 4-13.

According to PhRMA, "these alliances are diverse in nature and may involve domestic and foreign pharmaceutical companies, biotech firms, university research centers, contract research organizations, or other parties. Strategic alliances often allow pharmaceutical companies to draw upon others' research expertise, bring products to market more rapidly, and more effectively commercialize products after approval by FDA." PhRMA, *Pharmaceutical Industry Profile 2000*, p. 70.

[28] Shearson, Lehman, Hutton Securities, *Pharmaceutical Profiles*, Feb. 1990.

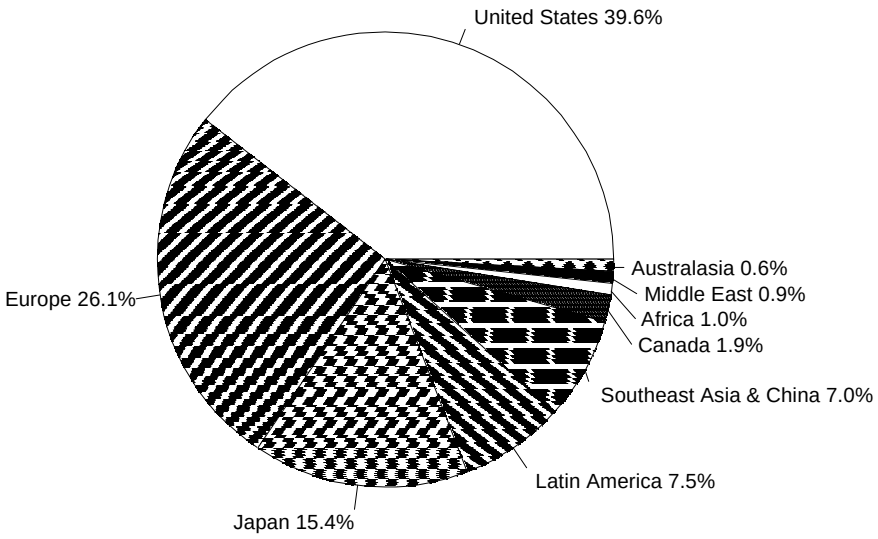
[29] "World-wide Pharmaceutical Market, 1999," found at http://www.ims-global.com/insight/world_in_brief/review99/year.htm and retrieved on Sept. 26, 2000. According to IMS HEALTH, a healthcare information company, data collected from a sample of representative companies (e.g., retail pharmacies and drug stores) within a country were used to project an overall total for the country. They state, however, that these data do not provide "comprehensive coverage" for products mainly used in hospitals or clinics.

[30] "10 Largest Pharmaceutical Markets in the World,1999," found at http://www.ims-global.com/insight/world_in_brief/review99/largest.htm and retrieved on Sept. 26, 2000.

[31] PhRMA, *Pharmaceutical Industry Profile*, p. 89.

[32] EFPIA, *The Pharmaceutical Industry in Figures*, p. 19.

Figure 1-3
World pharmaceutical market, 1998



Source: Obtained from PhRMA (*Pharmaceutical Industry Profile 2000*, p. 89) and used with their permission. The original source was *IMS HEALTH, 2000*. Graphic presentation rearranged by Commission staff.

products; a "steady stream" of new products entering the market; and the changing mix of products.[33]

Pharmaceutical Development, Pricing, and Expenditures

The development of pharmaceuticals, as well as their subsequent pricing, is affected by numerous factors.[34] As stated in the Commission's 1991 study on pharmaceuticals, for example, the level of innovativeness of the pharmaceutical industry in a given country depends on the industry's level of R&D spending and its reinvestment of sales revenues in R&D. Domestic or foreign government policies that reduced such revenues and, therefore, R&D expenditures may

[33] PhRMA, *Pharmaceutical Industry Profile*, p. vii. PhRMA cites IMS HEALTH as the source of this information.

[34] For example, in 1995, under the Uruguay Round Agreement, the United States and 16 other countries agreed to eliminate their most-favored-nation duties on about 7,000 pharmaceuticals and chemical intermediates used primarily for the production of pharmaceuticals, maintaining the option to review and update the list of products periodically. This duty-elimination could potentially affect the prices of pharmaceuticals if any portion of the eliminated duties are put to this use. As of the Commission's last examination of this subject matter, however, it was found that "The duty elimination resulting from the zero-for-zero agreement in pharmaceuticals is difficult to link directly to the various industry changes that have occurred during 1995-96 because of the likely impact of other economic factors during the period." USITC, "The Uruguay Round Elimination of Duties on Pharmaceuticals: Developments in the 2 Years Since Implementation" *Industry, Trade, and Technology Review,* Oct. 1997, p. 1.

potentially weaken the competitiveness of the pharmaceutical industry in a given country and, therefore, affect the global pharmaceutical industry.[35]

Representatives of the pharmaceutical industries in the United States and Europe have expressed concerns about the impact of government programs on the industry's ability to maintain innovative research programs.[36] For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) stated that "the United States' reliance on free market pricing has . . . established its clear leadership in pharmaceutical innovation."[37] They state, however, that "in most foreign markets, PhRMA member companies are confronted by a variety of government actions that stifle market-based competition from innovative products and limit patient access to new pharmaceuticals."[38]

In Europe, where price-control and cost-containment programs have been in effect in most countries for many years, several industry sources consider the pharmaceutical industry as becoming less competitive. According to a recent statement by EFPIA:

> The best guarantee of the European pharmaceutical industry's long-term competitiveness is its ability to pay for R&D. This ability largely depends on the success of products already on the market, and in particular on Europe's attitude to innovative products. In many European countries, the launch prices of patented products have been driven so low that they no longer generate a sufficient return to enable companies to recoup all their research costs before the patent expires. This is one of the root causes of the slow but steady erosion of European pharmaceutical industry competitiveness over the years.[39]

National patent systems also affect the development and pricing of pharmaceuticals.[40] Patents allow for a period of market exclusivity for a given pharmaceutical product, during which the innovative firm has the opportunity to recoup some of its R&D expenditures. These funds reportedly can then be used either in the development of other innovative products or for other purposes. During the 1980s, however, the effective patent terms for individual products (i.e., the patent term remaining after the product is granted national marketing approval) became considerably shorter in the United States, Western Europe, and Japan, given increases in the time needed to bring new products to market. Patent restoration programs enacted in the United States

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[35] USITC, *Global Competitiveness*, publication 2437, pp. 1-2, 1-4-1-5. Examples of government policies examined in that report as potentially reducing an industry's competitiveness included national price controls and cost-containment programs. It was noted in the study that, when assessing competitiveness, "because the pharmaceutical industry relies heavily on R&D [and] product innovation, assessments of the industry often focus on R&D productivity as well as output measures such as the number of globally-successful [new chemical entities]."

[36] This issue has been of ongoing concern to the U.S. and foreign industries. For example, the Commission's earlier study on this issue noted that the relatively "unencumbered U.S. economy," which allowed for continued high levels of R&D investment, was one of the main reasons for the U.S. industry's continued competitiveness. USITC, *Global Competitiveness*, publication 2437, pp. 1-4-1-5.

[37] PhRMA's submission of information in investigation No. 332-419, Aug. 4, 2000, p. 4 (see appendix G).

[38] Ibid., p. 2.

[39] EFPIA, *The Pharmaceutical Industry in Figures*, p. 21.

[40] The duration of national patent terms appears to be converging, perhaps as a result of various multilateral agreements implemented in the last two decades.

and Japan (and the intellectual property principle of the Supplementary Protection Certificate implemented in the European Union (EU)) have helped offset this erosion in the period of market exclusivity. (For more information on this topic, see chapter 3.)

One effect of improved intellectual property rights and a freer market climate in a given country can be increased investment in that country. For example, according to PhRMA and Canada's Research-Based Pharmaceutical Companies (Rx&D), the relatively high ratios of R&D expenditures to sales in Canada and Germany in 1998 were largely the result of improvements in the individual market climates for pharmaceuticals in the two countries. The level of R&D spending in each of the two countries reportedly decreased while compulsory licensing[41] was in effect in Canada and reference prices[42] were used for all products in Germany. Once compulsory licensing ended in Canada in the early 1990's and once patented products approved in Germany after January 1, 1996, were excluded from reference pricing while under patent, R&D spending increased in each country. In Canada, subsequent to the passage of Bill C-91 and the strengthening of the national patent system, the effective patent term for pharmaceuticals increased from about 6-7 years to 10 years.[43] R&D expenditures increased by over 700 percent during 1987-98, and the ratio of R&D spending to sales doubled during the same period [44] (For more information, see the sections in chapter 4 on pricing in Canada and Germany).

In general, overall healthcare expenditures have been increasing in many of the countries under consideration [45] and, as many sources indicate, so has the share of the total accounted for by prescription pharmaceuticals (see table 1-3 and figure 1-4). Different demographics and prescribing trends in each of the countries also contribute to the higher expenditures. Spending, whether on prescription pharmaceuticals as a percentage of overall healthcare costs or on a per-capita basis, varies significantly between countries and is generally higher in countries considered by several sources to be higher consumers of pharmaceuticals (see table 1-4). However, although many consider pharmaceuticals to be a cost-effective tool used to treat and, in some cases, reduce the disabling effects of many health conditions, as well as possibly reducing the need for hospitalization,[46] many countries are increasingly seeking ways to contain costs related to national consumption of pharmaceuticals.

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[41] Compulsory licensing is defined as "permission to use intellectual property, compelled by the Government in order to accomplish some political or social objective. Compulsory licensing forces an intellectual property owner to allow others to use that property at a fee set by the Government." J. Thomas McCarthy, *McCarthy's Desk Encyclopedia of Intellectual Property*, The Bureau of National Affairs, Inc., 1991, pp. 51-52.

[42] Reference pricing is defined as "a system for determining the maximum reimbursement amount for approved categories of pharmaceutical products prescribed by physicians." "Reimbursable products are placed in clusters or groups of drugs that have 'interchangeable' chemical characteristics or are considered to be 'therapeutically equivalent' when prescribed for a particular medical condition. Each group of products is given a single 'reference' price which then becomes the mandated average or maximum price at which all products in the group are reimbursed." William Looney, *The Costs and Consequences of Reference Pricing: A Flawed Experiment in Drug Payment Reform*, PhRMA, Mar. 1999, pp. 6-7.

[43] Rx&D, *Annual Review, 1999-2000: Patients are Our Purpose*," 2000, Canada, p. 13.

[44] Ibid., p. 14.

[45] The Organisation for Economic Co-operation and Development (OECD) dataset contains data through 1999; data for recent years, however, are not available for as many countries as in 1997.

[46] Elizabeth Helms, International Patient Advocacy Association, Testimony Before the Senate Committee on Health, Education, Labor and Pensions on "Prescription Drugs: What Drives Increases?" on July 18, 2000, p. 2; The Boston Consulting Group (BCG), *Ensuring Cost-Effective Access to Innovative Pharmaceuticals: Do Market Interventions Work?*, April 1999, p. 2; and EFPIA, *The Pharmaceutical Industry in Figures*, p 37.

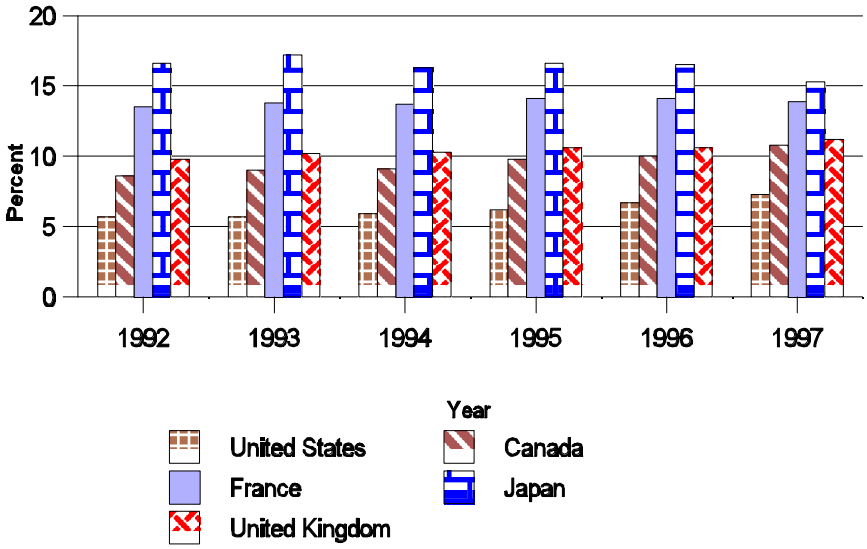
Table 1-3
Healthcare and prescription pharmaceutical expenditures and the share of the population 65 years of age and older, by country, 1992-97

Country	1992	1993	1994	1995	1996	1997
	Value (million dollars)					
Healthcare expenditures:						
United States	822,359	884,009	931,862	976,565	1,022,278	1,070,366
Canada	57,902	55,793	53,707	54,465	55,590	56,490
France	124,474	123,783	130,521	151,578	151,249	135,280
Germany	195,617	189,988	205,317	251,238	253,585	221,636
Italy	103,754	84,435	84,992	86,690	98,463	96,378
Japan	235,578	282,498	323,348	370,739	326,387	311,251
Mexico	16,231	18,045	19,586	14,063	15,132	18,939
Russia	(1)	(1)	(1)	(1)	(1)	(1)
United Kingdom	73,535	66,109	72,780	78,640	82,883	88,389
Prescription pharmaceutical expenditures:						
United States	46,598	50,632	55,189	61,021	68,890	78,545
Canada	4,982	5,045	4,864	5,319	5,535	6,096
France	16,784	17,103	17,912	21,342	21,159	18,810
Germany	(1)	(1)	(1)	(1)	(1)	(1)
Italy	(1)	(1)	(1)	(1)	(1)	(1)
Japan	39,070	48,593	52,685	61,723	53,909	47,727
Mexico	(1)	(1)	(1)	(1)	(1)	(1)
Russia	(1)	(1)	(1)	(1)	(1)	(1)
United Kingdom	7,179	6,715	7,463	8,298	8,786	9,902
	Quantity (percent)					
Prescription pharmaceutical expenditures as a share of total healthcare expenditures:						
United States	5.7	5.7	5.9	6.2	6.7	7.3
Canada	8.6	9.0	9.1	9.8	10.0	10.8
France	13.5	13.8	13.7	14.1	14.1	13.9
Germany	(2)	(2)	(2)	(2)	(2)	(2)
Italy	(2)	(2)	(2)	(2)	(2)	(2)
Japan	16.6	17.2	16.3	16.6	16.5	15.3
Mexico	(2)	(2)	(2)	(2)	(2)	(2)
Russia	(2)	(2)	(2)	(2)	(2)	(2)
United Kingdom	9.8	10.2	10.3	10.6	10.6	11.2
Share of population 65 years of age and older:						
United States	12.5	12.5	12.6	12.6	12.5	12.5
Canada	11.6	11.7	11.8	12.0	12.1	12.3
France	14.5	14.7	15.0	15.2	15.4	15.7
Germany	15.1	15.1	15.2	15.2	15.4	15.7
Italy	15.1	15.4	15.7	16.1	16.4	16.7
Japan	12.8	13.3	13.7	14.2	14.7	15.1
Mexico	4.1	4.1	4.2	4.3	4.4	4.4
Russia	(1)	(1)	(1)	(1)	(1)	(1)
United Kingdom	15.8	15.8	15.8	15.8	15.8	15.8

[1] Not available in the Organisation for Economic Co-operation and Development (OECD) dataset.
[2] Not available.

Source: Compiled by the Commission using data in the CD-ROM database developed by OECD and the Centre de Recherche, d'Etude, et de Documentation en Economie de la Sante (CREDES), *OECD Health Data 2000: A Comparative Analysis of 29 Countries*.

Figure 1-4
Prescription pharmaceuticals' share of healthcare expenditures, 1992-97



Source: Compiled by the Commission from data contained in *OECD Health Data 2000*.

Table 1-4
Healthcare spending as a share of GDP in the countries under consideration and prescription pharmaceuticals on a per capita basis, 1997

Country	Healthcare spending as a share of GDP	Prescription pharmaceuticals on a per capita basis
	Percent	
United States	13.6	$293
Canada	9.3	203
France	9.6	321
Germany	10.5	([1])
Italy	8.4	([1])
Japan	7.4	378
Mexico	4.7	([1])
Russia	([1])	([1])
United Kingdom	6.7	168

[1] Not available in the OECD dataset.
[2] Not available.

Source: Compiled by the Commission using data in *OECD Health Data, 2000*.

Many industry observers, including consumers, believe that increased expenditures for prescription pharmaceuticals in the United States are largely the result of price inflation. Others, however, have indicated that the higher prescription drug expenditures and their higher share of total healthcare expenditures in the United States are not necessarily just the result of pharmaceutical pricing, and increases thereof, but are also the result of additional factors, including:[47]

- ❏ increased prescribing and accessibility of medications (see figure 1-5) for a growing U.S. population in general as well as for the increasing number of senior citizens;[48]
- ❏ new generations of medications, many more expensive than older products, entering the market at a faster rate;[49] and
- ❏ increased budgets for advertising products directly to consumers.

For example, senior citizens are increasingly likely to develop chronic conditions (e.g., cardiovascular disease and osteoporosis) as they age. This has had the dual result of increased prescribing of existing products and increased efforts by innovative companies to develop new products to better manage such diseases. In addition to potentially developing more chronic conditions, the number of senior citizens is also increasing worldwide (see table 1-3). In the United States, the number of people 65 years and older is expected to increase by 17 percent during 1995-2010, from 33.5 million to 39.4 million; by 75 percent, to over 69 million, during 2010-30; and then by 14 percent, to about 79 million, during 2030-50.[50] Japan, however, has perhaps seen the largest rate of increase to date; the percentage of the total Japanese population

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[47] Elizabeth Helms, Testimony before the Senate Committee on Health, Education, Labor and Pensions on July 18, 2000, p. 2; Carlos Ortiz, Director of Government Affairs, CVS Pharmacy, Inc., Testimony before the Senate Committee on Health, Education, Labor and Pensions on "Prescription Drugs: What Drives Increases?" on July 18, 2000, p. 1; and Stanley S. Wallack, Ph.D., Executive Director, Brandeis University, Schneider Institute for Health Policy, Testimony before the Senate Committee on Health, Education, Labor and Pensions on "Prescription Drugs: What Drives Increases?" on July 18, 2000, p. 2.

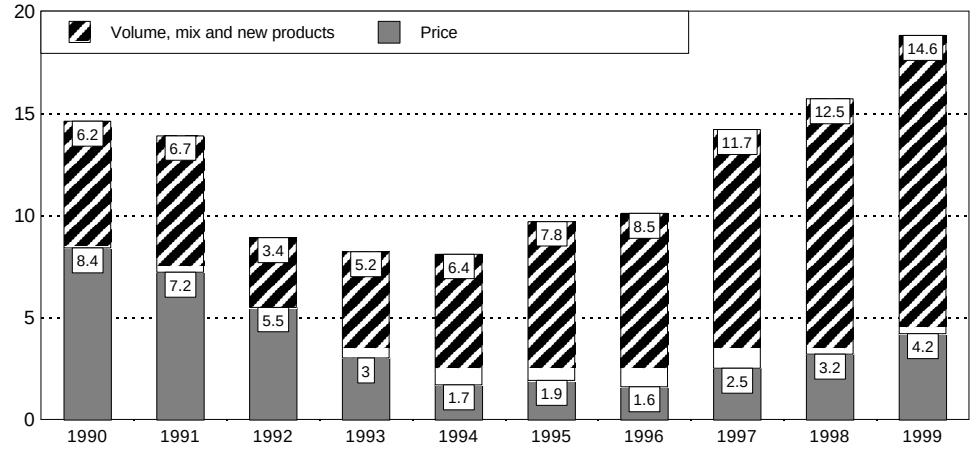
In Europe, market growth is largely attributed to the increasing level of national healthcare coverage provided within countries, as well as to the introduction of new products that can cure previously "incurable" diseases and "socio-economic factors" (e.g., growth in the size of the national populations and the increasing number of people older than 65). EFPIA, *The Pharmaceutical Industry in Figures*, p. 39.

[48] According to the BCG study, "Tight control of one aspect of drug spending fails to address the other drivers of spending and may even encourage inappropriate prescribing as many observers have suggested of the Japanese system (in which physicians also dispense drugs)." The authors caution that the inappropriate use of pharmaceuticals, or overprescribing (i.e., either the prescription of inappropriate medicines, the prescription of the wrong dose(s), or both; antibiotics are cited as an example of a product grouping that can be overprescribed) can result in increased overall healthcare spending. This results from the costs of the products themselves and potential associated increases in other healthcare costs. As such, the study states that "the 'appropriate' use of pharmaceuticals is a critical component of any health system." BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, pp. 4-5, 19.

[49] See also IMS HEALTH, "Five Year Forecast of the Global Pharmaceutical Markets," *Market Report*, found at http://www.ims-global.com/insight/report/global/ na_europe.html and retrieved on Sept. 26, 2000. IMS HEALTH also cites "volume gains resulting from increased prescription drug coverage for Medicare and Medicaid recipients under managed care programs" as growth factor.

[50] "Demographic Changes: Growth of the Elderly Population," *Aging Into the 21st Century*, dated May 31, 1996, found at http://www.aoa.dhhs.gov/aoa/stats/aging21/demography.html and retrieved on Sept. 26, 2000.

Figure 1-5
U.S. prescription pharmaceuticals market: Total sales growth rates, 1990-99



Note: Prior to 1993, market includes only retail pharmacy and nonfederal hospital distribution channels. From 1993-1998, market includes six audited channels: retail pharmacies, nonfederal hospitals, staff-model HMO's, clinics, long-term care, and federal facilities. Growth rates reflect percent change in sales dollars for specified calendar year versus previous calendar year.

Source: Obtained from PhRMA (*Pharmaceutical Industry Profile 2000*, p. 58) and used with their permission. The original source was IMS HEALTH, *Retail and Provider Perspective™, 2000.*

over 65 years almost doubled from 9.0 percent in 1980 to a projected 17.1 percent in 2000. During 1992-97 alone, the share of the Japanese population accounted for by senior citizens increased by 2.3 percentage points compared with changes in the other countries under consideration ranging from zero (United States and the UK) to 1.6 percentage points (Italy). (For more information, see the section on Japanese pricing of pharmaceuticals in chapter 4).

CHAPTER 2
FOREIGN MARKETS AND U.S. PRICES

Introduction

The global markets for patented pharmaceuticals are characterized by producers who have a great deal of market power derived from the temporary monopolies granted by the patent system; by an array of purchasers who can also influence prices; and by regulators in a wide range of markets exerting different degrees of control over product quality, marketing, and pricing. The patent system allows firms to recover the costs of developing their products and to reward the risks associated with such investments. Purchasers range from individuals filling their prescriptions at a local pharmacy (which may be an independent outlet or part of a national chain) to hospitals to large prescription benefit plans or national insurance providers. Finally, regulators in different countries and different segments of the health services system have a say in the development and testing of drugs, advertising, and (in some cases) the pricing and delivery of products. Further, governments are involved in the system not only as regulators, but as providers of basic research and as purchasers of drugs through military and government employee health plans, national health services, and other channels.

A major characteristic of the pharmaceutical industry is the large fixed cost of research and development (R&D) of innovative drugs. (For more information, see chapter 3.) More specifically, pharmaceutical R&D is a *global joint cost*, meaning the fixed cost is the same regardless of the number of users served worldwide, and hence cannot be rationally allocated to individual users. Other industries that are commonly subject to price regulation, including telephone, gas, and electricity, are also characterized by large fixed costs. For these industries, however, such capital costs are generally local to the country and more easily assigned to consumers within that country.

The high product development costs in the pharmaceutical industry require some long-term means by which developers can recover these costs. Patent monopoly power, which allows firms to set prices above marginal cost, is one such means, though not necessarily the only one; various forms of subsidy, for example, help defray these costs. The variety of purchasers in the market, in turn, allows the market to be segmented (with different prices charged in different segments) in ways that, on the one hand, allow producers to cover their costs, and on the other hand, allow markets to be served that might not be served if global uniform pricing was the rule. In addition, regulatory systems create market segments by establishing different national or subnational treatment and marketing regimes. In some cases, regulators have sought to eliminate distinctions between market segments.

This chapter examines the determinants of pharmaceutical prices in markets structured by patent monopolies and segmented purchasers, explores the role of regulation, and reviews the literature on methodologies applied to assess the possible linkages between foreign regulation and U.S. prices. The review is presented in three sections: (1) a discussion of the economic determinants of pharmaceutical prices, including market segmentation, price discrimination,

regulatory behavior, and other issues; (2) a discussion of methodological issues in measuring pharmaceutical prices; and (3) a methodology proposal for future research.

Studies reviewed in this chapter indicate that U.S. prices for prescription products generally tend to be higher than those in most of the countries under consideration, though the magnitude of the gap is difficult to measure.[1] The U.S. General Accounting Office (GAO) found that prices for an aggregate market basket of 121 drugs were 32 percent higher in the United States than in Canada. The U.S. House of Representatives Minority Staff Internal Report concluded that retail prices in Maine averaged 72 percent higher than those in Canada and 102 percent higher than those in Mexico. The Public Citizen Health Research Group found that U.S. prices for antidepressant and antipsychotic drugs were 1.7 to 2.9 times higher than prices in Canada, Mexico, and European countries. Danzon and Kim, and Danzon and Chao examined prices between the United States, Canada, and Europe and generally found smaller price differences.

All measurements of overall drug prices, including those surveyed for this report, require choices about relevant samples and means of weighting prices, among other things. Such choices depend on the judgment of researchers in the context of specific analyses and can significantly affect the findings. A single, definitive, unbiased measure of comprehensive price differences does not exist.

The large variety of pharmaceutical products, different medical practices and patterns of pharmaceutical use among countries, and different classes of purchasers within countries make international price comparisons difficult. Other factors that make such comparisons difficult include–

- international differences in consumption patterns;
- international variations in dosages, concentrations, strengths, pack sizes, and units of measurement;
- various courses of therapy;
- the nature of distribution chains;
- taxes and subsidies;
- the relative weights given to various consumption patterns;
- the availability of many products in patented and generic versions; and
- the use of exchange rates or purchasing power parity for currency conversion.

[1]Several international price comparison studies have been completed, with varying results. A more detailed review of economic literature on international price comparisons follows later in this chapter.

Economic Determinants of Pharmaceutical Prices

The international market for pharmaceuticals, and the determination of prices across countries in the global market, are influenced by the following key factors.

- ***Large fixed costs of research and development, which are global in nature***
  According to industry sources, about 20 percent of the value of U.S. sales of research-based pharmaceuticals is expected to be devoted to R&D in the year 2000, compared with 4 percent for all U.S. industries.[2] Another study indicates that among EU countries, R&D spending as a percentage of total production varied from about 9 percent in Italy to almost 17 percent in the UK in 1993.[3] These R&D expenditures represent costs on a global basis, that is, R&D expenditures remain the same regardless of how many consumers or countries are served by the product. Because these costs cannot be easily attributed to any particular consumer or country, the pharmaceutical industry faces the problem of how to assign costs to the different countries they serve.

- ***Market power granted to producers through patent protection***
  On the supply side, the government grants patents to pharmaceutical producers to help maintain product innovation. Patents help drug firms cover the fixed costs of research and development by providing significant market power to individual firms in setting prices.

- ***Buying power of large purchasers versus smaller ones (monopsony power)***
  On the demand side, large and small purchasers have varying degrees of market power. For example, large consumers such as HMOs, PBAs, government programs, or other such groups arguably have more bargaining power in drug purchases than do individual retail purchasers.

- ***Different price controls and other regulations across countries***
  Market regulations affect both the supply and demand sides, and vary significantly across countries. Direct and indirect price controls limit the amount of reimbursements available to drug producers, and other controls limit profits, coverage, and other factors affecting prices. Discussion of specific price control and cost-containment programs in each of the G-8 countries and Mexico is provided in chapter 4. Studies reviewed in this chapter indicate that such regulations affect prices within the home country, but there is less evidence that regulations in one country directly affect prices in other countries.[4]

[2] PhRMA, *Pharmaceutical Industry Profile 2000,* p. 20.

[3] A. Earl-Slater, "Pharmaceuticals," in P. S. Johnson (ed.), *European Industries*, Edward Elgar, 1993. Cited in W. Duncan Reekie, *Prescribing the Price of Pharmaceuticals* (IEA, London: 1995), p. 14.

[4] For example, see U.S. General Accounting Office, "Prescription Drugs: Companies Typically Charge More in the United States Than in Canada," GAO-HRD-92-110, Washington, DC, 1992, p. 2. Also see Patricia M. Danzon and Jeong D. Kim, "International Price Comparisons for Pharmaceuticals: Measurement and Policy Issues," *Pharmacoeconomics*, 14, Suppl. 1, 1998, p. 123.

As discussed below, two possible ways in which regulations in one country may affect prices in another are parallel trade[5] in drugs and the use of international reference pricing.[6]

- ***Segmentation of markets (by private market, government program, or internationally)*** Because they have market power, drug firms are able to sort customers by different criteria (segmentation) and charge different prices to each group (price discrimination). Segmentation can take place along many lines. This is one way consumers can be segmented, but not the only way. Criteria separating consumers in one market from those in another can include–

  - the relative size of the buyer (monopsony power);
  - the sensitivity of consumers to change in price (price elasticity of demand);
  - national regulatory regimes;
  - patent protections;
  - geography and customs restrictions;
  - the point of purchase along the distribution chain;
  - branded-drug purchases versus generic drug usage;
  - chronic versus acute illness; and
  - cash versus insurance sales.

A complex combination of all these factors influences pharmaceutical prices. The most extensive discussion in this report centers on how market segmentation occurs and how different prices can be charged to different groups of consumers. If consumers in different market segments can be totally isolated from each other, there is little economic reason why prices in one segment would affect prices in another–for example, why prices in one country would affect prices in another. Theoretically, reference pricing systems and parallel trade appear to be factors that can break down the ability of a firm to segment markets across national borders and allow indirect transmission of prices from one country to another. Another mechanism for breaking down segmentation is a uniform pricing strategy, where in response to parallel trade, a pharmaceutical firm may choose to charge the same price for all countries, thus affecting the prices around the world. Systematic parallel trade currently exists mostly within the EU; in the United States, recently introduced legislation would permit parallel imports to enter the United States.

The Economics of Price Discrimination and Market Segmentation[7]

For market segments to be preserved as distinct markets, it must be possible for a firm to practice *price discrimination*, i.e., to sell essentially the same product to different customers at different prices that are not directly related to the supply cost. This ability depends on several conditions.[8] The first is that the seller must have some market power, or ability to influence prices

[5] Parallel trade is the importation of products from countries with low cost by countries with higher costs. This practice is discussed more fully later in this chapter.

[6] International reference pricing occurs when prices in one country are controlled in a way that makes them equal or proportional to prices in another country or to the average price in a set of countries. This practice is discussed more fully later in this chapter.

[7] Much of the following discussion is based on F. M. Scherer and David Ross, *Industrial Market Structure and Economic Performance* (Boston: Houghton Mifflin, 1990), pp. 488-516. See also Hal Varian, "Price Discrimination," *Handbook of Industrial Organization*, Volume I, edited by R. Schmalensee and R.D. Willig, Elsevier Science Publishers, B.V., 1989, p. 598.

[8] Because different prices can reflect varying transportation or other costs and because price

(continued...)

conditions.[8] The first is that the seller must have some market power, or ability to influence prices charged in the industry–a firm with market power can raise prices without losing all of its customers. Second, the firm must be able to segment its market into groups that respond to changes in price differently (different effective demand elasticities). And third, arbitrage must be limited; low-price customers ought not to be able to resell the product to high-price customers. These criteria are generally met for the markets in patented pharmaceuticals.

Price Discrimination and Fixed Costs

There are two types of production costs a pharmaceutical firm tries to recover when pricing drugs: variable costs and fixed costs. Variable costs depend on the amount of output a drug company produces–i.e., the labor and materials required to produce given quantities of drugs. Fixed costs are expenditures that are the same regardless of whether a large quantity of output is produced or none at all. Fixed costs for innovative pharmaceuticals are large because of the initial research and development required to put a new drug on the market.

At the beginning of this chapter the connections between high fixed costs, patent-protected monopoly power, and the ability to segment markets and price discriminate were described. Appendix F provides more details on how a firm may set prices when it is able to price discriminate. (The appendix also discusses a particular, socially efficient, form of regulated price discrimination known as "Ramsey pricing.") As a result of such price discrimination–

- ❑ Consumers most sensitive to price changes (i.e., those with elastic demand) will pay less than those who are not as sensitive (those with inelastic demand);[9]
- ❑ The large fixed costs of research and development will be covered;
- ❑ Profits will be higher than with uniform pricing; and
- ❑ Compared with uniform pricing, some forms of price discrimination may be advantageous on a social welfare basis because it assures that some low-price sales would take place in markets that otherwise would likely not be served at all.

Appendix F also discusses the dynamic nature of this pricing strategy in the pharmaceutical industry. Competition in the pharmaceutical industry is based not only on price, but also on the introduction of new patented drugs–as well as on the expiration of patents on older drugs. With the ability to charge different prices to different market segments, the introduction of new drugs provides drug firms with new or changing market segments.[10] As consumers react to this changing availability of new and older drugs, producers have the incentive to adjust their pricing strategies among changing market segments. Their optimal pricing scheme, however, will remain market segmentation and price discrimination.

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[8]Because different prices can reflect varying transportation or other costs and because price discrimination can be present even if all consumers are charged the same price, a better way to describe price discrimination would be the sale of two or more similar goods at prices that are in different ratios to marginal costs.

[9]See Frank J. Ramsey, "A Contribution to the Theory of Taxation," *Economic Journal* 37 (March 1927), pp. 47-61. A discussion appears in Scherer and Ross (1990), pp. 498-499.

[10]Duncan Reekie, "The PPRS: Regulations Without a Cause?", *Should Pharmaceutical Prices Be Regulated? The Strengths and Weaknesses of the British Pharmaceutical Price Regulation Scheme*, Institute of Economic Affairs Health and Welfare Unit, 1997, p. 31.

Market Segmentation in Pharmaceuticals

With a degree of market power,[11] pharmaceutical producers can group their customers by a multitude of criteria[12] (or find them grouped by geographic, regulatory, or other circumstances) and more or less effectively price discriminate, preventing each group from making purchases from another group's market.[13] It is for this reason that the same price for a given drug is not charged to all consumers.[14] International market segmentation–or grouping consumers country by country–is only one of many ways drug markets are segmented. This section briefly discusses some of the criteria used to segment drug markets.

Within a given country, segmentation can be based on criteria found within private markets or within government benefit programs, as well as by other criteria such as branded versus generic drug use or chronic versus acute illness.[15] Internationally, markets might be segmented on the basis of different regulatory regimes, patent protections, consumer demand elasticity, geography and customs restrictions, and the role of doctors and insurance companies.

Segmentation in the private market

In the United States, the private market includes retail (comprising chain drug stores, mass merchandisers, independent pharmacies, supermarket pharmacies, and mail-order pharmacies); wholesale; hospital; HMOs and other managed care organizations and providers (such as clinics, long-term healthcare facilities, nursing homes, outpatient facilities, and physician offices); and the Internet.[16] Nationwide, there are more than 30,000 pharmacies operated by chain pharmacy companies, supermarkets, and mass merchants. In addition, there are another 20,000 independent pharmacies.[17] Mail-order pharmacies account for about 12 percent of the total retail prescription market, including sales from Internet pharmacies.[18]

Segmentation by size of buyer is apparent in drug sales to insurance companies, hospitals, HMOs, and other managed care organizations. These institutions arguably have their own market power, the ability to bargain more advantageously with large sellers than do small groups or individual consumers.[19]

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[11]The producer must not be a price-taker, as is the case in perfect competition. With some monopoly power, a producer has the ability to raise prices without losing all of its market share.

[12]F.M. Scherer and David Ross, *Industrial Market Structure and Economic Performance*, p. 489.

[13]Hal Varian, "Price Discrimination," p. 599.

[14]James M. Henderson and Richard E. Quandt, *Microeconomic Theory*: *A Mathematical Approach*, Third Edition, McGraw-Hill Publishing Company, 1986, p. 182.

[15]National Health Policy Forum, *Issue Brief: Pharmaceutical Market Dynamics*, brief No. 755, Wednesday, May 31, 2000.

[16] Ibid.

[17]National Association of Chain Drug Stores, *Industry Facts*, found at http://www.nacds.org/ industry/industry_fr.html and retrieved July 28, 2000.

[18]National Health Policy Forum, *Issue Brief: Pharmaceutical Market Dynamics*, brief No. 755, Wednesday, May 31, 2000.

[19]Congressional Research Service (CRS), The Library of Congress, CRS Report for Congress, *Prescription Drugs: Factors Influencing Their Pricing*, updated Feb. 3, 1998, p. CRS-7.

Segmentation related to Government programs

A pharmaceutical producer may find its market segmented through various Government benefit programs. For example, in the United States, the Federal market includes such programs as the Federal Employees Health Benefits program, the Department of Veterans Affairs and its Federal Supply Schedule, Medicaid, and various public health service programs. Other U.S. Government programs have legislated drug pricing and reimbursement methodologies.[20] With bargaining power similar to that of a large private buyer, the U.S. Government can influence drug prices by requiring drug manufacturers to provide rebates to States for Medicaid and the U.S. Department of Veterans Affairs drug purchases.[21] This market power creates a market segment separate from that of consumers with no such influence.

International market segmentation

According to several studies, prices for pharmaceuticals can differ significantly across countries,[22] reflecting differences in healthcare systems as well as in income and other factors.[23] Trade barriers might be a cause of market segmentation; however, in the EU, drug price differentials between member States have remained despite the removal of tariff barriers.[24] Segmentation can be based on differences in regulatory regimes, patent protections, consumer demand elasticity, consumption patterns, geography and customs restrictions, the role of doctors and insurance companies, and other criteria.

Regulatory differences between countries mean that drug producers can sort customers by the effects government restrictions have on drug demand. A possible reason for higher prices in the United States is that Canada, Mexico, and most European countries have government systems for negotiating drug prices or controlling costs. There are fewer such regulations in the United States. Various forms of market regulation include direct price regulation, manufacturer-specific budgets (revenue limits), internal reference price limits on reimbursement, rate-of-return regulation, physician drug budgets, patient copayment systems, and managed care systems.[25] These differences across countries provide criteria for drug producers to use in segmenting markets internationally.

Patent and intellectual property rights protection also varies between countries. Patent regimes can vary in terms of the application process, clinical trials, approval time, duration of patent, strength of patent laws, level of patent enforcement, patent expiration rules, role of brand-name substitutes, role of generics, and other factors. Market segmentation can focus on these differences. (For more information, see Chapter 3.)

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[20]National Health Policy Forum, *Issue Brief: Pharmaceutical Market Dynamics.*

[21]CRS, *Prescription Drugs: Factors Influencing Their Pricing*, p. CRS-8.

[22]As discussed earlier, international price comparisons of pharmaceuticals are subject to a number of difficulties. The number and nature of these problems suggest that comparisons should only be used with extreme care if at all. Duncan Reekie, *Should Pharmaceutical Prices Be Regulated? The Strengths and Weaknesses of the British Pharmaceutical Price Regulation Scheme*, p. 21.

[23]Patricia M. Danzon, "The Economics of Parallel Trade," *Pharmacoeconomics*, 13(3), 1998, p. 294.

[24]Patricia M. Danzon, "Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU," *International Journal of the Economics of Business*, Vol. 4, No. 3, 1997, p. 302.

[25]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, The AEI Press, Washington DC, 1997, p. 16.

Breakdown of Market Segmentation

If a pharmaceutical firm is not able to maintain or create market segments, there is reason to believe that regulations in one market or country could affect prices in another segment or country. As mentioned above, anything that diminishes the ability to sort customers by group, by product, by individual,[26] or to prevent resale or arbitrage between segregated groups,[27] may result in a breakdown of market segmentation.[28]

Market segmentation of pharmaceuticals may be diminished by a number of factors. Two of these include parallel trade[29] and reference pricing.[30] Parallel trade takes place where a good has significantly different prices in two or more different markets. Traders buy in low-price markets (such as France or Greece) and resell in higher price markets (such as the United Kingdom, Germany, and the Netherlands). It is a form of arbitrage that helps prices in different countries converge.[31] Parallel trade has been upheld by the European Court of Justice as consistent with principles of free trade within the EU. Opportunities for parallel trade might be increasing owing to, among other factors: (1) the 1995 launch of the European Agency for the Evaluation of Medicinal Products, which can grant simultaneous approval of new drugs throughout the EU, and (2) the accession to the EU of lower-price countries and the growing links with Eastern Europe.[32]

In the United States, parallel trade is the subject of recent legislation that considers allowing U.S. druggists and wholesalers to import drugs. In 1999, U.S. Representatives Bernie Sanders of Vermont, Jo Ann Emerson of Missouri, and Marion Berry of Arkansas proposed a bill entitled the International Prescription Drug Parity Act. A modified version of the bill, allowing pharmaceutical companies the right to decide whether or not to reimport drugs, was signed into law as part an agriculture bill in October 2000.[33]

Parallel trade diminishes a drug producer's ability to segment markets because consumers in one segment are making purchases from another. As supply increases in the high-price segment and decreases in the low-price segment, the gap in prices would tend to decrease. Similar effects are realized from the use of reference pricing, in which levels of reimbursement to drug producers are fixed for a particular product or group of products.[34] The government or insurer sets a single

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[26]F.M. Scherer and David Ross, *Industrial Market Structure and Economic Performance*, p. 489.

[27]Hal Varian, "Price Discrimination," p. 599. This source states that several common mechanisms can be used to prevent resale in various industries: some goods, such as services or electric power, are difficult to resell because of the nature of the good; tariffs, taxes, and transportation costs can impose barriers to resale; a firm can contractually restrict resale, as is the case with software manufacturers who offer educational discounts to students who sign an agreement not to resell; and a firm can modify its product, making consumers in one market segment "self-select" the version they prefer and reject versions sold to different segments.

[28]Commission staff interview with Patricia M. Danzon on July 24, 2000.

[29]Patricia M. Danzon, "The Economics of Parallel Trade," p. 293.

[30]Duncan Reekie, *Should Pharmaceutical Prices Be Regulated? The Strengths and Weaknesses of the British Pharmaceutical Price Regulation Scheme*, p. 76.

[31]Ibid.

[32]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, pp. 84-85.

[33]*Washington Post*, "Clinton Signs $80 Billion Agriculture Bill," October 29, 2000, p. A5.

[34]Duncan Reekie, *Should Pharmaceutical Prices Be Regulated? The Strengths and*

(continued...)

reimbursement (reference) price for all products in a cluster. In theory, the manufacturer is free to charge a price above the reference price, but in that case, the patient must pay the difference as an excess out-of-pocket charge.[35]

Reference prices can be set in a number of ways. For example, in 1996, Italy imposed a form of reference pricing which limits reimbursement to the price of the cheapest product in a given therapeutic class.[36] Other countries have used reference prices based on existing generic equivalents. Of importance to market segmentation is reference pricing that establishes a limit on reimbursement based on the average foreign price of the same drug.

Parallel trade "exports" low prices from low-price countries to other potentially higher-price countries. Reference pricing has been argued to have the same effect because it reduces prices "across the board" to foreign price levels. Reference pricing has been described as an equivalent to 100 percent parallel trade.[37]

Other Related Issues

Welfare Implications of Price Discrimination

When a drug producer charges different prices in different market segments, it may not only maximize profits but also have significant welfare effects on consumers. If all consumers are charged the same price, the price-sensitive consumers will reduce their demand by more than the price-insensitive consumers, and the result will be a loss in welfare relative to the segmented market situation. The most price sensitive consumers, generally those least able to pay, may drop out of the market altogether, even though they might have been willing to pay a price sufficient to cover the marginal costs. Their consumption at a marginal-cost price would not add to the joint fixed costs of a producer. More simply stated, the literature suggests that if a uniform price is charged for all markets and all countries, some markets might end up with no innovative drugs at all.[38]

Free-Rider Issue and Total Revenues

Since price discrimination based on price elasticities means that prices in drug markets are set according to consumers' willingness to pay, consumers (or their insurers, or national regulatory bodies) might benefit from concealing their willingness to pay. There may be "temptation and leverage for regulators and major purchasers to force prices down to marginal cost."[39] A country might impose regulations that limit prices to cover operating costs within the country, but not provide any contribution to the global joint costs of research and development. Such consumers

[34](...continued)
Weaknesses of the British Pharmaceutical Price Regulation Scheme, p. 76.

[35]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 19.

[36]Duncan Reekie, *Should Pharmaceutical Prices Be Regulated? The Strengths and Weaknesses of the British Pharmaceutical Price Regulation Scheme*, p. 76.

[37]Patricia M. Danzon, "The Economics of Parallel Trade," p. 294.

[38]See, for example, Scherer and Ross, *Industrial Market Structure and Economic Performance*, pp. 494-496.

[39]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 13.

and countries can be viewed as free-riders. These practices do not necessarily cause any change in the prices charged in other countries, but the resulting decrease in total revenues for the drug firm will likely mean less innovation and fewer new drugs introduced on the market.

According to one expert, cost-shifting (the argument that low prices in one market are shifted into higher prices in other markets) is generally unlikely.[40] A profit-maximizing firm will choose optimal prices in separate markets. A change in conditions in one market will not necessarily change the conditions, or optimal prices, in another.

Welfare Effects of Parallel Trade and Reference Pricing

As indicated earlier, parallel trade and reference pricing create "spillovers" of prices in one market segment (or country) to prices in another. The regulation of pharmaceutical prices in one country can directly affect the revenues of research-based pharmaceutical firms, regardless of their country of origin. According to some literature, in addition to this direct effect on revenues, possible indirect effects can occur when low prices in one country spill over to affect prices in other countries. These spillovers can cause a cross-national multiplier effect, where stringent price regulation in one country can reduce the total revenues of multinational drug firms by a factor larger than the direct effect in the country that initiates the regulation.[41]

Although price discrimination across market segments is considered to be more profitable than a uniform pricing policy, in the long run, a drug producer's best strategy when faced with the threat of parallel trade or international price comparisons is to set a uniform price in all countries that are linked either by such trade or price comparisons. This is essentially a market acknowledgment that the distinction between two segments has been broken, that there is now in effect a single segment, with a single price. The revenue loss for the firm would be smaller under uniform pricing than would occur if differential pricing were attempted and defeated by parallel trade or reference price linkages.[42] The resulting uniform price should lie between the prices that would have been charged without the threat of parallel trade or reference pricing.

In this situation, consumers in the traditionally low-priced country are worse off because they now face a higher uniform price. The short-run effects of uniform pricing would seem to benefit consumers in the higher priced country, as the price they face would be lower (though the lower prices of goods bought through parallel trade would likely accrue to intermediaries such as parallel traders, wholesalers, and retail pharmacists, while consumers would continue to pay the higher, regulated price).[43] As mentioned earlier, however, the long run effect would seem to be that all consumers could be worse off if lower total revenues for pharmaceutical firms mean less research and development, and thus fewer new drugs on the market.[44]

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[40]Ibid.

[41]Ibid., pp. 84-85.

[42]Patricia M. Danzon, "The Economics of Parallel Trade," p. 299.

[43]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 86.

[44]Ibid., p. 87.

costs of research and development.[45] This framework is widely used in economic literature to describe the drug industry, but there are other possibilities. One alternative is that drug companies maximize total revenues. There is an economic distinction between maximizing revenues and maximizing profits.

According to a study by Sager and Socolar, drug manufacturers "do not set prices to cover research costs. They set prices as high as they can, in hopes of maximizing revenue. When they face little pressure from competing manufacturers, as when they enjoy a monopoly or an oligopoly, they are able to set very high prices."[46] According to this study, the causes of high prices in pharmaceuticals include government inaction in the face of price regulation in other countries, lack of competition, high profits in the U.S. pharmaceutical industry, manufacturers' pricing strategies, and market conditions that exacerbate income inequalities by favoring large buyers over out-of-pocket purchasers.[47]

Foreign Regulatory Behavior and Foreign Prices

There are many types of pharmaceutical market regulation seen across the G-8 countries and Mexico. The United States appears to have higher prices than most countries[48] and less regulation,[49] and some of the countries with the strongest regulations appear to have among the lowest prices (France and Italy for example). This suggests that price controls have an effect on prices within a given country. More complete discussion of individual countries and price control or cost-containment programs is provided in chapter 4.

Governments cite several reasons for drug market regulation. First, governments use regulations as a means to reduce public expenditures on health.[50] A second objective is to promote industrial policy goals of domestic employment, investment, and international competitiveness.[51] Additionally, the third-party payment characteristic of prescription drug consumption is cited as

[45] Commission staff interview with Patricia M. Danzon on July 24, 2000.

[46] Alan Sager and Deborah Socolar, Boston University School of Public Health, *Access and Affordability Monitoring Project, Affordable Medications for Americans: Problems, Causes, and Solutions, for Presentation to the Prescription Drug Task Force*, United States House of Representatives, July 27, 1999, p. 9.

[47] Ibid., pp. ii-iii.

[48] Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 31. The difficulty of international price comparisons was discussed earlier in this chapter.

[49] U.S. General Accounting Office, "Prescription Drugs: Companies Typically Charge More in the United States Than in Canada," GAO-HRD-92-110, Washington, DC, 1992, p. 10.

[50] Michael L. Burstall, Bryan Reuben, and Anthony Reuben, "Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective," *Drug Information Journal*, Vol. 33, 1999, p. 669.

[51] Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 15.

justification for regulation–patients consuming drugs or the doctors that prescribe them often have a financial stake in consumption decisions.[52] Some methods of pharmaceutical regulation include–

- ❑ direct control of prices for new and/or existing medicines on a product-by-product basis;
- ❑ indirect price control by limiting reimbursement, and operating a reference pricing system;
- ❑ profit controls; and
- ❑ mandatory cuts or freezes in medicine prices generally.

Supply-Side Measures

Cost-containment measures can be divided into supply-side and demand-side policies. Supply-side policies affect the manufacturer and distributor, and may involve reference pricing, positive and negative lists, price controls, and profit controls, among other things.[53]

Direct price controls in France, Italy, Spain, and other countries require that prices of new products and changes in the prices of existing products be approved if they are to be reimbursed by the social insurance system. Several criteria can be used to regulate prices: internal comparisons with existing products, therapeutic merit, or contribution to the domestic economy and labor force.

Reference pricing has been introduced in many countries, including Germany (1989), the Netherlands (1991), Sweden (1993), and Denmark (1993). Health authorities establish a "reference price" that will be reimbursed for different single products or therapeutic classes. Patients who prefer more expensive products are required to pay the difference. Reference pricing can create competition between products within a cluster of drugs for prices above the reference price. However, some studies question the effect on those products priced below the reference price.[54] According to pharmaceutical industry representatives, prices of those products with market prices which would be below the reference price are usually raised to the reference level because there is less incentive to charge a lower price.[55] The impact of reference pricing on drug spending depends on how broadly the product clusters are set, and how the reference prices are set.

Positive and negative lists are used to classify drugs according to their eligibility for reimbursement. Drugs on the positive list are reimbursed; those on a negative list are not. An objective of these lists is to eliminate "useless" drugs, or those of questionable efficacy.[56] A problem encountered has been the difficulty of denying popular drugs, even if they are seen as not medically effective.

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[52] Michael L. Burstall, Bryan Reuben, and Anthony Reuben, "Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective," p. 669.

[53] National Economic Research Associates (NERA), *Market Segmentation: A Report for ESPG of EFPIA*, London, Mar. 1996, pp. 2-4.

[54] Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, pp. 19-20.

[55] PhRMA, Written Submission, Aug. 4, 2000, p. 4.

[56] Michael L. Burstall, Bryan Reuben, and Anthony Reuben. "Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective,"p. 669.

Rate-of-return regulations such as the Pharmaceutical Price Regulation Scheme in the United Kingdom regulate profits instead of prices. In such a system, companies themselves can determine the launch prices of new drug products, but they face a constraint on total rate of return on capital for their total portfolio of different products being reimbursed by the government. Although this system of profit control more explicitly recognizes the need to cover the large fixed costs of research and development, one argument suggests that it creates other potentially distorting effects, such as incentives for creative accounting and distorted incentives for real resource use to maximize the base on which returns are calculated, and thus the allowed profits.[57]

Demand-Side Measures

Demand-side pharmaceutical regulations target the prescriber and the patient. Such measures include patient copayments, budgets for doctors, incentives to prescribe generic equivalents or parallel imports, transfer of products from prescription to over-the-counter (OTC) status, and advice and guidelines for doctors and other prescribers. Some of these are described below.

Patient copayment schemes have a number of effects. First, they transfer some of the burden of drug expenditures from the social insurance system to the patient. In addition, copayments may reduce the overall level of drug consumption.[58] The United Kingdom operates a system of fixed copayments, where the consumer pays the same fee irrespective of the product purchased. Such a scheme might favor consumers buying expensive drugs or large packs.

Physician drug budgets place physicians directly at risk for the financial consequences of their prescribing habits. Doctors, who generally do not directly profit from dispensing drugs, may nevertheless have an incentive to use prescriptions as a means of stimulating additional patient visits.[59] Physician drug budgets aim to remove such incentives. In the United Kingdom, the National Health Service disseminates information on drug prices and notifies individual physicians when their prescribing costs exceed the norm for their given specialty. Such restrictions have had success in reducing drug expenditures, though it has proven difficult to enforce collective sanctions on doctors.[60]

[57]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 21.

[58]Michael L. Burstall, Bryan Reuben, and Anthony Reuben. "Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective," p. 675.

[59]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 24.

[60]Michael L. Burstall, Bryan Reuben, and Anthony Reuben. "Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective," p. 675.

Methodological Issues in Measuring Pharmaceutical Prices

Comparing pharmaceutical prices in the United States with those in other countries first requires an accurate measure of the prices to be compared. Numerous studies have evaluated global drug prices, but the results vary significantly. This section describes some principles that should be used in making drug price comparisons, the complexities involved in such an exercise, and a review of several price comparison studies found in the literature.

Price Comparison Principles

International drug price comparisons are sensitive to measurement methods. Different choices can reverse the relative price ranking of two countries. For a price comparison to be meaningful, it should–

- ❑ compare similar products in similar markets at similar times;
- ❑ use a representative sample of the drugs on the market of the countries to be compared;
- ❑ be based on a similar point in the distribution process;
- ❑ be based on actual transactions that account for discounts, rebates, tied sales, or other factors that influence price; and
- ❑ address issues related to currency conversions such as exchange rates or purchasing power parity measures.

Some key components of price comparisons are briefly discussed below.

Similar Products in Similar Markets at Similar Times

Pharmaceutical usage varies across countries because of differences in medical problems, medical culture, government regulation, and personal preferences. Moreover, although many products are patented products, others also have generic versions. These differences have resulted in an extremely large number of pharmaceutical products. Even when products are ostensibly similar, consumption varies in terms of dosage, strength, packaging, and means of delivery. Drug products in two countries might match in terms of one or more of these criteria, but likely not all of them. All of these factors may affect the price of the final product. The great variety of products across countries makes identifying similar products for comparison very difficult.

One approach to the diversity of products is to compare the price of the molecule, which is the volume-weighted average of prices charged by all manufacturers of the basic compound. This approach makes comparisons possible when there may only be overlap between the products in different countries at the active-ingredient level, and it may be the only feasible procedure in some cases. Nevertheless, it blurs some distinctions, such as differences between brands, between generic and brand-name drugs, and between OTC and prescription drugs. Sometimes other characteristics can be combined with the molecule-based approach. For example, prices could be gathered on a certain molecule in a particular type of package.

Part of the similar-product issue is defining the precise quantity unit about which to gather price information. Possible quantity units include price per pill, price per daily dose, price per course of therapy, and price per gram of active ingredient. Differences among countries in dosage forms, package sizes, strengths, and other factors imply that the choice of a quantity unit affects prices.

As previously discussed, prices may vary in different market segments within the same country. This is particularly true when part of the market is private and part is public or controlled by government regulation or when there are large institutional purchasers and small purchasers. One approach would be to compare the prices in similar market segments across countries; however, markets may be segmented differently in different countries. Price data should be collected in a way that corresponds to the amount of sales in different market segments within a country. This approach will permit a determination of whether price differences are due to differences in the same market segments across countries or to a different mix of market segments in the countries.

Almost all studies compare prices across countries at approximately the same point in time. Because changes can occur in a drug's patent status, in price regulations, and in foreign exchange markets, studies based on multiple time periods provide more robust results. Time-series data permit an examination of trends in relative prices and correlations with other causative factors. However, the difficulty in gathering data has precluded such an analysis of price trends and therefore, most studies have only analyzed data at a single point in time.

Representative Samples

The goals of the study dictate the type of sampling procedures to be used. Some specific-issue studies have gathered price data only on a small subset of the pharmaceutical market. If the study's purpose is national policy analysis, then a more comprehensive approach is needed. In this case, prices should be gathered for products that are representative of the entire set of products available in the countries under comparison, and, as previously mentioned, prices should be gathered for a representative sample of the market segments within a country.

A full welfare analysis, which would evaluate how a representative domestic consumer would fare if he or she faced prices in a comparison country for some group of goods, would require information about the demand characteristics for the goods under comparison. Price indexes approximate the actual welfare change and only require information about prices and quantities, which are used to weight the prices according to their importance in expenditures of one of the countries. The Laspeyres index uses the base period/country quantity weights, and the Paasche index uses the comparison period/country quantity weights. The Fisher and Divisia indexes use an average of the observed quantities as weights. For example, in a price comparison between the United States and Canada, the Laspeyres index weights each price by the volume of consumption in the United States, while the Paasche index uses Canadian weights. The Laspeyres index is appropriate if the policy question is what the costs of medicines would be to U.S. consumers if they faced Canadian prices. This assumes that U.S. consumers would not switch to Canadian consumption patterns even if faced with Canadian prices. Because consumption patterns vary from one country to another, the use of different indexes and their various weighting schemes can reverse the price ordering between two countries.

A representative sample of pharmaceutical products is also likely to be large given the large number of products. A price index is a convenient way to summarize the results in which the prices are weighted by some combination of expenditure shares in the countries under comparison. If a simple unweighted average of price comparisons is calculated, it implicitly assumes that all of the products are weighted equally, an often unrealistic assumption.

Pharmaceutical products can be classified in a variety of ways, such as patented versus generic, generic versus brand name, OTC versus prescription, or innovative versus mature product. Certain classifications are more important for some countries than others. For example, generic products accounted for nearly half of the drug prescriptions in the United States in 1998, though this fraction is lower in many other countries.[61] To be fully representative, the sample should include drugs from these different classes in proportion to their prevalence in national expenditures.

A tradeoff exists between the need to compare only similar products and the need to have a truly representative sample of a country's pharmaceutical market. If products under comparison are required to match in all dimensions (active ingredient, brand, type of dose, strength, pack, and so forth), the sample size could be very small and not representative of the available drugs in the given country.

Point on Distribution Chain

Prices for pharmaceuticals can be measured at different points along the distribution chain: the ex-manufacturer price, the ex-wholesale price, and the retail price. The retail price differs from the ex-manufacturer price because of the wholesale and retail distribution markups. Further gaps are created by value-added taxes, other fees, and transportation and handling costs. These factors can vary across products, manufacturers, and countries of origin and destination. If retail price comparisons are to be used to make inferences about ex-manufacturers' prices, information on wholesale and retail margins is required. To be meaningful, comparisons must be made at the same distribution point or account for margins and any relevant costs such as transportation and handing costs.

Actual Transactions

Actual transaction prices frequently vary considerably from published price lists and from prices that traders report if simply asked to state a transaction price. Also, many firms offer price discounts that might be based on volume purchased over some long period of time, promptness of payment, class of customer, location, or on other factors. For these reasons, studies based on actual transaction prices adjusted for any discounts, rebates, and so forth, are more reliable than those based on published price lists, orally reported prices, and secondary sources. Owing to the large number of transactions, pharmaceutical price comparisons have often relied on non-transaction price data; some studies have even compared data obtained by one method in one country with data obtained by another method in another country.

[61] Patricia M. Danzon,"Price Comparisons for Pharmaceuticals: A Review of U.S. and Cross-National Studies," The AEI Press, Washington, D.C., 1999, p. 11.

Foreign Currency Conversions

Because exchange rates deviate from purchasing power parity (PPP), conversions made on the basis of exchange rates will differ from those made on the basis of PPP. While PPP conversions are arguably more apt for comparisons at the final consumer level, exchange rates are better suited for regulatory purposes. Exchange rates determine a producer's actual revenues from foreign sales in terms of domestic currency. Most international price comparisons have used exchange rates at the time of the study to convert prices to a single currency.

Review of Price Comparison Studies

The following list represents some recent pharmaceutical price comparison studies–

- U.S. General Accounting Office, 1992[62]
- *U.S. House of Representatives Minority Staff International Report*, 1998[63]
- Public Citizen Health Research Group, 1997[64]
- Danzon and Kim, *Pharmacoeconomics*, 1998[65]
- Danzon and Chao, *Journal of Health Economics*, 2000[66]

The results of these studies vary considerably and are influenced by the methods used to collect and analyze prices. This section will briefly describe these studies and highlight the significant differences in their respective conclusions.

U.S. General Accounting Office, 1992[67]

This GAO study found that U.S.-Canadian price differences at the ex-manufacturer level varied widely. U.S. prices ranged from 44 percent lower to 967 percent higher than the Canadian prices. Most drugs studied were found to be more expensive in the United States. Of the drugs compared, 98 were priced higher in the United States and 23 were priced lower. Almost half of the 121 drugs studied were priced over 50 percent more in the United States than in Canada.[68] The aggregate basket of 121 prescriptions would cost 32 percent more in the United States than in Canada. The study concluded that the price differences are largely attributable to actions taken

[62]U.S. General Accounting Office, "Prescription Drugs: Companies Typically Charge More In the United States than in Canada," GAO-HRD-92-110, Washington, DC, 1992.

[63]Minority Staff International Report, Committee on Government Reform and Oversight, U.S. House of Representatives. "Prescription Drug Prices in the 1st Congressional District in Maine: An International Price Comparison," October 24, 1998, p. 1.

[64]Public Citizen Health Research Group, *International Comparison of Prices for Antidepressant and Antipsychotic Drugs*, Washington, D.C., 1997, p. 1.

[65]Patricia M. Danzon, and Jeong D. Kim, "International Price Comparisons for Pharmaceuticals: Measurement and Policy Issues," p. 115.

[66]Patricia M. Danzon, and Li-Wei Chao, "Cross-National Price Differences for Pharmaceuticals: How Large and Why?" *Journal of Health Economics*, Vol. 19, 2000, p. 1.

[67]U.S. General Accounting Office, "Prescription Drugs: Companies Typically Charge More In the United States than in Canada," GAO-HRD-92-110, Washington, DC, 1992.

[68] Ibid., p. 12.

by Canada's Federal and Provincial governments to restrain drug prices, not to any differences in manufacturers' costs between the two countries.[69]

The study purported to compare the manufacturers' component of the prices of drugs bought by retail pharmacies in the United States with the prices of similarly purchased drugs in Canada. The GAO obtained U.S. ex-manufacturer prices from the Wholesale Acquisition Cost (May 1, 1991), as marketed by Medi-Span, a private firm that gathers pharmaceutical information. Canadian prices were the Best Available Price as reported in the Ontario Drug Benefit Formulary, February 1991. U.S. drug prices were listed for specific package sizes, but most Canadian prices were unit prices (per tablet or capsule), almost always based on the largest package of a given drug sold in Canada. The Canadian unit price was converted to a price per package by multiplying by the number of units in the U.S. package. The quantity unit was the package that represented the typical U.S. package size.

The GAO initially selected the 200 most frequently dispensed drugs by U.S. drug stores; these represented 54 percent of all prescriptions dispensed in 1990. It matched 121 drugs by brand name, manufacturer, dosage strength, and dosage form in both the United States and Canada. The remaining 79 drugs were excluded because of differences in dosage, prescription versus OTC usage and availability in both countries, and because some generic drugs sold in the United States were manufactured by a company with no affiliate in Canada.[70] The study used the May 1, 1991, exchange rate to convert Canadian prices to U.S. dollars.

The GAO study compared both the prices of individual drugs in Canada and the United States and an aggregate cost of purchasing a common prescription for all 121 drugs included in the study. GAO was unable to weight individual drug price differences by relative sales volume because U.S. sales information was not available for each drug.[71] The GAO was reasonably successful at comparing similar products. For each selected drug, it matched brand, strength, dosage form, and prescription versus OTC. Nevertheless, the Canadian prices appear to be based on a larger package size than the U.S. package, which implies a lower Canadian unit price.

A sample that includes 54 percent of the prescription market appears comprehensive, but Danzon criticized it for being based on only small, unrepresentative samples of leading brand prescription drugs sold by the same originator company in all countries.[72] The GAO did not place any error bounds on either its individual or aggregate estimates, so it is difficult to provide a definitive assessment of sample adequacy. It did, however, exclude manufacturers' discounts to Medicaid, many managed-care programs, and mail-order pharmacies, which are important segments of the U.S. market, and it appears that OTC drugs were not included in the sample. These factors bias the U.S. prices upward.

The inability to create a price index based on quantity makes the estimate of the aggregate pharmaceutical market basket suspect because all drugs are equally weighted regardless of their prevalence in expenditures. Not knowing the details behind the data collection methods of the secondary sources used for the price data makes it difficult to assess whether the prices are at the same distribution point. The prices were not, however, actual transaction prices, and how they

[69]Ibid., p. 2.

[70]Ibid., p. 10.

[71]Ibid., p. 11.

[72]Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, p. 32.

accounted for discounts, transportation and handling costs, and other factors cannot be discerned. The reported information indicates that U.S. prices were likely biased upward owing to sample selection issues, and Canadian prices were likely biased downward owing to the package size issue.

U.S. House of Representatives Minority Staff International Report, 1998[73]

The 1998 Minority Staff International Report concluded that the average price in Maine to retail customers who buy their own drugs is 72 percent higher than the average price in Canada, and 102 percent higher than the average price in Mexico.[74] The study concludes that "drug manufacturers appear to be engaged in 'cost-shifting.' They charge low prices to consumers in Canada and Mexico and appear to make up the difference by charging far higher prices to senior citizens and other individual consumers in the United States."[75]

This study is based on prices of 10 patented nongeneric drugs with the highest annual sales to older Americans in 1997. The sample is based on a survey of six independent pharmacies and three chain stores in Maine's First Congressional District, four pharmacies in Canada, and three pharmacies in Mexico. The study used the same strength, dosage form, and package size as the GAO study when possible. If the drugs were not included in the GAO report, the study used the most common dosage, form, and package size as indicated in the *Drug Topics Red Book*.

Several drugs from Mexico were unavailable in the same dosage and form. When dosage did not match, comparisons were based on linear equivalents. For example, the report compared the cost of sixty 5-mg. Zocor tablets in the United States to thirty 10- mg. tablets in Mexico. This type of adjustment of the quantity unit could have biased the results.

Another potential source of bias is the study's reliance on a small sample of only 10 products, which were all brand-name products and market leaders by dollar volume of U.S. sales. Prices were reported for individual retail sales and may exclude sales through HMOs and insurance plans that use their market power to lower drug costs to participants; thus some important market segments may have been ignored. Also, data were gathered from a small number of pharmacies and may not be representative of total sales in the countries involved.

The method of price-indexing is another issue in the study. The 10 drugs were weighted equally, ignoring differences in market shares. The price differences for individual drugs ranged between 23 percent and 136 percent for the United States versus Canada and between 20 percent and 280 percent for the United States versus Mexico. Because consumption levels are not taken into account, the reported average price differences between countries is very sensitive to adding or deleting drugs from the sample.[76]

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[73]Minority Staff International Report, "Prescription Drug Prices in the 1st Congressional District in Maine: An International Price Comparison."

[74] Ibid., p. 2.

[75]Minority Staff International Report, "Prescription Drug Prices in the 1st Congressional District in Maine: An International Price Comparison." p. 2.

[76] Patricia M. Danzon, *Price Comparisons for Pharmaceuticals: A Review of U.S. and Cross-National Studies*, p. 29.

The reported prices appear to be at a similar distribution point–i.e., retail sales. The prices appear to be based on oral reports of pharmacists instead of on actual transactions. A currency conversion using exchange rates was used. In summary, the small sample size severely limits the generality of the conclusions reached in this study.

Public Citizen Health Research Group, 1997[77]

This study concluded that the average acquisition costs for eight innovative antidepressant and antipsychotic drugs were 1.7 to 2.9 times higher in the United States than in the other countries involved.[78] In this study, the price of the average acquisition costs to a pharmacist of a 30-day supply were compared for these drugs. The data were obtained in 1997 from English-speaking pharmacists willing to participate in the study from Canada, Mexico, the United States, and all countries in the EU. U.S. wholesale costs were obtained from the National Prescription Audit–1996.

In this narrowly defined study, care was taken to compare similar products. Besides matching the molecule, packaging had to conform to the 30-day-supply criterion. Points in time were similar but not exactly the same. The distribution point (pharmacist acquisition cost) was similar in each country; Greece was eliminated when researchers were unable to obtain data at that level. Costs in other currencies were directly converted to U.S. dollars using the exchange rate at the time costs were collected. The authors did not elaborate as to whether the costs were based on actual transactions and adjusted for any discounts or other requirements. The sample of eight drugs is considered to be an extremely small sample of more expensive innovative drugs and not likely to be representative of the overall pharmaceutical market. Similarly, the foreign data used are based on the report of a single pharmacist in each country and may not be representative of the overall prices for those products in those countries. These sample selection concerns severely limit the generality of the conclusions of this research.

Danzon and Kim, 1998[79]

Danzon and Kim presented a study of relative drug prices in the United States and eight other countries: Canada, Germany, France, Italy, Japan, Switzerland, Sweden, and the United Kingdom.[80] This study explored different price-indexing methods, product definitions, and quantity units; it generally found smaller price differences and, in some cases, foreign prices that were higher than U.S. prices. The study concluded that international drug price comparisons are sensitive to methodological issues, such as sample selection, quantity unit, and the relative weight given to consumption patterns in the countries being compared.

The data were from Intercontinental Medical Statistics (IMS) for sales of single- molecule cardiovascular products between October 1991 and September 1992. Sales were at the manufacturers' level and did not include sales to large purchasers, such as managed care organizations, HMOs, and non-pharmaceutical outlets. Sales did, however, include generics and some OTC products.

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[77]Public Citizen Health Research Group, *International Comparison of Prices for Antidepressant and Antipsychotic Drugs*, p. 1.

[78] Ibid.

[79]Patricia M. Danzon and Jeong D. Kim, "International Price Comparisons for Pharmaceuticals: Measurement and Policy Issues," p. 115.

[80]Ibid., p. 123.

Products were defined either by International Product Name (IPN) or by molecule and therapeutic category (MOL/ATC). IMS assigns two drug products the same IPN if two of three conditions are met: (1) the same chemical composition or (2) the same brand name, or (3) produced by the same corporation, including majority-owned subsidiaries. MOL/ATC definitions identify drug products by their active ingredient (molecule) and 4-digit anatomical therapeutic class. Two separate quantity units were used: IMS standard units (SU), which consist of one tablet, one capsule, 5 ml. of liquid, or other proxies for a single dose, and number of grams (KG) of active ingredient. Because average strength per dose can vary significantly across countries, these two measures can yield dissimilar results. Strength per dose is higher in the United States than in many countries, so comparisons based on SU showed a greater price difference between the United States and other countries than did comparisons based on KG. This was especially true in the case of Japan, where doses are reportedly weaker than in other countries.[81]

The report presents three indexes (Laspeyres, Paasche, and Fisher) and unweighted relative prices.[82] As noted above, the use of different indexes influences the resulting price comparisons. For example, depending on the price index used, pharmaceutical prices in Canada could be as much as 6.9 percent lower than in the United States, but as much as 116.6 percent higher (see table 2-1). Also, foreign prices appear lower when price indexes are based on foreign consumption weights. This phenomenon is known as the Gerschenkron effect, a reason for which is that countries consume relatively more of the products that are relatively inexpensive.

The IPN or MOL/ATC product definitions result in similar products being compared in most product dimensions. The use of the IMS standard unit and the number of grams is preferable to using package size, which has shown much variation across countries. The sample from the United States included 354 products based on IPN definitions and 105 based on molecule definitions. Using the IPN definitions, matching products accounted for less than half of sales in the United States for five of the eight countries; the share was generally over 90 percent when using the MOL/ATC definitions.

Coverage included generics and some OTC drugs, although some discount sales were eliminated. Although coverage in this study was one of the broadest, the sample consisted entirely of cardiovascular drugs, which limited its generality. The distribution points were manufacturers' prices, although the details of IMS's data gathering process were not presented in detail, precluding a determination of whether the data were based on transaction prices.

[81]Ibid., p. 124.

[82]The Laspeyres index uses U.S. quantity weights; the Paasche index uses foreign quantity weights, and the Fisher index is the geometric mean of the Laspeyres and Paasche indexes.

Table 2-1
Price indexes relative to the United States, single molecule cardiovascular drugs, all dosage forms, 1992

Index	US	Canada	Germany	France	Italy	Japan	Switzerland	Sweden	UK
Matched by IPN									
Laspeyres-KG	1.000	1.062	0.816	0.426	0.611	2.789	0.625	0.718	0.720
Laspeyres-SU	1.000	0.969	0.754	0.620	0.865	0.713	0.791	0.653	0.686
Paasche-KG	1.000	1.046	0.542	0.378	0.418	0.987	0.574	0.562	0.606
Paasche-SU	1.000	0.973	0.308	0.447	0.488	0.555	0.688	0.542	0.620
Fisher-KG	1.000	1.054	0.665	0.401	0.505	1.659	0.599	0.635	0.661
Fisher-SU	1.000	0.971	0.482	0.526	0.650	0.629	0.738	0.595	0.652
Unweighted-KG	1.000	1.009	0.888	0.398	0.566	1.157	0.727	2.277	0.791
Unweighted SU	1.000	0.948	0.824	0.459	0.651	0.498	0.743	0.780	0.707
N[a]	354	68	41	37	48	33	39	37	68
Matched by MOL/ATC									
Laspeyres-KG	1.000	1.166	0.882	0.502	0.704	1.191	0.747	0.871	0.646
Laspeyres-SU	1.000	0.954	0.828	0.659	0.920	0.740	0.885	0.694	0.587
Paasche-KG	1.000	1.016	0.560	0.449	0.504	0.868	0.644	0.677	0.459
Paasche-SU	1.000	0.908	0.587	0.595	0.656	0.620	0.833	0.667	0.463
Fisher-KG	1.000	1.088	0.703	0.475	0.596	1.017	0.693	0.768	0.544
Fisher-SU	1.000	0.931	0.697	0.626	0.777	0.677	0.859	0.680	0.521
Unweighted-KG	1.000	2.166	1.940	0.636	0.961	3.728	1.389	1.184	0.805
Unweighted SU	1.000	1.672	1.865	0.707	1.080	0.877	1.566	1.027	0.795
N[a]	105	52	64	54	57	59	45	43	62

Note–N refers to the number of distinct dosage forms, strengths, not the number of molecules; IPN = International Product Name (IMS); KG = kilogram; Laspeyres = US quantity weights; MOL/ATC = molecule and therapeutic category; Paasche = foreign quantity weights; and SU = standard units (IMS).

Source: Patricia M. Danzon, and Jeong D. Kim, "International Price Comparisons for Pharmaceuticals: Measurement and Policy Issues," *Pharmacoeconomics*, 14, Suppl. 1, 1998, p. 115.

Danzon and Chao, 2000[83]

Danzon and Chao undertook a similar approach, comparing drug sales through retail pharmacies between October 1991 and September 1992 for seven countries. The study uses the same IMS database to compare the U.S. prices with those in Canada, France, Germany, Italy, Japan, and the United Kingdom. The sample included all molecules that are available in the United States and the comparison countries; the bilateral subsamples ranged from 365 molecules for the United States-Japan comparison to 438 molecules for the United States-Germany comparison.

The Laspeyres price index for the larger sample shows smaller price differences than were reported in other studies. Laspeyres indexes for Canada and Germany were 2.1 percent and 24.7 percent, respectively, higher than for the United States; those for Japan, Italy, the United Kingdom, and France were 11.6 percent, 12.9 percent, 16.6 percent, and 32.2 percent, respectively, lower than the United States. With the Paasche indexes, all countries had lower prices than the United States. The SU and KG quantity units also led to significant differences among countries owing to the systematic differences in grams per standard unit (see table 2-2, published in a related study by Danzon). The main factors lowering prices in other countries were lower prices for older molecules and for therapeutic value. These factors were strongest in countries with strict price regulation, such as France, Italy, and Japan. Competition by generic drugs is effective in lowering prices in the United States and in other less regulated markets, such as Canada, Germany, and the United Kingdom.

Table 2-2
Price indexes in selected countries, relative to the United States, 1992
(all single-molecule drugs, matched by MOL/ATC, outpatient pharmacy)

Country	Laspeyres-KG	Laspeyres-SU	Paasche-KG	Paasche-SU	N
United States	1.000	1.000	1.000	1.000	922
Canada	0.870	1.030	0.664	0.447	458
Germany	0.972	1.273	0.521	0.368	471
France	0.570	0.701	0.416	0.326	412
Italy	0.739	0.907	0.331	0.465	406
Japan	1.282	0.923	0.486	0.448	396
Switzerland	1.049	1.444	0.657	0.465	308
Sweden	0.811	1.089	0.566	0.370	261
United Kingdom	0.678	0.761	0.479	0.465	453

Note.—N refers to the number of distinct dosage forms, strengths, not the number of molecules; IPN = International Product Name (IMS); KG = kilogram; Laspeyres = US quantity weights; MOL/ATC = molecule and therapeutic category; Paasche = foreign quantity weights; and SU = standard units (IMS).

Source: Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policies Versus Global Interests*, The AEI Press, Washington D.C., 1997, p. 31.

[83]Patricia M. Danzon and Li-Wei Chao, "Cross-National Price Differences for Pharmaceuticals: How Large and Why?", p. 1.

This study, which used the most comprehensive sampling procedure of all studies reviewed, although the data are 9 years old, points to some of the limits of international price comparison. The diversity of products, prices, and volumes, makes generalization difficult. Again, depending on the methodology chosen, differences between prices of drugs in foreign countries and prices in the United States can be large, small, positive or negative.

Methodology for Further Research

Currently available research has generally not addressed the question of whether and to what extent price regulations in other countries influence the price of comparable drugs in the United States, although Danzon and Chao, in previously discussed research, have examined some of the determinants of pharmaceutical prices within different countries. If the Commission were requested to undertake additional work on the determinants of prescription drug prices and the influence of foreign price controls on U.S. prices, the following issues could potentially be explored, but it is not clear that a precise answer to the question could be found. First, a data-intensive international price comparison study could attempt to provide an updated comparison of drug prices in the United States and abroad. Second, an industry survey could be attempted to provide a more extensive assessment of market segmentation in the pharmaceutical market. Finally, future research could use quantitative and qualitative methods to analyze parallel trade and reference pricing, and may give an indication of whether this breakdown in market segmentation provides a way for foreign price controls to affect U.S. drug prices.

Further research in this area by the Commission would be costly (given the size of the Commission's budget), and it cannot be determined in advance the extent to which future research would be able to definitively answer specific questions about the international linkages between national pricing policies and their effect on prices in other countries. The Commission is aware of only one source of data for international drug price comparisons. These data are proprietary and would have to be purchased at a significant cost and their suitability for the intended research has not been fully assessed. It should be noted that any price comparison would remain subject to the difficulties highlighted in the price comparison section of this study (e.g., the selection of market baskets and index numbers, with definitions of specific commodities to be measured and markets to be compared). Simple measures of overall price differences are inherently oversimplifications, and cannot be expected to be simultaneously definitive, unbiased, and comprehensive. However, taken in the context of carefully formulated questions or comparisons, price comparisons may provide meaningful information.

An assessment of the degree of market segmentation would require a survey of pharmaceutical drug manufacturers and purchasers and the results would be dependent on the quality and quantity of responses to such a survey. Markets for parallel imports–gray market goods–are by their nature difficult to measure, but a small number of studies have used surveys of exporters to quantify the extent and significance of parallel trade. Such survey data, if available, might allow an assessment of breakdowns in market segmentation in the pharmaceutical industry.

Econometric modeling could be attempted to further analyze why international price differences exist, provided the required data are available. Such modeling would consist principally of updating the work already done in the literature cited above. Such a model might be able to assess the extent to which cross-national price differences reflect differences in product characteristics, as well as in regulatory regimes. As far as the Commission is aware, research by

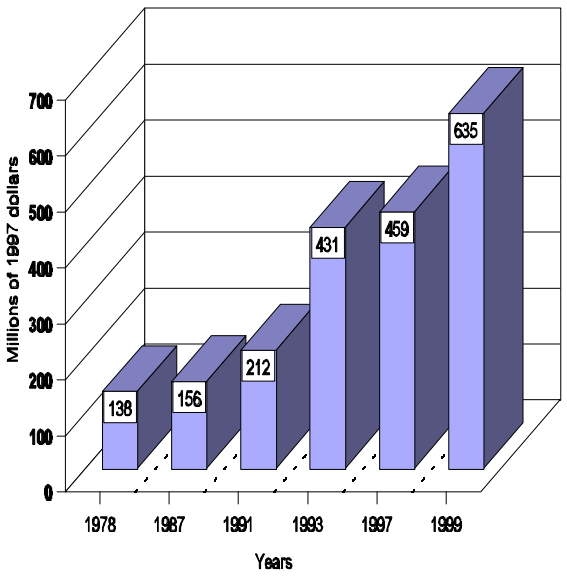
scholars in this subject area has not examined whether and to what extent regulatory regimes in certain countries may have affected prices in other countries.

Finally, it should be noted that such work, because it involves acquiring a data base, surveying the industry, and preparing econometric models, would take considerable time to complete.

CHAPTER 3
PRODUCT DEVELOPMENT

The drug development process from discovery to market can take as long as 12-15 years (on average), depending on the country involved. The process generally starts with the basic research needed to identify potential products, progresses to extensive clinical trials, and culminates in national approval by the appropriate approval body.[1] Substantial levels of R&D expenditures are reportedly needed, estimated to average about $500 million (1990 dollars)[2] or more per product for U.S. firms conducting global research compared with about $635 million for European Union (EU) firms (1997 dollars; see figure 3-1).[3] Moreover, there is also a great deal of risk involved, primarily in the form of failed products. In the United States, only 1 of about 5,000 compounds initially evaluated as potential products is actually approved. Moreover, "on average, only three out of ten generate revenues that meet or exceed average costs."[4] The development processes and the patent systems in each of the countries are described below; table 3-1 summarizes data for each country.

Figure 3-1
The average cost (EU) to bring pharmaceutical products to market, 1978-99



Source: EFPIA, *The Pharmaceutical Industry in Figures,* p. 21. Reprinted with permission from EFPIA. Converted to dollars by the Commission.

[1] In the European Union (EU), one of three routes for approval can be followed–the centralized procedure at the EU level, the mutual recognition procedure, or the national procedure (for more information see the section on product approvals in the EU).

[2] PhRMA, Written Submission, Aug. 4, 2000, p. 1.

[3] EFPIA, *The Pharmaceutical Industry in Figures*, p. 23; Lehman Brothers, *The Trend Towards Pharmaceutical Megabrands*, Nov. 15, 1999, p. 2; and "Recent Estimates of the Cost of Developing New Drugs," *PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2000*, p. 65. EFPIA cites the following sources for the data: Hansen, 1979; Wiggins, 1987; Di Masi et. al., 1991; Office of Technology Assessment, 1993; Meyers & Howe, 1997; and the Office of Health Economics & Lehman Brothers, UK, 1999.

According to *The Trend Towards Pharmaceutical Megabrands*, in addition to the $500 million for R&D, Astra-Zeneca estimates that an additional $250 million is needed for marketing if a megabrand product is to be created. This would result in combined R&D and marketing expenditures of about $750 million. The PAREXEL reference includes the following quote (Nov. 1998) from Dr. Joseph DiMasi, Director of Economic Analysis, Tufts Center for the Study of Drug Development: "There is every reason to believe that the cost [of drug development] is higher for drugs coming onto the market now–$500-$600 million or more is not an unreasonable estimate for the cost of drug development."

[4] PhRMA, Written Submission, p. 1; and PhRMA, *Pharmaceutical Industry Profile 2000*, p. 29. This result was based on products introduced during 1980-84.

Table 3-1
Pharmaceuticals: Selected information

Country	Domestic market's share of world market,1998 (percent)	Prescription products' share of total national health spending, 1997 (percent)	Annual R&D outlays, 1998 (millions of dollars)	Length of time for national approval process,1999[1] (months)	Length of patent term; patent term restoration or SPC? (years)	Compulsory licensing possible?	Price controls/cost-containment systems currently implemented
United States	36	7.3	17,223	About 12 [2]	20; Yes	No	In general, pharmaceutical companies operating in the United States can price products freely. However, participation in some Federal and State buying programs requires some controls, including rebates and discounts. Many private-sector programs (e.g., managed-care programs) reportedly negotiate their own price discounts. Although U.S. patients generally have access to any pharmaceutical on the market, some organizations (including the U.S. Department of Defense and the U.S. Department of Veterans Affairs) have reportedly implemented the use of formularies (i.e., listings of medicinal substances and formulas), which can restrict the products patients receive.
Canada	2	10.8	879	18-19.4[3]	17 or 20;[4] No [5]	Yes	Pharmaceutical companies are technically "free" to set their own prices for drugs. However, the suggested prices of patented medicines must be reviewed by the Patented Medicine Prices Review Board.
EU: France	6	13.9	2,718	7-24[6]	20; Yes	Yes	Prices have historically been controlled directly by the Government on a product-by-product basis. Decisions on reimbursement and prices are negotiated between the Comite Economique du Medicament (which includes representatives of economic ministries and outside experts) and the individual companies.
Germany	6	([7])	3,092	7-24[6]	20; Yes	Yes	A reference pricing system is used with the groupings decided by the Federal Association of Physician and Sickness Funds (excluding the industry).The Federal Association of Company-Based Insurance Funds then fixes reference prices after taking expert, including industry, views into account. At least some patented products are excluded from regulations based on this scheme.
Italy	4	([7])	851	7-24[6]	20; Yes	Yes	The licensing, classification, and reimbursement of new medicines is overseen by the Ministry of Health (with the advice of the Drug Commission). Parties are tied to the average of prices in France, Spain, Germany, and the UK, adjusted for purchasing power parity. Italy does not control the prices of pharmaceutical products it does not reimburse. It also does not control the price of OTC drugs, although OTC prices cannot be raised more than once a year.
UK	3	11.2	4,144	7-24[6]	20; Yes	Yes	The pricing of new medicines is free of regulation, subject to a control on profits from sales to the National Health Service embodied in the Pharmaceutical Price Regulation Scheme. Companies can apply for permission to raise prices only if their profits are below a given level.

See footnotes at end of table.

Table 3-1 (continued)
Pharmaceuticals: Selected information

Country	Domestic market's share of world market, 1998 (percent)	Prescription products' share of total national health spending, 1997 (percent)	Annual R&D outlays, 1998 (millions of dollars)	Length of time for national approval process,1999[1] (months)	Length of patent term; patent term restoration or SPC? (years)	Compulsory licensing possible?	Price controls/cost-containment systems
Japan	14	15.3	5,200	30-48	20; Yes	Yes	The Ministry of Health and Welfare fixes the introductory price of every new prescription brand-name drug through negotiation with its manufacturer. Japanese physicians generally dispense the drugs they prescribe. The Government sets the reimbursement price; the dispensing physician or hospital receives reimbursement from the social insurance program. The dispensing physician or hospital can thus profit from any margin between the reimbursement price and the manufacturer's price.
Mexico	([7])	([7])	([8])	6-8	20; Yes	Yes	The Mexican Government is the largest producer of pharmaceuticals in Mexico. The Institute Mexicano de Seguro Social is the largest purchaser of pharmaceuticals, and can impose its prices on drugs sold in the public sector. In the private sector, retail prices are limited by Mexico's Department of Commerce and Industrial Development's (SECOFI)Department of Standards and Acquisition. The Government must approve all final retail prices.
Russia	([7])	([7])	([9])	6	20; No	Yes	A price-control system for certain essential pharmaceuticals was introduced in Russia by decree No. 347, "On Measures for State Control over Pricing on Medicines," effective March 29, 1999. The decree provides Government control over market prices, setting an upper limit to the selling price. Prices are registered at the Federal level, but it is up to local officials to implement the controls.

[1] These data may also include approval times for generic products. Generic products are generally approved on a faster basis than innovative products. The approval time is intended to represent the time taken by the national agency to review and approve new drug applications. This time is not considered to include the time taken to perform clinical trials.

[2] Defined by the U.S. Food and Drug Administration (FDA) as the median approval time for new drug applications (does not include the approval time for generic products). According to an FDA representative, FDA's goals are to act on new drug applications in either 6 months for priority applications or 10-12 months for standard applications. This action could be in the form of either approving the drug, not approving it, or approving it conditionally while seeking more information from the applicant.

[3] According to a representative of Canada's Research-Based Pharmaceutical Companies (Rx&D), the difference in approval times can be attributed to the fact that the data were obtained from different sources using different survey data. Rx&D obtained the estimate of 19.4 months by surveying its members (i.e., innovative companies); the Therapeutic Products Programme of Health Canada 's estimate of 18 months was reportedly obtained from a survey of a broader group of companies.

[4] The term of a patent based on an application filed before October 1, 1989, is 17 years, measured from the date that the patent was issued. The term of a patent based on an application filed on or after October 1, 1989, is 20 years, measured from the filing date of the application.

[5] The term of any individual patent may be extended by an Act of Parliament, but that is rare.

[6] According to a representative of EFPIA, although the EU mandates that member States have 210 days to nationally authorize a drug, the actual times may vary; no data are reportedly available regarding actual times. Commission staff telephone interview with a representative of EFPIA on Oct. 25, 2000.

[7] Not available.

[8] Most R&D is conducted at the Mexican Centre of Pharmaceutical Development & Research (a joint government/industry venture funded by hospitals, universities, and research centers).

[9] Most Russian companies reportedly do not conduct primary research.

Sources: FDA (U.S. approval times); IMS HEALTH (1998 market data); *OECD Health Data, 2000* (prescription products' share of total health spending); and national trade organizations (annual R&D outlays). The various sources for remaining data are noted in this chapter and in chapter 4.

United States

Various sources note that the U.S. pharmaceutical industry's high level of innovation, fostered by factors such as the industry's level of R&D spending and the "market-driven competition" in the U.S. market which encourages such investment, has allowed it to remain globally competitive.

Most new drugs may not be commercially marketed in the United States unless they have been approved as safe and effective by the U.S. Food and Drug Administration (FDA). According to an FDA representative, FDA's goal is to act on new drug applications in either 6 months for priority applications or 10-12 months for standard applications. This action could be in the form of approving the drug, not approving it, or approving it conditionally while seeking more information from the applicant.

R&D Costs and Expenditures

The U.S. industry has traditionally maintained a strong position in the world pharmaceutical market, largely because of the level of innovation maintained by the industry.[5] During 1975-94, for example, the U.S. industry developed 45 percent of the 152 drugs launched globally.[6] The U.S. industry attributes its ability to maintain this level of innovation despite the high cost of developing pharmaceuticals and the high product-failure rate to several factors, including its level of R&D spending and the "market-driven competition" in the U.S. market which encourages such investment.[7] During 1990-2000, annual R&D spending by the U.S. industry increased from $6.8 billion to an estimated $22.5 billion, or by about 231 percent.[8] The percentage of revenues reinvested in R&D also increased during these years, from 18 percent to 21 percent.

The development of patented prescription drugs in the United States, whether discovered in-house or licensed from other companies, can take as long as 12-15 years on average from discovery to marketing. As in the development process in other parts of the world, several factors are taken into consideration when companies decide to pursue research in certain therapeutic areas, including the degree of information currently available regarding the mechanism(s) of a particular condition and the current status of research conducted to date in the scientific community on that condition and on products intended to treat it. Given the often rapid diffusion of scientific findings among research scientists, a number of firms might start discovery efforts in the same therapeutic area(s) at the same time. The first product to reach the market, whether or not a "blockbuster" product,[9] usually earns a significant degree of market recognition. Although subsequent products

[5] USITC, *Global Competitiveness*, publication 2437, p. 1-4. See also PhRMA, Written Submission, p. 1, and PhRMA, *Pharmaceutical Industry Profile 2000*, p. 90.

[6] PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 90. A global drug is defined as one marketed in the United States, Japan, France, Germany, the UK, Italy, and Switzerland.

[7] PhRMA, Written Submission, p. 1; PhRMA, *Pharmaceutical Industry Profile 2000*, p. 90; and USITC, *Global Competitiveness*, publication 2437, p. 1-4.

[8] PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 114.

[9] Defined as a product with annual sales of over $1 billion. Lehman Brothers, *The Trend Towards Pharmaceutical Megabrands*, p. 2.The article states that many blockbuster pharmaceuticals have been introduced in recent years and that such products have accounted for an increasing share of world

(continued...)

intended for similar use then need to differentiate themselves to gain market share, industry sources state that many of these latter products are generally more successful in the market because they are based on more recent scientific discoveries.[10]

The U.S. industry also participates in "public-private research collaboration" with National Institutes of Health (NIH).[11] Cooperative Research and Development Agreements (CRADAs) exemplify one type of such collaboration. CRADAs, created as part of the 1986 Federal Technology Transfer Act, provide a "forum through which NIH scientists and commercial firms could expedite the transfer of expertise and technology from NIH laboratories to encourage the development of improved healthcare products, processes and services."[12]

Government participation occurs largely in the basic research and translational research stages, with the companies generally pursuing the development process. The typical output of a CRADA is said to be "new knowledge"[13] and it is "ultimately, the collaborator [who] is responsible for commercialization of a new product, process or service."[14] It was estimated in a 1993 study that 92.4 percent of the new chemical entities approved in the United States during 1981-90 (or about 181 products) resulted from research conducted by private industry; 1 percent reportedly resulted from Government research programs.[15]

As noted in figure 3-2, the drug development process has several distinct phases, each of which takes several years to complete. Following completion of the initial research phase and preclinical testing (on average about 6.5 years), an investigational new drug application (INDA) is filed. Three phases of clinical testing then follow, with the patient population increasing substantially in each phase (total time is, on average, about 7 years). The final phase in the development process is the filing of the new drug application (NDA) with the U.S. Food and Drug Administration (FDA).[16]

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[9] (...continued)
pharmaceutical sales. However, the article further states that many blockbusters would not be considered megabrands using AstraZeneca's definition because they achieved the requisite high levels of return in their first 5-10 years on the market rather than in the first 2.

[10] USITC, *Global Competitiveness*, publication 2437, pp. 4-17 to 4-18.

[11] Ibid., p. 23.

[12] "Cooperative Research and Development Agreements (CRADAs)," found at *http://www4.od.nih.gov/ofm/PRIMER97/cradas.stm* and retrieved on Sept. 21, 2000. The website notes that "CRADAs have been proven to be a cost-effective way for companies to leverage their own research and development efforts. In turn, the stewardship of public funds for support of biomedical research is maintained and national economic and social interests are strengthened."

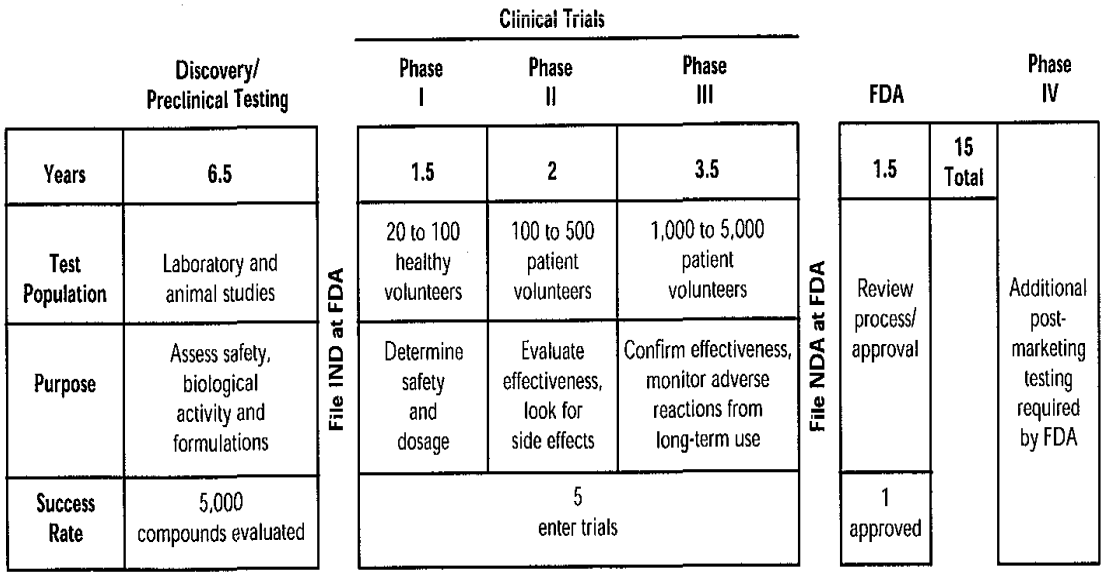
[13] PhRMA, *Pharmaceutical Industry Profile, 2000*, p. 25. EFPIA states that "unlike their European competitors, American companies have for several years benefitted from the U.S. Government's growing interest in leading-edge technologies" and from a large domestic market for their innovative products. EFPIA, *The Pharmaceutical Industry in Figures*, p. 23.

[14] "Cooperative Research and Development Agreements (CRADAs)," found at *http://www4.od.nih.gov/ofm/PRIMER97/cradas.stm* and retrieved on Sept. 21, 2000.

[15] K. Kaitlin, N. Bryant, and L. Lasagna, "The Role of the Research-Based Pharmaceutical Industry in Medical Progress in the United States," *The Journal of Clinical Pharmacology*, Vol. 33, May 1993, pp. 413-414.

[16] *New Drug Approvals in 1999*, p. 18.

Figure 3-2
The drug development and approval process



Source: PhRMA, *New Drug Approvals in 1999*, p. 18. Reprinted with permission from PhRMA.

Drug Approval Process

The Federal Food, Drug, and Cosmetic Act (FDCA)[17] was passed in 1938. The FDCA, administered by the FDA, is the major statute regulating marketing approval for new drugs on a Federal level in the United States. Generally, a new, patented drug may not be commercially marketed in the United States unless it has been approved as safe and effective by the FDA on the basis of the NDA submitted by the sponsor of the drug.[18] The NDA must contain acceptable scientific data, including the result of the tests performed to evaluate its safety and substantial evidence[19] of effectiveness for the conditions for which the drug is offered. Figure 3-3 provides information regarding the NDA review process.

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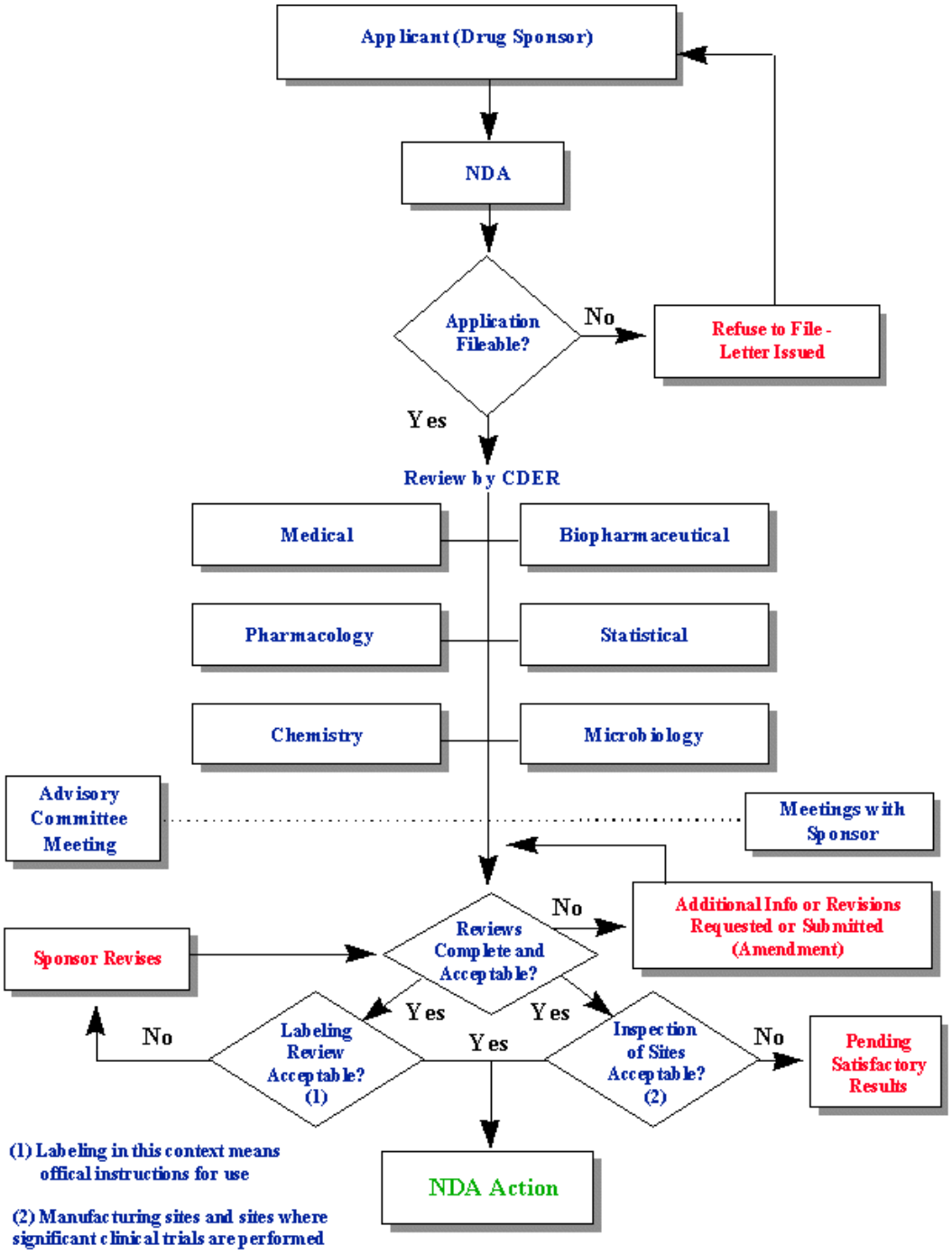
[17] 21 USC 301 et seq.

[18] Generic products are approved through a different process using an abbreviated NDA.

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

Figure 3-3
The NDA review process



Source: "The NDA Review Process," found at *http://www.fda.gov/cder/handbook/nda.htm* and retrieved on July 28, 2000.

According to information provided by FDA, the annual median approval time for all NDAs during 1998-99 was about 12 months compared with 27 months in 1987.[20] After fluctuating at levels between 21.8 months and 27 months during 1987-92, annual median approval times declined steadily during 1992-98. Under the Prescription Drug User Fee Act of 1992,[21] FDA's goal is to act on NDAs in either 6 months for priority applications (i.e., those considered to be an important therapeutic gain over existing products) or 10-12 months for standard applications.[22] This action could be in the form of approving the drug, not approving it, or approving it conditionally while seeking more information from the applicant. During 1992-99, median approval times for standards NDAs declined from 30.4 months to 13.8 months; those for priority NDAs declined from 16.8 months to 6.1 months.[23] In comparison, the median length of time needed in 1999 to approve generic products was almost 19 months.[24]

Patents[25]

The Term of a Patent

"A patent for an invention is the grant of a property right to the inventor, issued by the [U.S.] Patent and Trademark Office [(PTO)]. The right conferred by the patent grant is, in the language of the statute and of the grant itself, 'the right to exclude others from making, using, offering for sale, or selling' the invention in the United States or 'importing' the invention into the United States."[26] The PTO issues utility patents,[27] design patents,[28] and plant patents.[29] Utility

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[20] Data provided to Commission staff by a representative of the FDA on Oct. 19, 2000.

[21] According to a letter dated Nov. 12, 1997 from Donna Shalala, Secretary of Health and Human Services, to Senator James M. Jeffords, Committee on Labor and Human Resources, "Under [the Prescription Drug User Fee Act of 1992], the additional revenues generated from fees paid by the pharmaceutical and biological prescription drug industries have been used to expedite the prescription drug review and approval process."

[22] Commission staff telephone interview with a representative of FDA on July 28, 2000. The FDA representative stated that under the goals set forth in the Nov. 12, 1997, letter from the Secretary of Health and Human Services to Senator James M. Jeffords, there are annual incremental increases in the percent of applications to be acted on within 10 months. Two of the goals for fiscal year (FY) 2002 are that 90 percent of standard original NDA submissions filed in FY 2002 will be reviewed and acted upon within 10 months of receipt and that 90 percent of priority original NDA submissions filed in FY 2002 will be reviewed and acted upon within 6 months of receipt.

[23] Data provided to Commission staff by a representative of the FDA on Oct. 19, 2000.

[24] Ibid.

[25] Synopses of selected aspects of the patent laws of the United States, Canada, France, Germany, Italy, the United Kingdom, Japan, Mexico, and Russia are presented in order in this chapter. Owing to the limited focus of this investigation, these synopses do not summarize the patent provisions of international conventions, agreements, or treaties to which the United States or the other countries adhere, nor do they discuss European or Eurasian patents. Much of the patent information for countries other than the United States was obtained from *World Patent Law and Practice* (Matthew Bender & Co., Inc. Patent Law and Practice); from the websites for the patent offices of the Governments of Canada, France, Italy, Japan, Mexico, and the United Kingdom; from the U.S. Department of Commerce, Commercial Law Development Program, Office of the General Counsel; and from the U.S. Patent and Trademark Office (PTO).

[26] "What Are Patents, Trademarks, Servicemarks, and Copyrights?," found at *http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm* and retrieved on Oct. 19, 2000.

[27] According to 35 U.S.C. § 101, "Whoever invents or discovers any new and useful process, machine,

(continued...)

patents, however, are by far the most common and most important patents for the pharmaceutical industry.[30]

A utility patent is issued for an invention consisting of a process, machine, manufacture, or composition of matter, or an improvement thereof. The term of a utility patent issued under the current law is 20 years. Although the patent goes into effect on the date that the patent is issued, the 20-year term is measured from the filing date of the application for patent.[31] To keep the patent in force for its full term, the patent owner must pay maintenance fees 3½ years, 7½ years, and 11½ years after the patent is granted.

The term of any individual patent may be extended by Act of Congress, however, this is a rare occurrence. In some instances, the term of a patent for certain pharmaceuticals, processes for using them, or processes for manufacturing them (as well as certain medical devices, food additives, and animal drug products), all of which are subject to regulatory approval prior to marketing, may be extended for a limited period through an administrative proceeding at the PTO. The extension of the patent term generally is equal to the period of delay for the regulatory review. The length of the extension will not exceed 5 years even if the delay for review lasted longer than 5 years, and the combined unexpired term and the extension will not exceed 14 years. The FDA assists the PTO in determining eligibility for such extensions.

Under certain circumstances, the term of a patent also may be extended if issuance of the patent was delayed because of a secrecy order, if a proceeding was pending before the Board of Patents and Interferences to determine whether granting a patent for a particular invention would interfere with a pending application or an unexpired patent, or for appellate review. The total duration of extensions for a particular patent for any of the aforementioned reasons cannot exceed 5 years.

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[27] (...continued)
manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." *Manual of Patent Examining Procedure (MPEP)*, Edition 7, Revision 1 (E7R1), February, 2000, found at *http://www.uspto.gov/web/offices/pac/mpep/27.txt* and retrieved on Oct. 19, 2000. Another definition for the type of product covered by a utility patent is any product made by man that is neither a design or a plant. Commission staff conversation with representatives of the PTO.

[28] According to 35 U.S.C. § 171, "Whoever invents any new, original, and ornamental design for an article of manufacture may obtain a patent therefor, subject to the conditions and requirements of this title." *MPEP*, E7R1.

[29] According to 35 U.S.C. § 161, "Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state, may obtain a patent therefor, subject to the conditions and requirements of this title." *MPEP*, E7R1.

[30] USITC, *Global Competitiveness*, publication 2437, p. 3-11.

[31] The term of a utility patent that was in force 6 months after the enactment of legislation implementing the Uruguay Round Agreements (i.e., on June 8, 1995) is 20 years from the filing of the application for patent or 17 years from issuance of the patent, whichever is greater. This term also was extended for any patent whose prosecution at the PTO lasted less than 3 years (i.e., any patent for which the interval between filing and issuance was less than 3 years).

Working a Patent and Compulsory Licensing

U.S. patent law does not require that a patent be "worked," that is, exploited, after it is granted. Hence, if the patentee fails to work the patent, the law imposes no penalty such as revocation of the patent. Nor does U.S. patent law provide for compulsory licensing, a Government-mandated granting to others of the right to use the patented invention at a fee set by the Government and to accomplish a specified objective. (For more on the U.S. patent system, see appendix H.)[32]

[32] However, statutes make certain technologies, such as those involving nuclear power or space vehicles, subject to compulsory licensing. Moreover, at least one court has ordered the licensing of a patent that was not worked.

Canada

In 1997, R&D expenditures in Canada amounted to $825 million, representing reinvestment of 15.7 percent of revenues, compared with less than 3 percent in 1979. According to representatives of Canada's Research-Based Pharmaceutical Companies and PhRMA, increases in investment have coincided with the progressive removal of compulsory licensing, which was phased out in two steps by the Canadian Government.

R&D Costs and Expenditures

R&D expenditures in the pharmaceutical industry in Canada have been growing steadily and significantly for over a decade. In 1997, R&D expenditures in Canada amounted to over $825 million, or 15.7 percent of total pharmaceutical sales,[33] compared with 6.9 percent in 1988, and 2.7 percent in 1979.[34] Pharmaceutical research spending in Canada increased by more than 700 percent during 1987-98. Much of the R&D conducted in Canada in 1998 was concentrated in Alberta, British Columbia, Ontario, and Quebec.[35]

In terms of expenditures, Canada accounted for 1.9 percent of the global pharmaceutical market in 1998. As a part of Canada's total healthcare spending in 1997, the most recent year for which comparable data are available for certain industrialized nations, 13.8 percent was accounted for by spending on all pharmaceuticals (including prescription and nonprescription products); this compares with a high of 21.2 percent in Japan and a low of 7.7 percent in Switzerland. In the United States such spending was moderate, at 10 percent.[36]

The development process required to bring a new drug to market in Canada is considered by industry sources to be "lengthy, complex, and expensive." It can take as long as 15 years (including preclinical and clinical research phases) and cost as much as $500 million or more.[37]

Drug Approval Process

Drugs are authorized for sale in Canada once they have successfully gone through the drug review process. A new drug application is reviewed by scientists in the Therapeutic Products

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[33] Rx&D, *Annual Review 1999-2000*, 2000, p. 14.

[34] PhRMA, *Pharmaceutical Industry Profile 2000*, Chapter 8, p. 108, found at *www.phrma.org/publications/industry/profile00/tocnf.html* and retrieved on July 27, 2000.

[35] *Approval Times in Canada 1999*, published by Rx&D, found at *www.canadapharma.org/en/whatsnew/index.html* and retrieved on July 31, 2000. According to Rx&D, the "brand-name pharmaceutical industry's investment in research and development in Canada has grown from just over $100 million in 1988 to an expected $1 billion in 2000."

[36] PhRMA, *Pharmaceutical Industry Profile 2000*, Chapter 7, p. 93. See also *OECD Health Data, 1999*. These expenditures include prescription and nonprescription products.

[37] *Approval Times in Canada 1999*, Rx&D. Rx&D referred to surveys conducted by the Tufts University Center for the Study of Drug Development in Boston, MA.

Programme (TPP) of Health Canada (and, on occasion, outside experts) to assess the safety, efficacy and quality of a drug.[38] The steps in the development of pharmaceuticals in Canada are as follows:

- ❏ Primary research and discovery of new compounds;
- ❏ Initial studies involving tissue cultures and small animals;
- ❏ Preclinical tests involving animal and laboratory tests to achieve proper dosage; and Clinical trials, authorized by TPP upon assessment of sponsor's application. The intent of trials is to research and gather information on the drug's dosage, effectiveness, and safety in humans. If the clinical trial studies prove that the drug has potential therapeutic value that outweighs the risks associated with its use, the sponsor may choose to file a New Drug Submission with the TPP.[39]

The New Drug Submission contains information and data about the drug's safety, effectiveness, and quality. It also includes the results of preclinical and clinical studies, details regarding the production of a drug, packaging and labeling details, and information regarding therapeutic claims and side effects. As part of the review process, the TPP then–

- ❏ Performs a thorough review of the submitted information, sometimes using external consultants and advisory committees;
- ❏ Evaluates the safety, efficacy, and quality data to assess the potential benefits and risks of the drug; and
- ❏ Reviews the information that the sponsor proposes to provide to healthcare practitioners and consumers about the drug (e.g., the label and product brochure).[40]

If the benefits outweigh the risks, and the risks can be mitigated, the drug is issued a Notice of Compliance, as well as a Drug Identification Number, which permits the sponsor to market the drug in Canada and indicates the drug's official approval in Canada.[41] However, if a drug is not approved, which might happen for several reasons such as insufficient evidence to support the safety, efficacy, and quality claims of the drug's sponsor, the sponsor has the right to resubmit its submission at a later date with additional information and supporting data, or to appeal the TPP's initial decision.[42]

The TPP seeks to maintain internationally competitive standards for the time involved in the review process, though it is dependent upon staff availability and pending workload. Although Canada has mutual recognition agreements with other countries which allow each country to accept the other's test results to some degree, thereby potentially reducing the development time and costs for such products,[43] representatives of the TPP have stated that there is no such agreement between

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[38] "How Drugs are Reviewed in Canada," Therapeutic Products Programme, Health Canada, Feb. 2000, found at *www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/fact-sht.html* and retrieved on July 26, 2000. The TPP is the national authority that regulates, evaluates and monitors the safety, efficacy, and quality of therapeutic and diagnostic products and vaccines available in Canada.

[39] "How Drugs are Reviewed in Canada," found at *www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/fact-sht.html* and retrieved on July 26, 2000.

[40] Ibid.

[41] Ibid.

[42] Ibid.

[43] "Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (the PER

(continued...)

Canada and the FDA.[44] Thus, products approved in the United States also have to undergo testing in Canada before being marketed. According to one source, Canada has recognized that its own limited resources have prevented it from attaining its goal of an approval process as rigorous and demanding as that of the FDA, and has been looking into establishing a system along the lines of that in the EU.[45]

The TPP states that the current process takes an average of 18 months, from the time of sponsor's submission to the TPP's marketing decision.[46] The patented pharmaceutical industry's trade association in Canada, Rx&D, states that the average time for the TPP to review and approval new drugs in 1999 was 591 days, or 19.4 months,[47] about 54 percent higher than the average time of 12.6 months for the FDA. It was the second straight year in which Canadian mean approval time increased over the low of 549 days achieved in 1997.[48]

Some drugs may also receive expedited review by the TPP through the Priority Review Process. If a drug promises to enhance the capacity to treat life-threatening or severely debilitating conditions, such as cancer, Acquired Immune Deficiency Syndrome, or Parkinson's Disease, for which there are few effective therapies, the TPP allows for a faster review of the sponsor's submission. Similarly, the TPP's Special Access Program (SAP) allows physicians to gain access to certain drugs that are not available in Canada. After approval for the SAP, a physician may

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[43] (...continued)
Scheme)," dated September 7, 1990, found at *http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/policy/issued/per_e.html*. According to the TPP's website, "On February 21, 1990, Canada became an official member of the Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (the PER Scheme), which is operated under the auspices of the European Free Trade Association (EFTA). The other members of the PER Scheme are Australia, Austria, Germany, Finland, Hungary, Iceland, Italy, Netherlands, Norway, South Africa, Sweden, Switzerland and the United Kingdom. The purpose of the PER Scheme is to facilitate the registration of pharmaceutical products through the exchange of evaluation reports between members. This eliminates the duplicate evaluation of scientific data required for registration, and contributes to international co-operation by mutually recognizing the evaluation efforts of the members."

[44] Commission staff telephone conversations with representatives of the TPP October 26-30, 2000. For more information on Canada's participation in the Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products, see *http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/policy/issued/per_e.html.*

[45] Ullrich K. Hoffmeyer and Thomas R. McCarthy, ed., "Canada," *Financing Health Care*, Vol. 1, 1994, p. 286. According to this source, the "limited resources" applied strictly to "insufficient manpower" in the Health Protection Branch, which would like to maintain "a 'detail-oriented' approach, such as that used by the US FDA." It is further stated in the reference that these limitations have resulted in Canadian authorities looking to the Europeans as the Canadian approval process is reviewed. However, this source provides no further discussion of how Canada may use the disparate avenues of EU review as a model.

[46] "How Drugs are Reviewed in Canada."

[47] According to a representative of Canada's Research-Based Pharmaceutical Companies (Rx&D), the difference in approval times can be attributed to the fact that the data were obtained from different sources using different survey data. Rx&D obtained the estimate of 19.4 months by surveying its members (i.e., innovative companies); the Therapeutic Products Programme of Health Canada's estimate of 18 months was reportedly obtained from a survey of a broader group of companies.

[48] *Approval Times in Canada 1999.* After exceeding 1,100 days during 1987-93 (reaching a high of 1,163 days in 1991), the average approval time in Canada declined to 682 days in 1994. Approval times continued to decline during 1996-97, reaching a low of 549 days, before increasing gradually during 1998-99 to 591 days.

administer the drug to a patient if conventional treatments have failed or are not promising. The exceptional drug is released only after the TPP has determined that the need is "legitimate" and the physician is "qualified."[49]

Patents

The Term of a Patent

The term of a patent based on an application filed before October 1, 1989, is 17 years, measured from the date that the patent was issued.[50] The term of a patent based on an application filed on or after October 1, 1989, is 20 years, measured from the filing date of the application. To keep the patent in force for its full term, the patent owner must pay annual maintenance fees.

The term of any individual patent may be extended by an Act of Parliament, but that is rare. The Canadian patent statute and the patent rules make no provision for extension of a patent term to compensate for time consumed by regulatory approval processes.

Working a Patent and Compulsory Licensing[51]

At any time more than 3 years after a patent is granted, the Attorney General of Canada or any interested person may apply to the Commissioner of Patents for relief on the ground that the patent has been abused. The exclusive rights under a patent are deemed to have been abused in any of the following circumstances:

- If the demand in Canada for the patented article or the article made by the patented process is not being met to an adequate extent and on reasonable terms;

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[49] "How Drugs are Reviewed in Canada."

[50] Background information provided in an Office of the United States Trade Representative (USTR) press release, dated Sept. 18, 2000, states, "On May 6, 1999, the United States initiated a WTO dispute settlement case against Canada for its failure to amend its patent law to comply with the TRIPs [Trade-Related Aspects of Intellectual Property Rights] Agreement, which requires that Canada provide a patent term of at least 20 years from the date that a patent application is filed for all patents existing on January 1, 1996. The Canadian Patent Act, however, provides that the term of patents based on applications filed before Oct. 1, 1989, is seventeen years from the date the patent is issued. On September 22, 1999, the WTO [World Trade Organization] established a panel to review this issue. The final panel report was released on May 5, 2000. Canada filed an appeal with the WTO Appellate Body on June 19, 2000." As stated in the body of the press release, the Appellate Body upheld the Panel's findings. USTR, "United States Wins WTO Case Challenging Canada's 17-Year Patent Term," Press release dated Sept. 18, 2000. See also WTO, Report of the Appellate Body, "Canada–Term of Patent Protection," dated Sept. 18, 2000 (AB-2000-7), found at *http://www.wto.org/english/tratop_e/ dispu_e/170abr_e.pdf* and retrieved on Sept. 22, 2000.

[51] In general, some or all of the compulsory licensing laws discussed in this report apply to patented inventions, which would include pharmaceutical patents or patented pharmaceutical inventions. In some instances, countries will also have compulsory licensing statutes that apply exclusively to pharmaceuticals.

- If, by reason of the refusal of the patent holder to grant a license or licenses on reasonable terms, the trade or industry of Canada or the trade of any person or class of persons trading in Canada, or the establishment of any new trade or industry in Canada, is prejudiced and it is in the public interest that a license or licenses be granted;
- If any trade or industry in Canada, or any class of persons engaged therein, is unfairly prejudiced by conditions that the patentee has attached to the purchase, hire, license, or use of the patented article or the article made by a patented process, or to the using or working of the patented process; or
- If it is shown that the existence of the patent, being a patent for an invention relating to a process involving the use of materials not protected by the patent or for an invention relating to a substance produced by such a process, has been utilized by the patentee so as to unfairly prejudice in Canada the manufacture, use, or sale, of any materials.

Two types of relief are the granting of compulsory licensing or revocation of the patent. If the Commissioner is satisfied that the exclusive rights under a patent have been abused, he may grant a compulsory license to the applicant. It may include terms such as precluding the licensee from importing any goods into Canada which, if made by persons other than the patentee or persons claiming under him, would be an infringement of the patent. If the Commissioner is satisfied that the exclusive rights under a patent have been abused in the manner designated (4) in the preceding paragraph, a compulsory license may be granted to the applicant and such of the applicant's customers as the Commissioner deems appropriate. If the Commissioner determines that the desired objectives cannot be met by compulsory licensing, he can order revocation of the patent, provided that such revocation is not at variance with any treaty, convention, arrangement, or engagement with any other country to which Canada is a party. The Commissioner also has the option of declining to order a compulsory license or revocation of the patent if he concludes that the desired objectives would not be obtained by those actions.[52] All orders and decisions by the Commissioner are appealable to the Canadian Federal Court.

If the parties consent or if the proceedings require any prolonged examination of documents or any scientific or local investigation that cannot, in the opinion of the Commissioner, be conveniently made before him, the Commissioner may refer the proceedings to the Federal Court for disposition.

In the past, Canadian law contained provisions for the compulsory licensing of pharmaceuticals specifically. Those provisions were abolished in 1993. (For more on Canadian compulsory licensing and its national patent system, see the sections in chapter 4 and appendix H, respectively.)

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[52] The considerations by which the Commissioner is to be guided in deciding whether to grant a compulsory license are the following: (1) He must try to secure the widest possible use of the patented invention in Canada with the patentee deriving a reasonable advantage from his patent rights; (2) he must try to secure for the patentee the maximum advantage consistent with the invention being worked by the licensee at a reasonable profit in Canada; and (3) he must try to secure equality of advantage among the several licensees and, for this purpose, may for due cause reduce the royalties or other payments accruing to the patentee under any license previously granted.

European Union

There are three pharmaceutical approval processes in the EU: authorization at a purely national level for a national market only (national procedure); authorization at a national level, and afterwards negotiated to be recognized in one or more other EU member States (mutual recognition procedure); and centrally, through the EU's European Agency for the Evaluation of Medicinal Products (EAEM) (centralized authorization procedure). Products recognized through the EAEM are automatically acceptable in all EU member States.

Most innovative new pharmaceuticals, and all pharmaceuticals derived from biotechnology, must be authorized centrally in the EU. In the centralized authorization procedure, testing is performed by the EAEM; once the EAEM approves a medicine, it directs the European Commission's Committee on Proprietary Medicinal Products (CPMP) to license the product.

EU-Level Regulation of Pharmaceuticals

The EU developed a regulatory regime for pharmaceuticals within the scope of EU legislation in 1965[53] with Directive (65/65/EEC),[54] which set initial minimal standards of pharmaceutical regulation at the national level. In 1975, one EU Directive (75/318/EEC) established basic standards of pharmaceutical testing in the member States, another (75/319/19) addressed minimum testing standards, and a third (75/320/EEC) established an intergovernmental Pharmaceutical Committee to oversee competition issues.

In 1985, the EU became committed to the ideal of a single market; soon afterwards, single-market measures began to be applied to the pharmaceutical sector. A 1989 Directive (89/105/EEC) called for minimum levels of pricing transparency within national frameworks. Also in 1989, the EU extended its previous Directives that established minimal testing and regulatory standards (89/342/EEC, 89/343/EEC, and 89/381/EEC). A 1991 Directive (91/356/EEC) established guidelines for Good Manufacturing Practices (GMP) standards for pharmaceuticals.

In 1992, the EU became a single market and EU industry legislation began to reflect the EU's concerns over pricing and distribution. In pharmaceuticals, this was characterized by five Directives related to pharmaceuticals: wholesale distribution guidelines (92/25/EEC), pharmaceutical classification (92/26/EEC), medicine labeling (92/27/EEC), medicine advertising (92/28/EEC), and further widening the scope of general pharmaceutical regulation overall (92/73/EEC).

These EU Directives must be implemented nationally, through member-state legislation. The EU has also issued a number of Regulations which directly affect the pharmaceutical industry. The most notable of these was the establishment of the European Agency for the Evaluation of Medicinal Products (EAEM) in 1993 (Council Regulation 2309/93). Other Regulations related to

[53] The European Economic Community became the European Community in 1985 and the EU in 1992; throughout this section, "European Union" denotes the EU's previous organizations as well.

[54] EU directives relating to pharmaceuticals can be found on *http://dg3.eudra.org/eudralex/vol-1/home.htm*.

pharmaceuticals include–

Regulation No. 297/95 (fees payable to the EAEM);
Regulation No. 540/95 (reporting adverse reactions of pharmaceuticals);
Regulation No. 541/95 (honoring nationally based marketing authorizations in other member States); and
Regulation No. 1662/95 (national implementation of EU marketing authorization procedures).

In 1996, the EU further expanded its examination procedures for applications for the transfer of marketing authorizations to other member States (Council Regulation 2141/96).

In addition to influencing regulations regarding pharmaceuticals directly, the existence of the European single market has caused member States to gradually harmonize many of their regulations for pharmaceuticals. In cases of dispute between member States over recognition (or a failure to reach consensus during the mutual recognition period), the EAEM mediates a solution, thus contributing further to member state harmonization.

Drug Approval Processes in the EU

There are three pharmaceutical approval processes in the EU: authorization at a purely national level for a national market only (national procedure); authorization at a national level, with subsequent recognition negotiated in one or more other EU member States (mutual recognition procedure); and centralized authorization, through the EAEM. Products recognized through the EAEM are automatically acceptable in all EU member States.

Centralized Authorization

The centralized authorization procedure through the EAEM is mandatory for certain biotech-derived medicinal products and optional for other innovative products.[55] (Because mutual recognition of national authorizations can be time consuming,[56] many pharmaceutical companies today choose centralized authorization even when they are not strictly required to do so.[57]) In this procedure, pharmaceutical companies established in the EU submit marketing authorization applications to the EAEM. The EAEM then coordinates the actions of representatives from all 15 member states, which evaluate the application and conduct clinical trials. Following scientific evaluation by EAEM, formal political authorization is granted by the European Commission's Committee on Proprietary Medicinal Products (CPMP). In the interests of speed and efficiency, the CPMP has pledged to take no more than 210 days to grant approval and translate all necessary documents into the 12 EU languages;[58] the resulting single-market authorization is valid throughout the EU. Speedy approval is particularly important to companies seeking to avoid delays in marketing their products in member States where the approval process is slower than average. As patent durations are standardized throughout the EU, delays in authorization cut into the useful life of patented drugs.[59]

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[55] EAEM authorization may be requested by companies developing innovative new products.

[56] This is a U.S. industry characterization. Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[57] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on August 3, 2000.

[58] Commission staff interview with representatives of PhRMA on Aug. 25, 2000.

[59] Companies can still face national delays as member state governments work out reimbursement

(continued...)

As with the Drug Price Competition and Patent Reform Term Restoration Act (Hatch-Waxman) legislation in the United States and similar legislation enacted in Japan, the European Community Council Regulation on the Supplementary Protection Certificate,[60] which took effect on January 1, 1993, was implemented primarily to offset the reduction in the effective patent life of a pharmaceutical product that resulted from delays in receipt of national marketing authorization. For example, in the United States, the average effective patent life without patent term restoration was 8.6 years during 1984-95, compared with 11 years in cases with patent term restoration.[61]

Unlike the legislation in the United States and Japan, however, a supplementary protection certificate (SPC) does not affect the patent term itself but instead provides for an additional period of market exclusivity,[62] which allows companies to recoup some portion of their R&D expenditures. Products in the EU are generally granted a 20-year term from the filing date of the application. However, since products cannot be marketed until they receive authorization, the average length of the effective patent life of a pharmaceutical can decrease as a result of delays incurred in obtaining market authorizations and by rapid entry of competing generic products once the patent expires. Decreases in the length of the effective patent life of a product, in turn, decrease the amount of time during which the innovative company may recover some part of its investment in the product.[63]

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[59] (...continued)
schedules for newly approved drugs; the length of this process varies among the member States.

[60] Council Regulation EEC No. 1768/92 of 18 June 1992 Concerning the Creation of a Supplementary Protection Certificate for Medicinal Products (OJ No. L182 of 2.7. 1992, p. 1), dated June 18, 1999, found at *http://dg3.eudra.org/eudralex/vol-1/pdfs-en/921768en.pdf* and retrieved on Sept. 15, 2000.

[61] Sheila S. Schulman, Joseph A. DiMasi, and Kenneth I. Kaitin, "Patent Term Restoration: The Impact of the Waxman-Hatch Act on New Drugs and Biologics Approved 1984-995," *The Journal of Biolaw and Business*, Vol. 2, No. 4, 1999. The study examined the average length of patent term restoration for products approved by the FDA during 1984-95. The findings are based on 207 approved applications for patent term restoration out of a total of 294 applications.

[62] U.S. International Trade Commission, *The Effects of Greater Economic Integration Within the European Community on the United States: First Follow-Up Report* (investigation No. 332-267), USITC Publication 2268, 1990, p. 6-80, and IMS HEALTH's "SPCs Worth Millions to Pharma Companies in Europe," found at *http://www.ims-global.com/ insight/nws_story_000417a.htm* and retrieved on Sept. 26, 2000.

Many in the industry regard an SPC as a "device" rather than a patent. As noted in the Commission's report on economic integration, the implementation of a product other than a patent meant that the provisions of the Munich Convention did not need to be modified. See also "Supplementary Protection Certificates for Medicinal and Plant Protection Products," found at *http://www.patent.gov.uk/ dpatents/ mpp/pdfs/spcs.pdf* and retrieved on Sept. 15, 2000; and "Supplementary Protection Certificates for Medicinal and Plant Protection Products: A Guide for Applicants (Revised January 1997)," found at *http://www.patent.gov.uk/forms/supp/pdfs/spctext.pdf* and retrieved on Sept. 15, 2000.

SPCs, as utilized in each EU country under investigation, are discussed under the subheading entitled "The term of a patent and supplementary protection certificates" in the following sections in this chapter on France, Germany, Italy, and the United Kingdom.

[63] According to IMS HEALTH, product sales are at their highest within the five-year period after the product's patent expires. They cite the example of sales of Prozac in the UK, where the product was introduced in 1986 and the patent expired in 1995, stating that "almost 80 percent of Prozac's sales [in the UK] over the last 10 years were accrued in the 5 years covered by the SPC." "SPCs Worth Millions to Pharma Companies in Europe," found at *http://www.ims-global.com/insight/ nws_story_000417a.htm* and retrieved on Sept. 26, 2000.

According to information provided by Information obtained by the German Patent and Trade Mark
(continued...)

An SPC provides up to 5 years of market exclusivity for a product once its patent expires; the total effective patent period (i.e., the sum of the patent term and the added market exclusivity period) may not exceed 15 years from the date of the first marketing authorization in the EU.[64] For example, if a product receives its first marketing authorization 5 years after patent application, then the effective life of the patent would be 15 years and no SPC would be granted. if the product receives such approval 10 years after the application, then the effective patent life would be 10 years and an SPC would add a maximum of 5 years of market exclusivity. If the approval takes 20 or more years, then no SPC would be issued; an SPC cannot be granted if a product's patent expires prior to the first marketing authorization[65] nor can a second certificate be granted to a product.[66] Currently the highest number of SPCs are said to have been granted in the UK (268) and Switzerland (272);[67] the numbers granted in France, Germany, and Italy are reportedly low.[68] Products already on the market prior to January 1, 1993, were covered on a country-by-country basis under a tiered schedule.[69]

National Procedure

Companies seeking authorization for nonbiotechnology or noninnovative medicines might pursue authorization at the national level. In this procedure, one member state authorizes a medicinal product for domestic use only. Owing to the limited market of individual member States, however, few companies today seek solely national authorization;[70] a more common course of action is to seek national authorization and then arrange mutual recognition of that authorization in other EU member States.

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[63] (...continued)
Office, "the [EU] Regulation did not have to be particularly implemented and transformed into German law for it is automatically binding in its entirety and directly applicable in Germany as well as in every Member State of the EU." Information obtained by Commission staff via an e-mail from a representative of the German Patent and Trade Mark Office received Oct. 13, 2000.

[64] Council Regulation EEC No. 1768/92; an internal memo prepared by PhRMA's office in Brussels describing the provisions of and the total intellectual property protection conferred by an SPC (Council Regulation 1768/92)and transmitted to PhRMA on Oct. 25, 1996; and *The Effects of Greater Economic Integration Within the European Community on the United States: First Follow-Up Report*.

[65] Council Regulation EEC No. 1768/92 and the PhRMA internal memo, transmitted within PhRMA on Oct. 25, 1996.

[66] Council Regulation EEC No. 1768/92, and *World Patent Law and Practice* at § 6.01 [3] [d] (rel. 103-12/99 Pub. 055).

[67] IMS HEALTH, "SPCs Worth Millions to Pharma Companies in Europe," found at *http://www.ims-global.com/ insight/nws_story_000417a.htm* and retrieved on Sept. 26, 2000.

[68] Ibid., and "Are SPC Filings on the Decline-Now R&D Development Times Are Shortening?", found at *http://www.ims-global.com/ insight/news_story/news_story_000417d.htm* and retrieved on Sept. 26, 2000. According to IMS HEALTH's Patents International Lifecycle service, France and Italy each had similar programs established by 1992 and, given their differing regulations, their final implementation of SPCs varied somewhat from the EU's procedure. IMS HEALTH also states that in 1999 more than 40 SPCs were granted in Italy, more than 30 were granted in the UK, and over 50 were applied for in Germany.

[69] An internal memo prepared by PhRMA's office in Brussels describing the provisions of and the total IP protection conferred by SPCs (Council Regulation 1768/92)and transmitted to PhRMA on Oct. 25, 1996.

[70] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

Mutual Recognition Procedure

The mutual recognition procedure is used for most nonbiotechnology pharmaceutical products. In this procedure, pharmaceutical companies established in the EU obtain a national marketing authorization in one EU member state, known as the "champion state" for that product.[71] The "champion state" then negotiates mutual recognition individually with one or more other member States.[72] In cases of dispute, the EAEM mediates.

[71] Ibid.

[72] Some sources note that the UK and Germany have the most efficient authorization procedures. Companies are sometimes prevented from applying for authorization in these countries, however, by the European Commission, which has mandated that companies must use all member States equally when using the mutual recognition procedure.

France

The French pharmaceutical industry has been one of the largest producers in the EU, with employment in recent years growing annually by approximately 1,000 jobs. According to one source, however, profits (about 5 percent of sales) have been lower than those in the United States and the UK.

The French industry has continued to consolidate. Two recent large mergers have been the merger of Sanofi and Synthelabo to form Sanofi-Synthelabo and the merger of Hoechst and Rhone-Poulenc Rorer to form the company Aventis.[73] Of the 300 pharmaceutical companies in France, approximately 40 percent have a majority of French capital; foreign companies (including many Japanese and U.S. companies) own the remaining 60 percent.[74] Investment has grown faster than sales over the past few years. Nevertheless, profitability in the industry has reportedly been only about 5 percent compared to 10 percent in the United States and the UK.[75]

R&D Costs and Drug Approval Process

The French trade association Syndicat National de l'Industrie Pharmaceutique (SNIP) has stated that the R&D cost of a new drug in France is on the order of $244 million. In the process, the French pharmaceutical industry typically identifies about 100,000 chemicals that are submitted for preliminary testing, out of which 100 may be eligible for more extensive preclinical testing. From this number, about 10 are submitted to clinical trials leading to one new drug. SNIP indicated that pharmaceutical companies take 5 years of in-house primary and preclinical testing (when receiving positive results) of a potential drug before it is submitted to clinical trials. The three clinical trial phases can take another 5-6 years to complete (again when receiving positive results) before the process for approval in the French market starts, which includes price and reimbursement level negotiations (requiring another 2 to 3 years).[76]

Patents

The term of a patent and SPCs

The term of a French patent is 20 years from the date that the application for patent was filed. To keep the patent in force for its full term, the patent owner must pay annual renewal fees.

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[73] Doris Leblond, "French Revolution," *European Chemical News*, Nov. 30-Dec. 6, 1988, pp. 43-44. Investment has grown faster than sales over the past few years; nevertheless, profitability in the industry is reportedly low (about 5 percent) compared with 10 percent in the United States and the United Kingdom.

[74] Syndicat National de l'Industrie Pharmaceutique (SNIP), *Pharmaceutical Industry*, found at *http://www.snip.fr*.

[75] Doris Leblond, "French Revolution."

[76] SNIP, "Research and Development," *The French Pharmaceutical Industry: Facts and Figures '99*, p. 33.

The term of a pharmaceutical patent can be extended by an SPC.[77] If the patented invention relates to a medicament, a process for obtaining a medicament, a product necessary for obtaining said medicament, or a process for the production of such a medicament, the patent owner can obtain an SPC, provided the owner is exploiting the patent in France and using it to produce a proprietary medicinal product that has been authorized for marketing in accordance with the Public Health Code.

According to a representative of the Institut National de la Propriété Industrielle (INPI), two sets of provisions regarding SPCs coexist in France: those of national origin (covered by French laws implemented in 1990 pending finalization of the EU-wide measure) and those covered by the provisions of the European Community Council Regulation on the Supplementary Protection Certificate. The representative states that SPCs granted in France since January 1, 1993, comply with the EU provisions; they differ from those originally granted under the 1990 provisions mainly in the way the amount of extra protection is calculated.[78] Whereas the EU regulation calls for the addition of a maximum of 5 years based on the time lost during regulatory approval such that the total effective patent period (i.e., the sum of the patent term and the added market exclusivity period) does not exceed 15 years from the date of the first marketing authorization in the EU, SPCs granted under the 1990 provisions can add up to seven years to the remaining term of the patent and that total protection under the French provisions (i.e., the duration of the patent and the extra time granted under an SPC) can be calculated in one of two ways: (1) "The legal duration of the patent (20 years from the date of filing the application) plus 7 years" or (2) "the difference between the legal duration of the patent (20 years) and a time span of 17 years counted from the date of the marketing authorization, whichever term comes first."[79]

Working a patent and compulsory licensing

French law imposes a working requirement on patent owners and provides for compulsory licensing. Three years after the grant of a patent or 4 years after the filing of the application for patent, a person can apply for a nonexclusive compulsory license under the patent. The license will be granted if, in the absence of a legitimate excuse, the patent owner (1) has not started to work, or made effective and serious preparation to work, the patented invention in the territory of the EU and (2) has not marketed the patented product in a sufficient amount to satisfy the needs of the French market. A compulsory license also may be obtained if working or marketing in France has been abandoned for more than 3 years.

Compulsory licensing is also available in the case of interdependent patents. The owner of a patent for an improvement on an invention patented by a third party may not work his invention without the consent of the holder of the earlier patent. Conversely, the owner of the earlier patent cannot work the patented improvement without permission from the owner of the improvement

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[77] *World Patent Law and Practice Source* (Matthew Bender & Co., Inc., Patent Law and Practice). Although this topical compilation characterizes an SPC as extending the patent term, other sources view the certificate as extending a period of market exclusivity.

[78] The protection device implemented in France in 1991 was called a Complementary Certificate of Protection (CCP). According to one source, "CCPs are still available in France for patents granted before December 31, 1991 . . ." Sheila S. Schulman, Joseph A. DiMasi, and Kenneth I. Kaitin, "Patent Term Restoration: The Impact of the Waxman-Hatch Act on New Drugs and Biologics Approved 1984-995."

[79] Correspondence via e-mail and telephone between Commission staff and a representative of INPI during Sept.-Oct. 2000.

patent. If it is in the public interest and the patented improvement constitutes an important technical progress in relation to the earlier patent, the owner of the improvement patent may obtain a nonexclusive license under the earlier patent in order to work his improvement patent. In addition, the owner of the earlier patent must receive a license under the improvement patent.

The application for a compulsory license must be filed in the District Court and must be accompanied by evidence that the applicant has been unable to obtain a license to work the invention from the owner of the patent and that the applicant is in a position to work the invention in an effective and serious manner. The court will specify the amount of royalties to be paid to the owner.

French law also provides for compulsory licensing of the following kinds of pharmaceutical patents: (1) patents for medicaments or the processes for producing them; (2) patents for products required for producing medicaments; and (3) patents for processes for producing such products. These patents may be subjected to compulsory licensing at the request of the Minister of Public Health when (1) the interests of public health require it and (2) the subject medicaments are being made available to the public in insufficient quantities or quality or at abnormally high prices. From the publication date of an order subjecting the patent to the Government-mandated licensing system, any qualified person may apply for a license to work the patent. The license will be granted by the Minister responsible for Industrial Property under specified terms, except for the royalties to be paid. In the absence of an amicable agreement approved by the Minister responsible for Industrial Property and the Minister of Public Health, the amount of the royalties will be determined by the District Court. (For more on the French patent system, see appendix H.)

Germany

According to the German pharmaceutical industry trade association, the German pharmaceutical industry's expenditures on R&D rank among the highest in Europe and R&D spending in Germany continuously increased during 1985-99, reaching $3.2 billion in 1999. Thirty-one innovative pharmaceuticals based on new chemical entities were introduced in Germany in 1999, surpassing the long-term average of 29 per year. Moreover, German-based companies launched two new pharmaceutical products on a worldwide basis in 1999.

The German agency responsible for approval of finished medicinal drugs marketed for human use is the Federal Institute for Drugs and Medicinal Devices in Berlin. Industry sources, ranging from trade associations to representatives of multinational companies, state that pharmaceutical approval practices in Germany are considered to be particularly efficient compared with those in most EU countries, leading many drug manufacturers which wish to pursue mutual recognition within the EU to seek initial approval in Germany.

R&D
Costs and Expenditures

The basic process of developing drugs in Germany is similar to that in the United States and other EU countries.[80] The average cost for development of a new drug in Germany is reported to be about $500 million or more over an average R&D period of 8-12 years.[81] Moreover, thousands of compounds must be screened in order to determine and focus on the development of one particular drug, which may or may not be successfully introduced into the marketplace.[82] As in the United States and most other EU countries, the fundamental R&D phases (basic research, preclinical trials, and three phases of clinical trials) are followed by the market authorization and approval process.[83]

The German pharmaceutical industry's expenditures on R&D rank among the highest in Europe. R&D spending in Germany increased continuously during 1985-99, although the rate of increase slowed over the period. In 1999, the R&D expenditures of 36 research-based pharmaceutical companies operating in Germany totaled $3.2 billion, representing an increase of 8.3 percent from the previous year. R&D expenditures increased by about 22 percent during 1996-99 compared with a fourfold increase in R&D spending during 1985-94. Approximately half the costs for R&D drug development are incurred during clinical testing.[84] Pharmaceutical R&D spending averaged about $210,000 per R&D employee, or 50 percent more than that in other German industry sectors.[85]

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[80] Commission staff telephone interviews with various private companies and trade groups in Germany.
[81] Ibid.
[82] EFPIA, *The Pharmaceutical Industry in Figures,* p. 21.
[83] Commission staff telephone interviews with various private companies and trade groups in Germany.
[84] *Statistics 2000,* Verband Forschender Arzneimittelhersteller (VFA), Berlin, July 2000, pp. 25-37.
[85] Ibid., p. 25.

Thirty-one innovative pharmaceuticals based on new chemical entities were introduced in Germany in 1999,[86] surpassing the long-term average of 29 per year. Moreover, German-based companies launched two new pharmaceutical products on a worldwide basis in 1999. According to representatives of the German pharmaceutical industry association, Verband Forschender Arzneimittelhersteller, products launched by the U.S. industry worldwide accounted for about 34 percent of the total (11 products).[87]

Drug Approval Process[88]

Pharmaceutical products must be approved for use by the Federal Institute for Drugs and Medicinal Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) before they can be placed on the market in Germany. During the approval process, data concerning the product's quality, efficacy, and safety are reviewed. BfArM requires renewal of product authorizations after 5 years, requiring another application and review.

The review process for product authorization can take anywhere from 7-24 months; generics are generally approved in less time than innovative products. Germany's pharmaceutical approval practices are considered to be particularly efficient compared with those in most EU countries, leading many drug manufacturers who wish to pursue mutual recognition within the EU to try to seek initial approval in Germany.[89]

Patents

The term of a patent and SPCs

The term of a German patent is 20 years, beginning on the day after the filing date of the application for patent. To keep the patent in force for its full term, the patent owner must pay annual maintenance fees for the third year and each subsequent year after the filing date of the application. It is possible, however, for payment of the fees to be postponed because of the patentee's financial situation.

Germany has implemented the European Community Council Regulation on the Supplementary Protection Certificate and thus provides SPCs for patented products that have been subject to an administrative procedure for market clearance. The same rights, obligations, and limitations that apply to the patent apply to the certificate. The patent owner must apply for an SPC within 6 months after obtaining authorization to market the product. The certificate will take effect at the end of the patent term for a period equal to the amount of time that passed between the filing of the application for patent and the date of the marketing authorization,

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[86] According to representatives of the VFA, these new chemical entities refer primarily to new drugs developed outside of Germany and subsequently approved for use in Germany.

[87] *Statistics 2000,* pp. 25-37.

[88] Information obtained from Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medicinal Devices (BfArM)) found at *http://www.bfarm.de/gb_ver/drugs/* and retrieved on July 23, 2000. Information was also obtained from a Commission staff telephone conversation with a representative of BfArM on Oct. 19, 2000.

[89] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on August 3, 2000.

reduced by a period of 5 years. The duration of the certificate cannot exceed 5 years. Hence, the protection period for innovative medicinal products can be extended to a maximum of 15 years.[90]

Working a patent and compulsory licensing

German patent law does not impose a required term for working a patent before a person can seek compulsory licensing of the patent. If it is indispensable to the public interest, the Government can issue a compulsory license for exploiting an invention when the applicant for patent or the patent holder has refused to permit such exploitation by another person who offered to pay the patent holder reasonable compensation and to furnish security therefor. German patent law also provides that, except as otherwise required by an international agreement, a patent can be forfeited if it is exclusively or mainly exploited outside of Germany. The forfeiture cannot occur, however, until more than 2 years after a final decision granting a compulsory license for the patent and then only if the public interest can no longer be satisfied by the grant of compulsory licenses.[91] Proceedings for the grant of a compulsory license or for the forfeiture of a patent must be instituted by bringing a legal action against the patentee in the Patent Court. Review by the Federal Court of Justice may be possible. The parties may be eligible for legal aid in the proceedings before the Patent Court and the Federal Court of Justice. (For more on the German patent system, see appendix H.)

[90] Information obtained by Commission staff via e-mails from representatives of the German Patent and Trade Mark Office received during Sept.-Oct. 2000. According to one of the e-mails, dated Oct. 13, 2000, "the above mentioned Regulation did not have to be particularly implemented and transformed into German law for it is automatically binding in its entirety and directly applicable in Germany as well as in every Member State of the EU."

[91] These restrictions do not apply, however, in the case of nationals of a foreign state that does not grant reciprocity in this respect.

Italy

Industry sources in Italy state that levels of R&D investment and expenditures before 1978 were low because Italy had no patent protection for pharmaceuticals until that year. Once the national patent system was implemented, however, R&D investments increased by a factor of four during the next 10 years. Although, according to EFPIA, the industry's R&D expenditures increased continuously through 1999, such expenditures are lower than many of the other countries covered in this study.

Italy began to alter its method of testing new pharmaceuticals in 1993, and requirements continue to evolve today. According to one source, products were often approved before 1993 on the basis of preclinical in-vitro and in-vivo tests and on clinical evaluation models; currently, evidence-based medicine is required.

R&D Costs and Drug Approval Process

Italy had no patent law regarding pharmaceuticals until 1978, significantly deterring R&D investment in the country. As a result, the Italian pharmaceutical industry generally focused on producing copies of nonpatented drugs.[92] However, R&D has increased significantly since Italy's institution of strong patent laws in 1978, when $145 million[93] was invested in pharmaceutical R&D. By 1988, over four times as much was invested, and the amount continued to increase,[94] reaching about $835 million in 1999.[95] Nevertheless, such expenditures were low relative to those of other EU members[96] and, as reflected in table 1-2, were among the lowest of the countries covered in this report.[97]

Pharmaceutical products are approved in Italy by the Commissione Unicadel Farmaco (CUF) in the Ministry of Health, which issues a license known as the Direzione-Generale dei Servizi Farmaceutici. Until the mid-1990s, authorization was granted in an average of 8-10 months, and in some instances could take 2 years. The promulgation of the EU's 1998

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[92] Sigma-Tau Pharmaceutical website, found at *http://www.sigma-tau.it/english/Deval.htm* and retrieved on July 31, 2000.

[93] Using 1978 conversion rates, as reported by IMF International Finance Statistics.

[94] Farmindustria Indicatori Farmaceutici, 1994, quoted in PhRMA's *Global Industry Patent Protection*, found at *http://www.phrma.org/publications/industry/profile00/chap8.html#9* and retrieved on July 27, 2000.

[95] Over half of Italian R&D is invested in Lombardy, near Milan. *European Health Care Systems and Pharmaceutical Markets*, Arzneimittel Zeitung 1995. In 1998, 285 pharmaceutical companies operated in Italy, many of which were very small operations; of the total, 150 Italian pharmaceutical companies employed 50 workers or fewer, 50 had over 250 employees. EFPIA, *The Pharmaceutical Industry in Figures*, p. 34.

[96] EFPIA, *The Pharmaceutical Industry in Figures*, p. 20.

[97] R&D expenditure data for Mexico and Russia were not available. However, as noted in table 1-2, R&D in Mexico is conducted largely at the Mexican Centre of Pharmaceutical Development and Research, a joint government/industry venture funded by hospitals, universities and research centers. Most Russian companies reportedly do not conduct primary research.

Transparency Directive[98] was intended to shorten authorization times.[99] According to a representative of EFPIA, although the EU mandates that member States have 210 days to nationally authorize a drug, the actual times may vary; no data are reportedly available regarding actual times.[100]

Italy began to alter its method of testing new pharmaceuticals in 1993, and requirements continue to evolve today. Before 1993, products were often approved on the basis of preclinical in-vitro and in-vivo tests and on clinical evaluation models. Currently, evidence-based medicine is required, and companies which received approval for their products using old methods may have to provide the CUF with new documents in order to maintain their approval.[101]

Patents

The term of a patent and SPCs

The term of an industrial invention patent is 20 years, measured from the filing date of the application for patent. To keep the patent in force for its full term, the patent owner must pay annual maintenance fees after the patent is granted. If the inventor is indigent, those fees may be suspended for the first 5 years of the patent term.

Upon application to the Italian Patent and Trademark Office, a patent owner can obtain an SPC extending the duration of the patent rights for inventions of medicines (or plant health products) in order to compensate for time lost between the date of the patent application and the authorization for marketing of the patented product. The period of supplementary protection provided by the certificate is measured from the expiration of the patent and is equivalent to the time that elapsed between the date of the patent application and the authorization for marketing of the product, minus 5 years. The term of the supplementary protection cannot exceed 5 years, however. An application for a certificate must be filed within six months from the date of the initial Ministerial Order authorizing marketing of the patented medicine (or plant health product), and must be accompanied by a receipt for payment of the prescribed fee.

Working a patent and compulsory licensing

Italian patent law requires that an industrial invention patent be worked in the territory of Italy to an extent that is not disproportionate to the needs of Italy. An exhibition of patented articles held in the territory of Italy for at least 10 days or for the entire duration of the exhibit (if it was less than 10 days) constitutes a working of the patent. However, the introduction into or sale in Italian territory of articles manufactured abroad does not constitute working.

Three years after a patent was granted or 4 years after the filing of the application for patent, if the latter date expires after the former one, the Italian Patent and Trademark Office can issue a compulsory license to an interested party who has applied for the license if any of the

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[98] Directive 98/48/EC.

[99] *Financing Health Care, Vol. 1*, p. 555.

[100] Commission staff telephone interview with a representative of EFPIA on Oct. 25, 2000.

[101] Pharmaceutical and Healthcare Industry News Database, 1999, found at *http://quicksearch.profound.com/ cg...74,FM=0,SEARCH=EW.PharmNewsletters* and retrieved on Aug. 2, 2000.

following circumstances exist: (1) The patent has not been worked, or has been worked to an extent disproportionate to the needs of the country, in production in Italy or importation from EU or World Trade Organization (WTO) member-countries; (2) for more than 3 years, the working of the patent has been suspended or reduced to an extent that is greatly disproportionate to the needs of the country; or (3) the patented invention cannot be used without prejudice to the rights of a patent granted on an application of prior date, and the invention of the later patent is a marked technical progress in the subject matter of the two patents. The applicant for a compulsory license must demonstrate that he was unable to obtain a voluntary license from the patent owner on equitable terms and conditions.

The Italian Patent and Trademark Office will not grant a compulsory license if the failed or inadequate working of the patent was caused for reasons beyond the control of the patent owner or his licensee. Lack of financial means and the lack of domestic demand, if the patented product is traded abroad, are not included among such reasons. If a compulsory license is granted, the licensee must pay the patent owner equitable remuneration. The decree granting the license will specify, among other things, the amount and the payment formalities.

An Italian patent can lapse if the patented invention is not exploited, or is not exploited sufficiently for the needs of Italy, within 2 years of the grant of the first compulsory license. (For more on the Italian patent system, see appendix H.)

United Kingdom

In the UK, pharmaceuticals are licensed by the Department of Health's Medicines Control Agency. Industry sources state that the UK's pharmaceutical approval practices are considered to be particularly efficient compared with those in other EU countries, leading many drug manufacturers which wish to pursue mutual recognition within the EU to try to seek initial approval in the UK.

R&D Costs and Drug Approval Process

In 1997, pharmaceutical R&D expenditure in the UK accounted for 8.6 percent of the global R&D expenditure, or about $3.8 million.[102] In 1998, 375 pharmaceutical companies operated in the UK,[103] and in 1999 it produced 19 of the world's 35 largest-selling drugs.[104] Pharmaceutical R&D totaled $4 billion in 1999, accounting for nearly 25 percent of all industrial R&D spending in the UK.[105] In the late 1990s, pharmaceuticals were the UK's largest manufactured export.[106] Unlike the status in many manufacturing sectors, the UK maintains a trade surplus in pharmaceuticals; in 1999, its pharmaceutical trade surplus was $4.2 billion.[107]

The UK's pharmaceutical licensing body is the Medicines Control Agency (MCA). In cooperation with the Committee on the Safety of Medicines, the MCA commissions and oversees clinical trials,[108] and ultimately grants product licenses. UK pharmaceutical approval practices are considered to be particularly efficient compared to other EU countries. Median approval time for new pharmaceuticals (including clinical trials) decreased during 1995-97, from a median of 18 years in 1995 to a median of 15 years in 1997.[109] This relatively short approval time has led many leading drug manufacturers which wish to pursue mutual recognition within the EU to seek initial approval in the UK.[110] In regard to postclinical review and authorization, according to a representative of EFPIA, the EU mandates that member States have 210 days to

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[102] Centre for Medicines Research, *International Report: Profile on the UK Pharmaceutical Industry in 1997 and 1998*, London, 1999, p. 4.

[103] EFPIA, *The Pharmaceutical Industry in Figures, 2000*.

[104] From Canadian Department of Foreign Affairs and International Trade website, found at *http://www.dfait-maeci.gc.ca/english/geo/europe/84216-e.htm* and retrieved on Sept. 20, 2000.

[105] Ibid.

[106] Burstall, Michael L., Bryan Reuben and Anthony Reuben, "Pricing and Reimbursement Regulation in Europe: an Update on the Industry Perspective," *Drug Information Journal*, Vol. 33, 1999, p. 669.

[107] From Canadian Department of Foreign Affairs and International Trade website, found at *http://www.dfait-maeci.gc.ca/english/geo/europe/84216-e.htm* and retrieved on Sept. 20, 2000.

[108] Individual clinical trials are conducted in accordance with those guidelines agreed upon by the EU, United States, and Japan at the International Conference on Harmonisation, and have been in place throughout the EU since June 1995. Anne Thyer, Medicines Control Agency, found at *http://www.socialaudit.org.uk/ 437391GG.htm* and retrieved Sept. 20, 2000.

[109] Centre for Medicines Research, *International Report: Profile on the UK Pharmaceutical Industry in 1997 and 1998*, p. 4.

[110] Maryann Slater, Foreign Service Commercial Officer, US Embassy, London, telephone conversation with Commission staff July 27, 2000, and Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

nationally authorize a drug. The actual times, however, may vary; no data are reportedly available regarding the actual times.[111]

One perceived drawback of the UK process, however, is its relative lack of transparency. Section 118 of the Medicines Act 1968 prevents authorities from disclosing any information about the process, and thus UK doctors are able to receive less information about approved drugs' clinical trial histories than doctors in the United States.[112] While there is no proof that doctors prescribe certain drugs less because they lack this information, the strict confidentiality of the UK's system remains controversial.[113]

Patents

The term of a patent and SPCs

The term of a UK patent is 20 years, measured from the filing date of the application for patent or such other date as may be prescribed in a rule approved by resolution of each House of Parliament. To keep the patent in force for its full term, the patent owner must pay an annual renewal fee, commencing at the start of the fifth year after the patent was granted. Although the UK patent statute makes no provision for extension of the term of a patent, the UK does issue SPCs to allow for an additional period of market exclusivity to offset delays incurred during the approval process.[114]

Working a patent and compulsory licensing

Three years after a patent is granted, or such other period as may be prescribed, any person may apply to the Comptroller of the UK Patent Office for a nonexclusive compulsory license under the patent.[115] The circumstances under which such a license may be granted depend in part on the nationality or domicile of the proprietor of the patent.

If the proprietor is a national of or is domiciled in a country that is a member of the WTO, the following are the permissible grounds for seeking a compulsory license: (1) the patented invention is a product for which demand in the United Kingdom is not being met on reasonable terms; (2) the proprietor has refused to grant a voluntary license on reasonable terms and the exploitation of another patented invention in the United Kingdom involving an important technical advance of considerable economic significance is being prevented or hindered, or the establishment or development of commercial or industrial activities in the United Kingdom is being unfairly prejudiced; or (3) because of conditions imposed by the proprietor on the grant of licenses under

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[111] Commission staff telephone interview with a representative of EFPIA on Oct. 25, 2000.

[112] House of Commons Hansard Debates for 15 January, 1993, found at *http://www.parliament.the-stationery-office.co.uk/pa/cm199293/cmhansrd/1993-01-15/Debate-4.html* on September 20, 2000.

[113] "Straw Bill is Little Use Against Drug Secrecy," *The Guardian*, September 20, 1999, found at *http://www.guardianunlimited.co.uk/freedom/Story/0,2763,201196,00.html* and retrieved on Sept. 20, 2000.

[114] "Supplementary Protection Certificates for Medicinal and Plant Protection Products," found at *http://www.patent.gov.uk/dpatents/mpp/pdfs/spcs.pdf*, and retrieved on Sept. 15, 2000; and "Supplementary Protection Certificates for Medicinal and Plant Protection Products: A Guide for Applicants (Revised January 1997)," found at *http://www.patent.gov.uk/forms/supp/pdfs/spctext.pdf*, and retrieved on Sept. 15, 2000.

[115] Inventions in the field of semiconductor technology are exempt from compulsory licensing.

the patent, the disposal or use of the patented invention, the manufacture, use, or disposal of materials not protected by the patent, or the establishment or development of commercial industrial activities in the United Kingdom is being unfairly prejudiced.

A compulsory license, if granted, will be predominantly for the supply of the market in the United Kingdom and will include conditions entitling the proprietor of the patent concerned to remuneration adequate in the circumstances, taking into account the economic value of the license.

If a compulsory license is requested for a patent whose proprietor is not a national or resident of a country that is a member of the WTO, the following are the permissible grounds for seeking the license: (1) The patented invention is capable of being commercially worked in the United Kingdom, but is not being so worked or is not being worked to the fullest extent reasonably practicable;[116] (2) the patented invention is a product and demand for it in the United Kingdom is not being met on reasonable terms or is being met to a substantial extent by importation from a country that is not a member State of the WTO; (3) the patented invention is capable of being commercially worked in the United Kingdom, but is being prevented or hindered from being so worked by the importation of a product from a country that is not a member State or, if the patented invention is a process, by the importation of a product obtained directly by means of that process from a country that is not a member State.

A compulsory license also may be sought if, by reason of the patent proprietor's refusal to grant a license on reasonable terms, (1) a market for export of any patented product made in the United Kingdom is not being supplied,[117] (2) the working or efficient working in the United Kingdom of any other patented invention which makes a substantial contribution to the art is being prevented or hindered, or (3) the establishment or development of commercial or industrial activities in the United Kingdom is being unfairly prejudiced. A compulsory license also may be sought if the manufacture, use, or disposal of materials not protected by the patent or the establishment or development of commercial or industrial activities in the United Kingdom is being unfairly prejudiced by the patent proprietor's conditions for the grant of licenses under the patent, the disposal or use of the patented product, or the use of the patented process.

If the Comptroller is satisfied that the manufacture, use, or disposal of materials not protected by the patent is unfairly prejudiced by reason of conditions imposed by the proprietor of the patent on the grant of licenses under the patent, or on the disposal or use of the patented product or the use of the patented process, he may order the grant of compulsory licenses under the patent to appropriate customers of the applicant as well as to the applicant.

Decisions on compulsory licensing may be subject to judicial review and may be the subject of arbitration. The Queen may, by Order in Council, prohibit the Comptroller from granting a compulsory license, except for purposes of the public interest, if the patented invention

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[116] If the Comptroller believes that insufficient time has elapsed for the invention to be so worked, he may postpone action on the application for a compulsory license for such period as he thinks will give sufficient time for the invention to be so worked. In addition, a compulsory license will not be ordered if the patented invention is being worked in a country that is a member State of the WTO and demand in the United Kingdom is being met by importation from that country.

[117] Any compulsory license granted on this ground will contain provisions that appear to be expedient for restricting the countries in which any product concerned may be disposed of or used by the licensee.

is being commercially worked in any relevant country [118] specified in the Order and demand in the United Kingdom for any patented product resulting from that working is being met by importation from that country. (For more on the UK patent system, see appendix H.)

[118] A "relevant country" is a country other than a member state or a member of the WTO whose law, in the Queen's opinion in Council, incorporates or will incorporate provisions treating the working of an invention in, and importation from, the United Kingdom in a similar way to that which the Order in Council would (if made) treat the working of an invention in, and importation from, that country.

Japan

Over 400 relatively small manufacturers focus primarily on serving Japan's domestic market, the second largest in the world. Exports are small, but in spite of a difficult business climate, according to PhRMA, Japanese firms have achieved success in global markets. Their current share of consumption within the global market is 15 percent.

JPMA states, however, that the recently adopted Good Clinical Practice guidelines have significantly affected the Japanese medical community's ability to conduct acceptable clinical trials. According to one U.S. government source, the industry's immediate response has been to move clinical trial operations offshore.

In 1998, 82 innovative pharmaceutical companies were operating in Japan,[119] most of which were small compared with global competitors. According to PhRMA, the Japanese companies have been perceived to be harder to rationalize and, thus, have been less likely than their global counterparts to consolidate.[120] This is changing, however. Four Japanese companies were acquired by foreign firms in 1999 and more acquisitions are expected as foreign companies strengthen their positions in the Japanese market, the second largest in the world.[121] Japanese pharmaceutical wholesalers have also been consolidating in recent years, decreasing from 579 in 1979 to 260 in 1997.[122]

R&D and the Drug Approval Process

The Japanese pharmaceutical industry has focused primarily on its domestic market; products of Japanese origin have consistently accounted for about 60 percent of that market.[123] In the early 1980s, however, the Japanese Government selected Japan's pharmaceutical industry for international expansion as the pharmaceutical industry was considered to be knowledge-intensive and resource-thrifty.[124] Despite adverse economic conditions in the early 1990s,[125] a difficult regulatory environment, and the lack of an international marketing infrastructure, Japanese companies have been relatively prolific in creating new drugs. Of the 265 drugs developed in the global market during 1970-92, Japan originated 29, second only to the United

[119] This is the number of companies belonging to JPMA, the innovative industry trade association.

[120] Commission staff interview with representatives of PhRMA on July 25, 2000.

[121] Benjamin Fulford, "Shakeout in Tokyo," *Forbes*, May 1, 2000, p. 94.

[122] JPMA paper, "Distribution System," found at *http://www.jpma.or.jp/12english/05sales/e-dist.html* and retrieved on July 19, 2000.

[123] USITC, *Global Competitiveness*, publication 2437, p. 4-8. The United States is Japan's biggest trading partner for pharmaceuticals and, in 1998, accounted for 36 percent of Japanese exports and provided 23 percent of Japanese imports. JPMA, *Data Book 2000*, p. 1-18

[124] USITC, *Global Competitiveness*, publication 2437, p. 3-21.

[125] McKinsey Global Institute (MGI), "Why the Japanese Economy Is Not Growing," retrieved July 27, 2000.

States during the same period;[126] drugs originated by the Japanese industry (e.g., Pravastatin and Famotidine) are ranked among the top-selling drugs globally.[127]

R&D Costs and Expenditures

In 1998, total R&D expenditures for the Japanese pharmaceutical industry were $5.2 billion.[128] After increasing from $5.1 billion in 1992 to $6.8 billion in 1995, the industry's R&D expenditures declined to $6.1 billion in 1996 and to $5.3 billion in 1997. In terms of individual company expenditures, Takeda, the leading Japanese pharmaceutical firm, invested $546 million in R&D in 1998, compared with an average R&D expenditure of $197 million for the 20 leading Japanese firms.[129] According to a representative of PhRMA, the average cost of developing an innovative pharmaceutical product in Japan is about $280 million.[130]

Drug Approval Process

Review times for NDAs in Japan have been much longer than in the United States or Europe[131] because Japan lacked a standardized review process. Industry sources indicate that in the past approvals generally took from 30 to 36 months but, in some cases, up to 48 months. Under the U.S.-Japan Enhanced Initiative for Deregulation and Competition (Enhanced Initiative),[132] Japan

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[126] William P. Looney, *Japan's Health Care System Today: New Challenges and New Opportunities*, Pharmaceutical Research and Manufacturers of America, Aug. 1997, p. 7.

[127] PhRMA, "PhRMA Proposal for NHI Drug Pricing Reform-Supporting Arguments," p. 26.

[128] The Japanese Government allocates less to medical research than does the United States but nonetheless spearheaded efforts to map the human genome in the late 1980s. Their subsequent research efforts suffered from underfunded research facilities as adverse economic conditions precluded further expenditure. Lack of expertise, inflexible funding mechanisms, and bureaucratic rivalries also hampered progress. Robert Triendl, "Absent Pioneer," *Far Eastern Economic Review*, July 13, 2000, p. 44.

[129] Japanese Pharmaceutical Manufacturers Association (JPMA), *Data Book 2000*, pp. 1-35, 2-19. Industry sources note that average R&D expenditures for the twenty leading global firms amounted to $1.7 billion.

[130] Information obtained by Commission staff via e-mail, dated Sept. 26, 2000, from a representative of PhRMA.

[131] The U.S. pharmaceutical industry continues to express concern about the barriers inherent in the Japanese pharmaceutical market. According to PhRMA, a drug "lag" has developed in which 130 out of 230 products launched world-wide since 1985 remained unavailable in Japan by 1997. Of the 130 unavailable products, 90 are in the clinical trial process currently, but 40 are not being tested at all. Five of the 10 top-selling drugs worldwide are not yet available in Japan. See PhRMA, "PhRMA Proposal for NHI Drug Pricing Reform–Supporting Materials for Presentation" Jan. 29, 1999 p. 14, and MGI, "Why the Japanese Economy Is Not Growing," retrieved July 27, 2000, p. 66.

[132] Office of United States Trade Representative, *2000 National Trade Estimate Report on Foreign Trade Barriers*, p. 191, found at *http://www.ustr.gov/reports/nte/2000/nte2000.pdf* and retrieved on July 14, 2000. The pharmaceutical industry was included in the U.S.-Japan Enhanced Initiative for Deregulation and Competition (Enhanced Initiative). The process began in 1997 to address regulatory and anti-competitive barriers for both foreign and domestic firms in Japan, and in 1998 the MHW made four commitments to facilitate market access to be finalized by April 1, 2002. They were as follows: (1) to recognize the value of innovation so as not to impede the introduction of new, more efficient, cost-effective products, (2) to ensure impartiality by allowing foreign manufacturers opportunities to state their opinions in the relevant councils on an equal basis with Japanese manufacturers and by providing opportunities to exchange views with MHW officials at all levels, (3) to shorten the approval process for

(continued...)

committed to reduce the approval period to 12 months as of April 2000. Other structural reforms have been made including the addition of reviewers; institution of a new team-review system that permits continuous and direct communication between reviewers and applicants; allowance for the continuation of clinical trials during the review process; and the elimination of the mandatory number of clinical trials.

The Ministry of Health and Welfare (MHW) is in charge of pharmaceutical regulatory affairs in Japan. During a reorganization in July 1997, the old Pharmaceutical Affairs Bureau was replaced by a new regulatory system that includes three parts; the Pharmaceutical and Medical Safety Bureau (PMSB), the Pharmaceutical and Medical Devices Evaluation Center (Evaluation Center) and the Organization for Pharmaceutical Safety and Research (Drug Organization).[133] Through these groups, the new organization handles activities from clinical trials through new drug application (NDA) approvals to postmarketing studies. Figure 3-4 summarizes the new, standardized process of approval for new prescription products resulting from the reorganization. NDAs are filed with the Evaluation Center. The Drug Organization checks the reliability of data and reviews the application for Good Clinical Practice (GCP) compliance. Next, a detailed review by an appropriate expert team at the Evaluation Center is undertaken. Applications are forwarded to the New Drug Expert Committee of the Central Pharmaceutical Affairs Council (CPAC) which is an advisory council to the MHW. Various committees of CPAC are consulted as required, and the application is discussed by the executive committee of CPAC. Finally, the minister of MHW conducts a final approval review and grants approval.

In the 1990's, Japan participated with the United States and the EU in the International Conference on Harmonization (ICH).[134] One result of the ICH was to increase the international utilization of clinical trial data,[135] thereby eliminating duplicate effort and allowing for the more rapid introduction of better drugs. Other topics included maintaining guidelines with the latest advances in technology and creating common technical documents for new drug applications.[136]

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[132] (...continued)
NDAs to 12 months by April 2000 and to speed the introduction of innovative pharmaceuticals, and (4) to expand acceptance of foreign clinical tests through the incorporation of ICH guidelines into Japanese regulations (by August 1998) and adopt an acceptance process that is transparent and void of inappropriate delays.

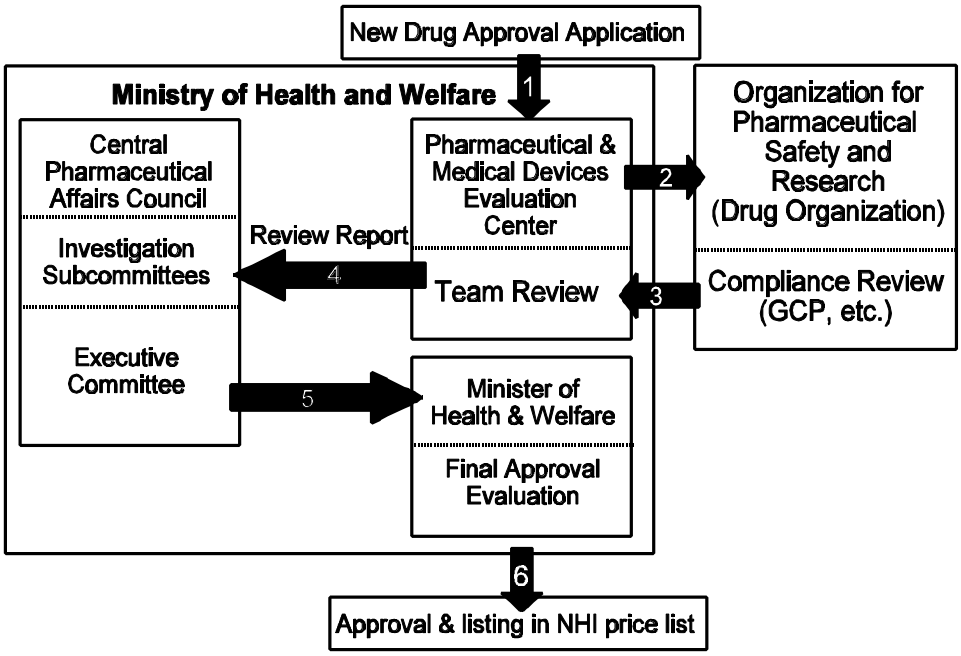
[133] JPMA, "1999 Pharmaceutical Administration and Regulations in Japan" retrieved July 12, 2000, p. 1.

[134] Restrictive regulations had in the past limited market access by foreign manufacturers of pharmaceuticals. This changed, however, as a result of various bilateral and multilateral initiatives. For example, the bilateral Market-Oriented Sector Selective (MOSS) talks in the mid-1980s changed regulations in place until then that prevented foreign manufacturers from applying for drug approvals on their own. Subsequent multilateral initiatives, such as the ICH and the Enhanced Initiative, addressed numerous issues, including clinical trials. For example, until the latter initiatives, foreign firms were handicapped by MHW requirements that all clinical testing on new drugs be done in Japan on resident Japanese citizens, which necessitated time-consuming and expensive duplication of clinical trials.

[135] JPMA, "1999 Pharmaceutical Administration and Regulations in Japan," retrieved July 12, 2000, p. 24.

[136] JPMA paper, "ICH Guidelines," found at *http://www.jpma.or.jp/12english/04newdrug/e-ich.html* and retrieved July 12, 2000.

Figure 3-4
New Drug Development and Approval



Source: JPMA, *1999 Pharmaceutical Administration and Regulations in Japan*. Reprinted with permission.

The GCP standards promulgated by the ICH in May 1996 and accepted by Japan in August 1998 have had a negative impact on Japan's ability to conduct research and development and present the Japanese medical community with a formidable challenge.[137] The new standards are completely different from previous Japanese practices for participants and the medical service providers that conduct such trials. For example, before the GCP standards were adopted, participants in Japanese clinical trials were allowed to provide informed consent orally. Now, written informed consent is required.[138]

Medical service providers that conduct clinical trials have already had difficulty meeting the new standards. Medical providers are now required to hire and train the clinical research coordinators and technical and support staff needed to conduct clinical trials which meet GCP standards.[139] The industry's immediate response to the new standards has been to move clinical trial operations offshore. Larger Japanese pharmaceutical firms (e.g., Takeda, Fujisawa, and Tanabe) have established clinical trial operations in the United States because medical facilities in Japan are not yet capable of undertaking clinical trials which meet GCP guidelines.[140]

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[137] Osamu Ebi, "Trends in the NDA Review Period and Facilitating Clinical Trials," *Update*, Vol. 16, found at *http://www.jpma.or.jp/12english/07publications/up016/e-up16-03.html*, and retrieved July 14, 2000.

[138] Kazutaka Ichikawa, "Recent Changes in Pharmaceutical Regulation," *Update*, Vol. 14 found at *http://www.jpma.or.jp/12english/07publications/up014/e-up14-04.html*, and retrieved July 14, 2000.

[139] Osamu Ebi, "Trends in the NDA Review Period and Facilitating Clinical Trials."

[140] Commission staff telephone interview with a representative of the U.S. Department of Commerce on July 17, 2000.

Patents

The Term of a Patent

The term of a Japanese patent is 20 years, measured from the filing date of the application for patent. The patentee must pay annual fees to keep the patent in force for its full term. The fee consists of a flat rate for each year of the term, plus an additional amount for each claim of the patent. The annual fee may be reduced, deferred, or waived, however.

With certain limitations and on the basis of an application filed with the Japanese Patent Office, the term of a Japanese patent may be extended for up to 5 years if it was not possible for the patentee to work the patented invention for 2 years or more owing to the necessity of obtaining approval or another disposition required by law to ensure safety in the working of the invention. The extension can be denied if the prescribed requirements are not met or if the requested extension exceeds the period during which the patented invention could not be worked.

Working a Patent and Compulsory Licensing

If a patented invention has not been sufficiently and continuously worked for 3 years or more in Japan, a person who intends to work the invention may request a nonexclusive license from the patentee (or the exclusive license holder, if any). The request cannot be made unless at least 4 years have passed since the filing of the application for patent. If the person and the patentee (or exclusive license holder) are unable to reach an agreement, the person who wishes to work the patented invention may ask the Japanese Patent Office for an arbitration decision on the matter. If there is a legitimate reason for the failure to sufficiently work the patented invention, the Japanese Patent Office will not grant a license. If the Japanese Patent Office grants the license, it will specify the consideration and the time and method of payment.

When the working of a patented invention is particularly necessary in the public interest, a person who intends to work the invention may ask the patentee (or the exclusive licensee, if any) for a nonexclusive license. If no agreement is reached, the person may ask the Minister for Trade and Industry for an arbitration decision on the matter. If the Minister finds that there is a legitimate reason for the failure to sufficiently work the patented invention, the Minister will not grant the license. If the Minister decides to grant the license, he will specify the consideration and the time and method of payment.

A person also may be entitled to a nonexclusive license by virtue of his prior use of the patented invention. A person is entitled to such a license if, when the application for patent was filed, that person had made an invention by himself without knowledge of the contents of the application, or learned the invention from another individual who made the invention by himself, or was commercially working the invention in Japan or making preparations therefor. (For more on the Japanese patent system, see appendix H.)

Mexico

According to one study, although domestic and multinational companies are involved in most phases of the Mexican pharmaceutical industry (R&D, manufacturing, and marketing), the domestic industry typically relies on product innovation that has been developed and imported by multinational firms. The Inter-Secretarial Commission of the Pharmaceutical Industry is responsible for overseeing the pharmaceutical industry and registering manufacturers.

In Mexico, prescription products include patented, generic, and "copy" products. According to a source in Mexico, generics are considered to be a rising market; copy products continue to pose a concern for U.S. firms (especially along the U.S.-Mexican border) as they continue to drive down the Mexican prices of prescription drugs manufactured by the original innovator.

Pharmaceuticals in Mexico

As in the United States, pharmaceuticals in Mexico are available either by prescription or as nonprescription (over-the-counter (OTC)) drugs. Many of the prescription products are patented, or innovative, pharmaceutical products. Generics and so-called copy products, also available by prescription, also are marketed in Mexico.[141] Historically, generics have not had a large share of the Mexican market, in part because of the relatively low prices of available patented products, the public's lack of understanding (and thus trust) of generics, and their reported record of poor performance; however, these trends may be slowly changing.[142] Generics are considered a rising market in Mexico (currently with a small profit margin) and, as a result of a change in health legislation in 1997, generics, previously only available through the public sector, became commercially available to the private sector for the first time.[143]
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Copy products, the result of weak patent protection that existed before 1991, have further limited the past need for generics. Copy products are very common in the Mexican market, particularly along the U.S.-Mexican border. They offer competition in the Mexican marketplace since they are generally offered at a lower price than the products manufactured by the original innovator. Copy products continue to be a major concern for U.S. companies which contend that they are losing market share because intellectual property rights are being

[141] A generic version of an innovative pharmaceutical product can be legally launched following the expiration of the patent on the innovative product; a copy product is one in which the original innovative product is still under patent in other countries.

[142] It is important to note that the Mexican Government has not been involved in manufacturing generics, unlike some other Latin American countries. NERA, *Mexico*, p. 81.

[143] Commission staff interview with U.S. Commercial Service representative (Mexico) on July 24, 2000. In addition to this legislation the Mexican Government is now publishing a registry (or standard) that contains new labeling for generic drugs that specifies their claims. The representative further states that Mexican physicians prescribe a generic drug first (by law) and subsequently the patented drug.

violated.[144] Further, U.S. pharmaceutical companies contend that U.S. citizens are at risk of jeopardizing their health and safety purchasing drugs which may not be safe or effective.[145]

In February 1998, the Mexican government published the Regulation for Health Products that further describes the guidelines used by the Secretariat of Health (SSA), or the Ministry of Health, to control the medicaments, vitamin and herbal products, medical equipment, supplies, and other health related products and services.[146] In some cases, vitamins and herbal supplements are classified as pharmaceuticals in Mexico, subjecting them to more restrictive testing, registration, and marketing regulations.[147] For example, the Mexican Government requires inspection and approval of manufacturing facilities in order to import and market vitamins, but will not conduct inspections in facilities outside of Mexico.[148] U.S. companies with production facilities in Mexico can obtain the sanitary license necessary to import and market vitamins in Mexico. Mexico continues to offer a good market for U.S. vitamins, nutritional supplements, and herbal products with a total estimated market for these products of over $520 million, and estimated annual growth of 15 percent for the next few years.[149]

R&D Costs and Drug Approval Process

Since 1991, Mexico has been, for the most part, self-sufficient in pharmaceutical production.[150] Both domestic and multinational companies research, develop, manufacture, and market pharmaceuticals in Mexico.[151] The government of Mexico points out a steady upward trend of foreign direct investment in the pharmaceutical industry.[152]

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[144] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[145] Ibid. The author of a recent journal article notes that the Mexican market has had a long-standing problem with effective regulation and enforcement in the pharmacy sector, leading to concerns over safety issues for generic products. The author further states the research sector's argument for tighter controls over how medicines are dispensed and how pharmacists are trained. Currently there is reportedly no legal requirement for pharmacists to have any professional training other than an apprenticeship. Rosalyn Chan, "Mexico: Striking a Balance Between Price and Innovation," *Pharma Pricing & Reimbursement*, PPR Communications Ltd., England, Jan. 2000, p. 22.

[146] Jesus S. Gonzalez, *Industry Sector Analysis (Mexico)*, U.S. & Foreign Commercial Service and U.S. Department of State, May 1999, p. 5.

[147] In the United States, vitamins and herbal products tend to be less regulated because they are considered food supplements.

[148] U.S. Trade Representative, *2000 National Trade Estimate Report on Foreign Trade Barriers*, p. 287.

[149] Gonzalez, Jesus S., *Industry Sector Analysis (Mexico)*, U.S. & Foreign Commercial Service and U.S. Department of State, May 1999, p. 1.

[150] Cantor, David J., *Prescription Drug Price Comparisons: The United States, Canada, and Mexico*, Congressional Research Service Report for Congress, Jan. 23, 1998, p. 4.

[151] NERA, *Mexico*, p. 77. According to the U.S. Foreign Commercial Service, U.S. pharmaceutical firms have had a presence in Mexico for forty to fifty years. The author of a recent journal article states that after the passage of the 1997 legislation the number of generic manufacturers in Mexico increased during 1998-99 from 110 to 160, or by about 45 percent. Rosalyn Chan, "Mexico: Striking a Balance Between Price and Innovation," p. 22.

[152] Mexico's Department of Commerce and Industrial Development's (SECOFI) Office of Directorate General for Foreign Investment notes that foreign direct investment for pharmaceuticals in Mexico increased from $118 million in 1995 to $307 million in 1999. SECOFI's Office of Directorate General for

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R&D Costs

For domestic companies, R&D is conducted largely at the Mexican Centre of Pharmaceutical Development and Research which is a joint government/industry venture funded by hospitals, universities and research centers.[153] The degree of government support, combined with the relatively low prices of pharmaceuticals in Mexico, provides little incentive for domestic companies to invest heavily in R&D. Instead, the domestic pharmaceutical industry typically relies on product innovation that has been developed and imported by multinational firms which accounted for nearly 70 percent of total pharmaceutical industry investment in Mexico in 1991.[154] As a result, most Mexican-owned firms specialize in the manufacture of copy and generic pharmaceuticals.

The Inter-Secretarial Commission of the Pharmaceutical Industry, a part of Mexico's Department of Commerce and Industrial Development (SECOFI), is responsible for over-seeing the pharmaceutical industry and registering manufacturers. On February 4, 1998, the Ministry of Health issued revised regulations on a wide range of health products and services.[155] These regulations explicitly state that in order to manufacture, prepare, mix, package, store, sell, import, export, prescribe, supply, or transport drugs, all companies must receive authorization from the Secretariat. The Regulations also describe the responsibilities and procedures for all establishments involved in all aspects of the manufacture, packaging, and selling of pharmaceuticals.

Drug Approval Process

The Pharmaceutical Control Bureau, under the SSA, is in charge of product registration. Approval is granted on the basis of a variety of factors, including efficacy, safety, and cost effectiveness.[156] On average, the application and approval process in Mexico takes 6-8 months.[157] Most drug manufacturers have few complaints about the speed of the overall approval process in Mexico.[158] However, industry concerns about the scientific thoroughness of testing have been raised; and resource shortages reportedly have, at times, forced the responsible Mexican authorities to subcontract testing to other institutions or prevented them from evaluating certain submitted products.[159] U.S. firms have also expressed concern about the protection of confidential test data during this process.[160]

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[152] (...continued)
Foreign investment, *Foreign Direct Investment in the Chemical Industry*, March 2000, table No. 4.

[153] According to NERA, over 90 percent of the funding for R&D performed by domestic companies comes from the Mexican government, and the total national budget spent on R&D was around $8 million in 1986. NERA, *Mexico*, p. 87 and 88.

[154] U.S. International Trade Commission, *Potential Impact on the U.S. Economy and Selected Industries of the North American Free-Trade Agreement*, USITC pub. 2596, 1993, p. 9-1.

[155] U.S. Foreign Commercial Service and U.S. Department of State Unofficial Translation of Feb. 4, 1998 Ministry of Health Regulations.

[156] NERA, *Mexico*, p. 81.

[157] This estimate by industry sources is based on foreign firms that have already had a manufacturing or distribution facility in place in Mexico for a substantial period of time.

[158] NERA, *Mexico*, p. 81, and Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[159] NERA, *Mexico*, p. 81.

[160] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical
(continued...)

In terms of manufacturing, however, Mexico benefits from a provision of the North American Free Trade Agreement (NAFTA) stipulating 50 percent local content for drugs purchased by the Mexican Government,[161] essentially requiring that pharmaceuticals be manufactured in Mexico in order to be sold in the Mexican market.[162] Although this provision expires in the 2000-01 time frame, U.S. companies tend to feel disadvantaged by this requirement.[163]

Patents

Mexico implemented its intellectual property laws (Ley de Patentes) in June 1991. Under this law, patent protection is in effect for 20 years from the filing date, or 17 years from the date granted upon payment of an annual fee.[164] The law did not provide for retroactive, or "pipeline," patent protection, meaning that all pharmaceuticals that were registered prior to 1991 are subject to competition from copy products.

With passage of the NAFTA, Mexican patent laws were substantially strengthened through regulations that were published in 1994. PhRMA believes that "the NAFTA, specifically Chapter 17, represents the highest standard of intellectual property protection ever achieved by the United States in an international agreement."[165] NAFTA provided legal protection for pharmaceutical patents, including pipeline protection for products that were already patented in the United States but not yet in Mexico. These protections took effect immediately upon implementation of the NAFTA. More recently, however, industry sources have stated that a lack of pipeline protection has been evident.[166]

The Term of a Patent

The term of a Mexican patent is 20 years, starting from the filing date of the application for patent. To keep the patent in force for its full term, the patent owner must pay fees to the government after the patent is granted.

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[160] (...continued)
industry on Aug. 3, 2000.

[161] North American Free Trade Agreement, Texts of Agreement and Implementing Bill, as set forth in the Statement Of Administrative Action and Required Supporting Statement, House Document 103-159, Vol. 1, Dec. 8, 1993, p. 1089.

[162] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000. It is also important to note here that although no formal complaint of WTO obligation violations have been issued against Mexico, a similar case was brought against Brazil by the United States regarding narrow provisions in the TRIPS Agreement (WT/DS199). According to the United States Trade Representative, the United States considers Brazil to be violating the TRIPS Agreement since it requires patent owners to manufacture their products in Brazil in order to maintain full patent rights. This case is currently in the consultation phase under the DSU.

[163] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[164] NERA, *Mexico*, p. 80.

[165] Alan F. Holmer, Testimony before the Subcommittee on Trade Committee on Ways and Means, U.S. House of Representatives, Mar. 18, 1997, found at *www.phrma.org/archive/2-18-97b.html* and retrieved on July 7, 2000.

[166] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

In the case of pharmaceutical products or processes for obtaining such products, the term of the patent may be extended for 3 additional years, provided that the patent holder grants a license to work the patent to a corporate entity with a majority of Mexican capital. The license must be granted in an agreement within 6 months from the grant of the patent or the date on which the competent Government authorities grant the sanitary registration allowing distribution of the product in Mexico, whichever is later.

Working a Patent and Compulsory Licensing

The Mexican patent law does not require that a Mexican patent be worked. However, 3 years from the date of grant of the patent, or 4 years from the filing date of the application, whichever is later, any person may apply for a nonexclusive compulsory license to work the patented invention if it has not been worked, unless there are justified technical or economical reasons for such nonworking. The license will not be granted if the patentee or a voluntary licensee has been importing the patented product or a product obtained by the patented process. Moreover, the patentee will be given 1 year to begin working the patent before a compulsory license will be granted. If such a license is granted, the deciding official will determine the amount of royalties to be paid to the patent holder and the compulsory licensee will have 2 years from the grant of the license to begin working the patent. If the licensee fails, without justification, to satisfy its working requirement, the Government can terminate the compulsory license at the request of the patentee. In addition, the patent can lapse if the patentee does not prove that the patent is being worked, or that there is a justified reason that it is not being worked, 2 years after the compulsory license was granted. (For more on the Mexican patent system, see appendix H.)

Russia

According to one study, development of new pharmaceutical products in Russia requires modernization of production facilities, including the introduction of Good Manufacturing Practice standards. However, the study indicates that new drugs are not likely to be developed in Russia until the patent protection system is strengthened.

Pharmaceuticals in Russia

The pharmaceutical sector was one of the fastest growing industries in the Russian economy, with a compound annual growth rate of 10 percent, prior to the devaluation of the ruble in August 1998.[167] In 1999, the pharmaceutical market in Russia was valued at $1.8 billion,[168] reportedly down from $3.1 billion in 1997.[169] Pharmacies supplied 80 percent of pharmaceutical sales in Russia, with the Moscow market alone accounting for 20 percent of the total Russian market.[170] Imports have accounted for a significant share of the market, reaching $1.6 billion in 1997 before decreasing to $1.2 billion in 1998 and $766 million in 1999, attributable in part to the effects of the devaluation.[171] Also, demand was diminished as real disposable per capita income fell 20 percent in 1998-99.[172]

Nonetheless, demand for pharmaceuticals in Russia outstrips domestic production, partly owing to the legacy of the former Soviet system, whereby most pharmaceutical manufacturing facilities were distributed among Council for Mutual Economic Assistance partner countries[173] to take advantage of specializations designed to optimize economies of scale. For example, during the former Soviet system, finished, dosage-form products came from companies such as Hungary-based Gideon Richter (which still has a well-established presence in the Russian market), while Russia made semifinished products (known as substances) used in pharmaceutical production. In recent years, however, Russian producers have been unable to compete with cheaper substances from China and India owing to rising costs for raw materials, high energy prices, outdated plant

[167] U.S. Department of State telegram No. 0841, "Food and Medical Supplies to the Primorskiy Krai," prepared by U.S. Consulate, Vladivostok, Dec. 10, 1998.

[168] Pyrabelisk, "Russian Drug Market," company located in London, contact at http://www.pyrabelisk.com.

[169] Ludmila Maksimova, "Financial Crisis Affects Pharmaceutical Market in Russia," Dec. 1998, found at *http://www.bisnis.doc.gov/bisnis/bulletin/9812phar.htm* and retrieved on July 10, 2000. However, other reports indicated that an estimate of $3.0 to $3.1 billion for 1997-98 is unjustified. See Pyrabelisk, "Russian Drug Market," company located in London, contact at http://www.pyrabelisk.com.

[170] Group of Companies Remedium, "Analysis of the Russian Pharmaceutical Market in 1999," (translated by Commission staff), found at *http://www.rmbc.ru/pbl/market19991.htm* and retrieved on July 12, 2000.

[171] Pyrabelisk, "Russian Drug Market."

[172] Group of Companies Remedium, "Analysis of the Russian Pharmaceutical Market in 1999."

[173] Tacis (prepared by Maxwell Stamp PLC), "Advice to the Pharmaceutical Sector as a Component of the Health Sector," June 17, 1997.

and equipment, and inefficient manufacturing processes.[174] About 90 percent of substances currently used in pharmaceutical production is now imported. Although imports of some substances have since become more expensive because of the ruble devaluation in 1998, the Russian industry continues to convert former production facilities for substances into facilities producing the end-product pharmaceutical products.[175]

Development of new pharmaceutical products in Russia requires modernization of production facilities, including the introduction of GMP standards.[176] Upgrades to former defense industry production facilities have begun, and Western pharmaceutical companies have partnered with Russian firms to promote production of generic products in Russia. However, new drugs are not likely to be developed in Russia until the patent protection and intellectual property rights systems are strengthened.[177] Drug development costs in Russia reportedly range from $100,000 to $300,000.[178]

Drug Approval Process

All pharmaceutical products[179] must be registered with the Ministry of Health (MOH), Bureau of Registration of New Pharmaceuticals and Medical Equipment; however, it is the MOH's Department of State Control Over Medicines and Medical Devices' Quality, Efficiency, and Safety that oversees the process. General registration requires the appropriate documentation and data, including, but not limited to, the application of the manufacturer or designated representative; list of medicinal components; certificate of quality and quality-control methods; results of preclinical research, pharmacological and toxicological research, and clinical research; and documents confirming registration outside of Russia, if applicable.[180] The general registration process takes 6 months and is valid for 5 years. An accelerated procedure is available for products that are equivalent to an original medicine already registered, pharmaceuticals included on the list of essential medicines, and pharmaceuticals received as humanitarian aid;[181] the minimum registration time period for this procedure is 3 months. Pharmaceuticals that have

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[174] Ibid., and V.I. Starodubov, "Measures of State Regulation of Pharmaceutical Support to the Population of the Russian Federation," *Zdravookhraneniye Rossiyskoy Federatsii*, June 30, 1999, pp. 3-9, translated by FBIS.

[175] A.A. Vespalov, N.V. Trifonov, S.A. Bespalov, and K.S. Khadzhibaronov, "Methodological Principles of Conversion of Defense Industry Enterprises into Enterprises Producing Pharmaceutical Materials," *Farmatisiya*, vol. 4, No. 4, July-Aug. 1999, pp. 400-442, translated by FBIS.

[176] GMP standards were introduced in Russia on Jan. 1, 2000. See Pyrabelisk, "Russian Drug Market."

[177] Pyrabelisk, "Russian Drug Market."

[178] Ibid.

[179] Includes new drugs, new combinations of previously registered drugs, drugs registered earlier but manufactured in other medicinal forms, and generic drugs. See Federal Law of the Russian Federation "On Pharmaceuticals," adopted by the State Duma on June 5, 1998, and approved by the Council of the Federation on June 10, 1998 (translated by FBIS), found at *http://199.221.15.211* and retrieved on July 11, 2000.

[180] "State Registration for Medical Products, Pharmaceuticals and Animal Origin Products in Russia," July 12, 1999, found at *http://www.bisnis.doc.gov/bisnis/isa/cert.htm* and retrieved on July 10, 2000.

[181] "State Registration for Medical Products, Pharmaceuticals and Animal Origin Products in Russia," July 12, 1999, found at *http://www.bisnis.doc.gov/bisnis/isa/cert.htm* and retrieved on July 10, 2000.

been registered with the MOH appear in the State Register of Medicines and can be used for medical applications.[182]

In addition to registration, importers of pharmaceutical products must obtain an import license approved by both the Ministry of Health and the Ministry of Foreign Economic Affairs and Trade, and a Russian quality certificate from Gosstandart, the Russian federal agency for certification of all products sold or used for mass consumption. Prior to February 2000, the United States and Russia had a Memorandum of Understanding (MOU) that streamlined the certification procedure for U.S.-produced drugs and biological products.[183] Those products already approved by the FDA theoretically were not subject to clinical trial requirements in Russia. However, in practice, U.S. pharmaceutical companies export their product to Russia from facilities in Europe and thus derive little or no benefit from the MOU. Consequently, there is little interest in renewing the MOU.[184]

The Government of Russia also requires pharmaceutical producers to obtain manufacturing licenses that contain a list of the drugs the enterprise is permitted to manufacture, data on the condition of manufacture, and the names of the persons responsible for production, quality, and labeling of the pharmaceuticals.[185] Licenses are issued within 2 months of the application filing date and are valid for 5 years.

Patents

Russia's 1992 patent law reportedly complies with the norms of the World Intellectual Property Organization, and includes procedures for deferred examination, protection for chemical products, and national treatment for foreign patent holders.[186] While the 1992 law provides protection, new drugs can take at least 10 years to develop, so only a few have been registered under the new law.

The Term of a Patent

The term of an invention patent is 20 years from the date that the application was filed with Rospatent. The patent statute contains no provisions for extension of the term.

Working a Patent and Compulsory Licensing

Compulsory licensing may be required if a patent is not used or is insufficiently used by the patent holder for 4 years after it was issued. In such circumstances, any person who is ready

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[182] One source indicated that Russian registration procedures resemble the national procedures of the EU. Association of International Pharmaceutical Manufacturers (AIPM), "Economic and Legal Framework for Non-Prescription Medicines," draft of July 21, 2000, p. 2.

[183] 59 F.R. 6054 and 61 F.R. 67036.

[184] Commission staff telephone interview with USAID official, July 31, 2000; and Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[185] Federal Law of the Russian Federation "On Pharmaceuticals," adopted by the State Duma on June 5, 1998 and approved by the Council of the Federation on June 10, 1998 (translated by FBIS), found at *http://199.221.15.211* and retrieved July 11, 2000.

[186] U.S. Department of State telegram No.14523, "Russia: Investment Climate Statement," prepared by U.S. Embassy, Moscow, July 19, 2000.

and willing to use the patented invention and who has been refused a voluntary license by the patent holder may apply to the Supreme Patent Chamber for a nonexclusive compulsory license. If the patent holder fails to prove a valid reason for his nonuse or insufficient use of the patented invention, the Supreme Patent Chamber must grant the license to the other person and determine the extent of use and the terms and order of the payments to the patent holder. The amount of the license payments must not be below the market price of the license.

Russian law also forces licensing in the situation of interdependent patents. If a patent holder cannot use his patented invention without infringing the rights of another patentee, the patent holder is entitled to demand that the other patentee enter a licensing agreement with him. (For more on the Russian patent system, see appendix H.)

CHAPTER 4
ESTABLISHMENT OF PHARMACEUTICAL PRICES WITHIN COUNTRIES

Pricing is considered by some to be one of the "main determinant[s] of margins, research capacities, and internationalization."[1] Several factors are involved in the pricing of pharmaceutical products, including, among others, costs of production, costs of regulation, profit, and perceived therapeutic value.[2] The pricing of pharmaceutical products also provides sales revenues that allow innovative firms an opportunity to recoup some of their R&D expenditures, some of which, in turn, can then be used in the development of other innovative products. As a result, pricing policies and cost-containment programs implemented by individual countries can have a significant impact on the industry, particularly in regard to R&D expenditures, because they may result in decreased revenues to the companies.[3]

Many countries have implemented price control policies, cost-containment programs, or combinations of both, to reduce healthcare expenditures, including the countries addressed in this study (see summaries provided below for each of the countries). Examples of such policies vary by country but can include reference pricing, international price comparisons, patient copayments, profit controls, spending controls, budgets for doctors, volume controls, controls on promotional spending,[4] and a shift towards generic products.[5] Among other things, these programs are intended to lower the portion of healthcare expenditures accounted for by pharmaceuticals as healthcare costs continue to increase in many countries (see table 1-4).

The success of such programs varies, depending on one's perspective (i.e., whether that of the implementing Government, domestic and foreign producers, or consumers). According to EFPIA, several countries have implemented successive programs before the impact of the previous one(s) has been determined. EFPIA asserts that these programs, "most of which seek

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

[2] Spilker, *Multinational Drug Companies*, p. 8.

[3] USITC, *Global Competitiveness*, publication 2437, pp. 3-18 to 3-19.

[4] Of the four countries within the EU considered in this report, only France and the UK have promotional spending controls. Donald Macarthur, *Handbook of Pharmaceutical Pricing and Reimbursement: Western Europe 2000*, Informa Publishing Group, London, 2000, pp. 1 and 4; and Elaine Last and Neil Turner, Ed., *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, 2000, Cambridge, UK, pp. 55, 61, 89, and 168. Information available about Canada and Japan indicates that neither country has controls on promotional spending, although Japan has reportedly imposed some restrictions on how companies promote products. *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, pp. 22 and 99.

[5] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, pp. 12-14; *Handbook of Pharmaceutical Pricing and Reimbursement: Western Europe 2000*, pp. 1 and 4; and *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, various pages.

only short-term gains," have a negative impact on the market and the competitiveness of the industry.[6]

Various organizations have examined different aspects of price controls and cost-containment programs (see chapter 2). Included among the more recent studies are one sponsored by Warner-Lambert and one commissioned by the Federal Ministry of Labour, Health and Social Affairs in Austria.[7] Both state that "appropriate measures" are needed and that the effects of price controls and cost-containment programs are more effective in the short term.[8] Moreover, according to the industry-sponsored study, complicated domestic "interlinkages" exist within national healthcare systems and there can be "unintended consequences of market interventions."[9] As stated in the study, their analysis–

> suggests that such [market interventions by national Governments] have been somewhat successful in curbing pharmaceutical costs in the short term, but have had little effect on longer-term spending trends. It is also the case that the very effort of controlling expenditures on pharmaceuticals, which are simply one component of health-care, results in increases in other cost components and increased overall spending.[10]

The study sponsored by the Austrian Federal Ministry states:

> The analyses of the individual countries show that the control strategies adopted have led to a "pendulum" which is typical of many fields of policy: as a reaction to an unsatisfactory situation, a number of fundamental changes are initiated, which cause the "pendulum" to swing in the opposite direction. When deficiencies or problems arise the "pendulum" begins to move back towards the initial situation. At present, the countries investigated in this study are in different stages of this cycle. Some of them have moved back to state intervention, while others are attempting to attain their goals by means of market instruments. Here

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[6] EFPIA, *The Pharmaceutical Industry in Figures,* p. 10.

[7] Respectively, BCG's *Ensuring Cost-Effective Access to Innovative Pharmaceuticals* and the Österreichisches Bundesinstitut für Gesundheitswesen (Austrian Health Institute), *Pharmaceuticals: Market Control in Nine European Countries*, Vienna, Nov. 1998. The latter study examined pricing and cost-containment programs in Austria, Denmark, France, Germany, Italy, the Netherlands, Sweden, Switzerland, and the United Kingdom.

[8] Austrian Health Institute, *Pharmaceuticals*, p. iv and BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 5. The authors of the Austrian study state that the reason such programs are generally effective on a short-term basis is the existence of "loop-holes" in each program. The effectiveness wanes once "the participants in the market have adjusted to the new situation and have learned to take advantage of its loopholes." Austrian Health Institute, *Pharmaceuticals*, p. iv.

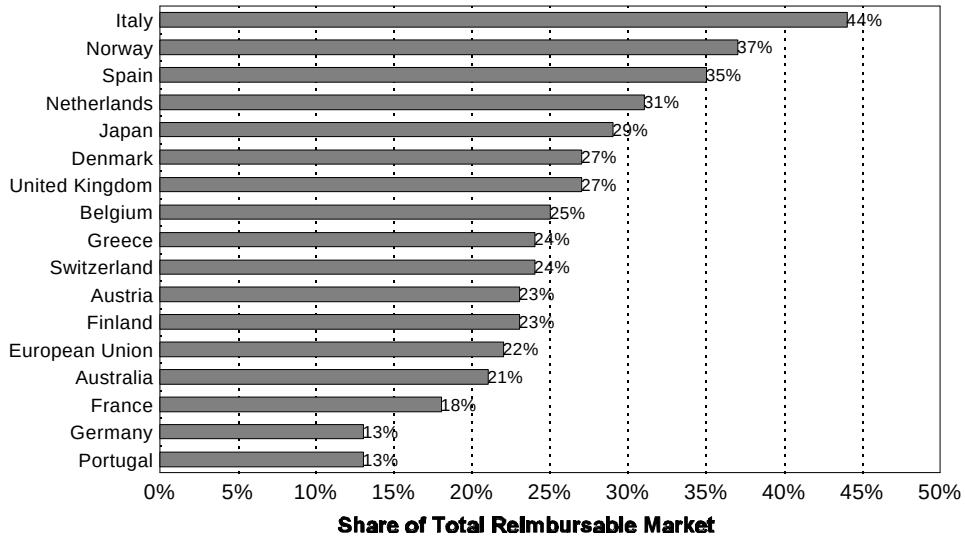
[9] BCG, *Ensuring Cost-Effective Access to innovative Pharmaceuticals*, pp. iii and 14.

[10] Ibid., p. 5. Examples of increased costs in other components of healthcare resulting from restrictions on pharmaceutical spending include increased referrals to specialists and hospitals; indirect costs include decreased productivity. One example cited by the study addresses a U.S. State Medicaid program that limited prescriptions to participants to three in a month. They state that although pharmaceutical consumption decreased by 35 percent under the program, nursing home admissions doubled. Once the prescription limitations were ended, pharmaceutical consumption and nursing home admissions reverted back to previous levels.

it is the duty of the policy makers to prevent extreme swings of the "pendulum" and to find an adequate mix of market interventions.[11]

Other reported effects of the reduction of national healthcare expenditures in some countries include a reduction in the revenues accruing to innovative companies, as well as the increased likelihood that older, lower cost products would be prescribed rather than newer, more innovative products.[12] Figure 4-1 presents the varying shares of total pharmaceutical sales subject to national reimbursement programs implemented in individual countries that were accounted for by patented, or innovative, products in 1996. Figure 4-2 presents information regarding market access delays in individual countries in 1998. The data, presented for a sampling of new products, reflect the delay between receipt of local approval and the subsequent market entry of the product.

Figure 4-1
Patented products' share of reimbursable pharmaceutical sales, 1996

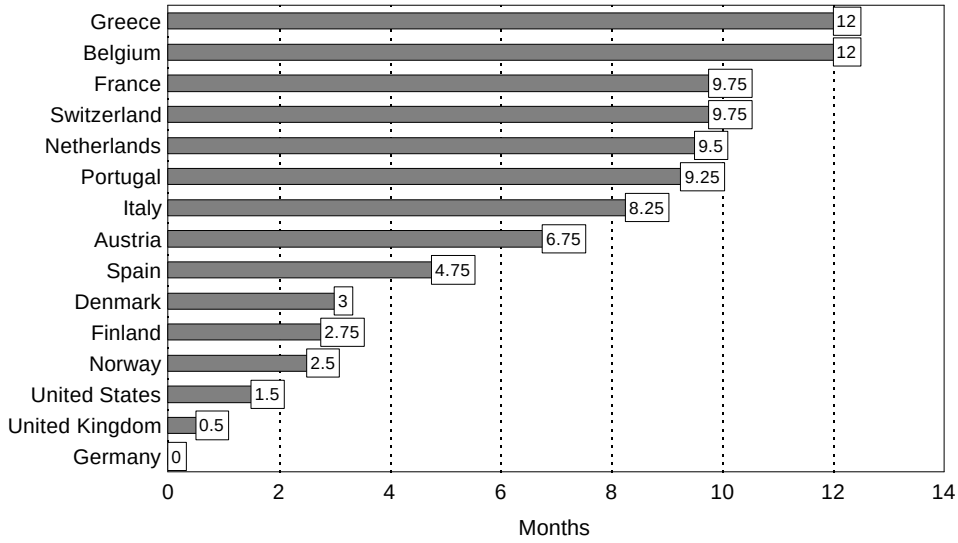


Source: Obtained from PhRMA (*Pharmaceutical Industry Profile 2000*, p. 95) and used with their permission. The original source cited was a Merck & Company analysis of 1996 IMS data, published in *PhRMA Pricing Review,* Dec. 1997. Comparable U.S. data for 1996 are not available.

[11] Austrian Health Institute, *Pharmaceuticals*, p. iv. The study also states, for example, that France made "repeated attempts" in the 1990s to reduce healthcare and pharmaceutical costs, instituting a number of reforms.

[12] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 6, and PhRMA, *Pharmaceutical Industry Profile 2000*, p. 93.

Figure 4-2
Market access delays across countries, 1998



Source: Obtained from Boston Consulting Group (*Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 25) and used with their permission. The original sources cited were interviews; EMEA; FDA; PhRMA, *1998 Industry Profile*; and BCG analysis. Graphic presentation rearranged by the Commission.

Comparable U.S. data for1996 are not available.[13] However, industry representatives suggest that the share of patented products subject to national reimbursement programs is higher in the United States than in Europe.[14] The industry also estimates that whereas patented products accounted for almost 30 percent of total reimbursement spending in Europe in 1998, they accounted for more than 60 percent of reimbursement spending in the United States.[15] Various factors may influence the U.S. market's greater consumption of patented products, whether reimbursed or not, including: less Government intervention in the domestic market; the ready availability of new products in the market because of the industry's continued innovation; the willingness of doctors to prescribe innovative products; and increased patient awareness of new products, in some cases enhanced by consumer advertising.[16]

Promotional expenditures, whether intended for doctors or the prospective consumer, have increased in recent years. The value of one type of promotion, "direct-to-consumer" advertising of prescription-only drugs, increased during 1989-94 from less than $100 million to about $200

[13] The original source of the data, presented in PhRMA's *Pharmaceutical Industry Profile 2000* on p. 95, was cited as a "Merck & Company analysis of 1996 IMS data, published in PhRMA Pricing Review, December 1997."

[14] Commission staff telephone interview with a representative of PhRMA on Sept. 20, 2000.

[15] Information obtained by Commission staff via e-mails, dated Sept. 22, 2000, from representatives of Merck.

[16] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, pp. 24, 30, and PhRMA, *Pharmaceutical Industry Profile, 2000*, p. 78. Except for Mexico and Russia, the BCG study looked at all of the countries under consideration in this report. The study cites Germany, the United States, and the UK as countries with "relatively less" government intervention in their domestic markets and France as a country with "considerable market intervention."

million; it then increased steadily during 1995-98 to almost $1.4 billion.[17] Such spending reportedly amounted to $905 million during January-June 1999.[18] One source contends that such spending may be one factor in increased costs of pharmaceuticals.[19] Controls on promotional spending have been implemented in several countries, including France and the UK.[20]

Various options, whether implemented singly or in concert, could be developed to contend with increasing pharmaceutical and healthcare costs in a given country. For example, one proposed approach focuses on little or no government-intervention.[21] In contrast, another suggests "the implementation of flexible systems that are continuously changed" so as to provide possible success on a long-term basis.[22] The former approach, found in the industry-sponsored study, suggests that free markets, or the introduction of "market elements" into healthcare systems while maintaining "equity" in coverage, can provide positive outcomes; these include incentives for product innovation and better, more appropriate, uses of the new pharmaceutical products that result from the increased innovation.[23] The study states that "approaches that leverage the economic incentives of all of the players–including pharmaceutical companies and other suppliers–are essential to ensure the successful outcome of a government policy."[24]

The Austrian study does not address the impact on innovation. It does, however, suggest that the latter approach, i.e., the implementation of flexible, changing systems, would include a combination of measures that would avoid excessive financial burden being placed on patients, increase the use of generics, and improve doctors' prescribing habits.[25]

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[17] Lehman Brothers, *The Trend Towards Pharmaceutical Megabrands*, p. 4. The number of products marketed increased during these years from 10 to 79. In comparison, advertising of OTC products is said to be greater than $2 billion.

[18] *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 176.

[19] "Prescription to Purchase: Is the Marketing of Prescription Medicine Leading to Overpriced, Overprescribed Drugs?,"dated Sept. 20, 2000, found at *http://abcnews.go.com/sections/living/ dailynews/ drugcosts000920.html* and retrieved on Oct. 3, 2000.

[20] *Handbook of Pharmaceutical Pricing and Reimbursement Western Europe 2000*, various pages. The individual price controls and cost-containment programs in each country will be discussed in later sections of this chapter. However, according to the *Handbook*, the overall intent of the control on promotional spending in France is to reduce the ratio of promotional spending to reimbursable sales to the following annual maximums: an average of 14-15 percent in 1999; an average of 12 percent in 2000; an average of 11 percent in 2001, and an average of 10 percent by the end of 2002. The *Handbook* states that, in the UK, where the companies' profits are controlled relative to their sales to the National Health Service (NHS), the promotional allowance is used to assess the company's profits. Each such allowance consists of the following: "a standard element of 6% of NHS sales, a fixed element of £464,000 [about $748,000], and a product servicing allowance for each active substance with NHS sales of £100,000 [about $161,000] or more in the year that the [company's annual financial return] relates."

[21] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 6.

[22] Austrian Health Institute, *Pharmaceuticals*, p. iv.

[23] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 6.

[24] Ibid.

[25] Austrian Health Institute, *Pharmaceuticals*, p. iv.

United States

In general, pharmaceutical companies operating in the United States can price their products freely. However, according to private- and public-sector sources, participation in some Federal and State buying programs is subject to some controls (e.g., rebates and discounts). Moreover, many private-sector healthcare programs (e.g., managed-care programs) negotiate their own price discounts. Although patients in the United States generally have access to any authorized pharmaceutical, some organizations have reportedly implemented the use of formularies, which can restrict the products prescribed.

Healthcare Coverage

The U.S. market is served by a variety of insurance plans, many of which are private. Many of these private plans, in turn, are managed-care plans (e.g., health maintenance organizations, or HMOs). HMOs reportedly provide prescription drug benefits to about 95 percent of their enrollees. Public-sector health plans include Medicare (for senior citizens), which does not provide prescription drug coverage, and Medicaid (primarily for low-income persons),[26] which does provide such coverage. Other public-sector plans cover the military (administered by the U.S. Department of Defense) and veterans (administered by the U.S. Department of Veterans Affairs).[27]

Pricing

The U.S. market is relatively free of Government-mandated price controls or cost-containment programs, and pharmaceutical firms can price their products freely. However, current Federal and State buying programs, many of which cover drugs, are said to require various forms of price controls, including rebates, discounts, price caps, and limits on price increases.[28] Such programs, which reportedly account for only 13 percent of the market,[29] include Medicaid, buying programs administered by the Department of Defense and the Department of Veterans Affairs, Public Health service grantees (e.g., community healthcare centers), and State pharmaceutical assistance programs for low-income persons.[30] Various private-sector programs, such as managed-

[26] According to PhRMA, almost 50 percent of all persons covered by Medicaid are in managed-care programs. PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 78.

[27] PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 64, and BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals: Do Market Interventions Work?,* pp. 60-61.

[28] PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 74, and BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals: Do Market Interventions Work?,* pp. 60-61.

[29] PhRMA, *Pharmaceutical Industry Profile, 2000,* p. 81. PhRMA states that should Government-imposed price-control systems be introduced as part of any plan implemented to provide prescription drug coverage to senior citizens under Medicare, the percentage of the market covered by "Government price regulation" would increase from the current level of approximately 13 percent to over 40 percent because "seniors comprise about one-third of the entire U.S. prescription medicine market."

[30] "Medicaid Drug Rebate Program," found at *http://www.hcfa.gov/ medicaid/drughmpg.htm,* and retrieved on Sept. 18, 2000; "Backgrounders and Facts: The Medicaid Rebate," found at *http://www.phrma.org/publications/* backgrounders/federal/rebate.phtml and retrieved on Sept. 29, 2000;

(continued...)

care programs, reportedly negotiate their own discounts. Some programs, including those of the Department of Defense and the Department of Veterans Affairs, reportedly have also implemented use of formularies.[31]

The pricing of innovative products in the United States is also affected by generic pharmaceutical products, which may reduce both the effective patent terms of patented, innovative products and their market share.[32] The annual share of the U.S. prescription drug market accounted for by generics grew continuously during 1984-99, increasing from about 19 percent of the total in 1984 to about 47 percent in 1999.[33] Sources have stated that the U.S. market for generic products is more competitive than that in Europe and that generic products in the United States are much lower priced than those in Europe.[34] More generic prescription products are expected to enter the U.S. market during the next 10 years as the patents expire on many of the innovative drugs currently marketed. Industry sources estimate that during 2000-05 alone, patents will expire on approximately 152 products, 64 of which are

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[30] (...continued)
and PhRMA, *Pharmaceutical Industry Profile, 2000*, p. 74-75. According to information provided by the Health Care Financing Administration, the Medicaid Rebate Program was created by the Omnibus Budget Reconciliation Act (OBRA) of 1990. This program "requires a drug manufacturer to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services for States to receive federal funding for outpatient drugs dispensed to Medicaid patients." The rebate for covered outpatient drugs as of January 1, 1996, was, for innovator drugs, "the larger of the average manufacturer price (AMP) per unit or the difference between the AMP and the best price per unit and adjusted by the CPI-U based on launch date and current quarter AMP" and, for non-innovative, or generic, drugs, "11% of the AMP per unit." The Veterans Health Care Act of 1992 amended the program such that a drug manufacturer is required to "enter into discount pricing agreements with the Department of Veterans Affairs and with covered entities funded by the Public Health Service in order to have its drugs covered by Medicaid." PhRMA states that an additional rebate is required if a product's price increase is greater than the CPI price increase for all items since 1990.

In regard to price discounts, PhRMA states that, as of 1992, "to have their products covered by Medicaid, manufacturers are required to sell innovator products to the [Department of Veterans Affairs, the Department of Defense, the Public Health Service] and the Coast Guard at or below Federal ceiling prices that are 24 percent below the manufacturers' average price to wholesalers for non-Federal customers, including hospitals and HMO's." They state that such discounts are not required for generics. PhRMA states that discounts offered to PHS grantees are equal to the Medicaid rebates. PhRMA also states that many of the Government programs, at either the Federal or State level, restrict the types of products that can be prescribed (i.e., patients would not have access to all products approved for sale in the United States), as well as reimbursement levels.

[31] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals: Do Market Interventions Work?*, pp. 26-27. Formularies generally restrict access to certain drugs. In this case, the formulary used is said to be "a restrictive cost-based national formulary [implemented] through a bidding process in which the low bidder almost always wins."

[32] Brand-name, patented, innovative products would not be competing with generic versions of themselves until their patents expire. However, generic versions of products in the same therapeutic class are often considered competitive with the patented innovative products.

[33] PhRMA, *Pharmaceutical Industry Profile, 2000*, p. 70.

[34] Ibid. and information obtained by Commission staff via e-mails, dated Sept. 22, 2000, from a representative of Merck.

considered to be “blockbuster” products. In comparison, patents expired on 83 products during 1995-99.[35]

Generic versions of many of these products are expected to enter the market during 2000-2005, albeit with a potential time lag resulting from varying patent-related issues (e.g., patent-term extensions under the Hatch-Waxman Act).[36] About 5-10 new generic products are expected to be introduced annually during 2000-03, compared with about 13-14 in 2004-05.[37] PhRMA states that generic products, within the first 18 months of their introduction, gained 47 percent of the market for innovative drugs first facing generic competition during 1989-90, compared with 72 percent of prescriptions for innovative products whose patents expired during 1991-92.[38]

[35] Lehman Brothers, *Global Pharmaceutical Sector Roadshow: Patents, Products, and Politics*, 1999, p. 11.

[36] Ibid., pp. 11, 25, and 26. According to the publication, the projected total value of the products going off patent during 2000-05 will increase to about $43 billion compared with about $11 billion for the products whose patents expired in 1995-98.

[37] Ibid., pp. 11, 25, and 26, and a Commission staff telephone conversation with a representative of Lehman Brothers on Oct. 19, 2000.

[38] PhRMA, *Pharmaceutical Industry Profile 2000*, p. 70. PhRMA cites the original source of this information as a working paper, H. Grabowski and J. Vernon, "Longer Patents for Increased Generic Competition: The Waxman-Hatch Act After One Decade," dated June 1995.

Canada

The Patented Medicines Price Review Board (PMPRB), an independent quasi-judicial agency, sets price caps at the Federal level for patented medicine in Canada using a reference pricing system based on an average of prices in seven other developed markets (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States). In this way, according to various sources, the PMPRB ensures that prices remain "reasonable" and not "excessive." Sources indicate that Provincial authorities, which bear a greater budgetary burden for healthcare than the Federal Government, retain the right to impose additional price control and/or related policies, such as reimbursement prices, that establish an effective price below the maximum price set by the PMPRB.

Healthcare Coverage

Because the Provinces incur a financial burden when paying for healthcare in Canada, the Provincial authorities are allowed discretion to construct and fund Provincial plans as they see fit. Consequently, there is a wide range of public healthcare coverage available across the Provinces, and within these general plans is a similarly wide range of prescription drug plans available to specific groups of the population.

At the Provincial level, there are a variety of cost-containment measures including generic substitution, and limits on the products to be reimbursed (as detailed in Provincial formularies). Among these plans are four common methods of keeping prices down for the qualifying citizen. They include deductibles, copayments, reimbursements, and maximum limits put on professional fees. Some Provinces, however, make themselves the exception by not requiring deductibles or copayments (e.g., in the Yukon, neither is used).[39]

The impact of such systems varies, however. Although some price comparisons have indicated that prices for pharmaceuticals are lower in Canada than in the United States (see chapter 2), other sources state that Canadian price controls and the use of formularies have had a negative impact on patients. One example cited is that of "forced" changes in the medicines prescribed for patients in British Columbia resulting from "year-to-year changes in the Provincial formulary," which, in turn, result from reference price changes.[40] Canadian patients are also reportedly subject to market access delays for new, innovative pharmaceuticals, in some cases

[39] National Pharmacare Cost Impact Study, Rx&D, found at *http://www.canadapharma.org/en/publications/special/palmer/e-appendix-b.html* and retrieved on August 22, 2000.

[40] PhRMA, Written Submission, p. 19. According to PhRMA, a 1997 survey of physicians found that 90 percent of their patients "were forced to change medications as a result of reference pricing" and that "the reported health implications of these shifts included adverse effects, worsened symptoms, and hospitalizations." PhRMA provides the following cite for this information: Canadian Association of Retired Persons, "CARP Survey: BC's New Drug Plan Hurts," Fifty Plus Net - CARP in Action, May 14, 1997.

because of tandem price negotiations at the Federal and Provincial levels.[41] Moreover, according to a recent StatisticsCanada report, "concerns have been expressed that efforts to control costs through copayments or by eliminating some drugs from formulary plans will reduce the use of medically necessary drugs. Several studies have shown that patients may reduce or abruptly terminate their use of prescription drugs when deductibles or copayments are required."[42]

Deductibles

A deductible is the most inconsistently offered cost-containment measure used by Provincial prescription drug plans in Canada. Of the 11 Provincial plans, 6 do not use deductibles under their most popular qualified-coverage programs that usually include seniors and those receiving social assistance.[43]

Copayments

Copayments are more common in Provincial prescription drug plans than deductibles. They are almost invariably applied as a percentage of the actual cost, ranging from 10 percent to 35 percent. Ontario, New Brunswick, and Prince Edward Island use a flat copayment scheme for seniors. Only the Yukon and Manitoba do not use copayments in their coverage. However, as with deductibles, conditional exceptions exist in some Provinces. In Prince Edward Island and in Newfoundland/Labrador, for example, there is no copayment required of recipients of social assistance. Furthermore, there are no copayments in Alberta for citizens falling under the plans for social assistance recipients, or for those receiving long-term care.[44]

Reimbursements and Professional Fees

Each of Canada's Provincial plans includes reimbursements to those who qualify for public health coverage and they each establish maximum limits on professional fees. The public cost allowance in each is determined by a formulary (i.e., a list of drugs for specific therapeutic classes). Each Province has also determined for itself how to limit professional fees (e.g., whereas some maintain flat fee limits, others determine the maximum fee allowed based on actual costs of drug acquisition). In Alberta, for instance, the maximum fee is broken down into three possible levels, based on a step, or ratchetlike, process: $9.70 for costs up to $74.99; $14.70 for costs between $75 and $149.99; and $19.70 for costs higher than $150.[45]

British Columbia's Plan

Understanding the diverse details of the 11 independent Provincial health plans may be made easier by a brief discussion of the Provincial drug plan in British Columbia. It appears to

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[41] Ibid.

[42] StatisticsCanada, "Prescription Drug Insurance," *Health Reports*, Spring 1999, Catalogue No. 82-003-XIE, Vol. 10, No. 4, p. 19.

[43] Rx&D, *National Pharmacare Cost Impact Study.*

[44] Ibid.

[45] Ibid.

be not only the Province covering the largest portion of its population with specific and individual plans, but also the Province with the most comprehensive plan.[46]

British Columbia's drug plan offers coverage to a variety of specific groups. Eligibility is extended differently to (1) seniors over 65, (2) residents in long-term-care facilities, (3) recipients of social assistance, (4) cystic fibrosis patients, (5) medically dependent children, and (6) all other Provincial residents.

Deductibles and copayments are available only to seniors and medically dependent children. Seniors are allowed an annual $200 deductible. There are no deductibles or copayments for any person falling in groups 2, 3, 4, or 5 mentioned above. All other Provincial residents have a $600 annual deductible, and must pay 30 percent of any remaining costs up to $2,000, at which point the government accepts all additional costs.

Reimbursements are available through the Low Cost Alternative Drug Listing, which limits reimbursements for drug costs to the actual acquisition cost of low-cost alternatives. The purchase of any higher priced drug of the same therapeutic class requires the patient to pay the difference between that drug and the low-cost alternative listed in the Provincial formulary.

In addition, the Provincial authorities cap professional fees for regular prescriptions at $7.55. The actual fee is determined by the individual pharmacy. Despite the cap, fees that do not exceed the Provincial average by more than 15 percent are still accepted.[47]

Pricing

The pricing system in Canada is a two-tiered system that relies on negotiated prices rather than on market forces. The Patented Medicines Price Review Board (PMPRB) first negotiates a final price for new (or "breakthrough") prescription drugs,[48] which acts as a price cap for the prices negotiated by each individual Province or Territory.[49] The intent of the PMPRB is that the price of a new patented drug at launch should not exceed the average price established by taking into account the prices in seven other markets (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States[50]).[51] Subsequently, prices are allowed to increase in step

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[46] Various Commission staff interviews with representatives of the industry and the PMPRB.

[47] Rx&D, *National Pharmacare Cost Impact Study.*

[48] Advertising to the consumer reportedly plays less of a role in the pricing of prescription drugs in Canada than in the United States. According to one source, direct-to-consumer advertising of prescription drugs is not allowed in Canada; advertising is intended for health providers only. *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 22.

[49] "PMPRB's Compendium of Guidelines, Policies and Procedures," found at *http://www.pmprb-cepmb.gc.ca/comp-e.html* and retrieved on Nov. 1, 2000. See also "Canadian Laws Control Prices and Limit Patients Rights," GlaxoWellcome Public Policy & Advocacy Department.

[50] The Canadian measurement of the U.S. price level used in its International Price Comparison recently changed. According to the PMPRB, International Price Comparisons will include the Federal Supply Schedule as a factor in establishing effective U.S. reference prices, effective Jan. 1, 2000, for all new and existing medicines. PMPRB Newsletter, Jan. 2000.

[51] PMPRB's Compendium of Guidelines, Policies and Procedures. On the PMPRB website, also see *http://www.pmprb-cepmb.gc.ca/pdf/broch-pri-e.pdf.* See also BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 51.

with the rate of inflation according to the Consumer Price Index.[52] For drugs with minor or no innovative therapeutic effect, prices are tied to those of existing drugs with similar effects.[53]

In addition to the Federal-level work of the PMPRB, prices are controlled through another mechanism at the Provincial and Territorial level. In British Columbia, for instance, a reference pricing regime applied by the Provincial authority limits prices at the Provincial level below those established by the PMPRB.[54] Under such a policy, the Provincial government sets a reimbursement price (reference price) for all products that are grouped in a specified therapeutic classification. This leaves the manufacturer free to charge any price below the PMPRB price, but it requires the individual patient to pay the difference between the Provincial price and the PMPRB price.[55] As the primary burden of healthcare budgeting falls on the Provinces in Canada, rather than on the Federal Government, regulation of pharmaceutical prices allows the Provinces to manage their healthcare expenditures more effectively.

Compulsory Licensing and Pricing

Compulsory licensing is "permission to use intellectual property, compelled by the government in order to accomplish some political or social objective. Compulsory licensing forces an intellectual property owner to allow others to use that property at a fee set by the government."[56] Of the countries under consideration, Canada is the only one that has actually applied compulsory licensing to pharmaceuticals. In Canada, while compulsory licensing was implemented, the "fee" was actually a percentage paid to the patent holder based on revenue from the sale of the product manufactured under the auspices of the compulsory licensing system imposed on the patent holder. (For more information on compulsory licensing in Canada, please see chapter 3.)

Canada commenced compulsory licensing of patented pharmaceuticals in 1923. In 1969, compulsory licensing of imported patent pharmaceuticals began by virtue of Bill C-102. However, with passage of Bill C-22 (Amendments to the Patent Act) in 1987, the compulsory licensing system began to erode. The Canadian Patent Act, "as modified by C-22," provided patent protection of 20 years from filing (the international standard); however, such protection was only

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[52] PMPRB's Compendium of Guidelines, Policies and Procedures. On the PMPRB website, also see *http://www.pmprb-cepmb.gc.ca/pdf/broch-pri-e.pdf*. See also BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 51. In principle, these maximum prices are strictly voluntary, but there are fines and other means available to the Government to ensure that prices, once set by the PMPRB, do not become "excessive." It is also worth noting that prices of patented drugs are monitored for the entire life of the patent.

[53] Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policy versus Global Interests*, The AEI Press, Washington, DC, 1997, p. 17. According to PhRMA, the PMPRB determines whether the price suggested is "reasonable" by placing the drug in one of three categories: a "breakthrough" product, a "line extension" product, or a "minor improvement" product. Each category specifies different standards in determining the "reasonable" price for the new drug. PhRMA, Written Submission, pp. 18-19.

[54] Patricia M. Danzon, *Price Comparisons for Pharmaceuticals*, p. 28.

[55] Patricia M. Danzon, *Pharmaceutical Price Regulation: National Policy versus Global Interests*, p. 19.

[56] J. Thomas McCarthy, *McCarthy's Desk Encyclopedia of Intellectual Property*, The Bureau of National Affairs, Inc., Washington, DC, 1991, pp. 51-52. The percentage fee referred to amounts to roughly 4-5 percent of sales revenue in Canada.

for new pharmaceutical products researched *and* discovered in Canada.[57] For other products, compulsory licenses could still be issued after 7 years from the date of marketing approval.[58] The goal of C-22 was to ease Canada into alignment with international standards. In return for Canada's willingness to compromise, it sought good-faith investment from the outside to raise the level of investment in Canada from 3 percent to 10 percent by 1996. The level was met by 1992, though it was unlikely to be sustained without greater measures taken up by the Canadian government.[59]

Subsequently, coinciding with the discussions over NAFTA, Patent Amendment Act of 1992 (Bill C-91) was enacted. Bill C-91 was considered to be a way of overcoming the remaining disincentives to investment and R&D by foreign drug companies in that it was expected to "adopt the patent regime proposed under the Uruguay Round of negotiations of the General Agreement on Tariffs and Trade (GATT) and embodied under the proposed GATT agreement"; it also established use of the 20-year patent term.[60] Although Bill C-91completed the termination of compulsory licensing with additional amendments to the Patent Act,[61] the intellectual property rights provisions of NAFTA also contributed to the demise of compulsory licensing for pharmaceuticals in Canada.[62] Subsequent to the strengthening of the patent system, R&D expenditures increased by over 700 percent during 1987-98, and the ratio of R&D spending to sales doubled during the same period.[63]

Some forms of compulsory licensing, however, endure in Canada. First, patented pharmaceuticals subject to compulsory licensing prior to December 20, 1991, were, in effect, grandfathered.[64] Those drugs sold after December 20, 1991, however, were free from compulsory licensing. Second, and more currently, Canada retains the right to impose compulsory licensing on a patented pharmaceutical if the patent-holding company chooses not to market and sell the drug in Canada. This enables the Canadian Government to ensure that such drugs are available nonetheless. Reportedly, this is the Canadian Government's way of ensuring that products that are patented are also products that are purchasable.[65] It is interesting to note, though, that while Canada currently reserves the right of compulsory licensing in these particular circumstances, it

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[57] *Potential Impact on the U.S. Economy and Selected Industries of the North American Free Trade Agreement*, p. 9-3.

[58] Ibid.

[59] Ibid. See also PhRMA, *Pharmaceutical Industry Profile 2000*, p. 105, found at *www.phrma.org/publications/industry/profile00/tocnf.html*, as of July 27, 2000, and PMAC Annual Review, 1998-99.

[60] *Potential Impact on the U.S. Economy and Selected Industries of the North American Free Trade Agreement*, p. 9-3; and "Stronger Patents and Curbs on Pricing in Canada," *SCRIP Magazine*, Sept. 1992, p. 55.

[61] Found at *www.canadapharma.org/en/about/generalhistory-rxd.html* and retrieved on July 31, 2000. By 1987, Rx&D membership had risen to 71 companies.

[62] *Potential Impact on the U.S. Economy and Selected Industries of the North American Free Trade Agreement*, p. 9-2.

[63] Rx&D, *Annual Review 1999-2000*, 2000, p. 14.

[64] Margaret Smith, "Patent Protection for Pharmaceutical Products," Background Paper, Library of Parliament, BP-354E, Nov. 1993, p. 8.

[65] While compulsory licensing was in effect in Canada, the patent holder was generally paid a royalty rate of 4 percent of the net selling price of the drug in final dosage form. *Potential Impact on the U.S. Economy and Selected Industries of the North American Free-Trade Agreement*, Jan. 1993, p. 9-2 (footnote).

has not acted on this option.[66] Industry sources, however, have expressed concern about the potential reinstatement of compulsory licensing for such products.

Canada's experience with compulsory licensing may provide some insights in regard to the role of compulsory licensing in setting prices. Industry sources in Canada have stated that the PMPRB was still responsible for setting prices while compulsory licensing was in effect and that the system had no direct effect on prices. They state, however, that compulsory licensing had a significant negative impact on investment levels in the Canadian pharmaceutical industry, particularly investment by research-based companies.[67] After declining while compulsory licensing was in effect, investment levels began to increase substantially once compulsory licensing was eliminated. According to Rx&D, the "brand-name pharmaceutical industry's investment in research and development in Canada" grew from about $100 million in 1988 to about $1 billion in 2000.[68]

[66] Conference hosted by the American Enterprise Institute at the Rayburn House Office Building on July 25, 2000. The comments are in reference to the presentation made by Neil Palmer, a Canadian consultant with expertise in Canadian health policy and a principal in the firm of Palmer D'Angelo.

[67] Commission staff telephone interview with a representative of Rx&D on Oct. 11, 2000.

[68] *Approval Times in Canada 1999*, published by Rx&D, found at *www.canadapharma.org/en/whatsnew/index.html* and retrieved on July 31, 2000.

European Union

While it is the EU's stated goal to create an internal market in the pharmaceuticals sector, this has not yet been achieved.[69] Although the EU has instituted a centralized authorization procedure for pharmaceutical products, it has generally not taken action on pharmaceuticals pricing. Instead, the EU has preferred to let member states retain their diverse health care systems and the pharmaceutical pricing and reimbursement policies that are controlled by national departments of health.[70] This has generally resulted in price differentials throughout the EU, leading to parallel trade. As noted in chapter 2, parallel imports are legal within the Union,[71] though the EU takes a strong line against parallel imports from non-EU countries.[72]

Some incidental costs associated with EU membership such as the value-added tax (VAT) and patenting fees also affect pharmaceutical prices. Although Directive 92/77/EEC mandates a minimum 5 percent VAT on pharmaceuticals, the EU allows many sectoral and national exceptions, until such a time as the EU implements a common VAT regime.[73]

[69] In 1998, the EU's Internal Market Council reiterated its desire to create a single internal market and started to draw up proposals for common pricing rules for OTC, generic, and patented pharmaceuticals. These proposals were echoed the following year, when the European Parliament endorsed them in a resolution calling for changes in pharmaceuticals trade regulations. So far, however, these proposals have not become law and national pricing and reimbursement policies remain in place in the different member states.

[70] According to the *Financial Times*, the EAEM has taken the initial step of internally ranking the cost effectiveness of drugs, a move that has raised industry concerns that such rankings might be tied to pricing or reimbursement policies, as is the case in countries such as Italy. *Financial Times*, June 22, 2000.

[71] Specifically, the EU's stance on parallel imports has been developed since 1974, when it ruled in favor of parallel trade in pharmaceuticals. In the mid-1970s, Roche sold Valium in the Netherlands for 24 percent less than in the UK. When a consortium of EU manufacturers requested the European Commission to intervene and stop this practice, the Commission refused. The resulting court case, referred to the European Court of Justice from the Dutch national courts, found that parallel trade was acceptable under the EU's founding Treaty of Rome (Centrafarm BV and Andriaan De Peijper v Winthrop BV, ECJ 16/74). See also, discussion in Joseph Weiler, "Introduction to the Law and Institutions of the European Union," Harvard Law School and European University Institute's Academy of European Law Online, found at website *http://www.law.harvard.edu/programs/JeanMonnet/course99w/Units/unit12.html* and retrieved on Aug. 2, 2000.

[72] Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[73] EFPIA, *The Pharmaceutical Industry in Figures*, p. 45.

France

The French National Health systems covers virtually the entire French population for at least part of medical costs. According to one source, supplemental insurance, to cover the cost of non-reimbursable expenditures, is offered by private insurance companies. Approximately 83 percent of total sales are of reimbursable drugs. Reimbursement for pharmaceuticals depends on the type of products purchased and the illness of the beneficiary.

According to EFPIA, the current system of price and expenditure regulation began in 1994 with a "framework agreement," the details of which vary over the years. In general, the government negotiates price reductions with companies on individual products. The government also sets annual limits on the level of expenditure that is reimbursable, and controls the amount of pharmaceutical advertising.

Healthcare Coverage

The French healthcare system, which covers virtually the entire population, is administered by several Government agencies and funded by the Social Security program. The Social Security program is funded by employee and employer contributions, which cover approximately 74 percent of healthcare expenditures.[74]

Pricing

Historically, healthcare has been decentralized; the French population has had the opportunity to choose their doctors, and doctors have had the right to dispense and charge what they want for pharmaceuticals. However, drug prices for products that are eligible for national reimbursement are tightly controlled, making French drugs among the lowest priced drugs in Europe.[75] In response, large quantities of drugs were used, helping to make France one of the largest consumers of drug products. In the early 1990s, partly in order to comply with the Maastricht regulations necessary for entrance into the EU, partly to deal with a recession and large deficit, and partly at the direction of a right-center government, France began the process of controlling national healthcare expenditures that is currently in effect.[76]

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[74] The remaining 26 percent of health expenditures are funded by copayments at the time of medical purchase. Approximately 80 percent of the population is covered by supplementary private insurance used to assist with copayments. The Economist Intelligence Unit (EIU) Limited 1999, *EIU Healthcare Global Outlook: France*, 1999, pp. 200-212. The EIU noted that the system has been replaced with a quasitax, the "Contribution Sociale Generalisee" (CSG), applied to the adult population at large.

[75] Furthermore, since the early 1970s, France has, at one time or another, used most of the price controls and expenditure-reducing procedures used in the EU. BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 13.

[76] Victorine Carre and Jean-Phillippe Cantan, "French Pharma Policy-A Revolution in Progress, *SCRIP Magazine*, May 1996, pp. 6-8.

Based on 1998 data collected by EFPIA, France was both the second largest producer and the second largest consumer of pharmaceuticals in the EU.[77] During 1992-97, prescription pharmaceuticals' share of total health expenditures increased from 13.5 to 14.1 percent (see table 1-3) before decreasing to 13.9 percent in 1998. A U.S. Embassy study of the French pharmaceutical industry noted that the increase during the early 1990s and that of earlier years was due, in part, to a growing and aging population, and the introduction of newer innovative, more costly, products.[78]

Prior to 1993, generic drugs were not a large portion of the market, owing primarily to the fact that primary drugs were priced very low, and there were no incentives for physicians or pharmacists to prescribe generic substitutes. The U.S. Embassy study stated that generic products had a value of $1.1 billion in 1996 and accounted for about 20 percent of hospital sales and 4 percent of pharmacy sales.[79] According to the study, a number of domestic and foreign companies were positioning themselves to produce generic drugs in France and that it was possible that generic products could gain a 10-percent market share by the year 2000. Another more recent source estimates that during the next 10 years more than 50 percent of the French market could be replaced by generic products as the patents on over 300 products expire.[80] But, according to the U.S. Embassy study, some sources believed that in order for this to occur generic products should be priced 30 percent lower than patented drugs and that doctors and pharmacists should have the correct incentives to substitute generic products for patented drugs.[81] As of 1999, French laws were modified so that pharmacists were allowed to substitute generic products for brandname products, reportedly resulting in expansion of the generic market.[82]

French pharmaceutical expenditure and pricing regulations have evolved since 1984. Often, a regulation affecting many drugs will take a number of years to complete, and the original intent of the regulation may well have changed as well.[83] The current regime of price controls began in 1993, when the French Government set up a drug pricing committee, the Comité Économique du Médicament (CEM).[84] The Committee had responsibility for, among other things,

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[77] In addition to pharmaceuticals, the French population generally consumes large amounts of medical services, including primary care doctor visits, hospital visits, special medical treatments, and specialty doctors. In 1998, French healthcare spending as a share of GDP was 9.6 percent (fourth only to the United States, Switzerland, and Germany), which represented an increase from 5 percent of GDP in 1970. Nevertheless, French expenditure on pharmaceuticals also appears to have increased. See EIU , "Healthcare Global Outlook: France," p. 216.

[78] Alain Levy, "Industry Sector Analysis: Pharmaceuticals," U.S. Embassy France, Aug. 1997, p. 5. The companies cited in the 1997 report included Bayer, Merck, Rhone-Poulenc Rorer, and Sanofi.

[79] Ibid., p. 11.

[80] "Over 50% of French Pharmaceutical Market Could Be Lost to Generics Over Next 10 Years," found at *www.ims-global.com/insight/news_story/0008/news_story_00080* and retrieved on Sept. 26, 2000.

[81] Alain Levy, "Industry Sector Analysis: Pharmaceuticals," U.S. Embassy France, Aug. 1997, p. 11. The companies cited in the 1997 report included Bayer, Merck, Rhone-Poulenc Rorer, and Sanofi.

[82] *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, pp. 53-54. According to this source, such substitution is limited to certain products.

[83] For example, early in 2000, the French labor minister, Martine Aubry, requested French pharmaceutical companies to reduce the prices of 658 drugs which did not qualify for a social security refund. However, the Government plans to negotiate reductions with each company over a number of years, and it is not obvious which products will actually be affected and what will be the size of the price cut. "French Set To Cut the Cost of Drugs," *European Chemical News*, Aug. 7-20, 2000, p. 8.

[84] As of January 1, 2000, the committee's name changed to Comité Économique des Produits de Santé.

(continued...)

negotiating with the pharmaceutical companies initially through the French trade association SNIP "an agreement which would define the criteria on which decisions would be based. These rules were intended to give the pharmaceutical companies the security of clearly defined rules, and transparency for the future."[85]

In 1994, the industry and the Government concluded a "framework agreement" which has been extended and modified every few years.[86] Under the agreement, individual companies voluntarily negotiate prices in exchange for limiting supply based on medically justified quantities and pharmaco-economic justification. Companies were also to limit promotional expenses. By October 5, 1995, 110 agreements had been signed. The Government also set limits on the growth of sales of reimbursable drugs sold in pharmacies. For example, in 2000, the rate of growth was to be 2 percent.[87] Moreover, the French Social Security Financing Law could impose a levy of 1.3 percent on 1999 sales of reimbursable products in order to finance social security budget overruns.

Pharmaceutical companies may set prices at any level they wish for prescriptions and generic drugs, but the prices of reimbursable drugs are extensively negotiated between the Government and the company. Approximately 83 percent of total sales are of reimbursable drugs. Then, the Government, through the CEM, negotiates prices with the individual pharmaceutical companies. To be considered for reimbursement, the companies must provide information on costs, promotion expenditures, and pharmaco-economic validity. If accepted, the drug is placed in one of the following reimbursable schedules: 100 percent for irreplaceable medical products; 35 percent for disorders that are generally not serious; and 65 percent for other products.

When a drug is accepted for reimbursement, then wholesale, pharmacy and hospital markups are also controlled. The VAT is set at 2.1 percent for reimbursed drugs and 5.5 percent for nonreimbursed drugs (compared with the country average VAT of approximately 20.6 percent in 1998). Pharmaceutical companies sell their drugs through the following vendors: wholesalers–80 percent; direct sales to pharmacists–5 percent ; and direct sales to hospitals–15 percent. Wholesalers add about 12 percent to the cost; pharmacies and hospitals, some 20 percent; and the VAT can add another 2 to 5 percent. In 1996 there were 331 full-line wholesalers, and they distribute throughout the EU.[88] According to a NERA study, by 1997, the three largest firms controlled 75 percent of the market.[89] The general population purchases all drugs (branded, generic, and OTC) through pharmacies and hospitals.

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[84] (...continued)
Comité Économique Médicament: Rapport d'Activité Année 1999, p. 1.

[85] Victorine Carre and Jean Phillipe Castan, "French Pharma Policy-A Revolution in Progress?," *Scrip Magazine*, May, 1996, pp. 6-8.

[86] EFPIA, *The Pharmaceutical Industry in Figures.*

[87] PhRMA, Written Submission, p. 20.

[88] Michael L. Burstall, Ed., *Pricing and Reimbursement in Western Europe 1998: A Concise Guide*, PPR Communications Ltd., Dorking, Surrey, England, 1998, p. 24.

[89] Michael L. Burstall and Konrad Wallerstein, "Chapter 5: Health Care Systems in France," Remit Consultants, p. 381.

Advertising is controlled in many ways. For example, a significant element in the 1994 framework agreement (which replaced State price regulation) was that the pharmaceutical companies would begin to commit themselves to limit advertising costs to inform the doctors on a rational use of the item in question. This voluntary restriction was a prerequisite for a higher selling price.[90] Advertising is also taxed, depending on the level of advertising; the tax rate ranges from 9 to 20 percent.[91]

[90] Ingrid Rosen, et al, *Pharmaceuticals: Market Control in Nine European Countries*, Austrian Health Institute, Vienna, Nov. 1998, pp. 71-72. Discussed also in European Health Care Systems and Pharmaceutical Markets : Facts and Trends, 1996, p. 34.

[91] "France," *Facts and Trends: European Health Care Systems and Pharmaceutical Markets*, Artze Zeitung Verlagsgesellschaft, 1996, pp. 31-34. Also see Donald Macarthur, *Handbook of Pharmaceutical Pricing and Reimbursement: Western Europe 2000*, p. 39.

Germany

Various publications indicate that approximately 90 percent of German citizens are covered under the statutory health insurance (SHI) system, while the more affluent are typically covered under private plans. The employee contribution to SHI health plans amounts to about 12-13 percent of salary with a maximum salary cap; the employee and employer each pay 50 percent. According to the publications, citizens over 65 pay less and coverage extends to outpatient drugs, unlike the U.S. system where slightly more than one-third of senior citizens reportedly have no coverage. Patients also make copayments based on the package size.

Industry sources indicate that pharmaceuticals in Germany are subject to a two-tiered pricing system which utilizes both reference pricing and free market pricing. According to the trade association for the German industry, approximately two-thirds of all prescription pharmaceutical prices in Germany were regulated by reference prices in 1998-99. Newly innovative patented drugs launched after December 31, 1995, are excluded from the reference system until patent expiration.

Healthcare Coverage

Germany is the largest pharmaceutical market in Europe, and along with France ranks at the top of the EU countries in terms of production.[92] The German healthcare system provides universal healthcare for all citizens and is decentralized as far as finance and delivery of services are concerned. It is reportedly based on between 450-1,000 sickness funds[93] through the statutory health insurance (SHI) system, which are self-governing nonprofit insurance funds organized on a local, company, occupational, or national basis and funded by employee/employer contributions and general taxation. In 1996, the average contribution rate ranged from 12 to 13 percent of monthly salary levels; employers and employees each carry 50 percent of these rates.[94] The SHI must accept all who qualify, together with dependents and pensioners, including the unemployed. The sickness funds cover about 90 percent of the population; persons whose income exceeds a certain level (i.e., about $2,900-$3,400 per month) are allowed to opt for

[92] In 1998, Germany's pharmaceutical output was about $20 billion. In addition, according to VFA, Germany succeeded in increasing its lead as the world's largest exporter of pharmaceuticals to $14.5 billion, of which $3.4 billion (23 percent) was shipped to the United States, Germany's most important market. VFA, *Statistics 2000*, pp. 10, 16-17.

[93] *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 57; D. Macarthur, *Handbook of Pharmaceutical Pricing and Reimbursement: Western Europe 2000*," Informa Publishing Group, 2000, p. 44; and Michael L. Burstall, Ed., *Pricing and Reimbursement in Western Europe 1998: A Concise Guide*, p. 27.

[94] Covered benefits, in addition to payment for pharmaceuticals, include hospital care; outpatient care; dental treatment; care for the disabled and infirm; and maternity services. Arzneimittel Zeitung, *European Health Care Systems and Pharmaceutical Markets, An Overview*, 1996, pp. 37-42.

private insurance instead, and about 8 percent do so. The density of primary care doctors is somewhat below the EU average.[95]

Germany also provides universal access to inpatient prescription drugs for people over age 65, much like Medicare coverage in the United States. In Germany, however, such coverage reportedly extends to outpatient drugs, unlike the U.S. system, where "slightly more than one-third of all elderly U.S. residents have no coverage whatsoever for outpatient drugs."[96] Senior citizens in Germany pay an annual premium for outpatient drugs based upon their ability to pay; there is no deductible, and copayments are limited to pack size[97] as in the reference price system. Maximum copayments for the elderly are reported not to exceed 2 percent of patient annual income. Those with chronic disease are limited to 1 percent of total income, while welfare recipients and those with incomes below a specified amount pay nothing.[98]

Long-term financial problems of the SHI system said to remain unresolved include high unemployment rates and the steady increase in life expectancy, which is increasing more rapidly in Germany than in other industrialized nations. The problems reportedly will continue to place a burden on the SHI system in the coming years.[99]

Pricing

The German prescription drug market is presently governed by a two-tiered reimbursement system that utilizes both reference pricing and free market pricing.[100] In 1998 and 1999, approximately two-thirds of all prescription pharmaceutical prices in Germany were regulated by reference prices;[101] generic drugs accounted for about 40 percent of all prescriptions.[102] Reference price regulation is a cost-containment system applying to drugs that are prescribed by doctors and dispensed by private pharmacies.[103] Individual patients are then reimbursed by the statutory sickness funds. Reference prices are revised frequently, usually on an annual basis. Generic

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[95] Michael L. Burstall, Ed., *Pricing and Reimbursement in Western Europe 1998: A Concise Guide*, "p. 27.

[96] D.A. Freund, D. Willison, G. Reeher, J. Cosby, A. Ferraro, and B. O'Brien B, "Outpatient Pharmaceuticals and the Elderly: Policies in Seven Nations," *Health Affairs*, May/June 2000, p. 261.

[97] "Pack size" is generally defined as the number of units dispensed under a prescription that combine the same level of active ingredient. If pills were dispensed, for example, the number of pills would determine the size of the "pack"for copayment purposes. A "large" pack would contain more pills than a "medium" pack which, in turn, would contain more than a "small" pack.

[98] D.A. Freund, D. Willison, G. Reeher, J. Cosby, A. Ferraro, and B. O'Brien, "Outpatient Pharmaceuticals and the Elderly: Policies in Seven Nations," *Health Affairs*, May/June 2000, p. 262.

[99] VFA, *Statistics '99*, p. 39.

[100] Commission staff telephone interviews with various private companies and trade groups in Germany, including Aventis, Pharma AG, Frankfurt; Bayer AG, Leverkusen; and the VFA, Bundesverband der Pharmazeutischen Industrie e.V. (BPI), Frankfurt, and PhRMA July/August 2000.

[101] VFA, *Statistics '99*, p. 53, and *Statistics 2000*, p. 64.

[102] VFA, *Statistics '99*, p. 53, and *Statistics 2000*, p. 43. Germany's statutory health insurance system is dominated by reference prices which reportedly place downward price pressure on prescription drugs and encourage the use of lower priced generic products.

[103] In 1996, there were more than 20,000 community pharmacies in Germany, or about 1 for every 4,000 inhabitants, the EU average. Their numbers are not controlled, and they have a monopoly on dispensing prescription-only products. Chain pharmacies are forbidden. Products used in hospitals are not subject to reference pricing.

manufacturers, in turn, may lower prices below reference prices and accept losses in revenue to maintain their price advantage relative to those on-patent drugs which have been reduced to reference price levels. The on-patent manufacturer may have one relative advantage, however, in that the original price advantage of generics and parallel imported drugs may potentially be reduced, leading to stabilization of market share for on-patent drugs.[104]

The reference price concept was introduced as part of the Health Care Reform Act implemented on January 1, 1989. Reference prices, as originally introduced, applied to patented and nonpatented pharmaceutical products. The system was changed in 1996, however, such that innovative patented drugs approved after December 31, 1995, were removed from the reference pricing system and reimbursed according to free market conditions.[105] According to present regulations, when these newly patented prescription drugs go offpatent they will reportedly again be subject to the reimbursement provisions of the reference system.[106] The market share of pharmaceuticals with patented substances, whether subject to reference pricing or not, was about 22 percent of the total German market in 1999.[107]

Reference prices are fixed reimbursement levels developed by managed healthcare providers (also known as the sickness funds) for various groupings of drugs established by a committee of physicians and the sickness funds under Germany's SHI system.[108] The system for developing reference prices is very complicated and is based in part on regression analysis. However, in principle, reference prices for prescription drugs should not be higher than the upper limit of the lower third of the existing product price range for the appropriate product grouping in Germany, and the patient should be required to copay the difference between the market price and the reference price.[109] According to some sources, reference prices are generally about 30 percent below the market price of the innovative pharmaceutical product.[110]

In practice, however, according to one source, it has reportedly not been feasible to sell products at prices higher than the reference price because the insured patients were generally not willing to copay out-of-pocket expenses, and doctors have been reluctant to prescribe drugs priced above the reference price.[111] Thus, reference prices in practice typically represent the fixed upper limit of reimbursement from the sickness funds, as well as a de facto upper limit of prices.[112] German pharmaceutical manufacturers are reported to be negatively impacted by reference prices because, in practice, they must lower their quoted prices to reference price levels established by the

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[104] U. Vorderwülbecke, *The German Reference Price System*, EU Pharmaceutical Law Forum 1999, Brussels, March 11-12, 1999.

[105] Commission staff telephone interview with a representative of VFA, July 2000. BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 54.

[106] Commission staff telephone interviews with representatives of VFA, July 2000.

[107] VFA, *Statistics '99*, p. 53.

[108] U. Vorderwülbecke, *The German Reference Price System*.

[109] Ibid.

[110] Arzneimittel Zeitung, *European Health Care Systems and Pharmaceutical Markets: An Overview*, 1996, p. 41, and discussions with a representative of the VFA, Sept. 2000.

[111] The doctor is the patient's main source of information about products. Reportedly, no advertising of pharmaceuticals is allowed in Germany. OTC drugs in some instances may be prescribed. About 80 percent of the total retail market for pharmaceuticals was prescribed by doctors for the treatment of SHI patients in 1999. VFA, Statistics 2000, p. 53.

[112] U. Vorderwülbecke, *The German Reference Price System*.

sickness funds to remain competitive.[113] In 1999, 94 percent of the reference-priced drugs were at or below reference price levels.[114] Figure 4-3 shows trend lines for reference prices, the prices of pharmaceuticals not subject to reference pricing, and the cost of living in Germany during 1992-99.

The change in the reference price system in 1996 was reportedly one of several results of joint efforts between the German Government and industry to address rising unemployment in the mid-1990s, a perceived reluctance by the industry to invest in Germany, and the threat of "de-industrialization."[115] The effort, known as "Investment Location Germany," resulted in four major decisions reportedly in favor of the research-based pharmaceutical industry beginning in 1996: (1) The exclusion of newly patented drugs launched after December 31, 1995, from the system of reference price clusters until patent expiration; (2) the cessation of mandatory dispensing of drugs brought into Germany by parallel imports; (3) the abandonment of plans to create a "positive list" as a screen for reimbursement by SHI; and (4) the encouragement (instead of discouragement) of biotechnology investment in Germany. Interim plans for healthcare reform based on an evaluation of new Government policy, however, have reportedly called for a "return to solidarity," or a return in part to the cost-containment policies of the past.[116] The new free market pricing system raised costs to healthcare providers, but reduced hospital costs.[117] It is uncertain how much of an effect this new system may have had on German physicians, who are required to operate under a regulated prescription drug budget system.[118]

Copayments

Beginning in 1994, patients were required to pay a flat amount per item based on package size. This cost has gradually risen and, since July 1997, the patient has been required to pay $5-$8 to the pharmacist depending upon package size, up to the cost for the drug itself; the difference between patient copayments and the actual drug price is paid as reimbursement to the pharmacist by the managed sickness fund or by private providers.[119] Payments based on package

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[113] Patricia M. Danzon, *Pharmaceutical Price Regulation, National Policies Versus Global Interests*, p. 19. The profile of 1997 retail prices of pharmaceuticals across Europe shows that German manufacturers received the lowest share of prices in Europe (54.8 percent). The markup ex-factory price is roughly twice as high in Germany as in the UK. VFA, *Statistics '99*, p. 23.

[114] U. Vorderwülbecke, *The German Reference Price System*.

[115] Correspondence via e-mail between Commission staff and a German industry representative on Aug. 3, 2000.

[116] Ibid.

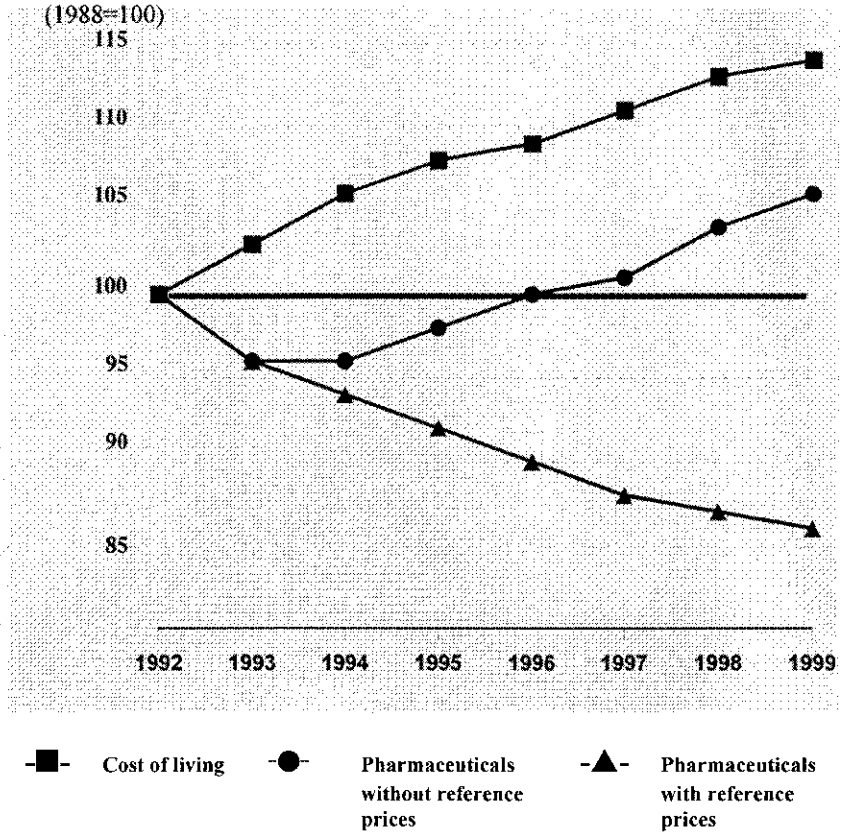
[117] Information based on Commission staff interviews with industry sources in Germany, July/August 2000.

[118] "Since 1994, Germany has had regional global budgets for prescribed medicines. Overruns were to be deducted in part from doctor's fees. Global budgets are now being replaced by indicative budgets for individual practices. They will be based on the number of patients treated by the physician, their age structure and the incidence of particular diseases. Doctors who exceed their budgets by more than 15 percent will be audited; those who exceed by more than 25 percent will have to repay the excess to the sick fund or face delisting."Michael L. Burstall, Ed., *Pricing and Reimbursement in Western Europe 1998: A Concise Guide*, p. 29. Despite the increase in VAT from 15 to 16 percent on April 1, 1998, SHI pharmaceutical market prices increased by only 0.4 percent. VFA, *Statistics '99*, p. 21.

[119] Michael L. Burstall, *Pricing and Reimbursement in Western Europe 1998: A Concise Guide*, pp. 28-29. Children under 18 and pregnant women are exempt, and concessions are made to the poor, the

(continued...)

Figure 4-3
Price trends of pharmaceuticals with and without reference pricing



Source: VFA, *Statistics Handbook 2000*, p. 45. Reprinted with permission from VFA.

size placed a greater relative price burden on the patient, especially for those prescriptions under reference pricing where the cost of the drugs is lower.[120] The share of reference price products in SHI prescriptions rose from 44.4 percent in 1994 to 63 percent during 1997-99, resulting in an annual cost savings to the SHI of $1.7 billion in 1999.[121]

[119] (...continued)
elderly, and the chronically sick. Another regulation increased copayments by about $0.60 for every 0.1 percent increase in patient contributions to the sick funds.

[120] Conversely, under the new free market pricing system, the healthcare provider is likely to experience a heavier relative cost burden as the difference between fixed patient copay and prices for new innovative, patented, approved drugs widens.

[121] VFA, *Statistics 2000*, p. 64.

Italy

The Italian Department of Health reimburses patients for the cost of many prescribed drugs. According to various publications, Italy's Department of Health controls the prices of pharmaceuticals that are reimbursed, according to a pricing system referenced against a basket of 12 EU member States. Publications indicate that prices are determined in negotiations between the Department of Health and pharmaceutical manufacturers, and are also affected by the degree of innovation, estimated sales, cost-benefit analysis, efficiency, therapeutic value, market forecasts, the economic impact on a company, and potential savings to the Italian health service overall.

Healthcare Coverage

The Italian population is provided healthcare coverage by the Servizio Sanitario Nazionale ((SSN); or the National Health Service).[122] Patients are reimbursed for the cost of many prescribed drugs.

Copayments were introduced in Italy in 1991 to control spending, following a gradual increase in the National Health Service[123] expenditure on pharmaceuticals.[124] Since 1996, copayments have been made in three categories. Class A drugs (1,450 drugs in 1995[125]), deemed to be the most efficient, are reimbursed fully; Class B drugs (290 drugs in 1995), which are less efficient, are reimbursed at 50 percent; Class C drugs (approximately 1,647 drugs in 1995), the least efficient, are not reimbursed at all. Nearly all drugs are Class A or Class C (44.5 percent and 49.9 percent, respectively).[126] In 1995, Class A and B drug prices were reduced 2.5 percent. A limit of $45 is applied to copayments per prescription. In addition, flat-rate fees are charged to patients (with some exceptions): $1.95 for one prescription item, and $3.90 for two or more items. In addition, general practitioners (GPs)[127] have some guidelines about what they can prescribe.

Pricing

The Italian market is overwhelmingly namebrand. In 1999, less than 1 percent of the prescription market in Italy consisted of generic products.[128] This results in significantly higher

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[122] BGC, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 54, and *Handbook of Pharmaceutical Pricing and Reimbursement Western Europe 2000*, p. 66.

[123] The SSN was created as a bureau within the Department of Health in 1978, replacing the Social Health Insurance System.

[124] Spending on pharmaceuticals was 14.0 percent of total health spending in 1989 and 15.2 percent in 1991 *Financing Health Care, Vol. 1*, p. 552.

[125] *European Health Care Systems and Pharmaceutical Markets*, Arzneimittel Zeitung, 1995.

[126] Michael L. Burstall, Bryan Reuben and Anthony Reuben,"Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective."

[127] GPs are comparable to American primary care physicians.

[128] Ibid.

costs, both for the Italian taxpayers who support the national health system in Italy and for individual patients who generally are not prescribed cheaper generic drugs.[129]

The cost of Italian pharmaceuticals has been rising since the late 1980s and early 1990s. In 1988, retail medicine prices in Italy were estimated to be 72 percent of the EU average; in 1989, 80 percent; and in 1991, 94 percent.[130] Various methods of cost containment are employed in Italy, including control of reimbursement prices, the publishing of "positive" and "negative" lists of efficient and inefficient drugs in order to encourage or discourage their use, and the use of patient copayments. Italy directly controls only the prices of pharmaceuticals that are reimbursed according to a reference pricing system. (Nonreimbursed and OTC drugs have no price controls, though the companies manufacturing them may not raise OTC prices more than once a year.)

Italy allows domestically produced pharmaceuticals to command higher costs. Until the 1993 overhaul of its pricing system, Italy regulated drug prices on the basis of costs. In 1994, the amount of reimbursement could not exceed a European "average," based on the prices of a given drug in France, Germany, Spain, and the UK. One problem reported with this system was determining exchange rates according to the Purchasing Power Parity rates of exchange, which were seen by many to be too low.[131]

The four-country averaging system was ruled illegal under European law in February 1997, and a new method of price reimbursement came into effect on July 1, 1998. All prices above the European average were lowered to it immediately, and all prices below the average were to be raised to it within 6 years. The new system uses real exchange rates and reflects an average of prices in 12 countries. Price negotiations for pharmaceuticals approved through the EU's centralized procedures were also extended to those approved via the decentralized procedure. This meant prices were to be fixed according to criteria such as degree of innovation, estimated sales, prices applied in other EU countries, and cost-benefit analysis. At the same time, Italy instituted direct negotiations with drug companies, and began to take into account efficiency, degree of innovation, therapeutic value, market forecasts, the economic impact on a company, and the potential savings to the Italian health service overall, in setting price reimbursement levels.[132]

Currently, Italy reimburses qualified prescription drugs whose prices reflect approved profit levels.[133] For drugs approved in Italy, wholesaler margins are fixed at 10 percent of the manufacturer's price. For drugs approved centrally through the EU, the wholesaler's price depends

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[129] *Financing Health Care, Vol. 1*, and Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[130] *Financing Health Care, Vol. 1*, p. 555.

[131] The EU threatened to invoke the infringement procedure against Italy because the average price system renders some imports unprofitable to market in Italy. In February 2000, the Italian Department of Health proposed that Italy retain its average price system but, in cases where this renders foreign products unprofitable, they will be able to determine pricing through a negotiation system. EFPIA, "Pricing and Reimbursement," March 30, 2000.

[132] Michael L. Burstall, Bryan Reuben and Anthony Reuben,"Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective."

[133] Sources state that generic products have to be priced "at least" 20 percent below the reimbursed original innovative product to be eligible for reimbursement. *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 82, and *Handbook of Pharmaceutical Pricing and Reimbursement: Western Europe 2000*, p. 71.

on the product price.[134] Pharmacy margins for reimbursed drugs are 40 percent of manufacturers' prices. In 1995, the manufacturer selling price was fixed at 50.9 percent of the consumer price. In addition to this, wholesalers are allowed a 17.8 percent margin, and pharmacists are allowed a 35.7 percent margin. VAT was lowered to 4 percent for drugs in 1995 (from 19 percent for OTC drugs and 9 percent for prescription drugs).

[134] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, pp. 41 and 54.

United Kingdom

In the UK, the National Health Service (NHS) provides universal health coverage. In turn, according to various publications, the UK's Department of Health regulates NHS expenditure on pharmaceuticals primarily by controlling the profits that drug manufacturers are allowed to make on sales to the NHS. The profit control program, called the Pharmaceutical Price Regulation Scheme (PPRS), is renegotiated every 5-6 years by the Department of Health and the Association of the British Pharmaceutical Industry (ABPI).

Various sources indicate that, under the PPRS, companies enter into yearly confidential dialogues with the Department of Health. Profits are determined by companies' level of long-term risk, investment in the UK, rate of return on capital, overall relationship with the NHS, and levels of exports.

Healthcare Coverage

The UK's National Health Service (NHS) provides comprehensive healthcare to all UK residents. Because the NHS pays for most drugs prescribed in the UK,[135] it is in the Government's interest to strictly control the cost of pharmaceuticals. Costs are contained in a number of ways, including price controls, profit controls, encouraging the use of generics and patient copayments, publication of "negative lists" of inefficient drugs to discourage and contain their use, issuing a "Selected List" of minor drugs that are not paid for by the NHS, and enlisting doctor participation to control drug expenditures. Since 1991, for example, GPs have the option of becoming "fundholder practices," which encourages further conservation of resources, including expenditures on pharmaceuticals.[136] Since its introduction, over half of UK GPs have opted to become fundholders, and have reduced spending on pharmaceuticals to a level up to 9.4 percent less than that of nonfundholding practices.[137]

In regard to copayments, UK patients either pay a standard fee for each prescription or a yearly fee that covers unlimited prescription costs. Spending by GPs is calculated monthly by The Prescription Analysis and Cost System (PACT). The copayment for prescribed drugs since April 1998 is $9.28 per item; this favors patients who are prescribed expensive and/or large amounts of pharmaceuticals. Many exceptions are granted; in 1997, 85 percent of prescription were free to patients.[138]

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[135] The NHS does not reimburse pharmaceuticals that are directly exported, OTC drugs, those sold outside the NHS, and those on a "negative list" of eight therapeutic categories.

[136] Fundholder practices receive a set amount of operating funds, determined by the National Health Service Executive, each year. Any excess funds at the end of the year can be appropriated by the practice. Practices which overshoot their budget can apply for extra money from the NHS.

[137] Spending habits of fundholders are surveyed by the UK Audit Commission; these results are cited in W. Duncan Reekie, *Medicine Prices and Innovations: An International Survey*, The Institute of Economic Affairs (London: 1996, p. 16.).

[138] Michael L. Burstall, Bryan Reuben and Anthony Reuben,"Pricing and Reimbursement Regulation in Europe: An Update on the Industry Perspective."

Pricing

Profit control

The UK is unique in the EU in controlling not only the prices of pharmaceuticals but also the profits allowed to manufacturers which sell their pharmaceuticals to the NHS. Price control began in 1957 with manufacturer participation in the Voluntary Price Regulation Scheme to control excess profitmaking. This form of cooperation between manufacturers and the Department of Health to limit the health budget was renamed the Pharmaceutical Price Regulation Scheme (PPRS) in 1978. Participation in the PPRS is not mandatory, though all firms that sell to the NHS do participate in PPRS negotiations.[139] The terms of the PPRS are periodically reviewed and target budgets of health spending are renegotiated between the Department of Health (which administers the PPRS) and the Association of the British Pharmaceutical Industry (ABPI). This normally takes place every 5 or 6 years; the last such negotiation took place in 1998-89.[140]

Through the PPRS, the Department of Health sets companies' profits according to three factors: level of long-term risk, investments in the UK (including R&D), and the rate of return on capital. Additional factors that are examined include a company's overall relationship with the NHS, levels of exports, and the amount of manufacturing that is carried out in the UK.[141] The terms of the PPRS also regulate corporate tax deductions that pharmaceutical companies can claim for R&D expenditures, and deductions companies can claim for sales promotion expenditures. There are no established guidelines governing the level or inter-relationship of all the aforementioned factors and prices; observers have been unable to determine a consistent set of determinants about the profit decisions made under the PPRS.[142]

The primary oversight mechanism used by PPRS committees is review of yearly confidential submissions (i.e., the Annual Financial Return (AFR)) with the Department of Health, required by all companies with annual sales to the NHS of over $31 million. In the AFR, revenue generated by sales to the NHS is distinguished from other sales revenue, so that profit allowances may be determined. The AFR also enables the Department of Health to calculate R&D rates; these are capped at 20 percent of sales to NHS for the industry in a given year, overall.[143] Although the rate of return on "allowable" capital varies between 17 and 21 percent, an automatic allowable margin tolerance of 25 percent also exists.[144] Companies whose sales in a year are 375 percent or higher than the capital invested in a given product reach the PPRS's profit ceiling. Because these companies' capital bases are assumed to be relatively small (this particularly affects subsidiaries of

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[139] Richard T. Rapp and Adam Lloyd, "'Civilized' Pharmaceutical Price Regulation: Can the U.S. Have It Too?", NERA Consulting Economists, found at the NERA website (*http://www.nera.com/search/searf.html)* and retrieved on Aug. 1, 2000.

[140] Generic prices are set by the Department of Health's Drug Tariff each month.

[141] According to industry, requirements that companies invest in R&D in the UK do not encourage real investment, but instead induces artificial and distorted investment for the sake of investment. Commission staff interview with representatives of PhRMA and the multinational pharmaceutical industry on Aug. 3, 2000.

[142] "'Civilized' Pharmaceutical Price Regulation: Can the U.S. Have It Too?"

[143] *Medicine Prices and Innovations: An International Survey*, p. 15.

[144] This used to be known as a "grey area" and is now called a "margin of tolerance." Currently set at 25 percent, the margin of tolerance means that companies are able to earn a profit up to 25 percent greater than their target range of profit; they are not allowed to raise prices unless their profit falls 25 percent *below* their target range of profit.

foreign companies), these companies are allowed to earn a profit based on their levels of sales instead of their capital base, limited to a 4.5 percent return on sales, with a 25 percent margin.

Initial launch prices of pharmaceuticals are not controlled. However, once manufacturers set an initial price, they must obtain official permission to raise it. If a company's total profits on branded sales to the NHS exceed the PPRS limit, a company can be forced to reduce prices; if profits fall below an approved level, the company may be allowed to increase product prices. If companies exceed their allowed profit, they must either repay the excess profits directly to the PPRS, or lower existing and future prices. Promotional spending is limited to a finite percentage of sales to the NHS.

Price controls

In addition to controlling profits and limiting price increases through the PPRS, the Department of Health periodically encourages comprehensive price restraint through unilateral freezes or reductions of the total health budget. A recent period of major price restraint occurred during 1990-92, during which pharmaceutical prices were frozen; prices were then lowered by 2.5 percent in 1993. In 1999, prices were lowered by 4.5 percent.[145]

The Department of Health also controls distribution costs. Wholesalers which sell to the NHS receive a 12.5 percent discount from the manufacturers' price. Pharmacies receive a standard dispensing fee for each prescription they fill; this is reimbursed at the wholesaler's list price. There is no VAT on NHS prescriptions; the VAT on OTC drugs and private prescriptions is 17.5 percent.

In a further attempt to ensure that inexpensive pharmaceuticals are purchased by the NHS, the Department of Health encourages pharmacists to buy parallel imports when they are cheaper than domestically produced pharmaceuticals.[146] Since 1991, pharmacists have been allowed to keep the difference between the listed reimbursement price and the price paid for imported pharmaceuticals. As noted by one source, the use of generic pharmaceuticals in the UK is increasing overall.[147] In 1999, the consumption of generic products was valued at about $2.3 billion, or about 23 percent of the prescription pharmaceuticals market.[148]

[145] This was modified in February 2000 by a regulation freezing prices on branded pharmaceutical products at January 20, 2000, levels for companies with sales of under £1 million (or about $1,540,000) in the 12 months to October 2000. The regulation also required the 4.5 percent price decrease for companies with sales to the NHS greater than this amount. The pricing freeze and pricing levels will be reevaluated in 2001.

[146] W. Duncan Reekie, *Medicine Prices and Innovations: An International Survey*, p. 18.

[147] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 41.

[148] *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, 2000, p. 166.

Japan

Various sources note that Japan's rapidly aging population threatens its system of universal, national healthcare (NHI). Annual expenditures grew by 4.9 percent per year since 1980 and totaled $204 billion in 1998. Recent economic declines have reportedly added pressure to contain the cost of NHI.

Sources have also indicated that with the increased pressure to control NHI costs, the system by which the MHW sets pharmaceutical prices in Japan has come under increased scrutiny. To date all plans for major reform to the system have been shelved.

Healthcare Coverage

The origin of the present day Japanese National Health Insurance (NHI) program dates to the passage of the Health Insurance Law of 1922 which provided insurance coverage for major occupational groups.[149] Gradual revisions to the law added those initially excluded, and the intent of the 1958 revision was to provide universal health insurance coverage. Unlike previous laws that focused on employment, the 1958 law focused on residence and mandated that all residents must join a health insurance plan. By 1961, a universal-access health insurance system was in place. This system, which is still in effect today, provides a comprehensive set of uniform benefits. It is financed by employer-employee contributions to either private employer-based or government insurance plans but provides government subsidies for certain groups. A persistent deficit has plagued the system as annual healthcare expenditures have risen steadily.[150] In spite of subsequent revisions to the law (most recently in 1997) that increased premiums and added or increased copayments, deficits have continued.

During the last two decades, the age distribution of Japan's population shifted significantly. The percentage of the total population age 65 and older almost doubled from 9.0 percent in 1980 to a projected 17.1 percent in 2000.[151] (This contrasted with other G-8 countries which have experienced much more moderate shifts.) Already, approximately one third of Japan's total healthcare bill is spent on services for the elderly,[152] and yet the shift is forecast to continue with the percentage of the population age 65 and older reaching 26.2 percent in 2020.[153] As the population has aged, demand for medical services has increased. Since 1980, annual expenditures for healthcare grew by 4.9 percent per year, and in 1998 the Japanese healthcare expenditures totaled $204 billion.[154] The aging population also squeezes NHI revenues which are financed by premiums that are tied to wages. The slow growth and turmoil of the

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[149] Laurene A. Graig, *Health of Nations-An International Perspective on the U.S. Health Care Reform*, 3rd ed. (Washington DC: CQ Press, 1999) p. 98.

[150] JPMA, "1999 Pharmaceutical Administration and Regulations in Japan," found at *http://www.jpma.or.jp/12english/01guide* and retrieved July 12, 2000, p. 72.

[151] Gerald F. Anderson and Peter S. Hussey, "Population Aging: A Comparison Among Industrialized Countries," *Health Affairs*, vol. 19, No. 3 (May/June 2000), p. 192.

[152] Graig, *Health of Nations*, p. 95.

[153] Anderson and Hussey, "Population Aging: A Comparison Among Industrialized Countries," p. 192.

[154] JPMA, *Data Book 2000*, p. 3-8.

Japanese economy during the last decade have added to the chronic deficits and have increased pressure to contain the cost of NHI.

Measures both to increase revenues and contain costs have been taken. In 1997, the financial burden borne by patients increased, as copayments doubled and premiums increased.[155] Some of the resulting cost containment measures have not been effective. For instance, according to a report by the Boston Consulting Group, overall spending on drugs increased by 59 percent between 1980 and 1993 in spite of the fact that Japan's price control mechanism drove pharmaceutical prices down by more than 60 percent over the same period. Increased spending was driven by increased prescribing volumes and the higher price levels of new drugs.[156] It should be noted that increased spending for pharmaceuticals did not keep pace with the increased healthcare spending, however. Pharmaceutical spending as a percent of total healthcare expenditures has declined steadily since the early 1970s.[157]

Pricing

Drugs containing new chemical entities (NCEs) are added to the NHI drug price list four times annually in March, May, August, and November.[158] The MHW through the Special Committee on Drug Prices (part of the Central Social Insurance Medical Council or Chuikyo) fixes the introductory price of every new ethical brand name drug through negotiation with the manufacturer. Generally, the price of a "comparator" product which is already on the market will be considered, and overseas prices in four countries (United States, United Kingdom, Germany, and France) are also taken into account. If a comparable product doesn't exist on the market or if the manufacturer wants to avoid the comparator-based system, it may seek to have the new drug price based upon cost calculation, but MHW reserves the final decision regarding the actual method used.

Drugs are also classified by usefulness and market size; the criteria in each of the categories are summarized in the tabulation below. Five of the categories allow a premium to be awarded to the new drug in question. Since 1997, 47 new drugs have been introduced, but none has received an innovation premium.[159]

Classification Based on Usefulness

A Innovative new drugs (standard premium: 40%; priority allocation: 20-60%)

B1 Useful new drugs I (standard premium: 10%; priority allocation: 5-15%)

B2 Useful new drugs II (standard premium: 3%; priority allocation: 1.5-4.5%)

C Other new drugs (no premium)

Classification Based on Market Size

A1 New drugs with extremely small markets (standard premium: 40%; priority allocation: 5-15%)

A2 New drugs with small markets (standard premium: 3%; priority allocation: 1.5-4.5%)

B Other new drugs (no premium)

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[155] Graig, *Health of Nations*, p. 95.

[156] BCG, *Ensuring Cost-Effective Access to Innovative Pharmaceuticals*, p. 19.

[157] PhRMA, "PhRMA Proposal for NHI Drug Pricing Reform-Supporting Arguments," Jan. 29, 1999, p. 61.

[158] JPMA paper, "Calculation of Drug Price" found at *http://www.jpma.or.jp/12english/03drug/e-calc.html* and retrieved July 12, 2000.

[159] Draft PhRMA report, July 25, 2000.

An additional factor is the R-zone (reasonable zone) which is the allowable margin between a medical facility's acquisition cost and the reimbursement price. Unlike the European Union and the United States, where the separation of the prescribing and dispensing of ethical drugs (bungyo) is well-established, medical facilities in Japan both prescribe and dispense ethical drugs.[160] According to JPMA, about 80 percent of ethical drugs in Japan move from pharmaceutical wholesalers to medical institutions (either hospitals or clinics).[161] Therefore, the R-zone (also known as the yakkasa) historically has been an important source of income for clinics and hospitals in Japan. This financial incentive led to the widespread practice of over-prescription of drugs in Japan,[162] but bungyo appears to be increasing as the R-zone has decreased.[163]

Prices are generally reviewed biennially by the MHW with the goal of bringing NHI prices closer to market prices. Drugs are subject to repricing if principal indications, efficacy, dosage levels, or market size change. Revised reimbursement prices are determined using a formula developed by the Chuikyo in 1991.[164] If the discount for the wholesale price of a drug is more than the R-zone, the price will be cut by the amount of the excess. In addition to revisions for specific drugs, from 1992 to 1998 the R-zone itself was reduced from 15 percent to 5 percent.[165] During this period prices were revised in three consecutive years (1996, 1997, and 1998). A new Drug Price Organization was established in October 2000. It is designed to provide the MHW with expert advice on the appropriate comparator to use and appropriate premiums to apply, if any.[166]

The use of generic drugs in Japan has been limited for three major reasons. As outlined above, pharmaceuticals are reimbursed based on a fee-for-service system; Japanese doctors are brand conscious and uncertain of the quality of generic drugs, and Japanese pharmacists cannot substitute drugs.[167] Also, it should be noted that because of Japan's universal healthcare system, Japanese patients are not sensitive to the cost of pharmaceuticals.

Two sources estimate that the share of generic drugs in Japan in 1999 was approximately 7.5-8.0 percent, by value, of the total prescription market.[168] The share of generic drugs is expected to increase as the pressure to contain costs continues to intensify. Prices for generic drugs are listed on the NHI drug price list at 80 percent of the price of the original drug unless another generic has already been listed. If that is the case, the price is set at that of the cheapest existing generic drug.

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[160] Although promotional spending is reportedly not controlled in Japan, some restrictions have been implemented on how companies promote pharmaceutical products. *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 99.

[161] JPMA, "Distribution System," found at *http://www.jpma.or.jp/12english/05sales/e-dist.html* and retrieved July 19, 2000.

[162] Graig, *Health of Nations*, p. 115.

[163] JPMA, "Bungyo," found at *http://www.jpma.or.jp/12english/05sales/e-bung.html* and retrieved July 19, 2000.

[164] JPMA, "1999 Pharmaceutical Administration and Regulations in Japan," retrieved July 12, 2000, p. 74.

[165] Ibid.

[166] Commission staff interview with representatives of PhRMA on July 25, 2000.

[167] U. S. & Foreign Commercial Service and U.S. Department of State, *Generic Drugs–Japan*, (Industry Sector Analysis), 1999, p. 6.

[168] Ibid., p. 6, and *Pharmaceutical Pricing & Reimbursement 2000: A Concise Guide*, p. 98. One of the sources, the Ethical Manufacturers' Association, is a Japanese organization of small to medium-size manufacturers of ethical and OTC drugs which is generally known as the organization of the generic drug producers.

Pricing Reform

On August 29, 1997 the ruling coalition parties' Health Insurance System Reform Committee announced a reform plan entitled "National Health Insurance for the 21st Century: Plan for Preserving Quality Medical Care and the Universal Insurance System."[169] The plan called for the existing NHI drug pricing system to be abolished and replaced with a Japanese version of reference pricing systems of the sort found in Europe. The proposal was not supported by industry[170] and ultimately was scrapped at the meeting of the LDP Research Council on Basic Medical Issues on April 13, 1999.[171] A market-based pricing reform proposal had been made by the industry through PhRMA in December 1998 but was likewise rejected in April 1999. Subsequently, the Japanese government announced that it is not prepared to undertake comprehensive restructuring of the reimbursement pricing program. Chuikyo, through the dedicated Committee on Drug Pricing Issues, has been reviewing the current NHI pricing system. Two main issues are the status of the R-zone method and pricing of long-term listed drugs.

[169] Reform of the NHI Drug Price System found at *http://www.jpma.or.jp/12english/03drug/e-reform.html* and retrieved July 12, 2000.

[170] Osamu Kido, "Review of 1998: The Japanese Economic Recession and the Pharmaceutical Industry," *Update*, Vol. 15, found at *http://www.jpma.or.jp/12english/07publications/up015/e-up15-01.html* and retrieved July 14, 2000.

[171] Mitsuo Yashiro, "Trends in NHI Price Reform and Outlook for the Future," *Update*, Vol. 17, found at *http://www.jpma.or.jp/12english/07publications/up017/e-up17-03.html* and retrieved July 14, 2000.

Mexico

Mexico's General Law of Health, implemented in 1984, guarantees the right of all Mexican citizens to healthcare. Approximately half of Mexico's population is covered by its social security system, while the other half is uninsured (but has the option of using Federal and State government services). Per capita spending on healthcare in 1997 in Mexico was $202.

Sources in Mexico have stated that the Institute Mexicano de Seguro Social is the largest purchaser of pharmaceuticals in Mexico and can impose prices on drugs sold in the public sector. According to a recent publication, retail prices in the private sector are limited by SECOFI's Department of Standards and Acquisition. Although the latter process has reportedly been relaxed over the past few years, the Government must approve all final retail prices.

Healthcare Coverage

In 1984, Mexico implemented the General Law on Health (Ley General de Salud). This law guarantees the right of all Mexican citizens to healthcare and describes the roles and responsibilities of all participants, including the federal and state governments, healthcare providers, and patients. According to a recent study, "the healthcare system in Mexico is comprised of three distinct segments:

> the social security system, paid for by employers, workers and tax payers;
> the governmental health system, financed by tax payers and users through copayments; and
> the private sector, which relies on out-of-pocket payments from users and insurance premia."[172]

Approximately half of Mexico's population, typically the middle and upper class, are covered by public insurance under Mexico's social security system.[173] Some individuals supplement this public coverage with private insurance. The second half of the population is uninsured, but can use Federal and State funded government services, usually in the form of copayments based on an individual's income.[174]

When comparing pharmaceutical development and pricing in Mexico versus the United States it should be noted that Mexico "is at a less advanced stage of economic development, has lower real wages and per capita incomes, and has lower prices for many goods and services."[175] In 1997, per capita spending on healthcare in Mexico was $202, compared with $3,998 in the United

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[172] National Economic Research Associates (NERA), *Financing Health Care: The Health Care System in Mexico*, August 1998, p. 1.

[173] Ibid., pp. 4 and 18.

[174] Ibid., p. 18. NERA estimates that about 10-15 million people do not have any access to healthcare services, mainly because of poverty, combined with a lack of education and/or lack of nearby facilities.

[175] Patricia M. Danzon, *Price Comparisons for Pharmaceuticals: A Review of U.S. and Cross-National Studies*, The AEI Press, Washington, DC, 1999, p. 32.

States.[176] In recent years, pharmaceuticals have accounted for a higher percentage of total healthcare spending in Mexico than in most Organisation for Economic Co-operation and Development (OECD) countries.[177]

Pricing

Overall, the Mexican Government is the largest domestic purchaser of pharmaceuticals.[178] In essence, there are two separate markets for pharmaceuticals in Mexico, the public and the private sectors. In the public sector, generic and copy drugs[179] are sold for low prices which are essentially set by the Government.[180] The Instituto Mexicano de Seguro Social is the largest purchaser of pharmaceuticals, and as such has the power to impose its prices on drugs sold in the public sector.[181] Patented products are mainly sold in the private sector, but retail prices are still limited by SECOFI's Department of Standards and Acquisition. Although this process has been relaxed somewhat, and manufacturers have been permitted to increase prices when they choose instead of during 3-month intervals as before, the Government must still approve all final prices.[182] Wholesale and retail margins are also set by agreement and through negotiations between the Government and the manufacturer; however, manufacturers are permitted to discount their prices.[183] In neither sector are pharmaceuticals subject to the VAT.

Pharmaceutical prices are substantially lower in Mexico than they are in the United States, although the gap has been narrowing somewhat since the 1980s. A recent report prepared by minority staff of the Committee on Government Reform of the U.S. House of Representatives found that the average prices for the top five drugs for senior citizens in the United States were 83 percent higher than the prices that Mexican consumers pay.[184] According to this report, the difference in price for certain brand-name products ranged from 3 percent for Zoloft to 262 percent for Prilosec. As a result of these lower prices, U.S. citizens reportedly have been traveling to Mexican border towns in rising numbers to purchase pharmaceuticals.[185]

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[176] Organisation for Economic Cooperation and Development (OECD), *"Health Data 2000: A Comparative Analysis of 29 Countries,"* OECD CD-ROM, 2000, France. NERA's estimate for Mexico's per capita spending on healthcare for 1998 was $185 as compared with OECD's estimate for the United States of $4,178.

[177] According to NERA, pharmaceuticals accounted for around 30 percent of total healthcare spending in Mexico in 1995 as compared with the United States, in which pharmaceuticals accounted for under 9 percent of total expenditures in that year. NERA, *Mexico*, p. 77.

[178] Cantor, *Prescription Drug Price Comparison*, CRS-5.

[179] As noted in chapter 3, a copy product is one in which the original innovative product is still under patent in other countries.

[180] In addition, the author of a recent journal article states that 20,000 Mexican pharmacies began to sell generic products in 1999, resulting in a 30 percent decrease in drug prices in that year. Rosalyn Chan, "Mexico: Striking a Balance Between Price and Innovation," p. 22.

[181] According to the U.S. Commercial Service (Mexico), about 80 percent of the Mexican population receives pharmaceuticals from the IMSS. Commission staff interview with U.S. Commercial Service (Mexico) representative on July 24, 2000.

[182] NERA, *Mexico*, p. 82.

[183] Ibid.

[184] Minority Staff, Special Investigations Division, Committee on Government Reform, U.S. House of Representatives, *Prescription Drug Pricing in the 7th Congressional District of Massachusetts: Overcharging Compared to Mexico and Canada*, 2nd report, Jan. 5, 2000, p. 8.

[185] According to PhRMA, approximately 25 percent of products purchased by U.S. citizens at the

(continued...)

The reasons for the price differences between pharmaceuticals sold in the United States and in Mexico are varied and often hotly debated. A CRS report attributes the differential mainly to international income inequality and the lower value of the peso.[186] According to CRS, the very prevalent role of the Government in the Mexican healthcare system further explains the lower prices for pharmaceuticals in Mexico. The Mexican Government, in an effort to provide broad access to pharmaceuticals, establishes maximum prices for these products. In addition, the Mexican Government, as the largest domestic purchaser with significant power, sells pharmaceuticals through its social security system, which could be further construed as public assistance to Mexican consumers.[187] (For more information about the CRS report, see chapter 2.)

Also, in 1992, industry sources contended that prior to the passage of NAFTA the public tendering or Government procurement system in Mexico discriminated against foreign-based pharmaceutical companies that sold patented products.[188] Chapter 10 of the NAFTA specified that Government agencies should work toward opening the government procurement market for pharmaceuticals in Mexico to U.S. and Canadian companies.[189] Although price controls have been relaxed and the Government procurement market for pharmaceuticals is more open in Mexico, prices for pharmaceuticals in Mexico reportedly continue to be lower, on average, than in the United States as a result of these combined Government actions.

Another reason cited for the price differences between Mexico and the United States is the fact that Mexico did not enact patent protection for pharmaceuticals until relatively late, and in such a way that resulted in a proliferation of copy products. Danzon notes that such copy pharmaceuticals have not been developed through expensive R&D, are less expensive, and weaken demand for the original, patented product.[190] As a result, a manufacturer that holds a patent on a particular pharmaceutical that is subject to copies must reduce its price if it is to compete. Finally, NERA reports that many prescription drugs are available in Mexico without prescription;[191] Danzon states that in such cases consumers can directly influence their choice of drug, as opposed to the choice being made for them by a doctor's prescription.[192] Other experts note that retailers (such as pharmacies) may offer pharmaceuticals at prices below the maximum Government price printed on the package.[193]

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[185] (...continued)
border may not be effective or meet minimum standards and, therefore, may "pose important health risks to the patient," and about 75 percent of those products that are not approved by the FDA are manufactured in facilities that are not certified by the U.S. Food and Drug Administration. Commission staff interview with representatives of PhRMA on July 13, 2000, and PhRMA, Written Submission, p. 29.

[186] Cantor, *Prescription Drug Price Comparisons*, CRS-3.

[187] Ibid.

[188] Pharmaceutical Manufacturers of America, press release, "Impact on the Pharmaceutical Industry of the North American Free Trade Agreement," Sept. 10, 1992.

[189] As of Jan. 1, 2002, all Mexican Government agencies are to fully open procurement procedures for pharmaceuticals. USITC, *Potential Impact on the U.S. Economy and Selected Industries of the North American Free-Trade Agreement*, pp. 9-2 to 9-3.

[190] Patricia M. Danzon, *Price Comparisons for Pharmaceuticals*, p. 34.

[191] NERA, *Mexico*, p. 77.

[192] Patricia M. Danzon, *Price Comparisons for Pharmaceuticals*, p. 34.

[193] NERA, *Mexico*, p. 94.

Russia[194]

Various sources indicate that the Russian pharmaceutical market is supplied largely by generic products because of their cost relative to that of innovative medicines and because of their long-term presence in the market. Budget constraints of local governments reportedly hinder the use of expensive, innovative medicines developed overseas because funding for reimbursable pharmaceutical products comes from local budgets.

Generic pharmaceutical products account for 83 to 91 percent of the pharmaceutical market in Russia, of which 70 percent are considered "old-generation" products, according to a recent report.[195] Prior to 1992, Russian patent law protected only the manufacturing process rather than the final product; as a result, many Western drugs have not been competitive owing to the existence of copies in the Russian market.[196] Old-generation products are relatively less expensive than newer generic products or innovative medicines, and doctors and patients alike are more familiar with these products.[197] Although most pharmaceutical products are sold on an OTC basis, prescriptions are used to identify drugs for specific ailments and dosages, and are required to obtain reimbursable drugs. Medical care in Russia is costly, prompting many people to go directly to a pharmacy for reliance on established OTC products and companies that are well known to them.[198] Pharmaceutical needs are funded by consumers, local budgets, and mandatory health insurance funds.[199]

A price-control system was introduced in Russia by decree No. 347, "On Measures for State Control over Pricing of Medicines," effective March 29, 1999, on medicines included in the "list of essential and most important medicines" eligible for reimbursement.[200] The decree provides

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[194] Commission staff contacted the Government of Russia and other entities via fax on July 24, 2000. Faxes were sent to the State Duma, Ministry of Public Health, Department of Licensing, Russian Agency on Patents and Trademarks, the Chamber of Commerce and Industry of the Russian Federation, and the All-Russia Market Research Institute. The Commission has since received two responses, one dated September 15, 2000, from the Ministry of Health of the Russian Federation, Department of International Cooperation and the other, dated Sept. 29, 2000, from the Russian Agency for Patents and Trademarks.

[195] Gregory Feifer, "Locals Raise Production of Generic Medicines," *The Moscow Times*, Apr. 4, 2000, found at *http://today.newscast.com* and retrieved on July 14, 2000.

[196] Mikhail Minkevich, "Drugs and Pharmaceuticals in Northwest Russia," Sept. 1998, found at *http://www.bisnis.doc.gov/bisnis/isa/9809phrm.htm*, retrieved July 10, 2000.

[197] One source reported that "the lack of information about new drugs and their prohibitively high prices encourage many doctors to resort to prescribing older, more familiar drugs, even if they are less effective than newer options." Oksana Yablokova, "Drug Rush Dizzies Doctors, Patients Alike," *The Moscow Times*, Apr. 13, 2000 found at *http://today.newscast.com* and retrieved on July 14, 2000.

[198] Oksana Yablokova, "Drug Rush Dizzies Doctors, Patients Alike," *The Moscow Times*, Apr. 13, 2000 found at *http://today.newscast.com* and retrieved on July 14, 2000.

[199] V.I. Starodubov, "Measures of State Regulation of Pharmaceutical Support to the Population of the Russian Federation," *Zdravookhraneniye Rossiyskoy Federatsii*, June 30, 1999, pp. 3-9, translated by FBIS.

[200] The list of essential and most important medicines was established by decree No. 478 of the Government of the Russian Federation, Apr. 15, 1996. Local governments develop their own lists based

(continued...)

for Government control over market prices in order to increase transparency of price formation in the regions of Russia,[201] and applies to all organizations holding licenses to manufacture, store, or sell medicines.[202] The registered price sets an upper limit to the selling price; price control is achieved by curbing trade mark-ups and limiting the number of suppliers in the distribution chain.[203] Prices are registered at the Federal level by the manufacturer or designated representative, but it is up to local officials to implement the controls on the basis of the guidelines outlined in the decree. As of August 10, 2000, the Russian Ministry of Health had registered prices on 5,699 pharmaceuticals from 343 manufacturers, of which 162 were domestic producers and 181 were foreign producers.[204]

The Ministry of Economics and the Ministry of Health are the Federal agencies responsible for monitoring the price-control system. The Ministry of Economics reviews and approves proposed prices, while the Ministry of Health registers prices, issues certificates, and communicates the prices to local officials. Prices of domestically manufactured products are registered in rubles, and imported pharmaceuticals are registered in foreign currency and in rubles.[205] Prices can be reregistered by repeating the registration process. Proposed prices can be submitted without a cost breakdown if they can be linked to reference prices in European countries.[206]

While markups vary across regions, one report indicated that, generally, wholesale prices are 10 to 15 percent higher than manufacturer prices; retailers add another 20 to 30 percent. Local authorities compile their own lists of essential medicines based on the Federal list of essential medicines and the specific needs of the region. Further, retail prices can vary depending on whether the product was obtained from distributors or manufacturers. Final selling prices are not required to meet the registered price plus markup, and pharmacies can and do sell products below the maximum allowed.[207]

The list of essential medicines eligible for reimbursement contains up to 10,000 different products (based on 394 active ingredients[208]). The list largely includes generic products; however, some patented prescription medicines do appear on the list. Approximately 30 million Russians are eligible for discounted medicines; pharmacies receive reimbursement from local agencies, depending on the eligibility of the patient and the regional healthcare budget.

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[200] (...continued)
on the Federal list of essential medicines.

[201] The Association for International Pharmaceutical Manufacturers (AIPM), "Introduction and Initial Findings of the Price Control System in Russia," presentation by Irina Stafeeva, Deputy Director, undated.

[202] Pharmaceutical products not considered "essential medicines" still must be registered with the Ministry of Health, but are not subject to price controls outlined in decree No. 347.

[203] AIPM, "Introduction and Initial Findings of the Price Control System in Russia," presentation by Irina Stafeeva, Deputy Director, undated.

[204] Ministry of Health of the Russian Federation, Department of International Cooperation, written submission to the Commission, Sept. 15, 2000.

[205] The exchange rate is based on the Russian Federation Central Bank rate on the date of registration.

[206] AIPM, "Economic and Legal Framework for Non-Prescription Medicines," draft of July 21, 2000, p. 3.

[207] Pyrabelisk, "Russian Drug Market."

[208] Forty-seven percent of the 394 active ingredients are not produced in Russia. See V.I. Starodubov, "Measures of State Regulation of Pharmaceutical Support to the Population of the Russian Federation," *Zdravookhraneniye Rossiyskoy Federatsii*, June 30, 1999, pp. 3-9, translated by FBIS.

Currently, pharmaceutical products are not subject to a VAT; however, the Russian Government recently proposed eliminating the VAT exemption for pharmaceuticals, except essential medicines.[209] The new draft tax code seeks to establish a 20-percent VAT on pharmaceuticals, active substances, and medical devices in order to increase revenues.[210] The Association of International Pharmaceutical Manufacturers (AIPM)[211] predicts that this proposal could (1) raise pharmaceutical retail prices by at least 20 percent; (2) adversely impact domestic producers, which import up to 90 percent of their raw materials, leading to supply shortages; and (3) increase the possibility of corruption.[212] The Russian Government's response to AIPM's concerns is not known at this time.

[209] "Russia Proposes 20% VAT for Medicines," *SCRIP*, No. 2556, July 12, 2000, p. 6.

[210] Ibid.

[211] AIPM represents over 50 international pharmaceutical companies in Russia.

[212] AIPM, press release "International Pharmaceutical Producers are Concerned About Possible Introduction of 20% VAT for Medicines," July 11, 2000.

Appendix A
Request Letter From the Committee on Ways and Means of the U.S. House of Representatives, Dated June 28, 2000

Rec'd 6-29-00

COMMITTEE ON WAYS AND MEANS

U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, DC 20515–6348

June 28, 2000

The Honorable Stephen Koplan
Chairman
U.S. International Trade Commission
500 E Street SW
Washington, DC 20436

Dear Chairman Koplan:

Under the authority of section 332(g) of the Tariff Act of 1930, 19 U.S.C. §1332(g), I am requesting that the Commission institute a fact-finding investigation relating to pricing of prescription drugs by certain U.S. trading partners. Specifically, I would like the Commission to determine the effect of the utilization of price controls on innovative medicines by the other G-8 countries or other countries that are signatories to the NAFTA on pricing for such drugs abroad and in the United States.

The Commission's review should include the following:

(1) the process by which prescription drug prices are established;

(2) the role of compulsory licensing in setting prices;

(3) a description of the costs associated with the development of prescription drugs, and a comparison of the authorized prices in the specified countries; and

(4) whether and to what extent price control systems utilized by such countries impact pricing for comparable drugs in the United States.

The Committee would appreciate receiving the study no later than 90 days after receipt of this letter. Thank you for your attention to this important matter.

With best personal regards,

Bill Archer
Chairman

Appendix B
Commission's Response Letter
to the Committee on Ways and Means,
Dated July 21, 2000

CHAIRMAN

UNITED STATES INTERNATIONAL TRADE COMMISSION

WASHINGTON, D.C. 20436

July 21, 2000

The Honorable Bill Archer
Committee on Ways and Means
United States House of Representatives
Washington, DC 20515-6348

Dear Chairman Archer:

In response to your letter of June 28, 2000, the U.S. International Trade Commission has instituted, pursuant to section 332(g) of the Tariff Act of 1930, an investigation entitled "Pricing of Prescription Drugs."

Enclosed for your information is a copy of the Commission's notice announcing institution of the investigation, which is being published in the *Federal Register*. The Commission expects to submit its report to you by September 29, 2000, as requested.

We have looked closely at the issues raised in your request and believe that a comparison of the authorized prices in the specified countries, and a comprehensive and in-depth analysis of the impact of foreign price controls on U.S. prices, would require a significantly longer study period.

Accordingly, the Commission will provide a report in 90 days that will address, in descriptive terms, the process by which prescription drug prices are established; the role of compulsory licensing in setting prices; a description of the costs associated with the development of prescription drugs; and provide a review of the literature that addresses the dynamics of the pharmaceutical market and cross-country comparisons. Further, we will provide a description of the analytical methods (and possibly an analytical framework) that could be used to analyze the question of whether and to what extent price control systems utilized by other countries impact pricing for comparable drugs in the United States. However, due to the complexity of the task, the Commission will not be able to respond fully to your request in a 90-day investigation.

The Commission is willing to undertake this additional analysis if you believe that it would be of assistance to the Committee. Any such investigation will require

further consultation between Committee staff and Commission staff as to its scope, terms of reference and duration.

Please continue to call on us whenever we can be of assistance to you.

Sincerely,

Stephen Koplan
Chairman

Enclosure

Appendix C
Federal Register Notice
(July 26, 2000)

DEPARTMENT OF THE INTERIOR

National Park Service

Draft Legislative Environmental Impact Statement, Timbisha Shoshone Homeland In and Around Death Valley National Park; Notice of Second Extension of Public Comment Period

SUMMARY: Pursuant to § 102(2)(C) of the National Environmental Policy Act of 1969 (P.L. 91–190 as amended), the National Park Service, Department of the Interior, has prepared a Draft Legislative Environmental Impact Statement (LEIS) assessing potential impacts of Congress establishing a proposed Timbisha Shoshone Tribal Homeland in and around Death Valley National Park, California. The Draft LEIS identifies parcels of land suitable for the Timbisha Shoshone Indian Tribe to establish a permanent homeland. In deference to public interest expressed to date from local governmental agencies, organizations, and other interested parties, the original 60-day public comment period has been extended for a total of 30 calendar days from the original July 22, 2000 deadline.

SUPPLEMENTARY INFORMATION: Interested individuals, organizations, and agencies are encouraged to provide written comments—to be considered any response must now be postmarked no later than August 21, 2000.

All responses should be addressed to the Superintendent, Death Valley National Park, P.O. Box 579, Death Valley, California 92328. If individuals submitting comments request that their name or/and address be withheld from public disclosure, it will be honored to the extent allowable by law. Such requests must be stated prominently in the beginning of the comments. There also may be circumstances wherein the NPS will withhold a respondent's identity as allowable by law. As always: NPS will make available to public inspection all submissions from organizations or businesses and from persons identifying themselves as representatives or officials of organizations and businesses; and, anonymous comments may not be considered.

To obtain a copy of the LEIS please contact Bettie Blake at (760) 786–3243. All other questions can be directed to Joan DeGraff at (760) 253–6830.

Dated: July 18, 2000.

James R. Sheveck,

Acting Regional Director, Pacific West Region.

[FR Doc. 00–18841 Filed 7–25–00; 8:45 am]

BILLING CODE 4310–70–P

DEPARTMENT OF THE INTERIOR

National Park Service

Golden Gate National Recreation Area; Correction to Notice of Proposed Year-Round Closure at Fort Funston and Request for Comments

CORRECTION: Public comments on this notice must be received by September 18, 2000.

Dated: July 17, 2000.

Donald Mansal,

Acting Superintendent, GGNRA.

[FR Doc. 00–18842 Filed 7–25–00; 8:45 am]

BILLING CODE 4310–70–M

INTERNATIONAL TRADE COMMISSION

[Investigations Nos. 731–TA–457 A–D (Review)]

Heavy Forged Handtools From China

Determinations

On the basis of the record [1] developed in the subject five-year reviews, the United States International Trade Commission determines, pursuant to section 751(c) of the Tariff Act of 1930 (19 U.S.C. 1675(c)) (the Act), that revocation of the antidumping duty orders on heavy forged handtools from China would be likely to lead to continuation or recurrence of material injury to an industry in the United States within a reasonably foreseeable time.

Background

The Commission instituted these reviews on July 1, 1999 (64 FR 35682) and determined on October 1, 1999 that it would conduct full reviews (64 FR 53958, October 15, 1999). Notice of the scheduling of the Commission's reviews and of a public hearing to be held in connection therewith was given by posting copies of the notice in the Office of the Secretary, U.S. International Trade Commission, Washington, DC, and by publishing the notice in the Federal Register on February 10, 2000 (65 FR 6626). The hearing was held in Washington, DC, on May 16, 2000, and all persons who requested the opportunity were permitted to appear in person or by counsel.

The Commission transmitted its determinations in these reviews to the Secretary of Commerce on July 19, 2000. The views of the Commission are contained in USITC Publication 3322 (July 2000), entitled Heavy Forged Handtools from China: Investigations Nos. 731–TA–457 (A–D) (Review).

By order of the Commission.

Dated: July 21, 2000.

Donna R. Koehnke,

Secretary.

[FR Doc. 00–18925 Filed 7–25–00; 8:45 am]

BILLING CODE 7020–02–P

[1] The record is defined in § 207.2(f) of the Commission's rules of practice and procedure (19 CFR 207.2(f)).

INTERNATIONAL TRADE COMMISSION

[Investigation 332–419]

Pricing of Prescription Drugs

AGENCY: United States International Trade Commission.

ACTION: Institution of investigation.

EFFECTIVE DATE: July 19, 2000.

SUMMARY: Following receipt of a request on June 28, 2000, from the Committee on Ways and Means (the Committee) of the United States House of Representatives, the Commission instituted investigation No. 332–419, Pricing of Prescription Drugs, under section 332(g) of the Tariff Act of 1930 (19 U.S.C. 1332(g)).

FOR FURTHER INFORMATION CONTACT: Elizabeth R. Nesbitt, Project Leader (202–205–3355) or Raymond L. Cantrell, Deputy Project Leader (202–205–3352), Office of Industries, or Michael Barry, Deputy Project Leader (202–205–3246), Office of Economics, U.S. International Trade Commission, Washington, DC 20436. For information on the legal aspects of this investigation, contact William Gearhart of the Office of the General Counsel (202–205–3091). Hearing impaired individuals are advised that information on this matter can be obtained by contacting the TDD terminal on (202) 205–1810.

BACKGROUND: The Committee requested that the Commission's report include the following information for Canada, France, Germany, Italy, Japan, Mexico, Russia, and the United Kingdom:

- The process by which prescription drug prices are established;
- The role of compulsory licensing in setting prices;
- A description of the costs associated with the development of prescription drugs, and a comparison of the authorized prices in the specified countries; and
- Whether and to what extent price control systems utilized by such countries impact pricing for comparable drugs in the United States.

The Committee plans to submit its report to the Committee by September 29, 2000.

Written Submissions: A hearing will not be held. Instead, interested parties are invited to submit written statements (original and 14 copies) concerning the matters to be addressed by the Commission in its report on this investigation. In addition to general information regarding prices and pricing practices prevalent in each of the countries under consideration, the Commission is particularly interested in comments regarding the question raised by the Committee in their request regarding the extent to which price control systems utilized by the countries under consideration impact pricing for comparable drugs in the United States. Commercial or financial information that a person desires the Commission to treat as confidential must be submitted on separate sheets of paper, each clearly marked "Confidential Business Information" at the top. All submissions requesting confidential treatment must conform with the requirements of § 201.6 of the Commission's rules of practice and procedure (19 CFR 201.6). All written submissions must conform with the provisions of § 201.8 of the Commission's Rules. All written submissions, except for confidential business information, will be made available in the Office of the Secretary of the Commission for inspection by interested parties. To be assured of consideration by the Commission, written statements relating to the Commission's report should be submitted to the Commission at the earliest practical date and should be received no later than the close of business on August 4, 2000. All submissions should be addressed to the Secretary, United States International Trade Commission, 500 E Street SW, Washington, DC 20436. The Commission's rules do not authorize filing submissions with the Secretary by facsimile or electronic means.

Persons with mobility impairments who will need special assistance in gaining access to the Commission should contact the Office of the Secretary at 202–205–2000. General information concerning the Commission may also be obtained by accessing its Internet server (http://www.usitc.gov).

List of Subjects: Prescription drugs, Price controls, Compulsory licensing.

Dated: July 21, 2000.

By order of the Commission.

Donna R. Koehnke,

Secretary.

[FR Doc. 00–18924 Filed 7–25–00; 8:45 am]

BILLING CODE 7020–02–P

INTERNATIONAL TRADE COMMISSION

[Inv. No. 337–TA–425]

Notice of Commission Determination Not To Review an Initial Determination Terminating the Investigation Based on Withdrawal of the Complaint

In the matter of certain spiral grill products including ducted fans and components thereof.

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined not to review the initial determination (ID) of the presiding administrative law judge (ALJ) terminating the above-captioned investigation on the basis of complainant's withdrawal of its complaint.

FOR FURTHER INFORMATION CONTACT: Donnette Rimmer, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202–205–0663.

SUPPLEMENTARY INFORMATION: The Commission instituted this investigation on January 26, 2000, based on a complaint filed by Vornado Air Circulation Systems, Inc. of Andover, Kansas ("Vornado"). 65 FR 4260.

On June 1, 2000, Vornado filed a motion to terminate the investigation without prejudice based on withdrawal of its complaint. On June 12, 2000, respondents, The Holmes Group, Inc., of Milford, Massachusetts, Holmes Products (Far East) Ltd. (Hong Kong), and Holmes Products (Far East) Ltd. (Taiwan), (collectively "Holmes"), and the Commission investigative attorney filed separate submissions in support of complainant's motion to terminate the investigation. On June 16, 2000, the presiding ALJ issued an ID granting complainant's motion.

No petitions for review of the ID were filed.

This action is taken under the authority of section 337 of the Tariff Act of 1930, 19 U.S.C. 1337, and Commission rule 210.42(h), 19 CFR 210.42(h).

Copies of the public version of the ID, and all other nonconfidential documents filed in connection with this investigation, are or will be available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street SW, Washington, DC 20436, telephone 202–205–2000. Hearing-impaired persons are advised that information on the matter can be obtained by contacting the Commission's TDD terminal on 202–205–1810. General information concerning the Commission may also be obtained by accessing its Internet server (http://www.usitc.gov).

By order of the Commission.

Dated: July 20, 2000.

Donna R. Koehnke,

Secretary.

[FR Doc. 00–18923 Filed 7–25–00; 8:45 am]

BILLING CODE 7020–02–P

INTERNATIONAL TRADE COMMISSION

Sunshine Act Meeting

AGENCY HOLDING THE MEETING: United States International Trade Commission

TIME AND DATE: August 2, 2000 at 2 p.m.

PLACE: Room 101, 500 E Street S.W., Washington, DC 20436, Telephone: (202) 205–2000.

STATUS: Open to the public.

MATTERS TO BE CONSIDERED:

1. Agenda for future meeting: none.
2. Minutes.
3. Ratification List.
4. Inv. Nos. 731–TA–850 (Final)(Tin-and Chromium-Coated Steel Sheet from Japan)—briefing and vote. (The Commission is currently scheduled to transmit its determination to the Secretary of Commerce on August 9, 2000.)
5. Inv. No. 731–TA–836 (Final) (Certain Ammonium Nitrate from Russia)—briefing and vote. (The Commission is currently scheduled to transmit its determination to the Secretary of Commerce on August 14, 2000.)
6. Outstanding action jackets: none.

In accordance with Commission policy, subject matter listed above, not disposed of at the scheduled meeting, may be carried over to the agenda of the following meeting.

Issued: July 21, 2000.

By order of the Commission:

Donna R. Koehnke,

Secretary.

[FR Doc. 00–19036 Filed 7–24–00; 3:35 pm]

BILLING CODE 7020–02–P

DEPARTMENT OF LABOR

Employment and Training Administration

Proposed Collection of the ETA 205, Preliminary Estimates of Average Employer Contribution Rates; Comment Request

ACTION: Notice.

Appendix D
Request Letter From the Committee on Ways and Means, Dated August 9, 2000

COMMITTEE ON WAYS AND MEANS

U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, DC 20515-6348

August 9, 2000

The Honorable Stephen Koplan
Chairman
U.S. International Trade Commission
500 E Street SW
Washington, DC 20436

Dear Chairman Koplan:

This is in further reference to the June 28, 2000, request by the Committee on Ways and Means for a section 332 study on prescription drugs and the Commission's July 21 response letter to the Committee, which suggests an initial report and a possible follow-up study to address the more complicated issues.

We recognize that our request for a comprehensive study in 90 days provides a very compressed time-frame given the number and complexity of the issues involved. After discussion between our staffs regarding the scope of the study and the resources required, we believe it is in our mutual interest to defer the delivery date of the Commission's initial report until December 1, 2000. This date should provide the Commission sufficient time to research and prepare the initial report as described in its July 21 letter. Our staffs will continue to discuss the various aspects, timing, and resource requirements of any additional follow-on work which may be requested.

With best regards,

Bill Archer
Chairman

Appendix E
***Federal Register* Notice**
(August 23, 2000**)**

INTERNATIONAL TRADE COMMISSION

[Inv. No. 337–TA–435]

Certain Integrated Repeaters, Switches, Transceivers, and Products Containing Same; Investigation

AGENCY: U.S. International Trade Commission.

ACTION: Institution of investigation pursuant to 19 U.S.C. 1337.

SUMMARY: Notice is hereby given that a complaint was filed with the U.S. International Trade Commission on July 20, 2000, under section 337 of the Tariff Act of 1930, as amended, 19 U.S.C. 1337, on behalf of Intel Corporation, 2200 Mission College Boulevard, Santa Clara, California 95052, and Level One Communications, Inc., 9750 Goethe Road, Sacramento, California 95827. The complaint alleges a violation of section 337 in the importation into the United States, the sale for importation, and the sale within the United States after importation of certain integrated repeaters, switches, transceivers, and products containing same by reason of infringement of claims 1, 3, 7–8, 13–19, and 23–29 of U.S. Letters Patent 5,894,410; claims 1, 3, 10–13, 15–16, and 19 of U.S. Letters Patent 5,608,341; and claims 1, 3, 5, 10, and 11 of U.S. Letters Patent 5,726,860. The complaint further alleges that there exists an industry in the United States as required by subsection (a)(2) of section 337.

The complainants request that the Commission institute an investigation and, after a hearing, issue a permanent exclusion order and a permanent cease and desist order.

ADDRESSES: The complaint, except for any confidential information contained therein, is available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street, S.W., Room 112, Washington, D.C. 20436, telephone 202–205–2000. Hearing-impaired individuals are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202–205–1810. Persons with mobility impairments who will need special assistance in gaining access to the Commission should contact the Office of the Secretary at 202–205–2000. General information concerning the Commission may be obtained by accessing its internet server (http://www.usitc.gov).

FOR FURTHER INFORMATION CONTACT: Juan Cockburn, Office of Unfair Import Investigations, U.S. International Trade Commission, telephone 202–205–2572.

Authority

The authority for institution of this investigation is contained in section 337 of the Tariff Act of 1930, as amended, and in section 210.10 of the Commission's Rules of Practice and Procedure, 19 CFR § 210.10 (1999).

Scope of Investigation

Having considered the complaint, the U.S. International Trade Commission, on August 16, 2000, *ordered* that—

(1) Pursuant to subsection (b) of section 337 of the Tariff Act of 1930, as amended, an investigation be instituted to determine whether there is a violation of subsection (a)(1)(B) of section 337 in the importation into the United States, the sale for importation, or the sale within the United States after importation of certain integrated repeaters, switches, transceivers, or products containing same by reason of infringement of claims 1, 3, 7–8, 13–19, or 23–29 of U.S. Letters Patent 5,894,410; claims 1, 3, 10–13, 15–16, or 19 of U.S. Letters Patent 5,608,341; or claims 1, 3, 5, 10, or 11 of U.S. Letters Patent 5,726,860; and whether there exists an industry in the United States as required by subsection (a)(2) of section 337.

(2) For the purpose of the investigation so instituted, the following are hereby named as parties upon which this notice of investigation shall be served:

(a) The complainants are—

Intel Corporation, 2200 Mission College Boulevard, Santa Clara, California 95052

Level One Communications, Inc., 9750 Goethe Road, Sacramento, California 95827

(b) The respondent is the following company alleged to be in violation of section 337, and is the party upon which the complaint is to be served:

Altima Communications, Inc., 2055 Gateway Place, San Jose, California 95110

(c) Juan Cockburn, Esq., Office of Unfair Import Investigations, U.S. International Trade Commission, 500 E Street, S.W., Room 401–Q, Washington, D.C. 20436, who shall be the Commission investigative attorney, party to this investigation;

(3) For the investigation so instituted, the Honorable Paul J. Luckern is designated as the presiding administrative law judge;

(4) The presiding administrative law judge is authorized to consolidate Inv. No. 337–TA–430 and this investigation if he deems it appropriate.

Responses to the complaint and the notice of investigation must be submitted by the named respondent in accordance with § 210.13 of the Commission's Rules of Practice and Procedure, 19 CFR 210.13. Pursuant to 19 CFR 201.16(d) and 210.13(a) of the Commission's Rules, such responses will be considered by the Commission if received not later than 20 days after the date of service by the Commission of the complaint and the notice of investigation. Extensions of time for submitting responses to the complaint will not be granted unless good cause therefor is shown.

Failure of the respondent to file a timely response to each allegation in the complaint and in this notice may be deemed to constitute a waiver of the right to appear and contest the allegations of the complaint and this notice, and to authorize the administrative law judge and the Commission, without further notice to the respondent, to find the facts to be as alleged in the complaint and this notice and to enter both an initial determination and a final determination containing such findings, and may result in the issuance of a limited exclusion order or a cease and desist order or both directed against such respondent.

Issued: August 17, 2000.

By order of the Commission.

Donna R. Koehnke,

Secretary.

[FR Doc. 00–21489 Filed 8–22–00; 8:45 am]

BILLING CODE 7020–02–U

INTERNATIONAL TRADE COMMISSION

[Investigation 332–419]

Pricing of Prescription Drugs

AGENCY: United States International Trade Commission

ACTION: Extension of dates for delivery of the initial report and for written submissions by interested parties for Inv. No. 332–419, Pricing of Prescription Drugs.

EFFECTIVE DATE: August 17, 2000.

SUMMARY: In response to a request on August 8, 2000, from the Committee on Ways and Means (the Committee) of the United States House of Representatives, the Commission has extended the date for reporting the initial results of its investigation No. 332–419, Pricing of Prescription Drugs, until December 1, 2000. The deadline for written submissions by interested parties has been extended to September 8, 2000.

FOR FURTHER INFORMATION CONTACT: Elizabeth R. Nesbitt, Project Leader (202–205–3355) or Raymond L. Cantrell, Deputy Project Leader (202–205–3362), Office of Industries, or Michael Barry, Deputy Project Leader (202–205–3246), Office of Economics, U.S. International Trade Commission, Washington, DC 20436. For information on the legal aspects of this investigation, contact William Gearhart of the Office of the General Counsel (202–205–3091). Hearing impaired individuals are advised that information on this matter can be obtained by contacting the TDD terminal on (202) 205–1810.

WRITTEN SUBMISSIONS: The deadline for written submissions has been extended until September 8, 2000. Interested parties are invited to submit written statements (original and 14 copies) concerning the matters to be addressed by the Commission in its report on this investigation. In addition to general information regarding prices and pricing practices prevalent in each of the countries under consideration, the Commission is particularly interested in comments regarding the question raised by the Committee in their request regarding the extent to which price control systems utilized by the countries under consideration impact pricing for comparable drugs in the United States. Commercial or financial information that a person desires the Commission to treat as confidential must be submitted on separate sheets of paper, each clearly marked "Confidential Business Information" at the top. All submissions requesting confidential treatment must conform with the requirements of § 201.6 of the Commission's Rules of Practice and Procedure (19 CFR 201.6). All written submissions must conform with the provisions of section 201.8 of the Commission's Rules. All written submissions, except for confidential business information, will be made available in the Office of the Secretary of the Commission for inspection by interested parties. To be assured of consideration by the Commission, written statements relating to the Commission's report should be submitted to the Commission at the earliest practical date and should be received no later than the close of business on September 8, 2000. All submissions should be addressed to the Secretary, United States International Trade Commission, 500 E Street SW., Washington, DC 20436. The Commission's rules do not authorize filing submissions with the Secretary by facsimile or electronic means.

Persons with mobility impairments who will need special assistance in gaining access to the Commission should contact the Office of the Secretary at 202–205–2000. General information concerning the Commission may also be obtained by accessing its Internet server (http://www.usitc.gov). Notice of institution of the investigation was published in the Federal Register of July 26, 2000 (65 FR 45986).

List of Subjects

Prescription drugs, Price controls, Compulsory licensing.

By order of the Commission.

Issued: August 17, 2000.

Donna R. Koehnke,

Secretary.

[FR Doc. 00–21503 Filed 8–22–00; 8:45 am]

BILLING CODE 7020–02–P

INTERNATIONAL TRADE COMMISSION

[Investigations Nos. 731–TA–864–867 (Final)]

Certain Stainless Steel Butt-Weld Pipe Fittings From Germany, Italy, Malaysia, and the Philippines

AGENCY: United States International Trade Commission.

ACTION: Scheduling of the final phase of antidumping investigations.

SUMMARY: The Commission hereby gives notice of the scheduling of the final phase of antidumping investigations Nos. 731–TA–864, 865, and 867 (Final) under section 735(b) of the Tariff Act of 1930 (19 U.S.C. 1673d(b)) (the Act) to determine whether an industry in the United States is materially injured or threatened with material injury, or the establishment of an industry in the United States is materially retarded, by reason of less-than-fair-value imports from Germany, Italy, and the Philippines of stainless steel butt-weld pipe fittings, provided for in subheading 7307.23.00 of the Harmonized Tariff Schedule of the United States.[1] Section 207.21(b) of the Commission's rules provides that, where the Department of Commerce has issued a negative preliminary determination, the Commission will not publish a notice of scheduling for the final phase of its investigation unless and until it receives an affirmative final determination from Commerce. Although the Department of Commerce has preliminarily determined that certain stainless steel butt-weld pipe fittings from Malaysia are not being sold, nor are likely to be sold, in the United States at less than fair value, for purposes of efficiency the Commission hereby waives rule 207.21(b) and gives notice of the scheduling of the final phase of the antidumping investigation No. 731–TA–865 (Final) under section 735(b) of the Act. The Commission is taking this action so that the final phases of the antidumping investigations may proceed concurrently in the event that Commerce makes a final affirmative antidumping determination with respect to Malaysia. If Commerce makes a final negative antidumping determination with respect to Malaysia, the Commission will terminate its antidumping investigation under section 735(c)(2) of the Act (19 U.S.C. 1673d(c)(2)), and section 207.2(d) of the Commission's rules.

For further information concerning the conduct of this phase of the investigations, hearing procedures, and rules of general application, consult the Commission's Rules of Practice and Procedure, part 201, subparts A through E (19 CFR part 201), and part 207, subparts A and C (19 CFR part 207).

EFFECTIVE DATE: August 2, 2000.

FOR FURTHER INFORMATION CONTACT: Christopher J. Cassise (202–708–5408), Office of Investigations, U.S. International Trade Commission, 500 E Street SW, Washington, DC 20436. Hearing-impaired persons can obtain information on this matter by contacting the Commission's TDD terminal on 202–205–1810. Persons with mobility impairments who will need special assistance in gaining access to the Commission should contact the Office of the Secretary at 202–205–2000. General information concerning the Commission may also be obtained by accessing its internet server (http://www.usitc.gov).

SUPPLEMENTARY INFORMATION:

[1] For purposes of these investigations, Commerce has defined the subject merchandise as follows: "Certain stainless steel butt-weld pipe fittings are under 14 inches in outside diameter (based on nominal pipe size), whether finished or unfinished. The product encompasses all grades of stainless steel and "commodity" and "specialty" fittings. Specifically excluded from the definition are threaded, grooved, and bolted fittings, and fittings made from any material other than stainless steel. The fittings subject to these investigations are generally designated under specification ASTM A403/A403M, the standard specification for Wrought Austenitic Stainless Steel Piping Fittings, or its foreign equivalents (e.g., DIN or JIS specifications). This specification covers two general classes of fittings, WP and CR, of wrought austenitic stainless steel fittings of seamless and welded construction covered by the latest revision of ANSI B16.9, ANSI B16.11, and ANSI B16.28. Pipe fittings manufactured to specification ASTM A774, or its foreign equivalents, are also covered by these investigations. These investigations do not apply to cast fittings. Cast austenitic stainless steel pipe fittings are covered by specifications A351/A351M, A743/743M, and A744/A744M."

Appendix F
Marginal Costs and Marginal Revenues

Marginal Costs and Marginal Revenues

An important economic concept used in this report is that of a "marginal" indicator. Drug producers (or producers of other products) can equate marginal revenue to marginal cost of production, and maximize their profits. A marginal cost is the cost of producing an additional unit of output–that is, given the amount already produced, marginal cost is how much it would cost a firm to produce one more unit. This amount can change as more output is produced, and likely increases as output increases.

Similarly, marginal revenue is the revenue a firm receives from selling an additional unit of output–that is, given the amount already sold, marginal revenue is how much a firm will receive as payment if it sells one more unit. Marginal revenue usually falls as output increases because consumer demand is sensitive to price. For example, assume an automobile manufacturer can sell 10 cars at $10,000 each. Total revenue would be $100,000. However, in order to sell 11 cars, the dealer must lower the price of all the cars to $9,500. Total revenue would be $104,500. Marginal revenue, the extra revenue the dealer gets for deciding to sell the 11th car is only $4,500.

Both marginal cost and marginal revenue vary according to output. A profit-maximizing firm should choose the output level where marginal cost and marginal revenue are equal. Intuitively, it is helpful to think about the producer if the two are not equal. If marginal revenue is greater than marginal cost, producing one more unit will mean greater profit. Conversely, if marginal cost is greater than marginal revenue, it is not smart to produce that last unit of output, and producing one fewer unit will mean greater profit. This is the concept applied to the pharmaceuticals industry in this report.

Price Discrimination and Ramsey Pricing

Price discrimination is present when the same commodity is sold at different prices to different consumers.[1] Considering how different prices could reflect varying transportation or other costs, or that price discrimination could be present even if all consumers are charged the same price, another definition would be more specific: price discrimination is present when two or more similar goods are sold at prices that are in different ratios to marginal costs.[2]

This assumes the ability of the firm to "segment" markets, or sort consumers by some criteria or set of criteria. As discussed in chapter 3, there are several criteria by which pharmaceutical firms may be able to sort their customers. If a drug firm has some pricing power in the market, and is able to maintain separation between groups of consumers, it can maximize its profits by charging different prices to each group of consumers. In this "third degree" price discrimination, consumers are sorted by their price elasticities of demand. Higher prices are charged to those consumers least sensitive to price (inelastic demand), and lower prices are charged to those consumers most sensitive to price (elastic demand). This pricing strategy can maximize the firm's profits, but can also have positive effects on total global welfare. (If one price is charged to all drug consumers, it is possible that some price-elastic countries could end up consuming no drugs at all.)

[1] Hal Varian, "Price Discrimination," *Handbook of Industrial Organization*, Volume I, edited by R. Schmalensee and R.D. Willig, Elsivier Science Publishers, B.V., 1989, p. 598.

[2] G. Stigler, *Theory of Price*, New York, Macmillan, 1987.

In an industry characterized by high fixed costs, such as the cost of research and development in the pharmaceutical industry, the marginal cost of producing a product remains below the average cost. Competitive pricing at the marginal cost level would be possible if the fixed costs were met out of public subsidies or by some other mechanism, but the usual way firms are allowed to recover these costs is through the grant of patent protection for a temporary monopoly in the product. Where it is possible, price discrimination by a monopolist will be more profitable than a uniform pricing policy. Ramsey showed that a solution essentially equivalent to third-degree price discrimination is also superior to uniform pricing from a social welfare perspective.[3] Briefly, the basic idea of "Ramsey pricing" is that, if an agency is regulating the price charged by a monopolist facing a segmented market, and the objective is to allow the monopolist to set prices sufficiently above marginal cost to recover the fixed costs (or some fraction of them), then prices in each market segment *I* should be set so that

$$P_i - MC_i = R(\frac{1}{e_i})P_i$$

In other words, the price should be set so that it exceeds marginal cost in proportion to the inverse of the demand elasticity e_i. R is set by the regulating agency between zero and one to adjust the outcome between simple marginal cost pricing (R=0) and the amount by which the monopolist would discriminate under third-degree price discrimination in the absence of regulation. The result means consumers most sensitive to price changes (elastic demand) will pay less than those who are not as sensitive (inelastic demand). Compared with charging the same price to all consumers, this pricing system is advantageous because it assures that some low-price sales would take place in markets that otherwise would likely not be served at all.

Dynamic Price Discrimination

Competition in the pharmaceuticals industry is based not only on price, but also on innovation. With the ability to charge different prices to different market segments, the introduction of new innovative drugs provides drug firms with new market segments.[4] Two characteristics of the market become important in the pricing strategy of a firm:

- ❑ Markets with price-elastic demand are charged lower prices than those with inelastic demand; and
- ❑ A firm with a new, innovative drug is likely to face a more inelastic demand than firms selling older drugs with more competitors.

Price discrimination becomes a dynamic process, where firms adjust prices in market segments to react to changing demand elasticities. A firm that introduces a new, innovative product with few substitutes can charge a higher price because the demand it faces is likely to be less sensitive to price (less elastic). This market power is supported during the life of a patent. When a drug comes off patent and generics are introduced (or close substitutes are found for an on-patent drug), competition will cause sellers to face

[3] See Frank J. Ramsey, "A Contribution to the Theory of Taxation," *Economic Journal* 37 (March 1927), pp. 47-61. A discussion appears in Scherer and Ross (1990), pp. 498-499.

[4] Duncan Reekie. "The PPRS: Regulations Without a Cause?" *Should Pharmaceutical Prices Be Regulated? The Strengths and Weaknesses of the British Pharmaceutical Price Regulation Scheme*, Institute of Economic Affairs Health and Welfare Unit, 1997, p. 31.

demand that is more sensitive to price. With more price elasticity, a lower price will be charged. Market segmentation remains a focus, but by introducing time into the analysis, this framework emphasizes not only the role of price in the pharmaceuticals industry, but also describes the importance of R&D, new products, and the role of changing conditions of competition.

Appendix G
Written Submissions From Interested Parties

Shannon S.S. Herzfeld
SENIOR VICE PRESIDENT
INTERNATIONAL AFFAIRS

PhRMA

August 4, 2000

Ms. Donna R. Koehnke
Secretary
U.S. International Trade Commission
500 E Street, S.W.
Washington, D.C. 20436

Dear Ms. Koehnke:

The Pharmaceutical Research and Manufacturers of America is pleased to submit its response to the U.S. International Trade Commission's request for information regarding pricing practices prevalent in the G-8 and NAFTA countries (Investigation 332-419). None of the information contained in our submission is considered by us to be "Confidential Business Information."

We appreciate the opportunity afforded us to submit comments.

Sincerely,

Shannon S.S. Herzfeld

Attachment

Pharmaceutical Research and Manufacturers of America
1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3481 • FAX: 202-835-3428 • E-MAIL: Sherzfeld@Phrma.org

The United States International Trade Commission
Fact-finding Investigation on
Price Controls and Other Market Access Barriers in G-8 and NAFTA Countries Faced by the American Pharmaceutical Industry

Submission of the
Pharmaceutical Research and Manufacturers of America (PhRMA)

"In some places, drug availability depends on whether the local health authorities are willing to pay their share. In other places, the introduction of a new medicine can be held up as drug makers spend months haggling with individual European governments over reimbursement prices. Elsewhere, the state bans altogether drugs it deems too costly."
The Wall Street Journal, July 21, 2000

Introduction

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to have the opportunity to provide comments concerning price controls and other market access barriers which are faced by our industry in G-8 and NAFTA countries.

PhRMA is a trade organization representing the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. This year, PhRMA members expect to invest over $26 billion in research and development efforts to identify and bring to market new drugs. They also employ almost a quarter of a million Americans in a variety of high-skill, high-wage jobs.

The U.S. research-based industry leads the world in the development of innovative medicines, currently accounting for about half of all new drugs; Europe is second, followed by Japan. This distinction rests in large part on the fact that the U.S. is the only country in the world that fosters pharmaceutical innovation through market-driven competition. The market environment in this country provides the incentive to invest in the very high cost, high-risk venture of new drug development. On average, it costs half a billion dollars to develop and bring to market a new drug. Only about 1 in 5,000 compounds tested ever becomes a marketed drug,[1] and of these, on average, only three out of ten generate revenues that meet or exceed average costs.[2]

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[1] DiMasi, J.A., "New Drug Development: Cost, Risk, and Complexity", Drug Information Journal, May, 1995.

[2] Grabowski, H., and Vernon, J., "Returns to R&D on New Drug Introductions in the 1980's", Journal of Health Economics, Vol. 13, 1994.

U.S. patients are the direct beneficiaries of the U.S. market-driven environment and the substantial investment in R&D that it fosters. In the last two years alone, PhRMA members have added over 100 new drugs to the nation's medicine chest, including important new treatments for cancer, AIDS and Alzheimer's disease. Right now, our members are developing more than 1,000 new medicines for heart disease, cancer, AIDS and hundreds of other diseases.

In most foreign markets, PhRMA member companies are confronted by a variety of government actions that stifle market-based competition from innovative products and limit patient access to new pharmaceuticals. Since the U.S. research-based industry is the world leader in the development of new medicines, our members and their innovative products disproportionately bear the brunt of these impediments. As a result, U.S. companies are denied the opportunity to compete fairly.

U.S. companies' sales in foreign markets are affected adversely by foreign government interventions in several ways. First and foremost, both direct and indirect price controls dissipate the premium for innovation which the market would otherwise bestow on a medicine with superior efficacy and/or fewer side effects. At the same time, local products are often sheltered from competition and subsidized. Moreover, the administrative hurdles erected by foreign governments unreasonably delay market access denying American companies revenue and the ability to benefit fully from intellectual property rights. These delays effectively foreshorten the effective patent life of U.S. products and PhRMA members are denied the opportunity to realize the full commercial value of a new drug. These interventions also erode intellectual property rights by reducing the net commercial returns from U.S. products.

While industry recognizes the right of governments to administer public budgets, the short-term perspective embraced by most G-8 members fetters market-driven competition in the health care industry, with particularly harsh consequences for innovative pharmaceuticals, a component heavily represented by "foreign" interests. This approach trades away long-term sustainability for near-term expediency. When foreign governments view cutting-edge innovative medicines as a problem rather than a part of the solution to controlling health care costs, they erect market access barriers to innovative goods. Given, in fact, that more and more medicines are discovered here, these actions most often hamper U.S. products. This is bad public health policy and bad economic policy. Limiting the availability of state-of-the-art medicines limits patient access to new drugs and risks destroying the financial incentive for privately sponsored research and development. This approach steps away from the bedrock principles of free trade where companies compete vigorously and products gain or lose market share based on their merits, not government selection.

Foreign Barriers to Market Access

A variety of interventions are employed by foreign governments that affect the prices and volumes of American pharmaceutical products available in their countries, ranging from outright controls on prices to caps on sales growth.[3] All of these government interventions have one feature in common: they distort free trade and hamper open competition by imposing a non-market-based approach to the purchase and consumption of pharmaceuticals. The following are four common examples of such government interventions.

Price Controls

Ever more frequently, governments promise universal health care benefits but budget for far less. One of the more common methods used by governments to curtail health care costs is by directly controlling prices charged by companies for their products. There are as many price control systems as there are governments that choose to control prices. The diversity of these mechanisms merely underscores the fact that none of them work, either alone or in combination.

Europe is case in point of the acknowledged failure of government-directed efforts to control pharmaceutical expenditures through the imposition of price controls. This fact was evident at least as far back as 1993, when the former head of the pharmaceuticals unit at the European Commission, Fernand Sauer, stated bluntly "most member states no longer believe that regulating prices is the long-term answer...[t]hey have seen the damage that it can create to their own industry and even to the social security system, because it fails to solve the problem."[4] Patients are poorly served, innovation is stifled and American products are penalized.

While the specific mechanics of each price control system differ from country to country, the end result is the same; i.e., after investing on average $500 million and spending 12-15 years of effort to discover, develop, and manufacture a medicine, when it comes time to sell a product, a government bureaucracy determines its value rather than doctors and their patients. If the return on investment is dictated or limited by a government, the high-risk, high-cost journey from drug discovery through development and marketing approval becomes much less attractive. Entrepreneurs are willing to take on high risks only if they have a chance of commensurate financial reward. In the fierce daily reward for capital, investors will direct their money elsewhere if at the end of the day the successful drug faces anti-innovative public pricing policies.

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[3] See Appendix 2 for a more detailed discussion of the specific mechanisms in place in the G-8 and NAFTA countries, excluding the U.S.

[4] "EC: The Euro Evolution," *Pharmaceutical Executive*, January 1993, p.36.

Reference Pricing

Another form of price control that has emerged in the last decade is reference pricing. Instead of establishing prices for individual products, a reference pricing system sets one public reimbursement price for all products grouped into a given active ingredient or therapeutic category.[5] Frequently these categories are overly broad and may group innovative new products with older products. In some cases such as the Netherlands, many new innovative medicines still under patent receive the same reference price as off-patent, old technology products. This practice denies any commercial premium for an improved product and, therefore, often harms the economic interests of U.S. research-based companies more than those of local industry.

From the public health perspective, reference pricing implicitly assumes that all medicines within a category are equivalent or appropriate for any patient with a specific illness. This ignores differences in the chemical preparation of an active ingredient, in the manufacture of and quality of the drug, in dosage form or application, and in efficacy and side effects. These important differences may have serious implications for patients and most certainly affect both supply and demand. But governments who adopt reference prices do not allow market forces to play out, fearing demand for newer, often imported, products would reduce interest in older products often made by local companies

As for achieving the goal of cost containment, reference pricing does not work. Such systems can be bureaucratic and costly to administer due to the complexity of defining categories for multitudes of products and administering prices. Moreover, establishing a reference price effectively discourages price competition among products. The reference price is in practical terms the artificially established market price. Those products with market prices which would be above the reference price (generally innovative products) must lower their prices so as not to exceed reimbursement rates; those products with market prices which would be below the reference price (often older products) usually raise their prices to the reference level. There is no incentive to compete by lowering prices; consumers are deprived of potential cost savings. Since developing a better medicine results in no additional revenue, research is discouraged. Thus, reference prices act simultaneously as price "ceilings" on more effective medicines discouraging research, and as price "floors" on less effective medicines reducing economic savings.

The United States' reliance on free market pricing has instead established its clear leadership in pharmaceutical innovation. This has generated considerable competition among innovative products in many therapeutic areas, and, after patent expiration, additional strong competition, especially from generics, leading to lower prices. In Europe, on the other hand, government

[5] In many countries, virtually all pharmaceuticals are reimbursed, so the government act of setting a reimbursement price is tantamount to setting the market price.

controls have lead to generics being priced significantly higher than in the U.S. These higher prices are essentially industrial subsidies to local generic manufacturers.

Global Budgets

Pressed by the urgent need to contain health care spending in an environment of open-ended entitlements and fiscal restraint, an increasing number of governments in Europe as well as Japan have adopted fixed global health care budgets. As in the case of reference pricing above, such measures shelter older, less effective and less cost-effective products, by keeping competition from innovative medicines at bay. Since older medicines are often produced locally, these measures indirectly and *de facto* constitute a trade barrier to U.S. products, unduly penalizing innovation and efficiency.

Two approaches are popular whereby governments declare at the start of the year the whole amount of public funds to be expended on drugs, and force the industry to bear the brunt of the shortfall if governments guess wrong. The first and increasingly favored approach is to link prices of pharmaceutical products to sales volumes. Once sales volumes surpass a targeted level, companies are forced to decrease prices so that total public expenditure reflects what was budgeted. The other approach is to require that either the collective pharmaceutical industry or individual companies return a portion or all of any budgetary overrun to the government in the form of a rebate or "clawback." Drug budgets are set arbitrarily without much recognition of the factors triggering increased drug-consumption. By requiring companies to make up the difference, politicians are insulated from the consequences of their under-budgeting and bureaucrats are insulated from the consequences of "guessing-wrong".

Global budgets impose a disproportionate burden on research-based companies because new, innovative products offer improved therapeutic relief and thus are the most likely to realize market growth. Through imposition of global budgets, innovative companies are penalized for introducing a new product into the marketplace that meets the medical needs of patients. Moreover, by legislating strict volume controls, governments are, in effect, setting quotas and removing incentives to compete by freezing or parceling out market share. Governments are further interjecting themselves into the market environment by effectively penalizing winners and insulating losers, a politically acceptable outcome when innovation comes from abroad as opposed to being home-grown.

The "Cost Effectiveness" Hurdle to Market Access

An emerging new barrier to market access for innovative pharmaceutical products is the use of health outcomes research, including cost effectiveness analyses, as a condition for reimbursement and thus market access. This

seemingly innocent practice is instead a subtle instrument which acts as a market barrier to innovative pharmaceutical products.

European and national health authorities assess a product's quality, safety and efficacy in order to determine whether to grant it a marketing approval. Fiscal authorities, however, are now erecting yet another hurdle which in effect second-guesses the public safety arm of government by requiring manufacturers to demonstrate their products' "cost effectiveness" in order to gain market access. This, of course, puts the cart before the horse since this information only comes to light through wide-scale use in the marketplace. Only through the tough test of real world use by doctors and their patients will a product's true therapeutic value and cost effectiveness be determined. Yet, this new approach, as practiced, for example, by the UK's National Institute for Clinical Excellence (NICE) and other groups throughout Europe, create an old-fashioned market barrier while wrapping it in economic modeling. In actuality, this hurdle denies patients, or limits their access to, the newest drugs that offer great therapeutic benefit and relief.

This form of market intervention invariably will target U.S. developed medicines because of this country's lead in pharmaceutical innovation. Like other measures noted above, creation of a "cost effectiveness" hurdle foreshortens effective patent life. Also, by delaying the introduction of new technology, this type of intervention artificially skews the playing field in favor of older drugs, usually manufactured by local companies.

Impact on Patent Protection and R&D

Because of the inherently high-risk nature of drug R&D, the United States' free market environment is a particularly conducive to the research and development of new medicines. So too is this country's strong intellectual property rights regime. Strong product patent protection is an important reason for the U.S.'s preeminence in high technology like pharmaceuticals. This is often missing, however, in other G-8 and NAFTA countries where full commercial valuation of U.S. patented pharmaceutical products is undermined through direct and indirect price control regimes.

R&D Risks

An extraordinary level of risk is inherent to the pharmaceutical R&D process. Decisions as to what therapeutic indication to pursue must be taken nearly two decades before a product may enter the market. When it finally does, marketplace conditions (and the ability to realize an adequate return on investment) most assuredly have changed. Research-based pharmaceutical companies compete vigorously to develop new medicines. As a result, competing products are often introduced faster than ever after the launch of a new product in a therapeutic class. This intensifying competition in the

pharmaceutical marketplace is shrinking the period of market exclusivity traditionally enjoyed by the inventor of breakthrough medicine as competing innovators arrive sooner and sooner. Like riding a bicycle, all innovative companies must consistently push forward or risk losing their commercial balance and being left hopelessly behind.[6]

This year, America's research-based pharmaceutical companies will invest $26.4 billion in R&D – a 10.1 percent increase over research spending in 1999.[7] PhRMA members have more than tripled their R&D expenditures since 1990 and have multiplied their R&D investment 13-fold since 1980.[8] This is a benefit for the American economy and American patient, but a strong concern for our trading partners – particularly those whose industries are failing to invest in their future.

Since effective patent lifetimes are becoming ever shorter, the window of opportunity for realizing a return on investment is ever narrower. Companies rely on highly successful products to recoup not only the R&D investment in those medicines, but also to cover the costs of the drugs that do not successfully make it to market. Without the ability to realize reasonable returns on R&D investments, companies will not attract the investment capital or generate the revenues needed to fund ongoing research and development.

While computers have eased the screening process of potential candidates, the actual development process through testing in humans to ensure a product's safety and efficacy has gotten ever more time and cost intensive. Very few of the products that finally clear all of the regulatory hurdles and reach the market become the sought-after so-called blockbuster products. Indeed, as noted above, only about 30 percent of the new drugs that reach the market ultimately produce revenues that match or exceed average research and development costs during their period of patent exclusivity.

Identifying new approaches to treat complex diseases and testing these potential new therapies to ensure safety and efficacy is a costly, risky and time-consuming process. While the National Institutes of Health (NIH) leads the way in basic research (with the research-based industry contributing to this effort), it is the pharmaceutical industry that leads the way in translating advances in medical knowledge into medicines that to help and heal patients.

Erosion of Ability to Realize the Value of a Patent

The R&D risks noted above underscore the critical importance of patent protection to the research-based industry. Companies not only need an effective

[6] PhRMA Annual Survey, 2000. Industry Profile Figure 5-5 (see Appendix 3).
[7] This reflects $22.4 billion spent within the United States by both U.S.-owned and foreign-owned firms, plus an additional $4 billion spent abroad by U.S.-owned firms.
[8] PhRMA Annual Survey, 2000. Industry Profile Figure 2-1 (see Appendix 3).

patent life for the new drugs that enter the marketplace, they also need the ability to compete in a market-driven environment that will determine the value of a new medication. Government market interventions abroad undermine the value of our industry's intellectual property by eroding effective patent life and distorting the normal market forces of demand, supply, and competition, so that the innovator never has the opportunity to ascertain the commercial value of his innovative product. In this country, doctors and patients get access to new drugs quickly and they – not government bureaucrats – determine the drug's worth in the market. If an innovative new product has a unique therapeutic value, doctors and patients will seek it out and the market will respond. If the anticipated demand is not realized, the market also will respond by not favoring the product. The free market gives a manufacturer the freedom to succeed or fail. These are the essential operating conditions of the market environment in which high-risk, long-term investment thrives. When these market highs and lows are dampened, so is investment.

A previous U.S. International Trade Commission (ITC) study found that government intervention in the form of price controls often results in decreased levels of R&D spending by reducing revenues that could be reinvested in R&D programs.[9] The Progressive Policy Institute reinforced the findings of the ITC by concluding that "price controls [on medicines used primarily by seniors] would discourage the development of drugs and biotechnology products for older and disabled Americans," and would "undermine competition by substituting federally mandated discounts for the hard work of negotiating prices that regularly occurs in the marketplace."[10]

Negotiations with governments on imposed prices, reimbursement, volume limits, formulary access or other interventions also delay market entry. First and foremost, this is bad for patients waiting for relief. It is also contrary to our principles of free trade and open markets. Additionally, as noted above, since the patent clock is ticking, these delay tactics erode the effective patent life of a product. This in turn eliminates part of the revenue which should be flowing during the period of market exclusivity, further diminishing the patent holder's ability to realize the full potential for realizing an adequate return on investment. Since more and more medicines are discovered in the U.S., these barriers work, in a disproportionate way, to the detriment of our industry's sales abroad.

These delays are not insignificant. For example, the average delay between marketing approval and market introduction for new products recently launched in Europe ranged from 10 to 12 months in Greece, Belgium, France and Switzerland. When, as in the U.S., the effective patent lifetime of an innovative medicine averages less than 11-12 years, the loss of a year is a

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[9] U.S. International Trade Commission, "Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals", U.S. International Trade Commission, 1991.
[10] McNeil, D., and Kendall, D., "Medicare Consumer Coalitions Helping Older Americans Afford Prescription Drugs", Progressive Policy Institute, May 1, 1999.

significant commercial penalty. It also expands the period of time where local, non-innovative industry remains shielded from competition.

Compulsory Licensing in G-8 and NAFTA Countries

The Uruguay Round's Trade-Related Aspects of Intellectual Property Agreement (TRIPS) recognizes that under very limited circumstances, a government which has granted a patent can take back this right with appropriate compensation to the patent holder. This "use of the subject matter of a patent without authorization of the right holder," (Article 31) would potentially come into being if the holder of the patent failed to make its product available in the market. While TRIPS authorizes this activity under very narrowly prescribed circumstances, none of the countries that are the subject of this study have invoked the TRIPS compulsory licensing provisions in order to ensure the supply of a medicine or otherwise enhance its negotiating position. Indeed, it is noteworthy that since the adoption of TRIPS in 1994, no compulsory licenses for any reason have been issued for a pharmaceutical product in any of the countries under review. This should not come as a surprise given that all of the countries, with the exception of Russia, were at the forefront of those advocating a strong international standard of patent protection within the TRIPS agreement.

Nevertheless, PhRMA member companies face the threat of compulsory licensing in the context of the price-setting process in some foreign markets. For example, if a company were to disagree with the decision taken by a government and, as a result, decide not to launch a product in the country, it could then face compulsory licensing. TRIPS does recognize the grant to a third party of a compulsory license for not working a patent locally, in other words for not placing a product on the local market after local marketing approval has been granted. This threat undermines the negotiating position of a U.S. company and its ability to realize the true commercial value of its innovative product.

Finally, the entire international patent system might be weakened if actions in the U.S. encourage G-8 countries to start to use compulsory licensing of pharmaceutical products. While G-8 countries have not done so in the past, they might do so if U.S. pharmaceutical manufacturers were reluctant to market products in their countries, because those products were reentering the U.S. market through parallel trade. Any U.S. legislative or regulatory actions which encourage parallel trade pose this risk which, while hypothetical now, should raise a point of caution among U.S. policy makers.

Conclusions

Among the factors explaining the success of the U.S.-based pharmaceutical industry are the public policies in this country that encourage private-sector investment in drug R&D, decentralize decision-making in

technology and capital markets, and place value on risk-taking entrepreneurship and diversity, fostering new ideas and innovation. [11]

In stark contrast to the U.S., the routine government interventions broadly practiced in foreign countries erect barriers to U.S. innovative medicines and penalize PhRMA members for bringing to market innovative new drugs. They categorically fail to accomplish their intended objective of creating substantial and sustainable cost savings, but also harm the interests of patients and jeopardize prospects for advances in health technologies through innovative pharmaceutical research. Without a doubt, they undermine the ability of the U.S. research-based industry to compete fairly and to realize the true commercial value of its products in foreign markets.

The result in Europe, as noted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), is that "[p]harmaceutical innovation is already shifting from Europe to the U.S. and the EU could eventually be reduced to the status of a purely consumer market which does not generate its own innovative products." This is most evident in the medically promising biotechnology sector, where Europe (and Japan) lag far behind the U.S. The latest data on the location of biopharmaceutical development work show that 63 percent of biotechnology-derived medicines are currently under development in the U.S., compared with 25 percent in Europe.[12]

In the United States, each pharmaceutical company prices its own prescription medicines based on market factors. Under the antitrust laws, pharmaceutical pricing and other commercial considerations are not discussed by or at the research-based industry's trade association, PhRMA, or otherwise between companies.

The freedom for each individual company to price its medicines based on competitive market factors is critical to private-sector discovery and development of new medicines to help and heal even more patients. While the new medicines are invaluable to patients, their families, and society, drug R&D is, as noted above, time-consuming, costly and risky.

New medicines benefit patients all over the world. Therefore, in evaluating the risks of drug research and development, it may be appropriate to measure its rewards by looking to global revenues since private investment requires an opportunity for a return on investment commensurate with the risk factors. The freedom for each individual company to price the medicines it invents, based on market factors, provides this opportunity.

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[11] "Economic Dynamism and the Success of U.S. High Tech", U.S. Senate, Joint Economic Committee Staff Report, October 1999.

[12] A more in-depth discussion is set forth in Appendix 4.

However, in too many foreign markets, and regrettably to a lesser extent in parts of the U.S. market covered by government price controls, such as Medicaid, federal ceiling prices, Federal Supply Schedule pricing requirements, and many state pharmaceutical assistance programs, governments control the prices that a pharmaceutical company can charge. The government thus limits the opportunity in the market for a return on investment, but does not limit any of the risks of the enterprise. This asymmetrical intervention in the market discourages private investment in drug R&D and adds layers of administrative costs and market access delays.[13]

Beyond these general statements, PhRMA is not able to comment on the specific effects of such foreign government price controls on each individual company's pricing practices in the U.S. market. Each company makes its own decisions regarding its prices, so presumably any effects from foreign government price controls vary from company to company, and perhaps from medicine to medicine within a company.

However, PhRMA member companies, as well as the research-based pharmaceutical companies of Europe, unanimously agree that free market forces should govern, rather than the layers of government intrusion found in most G-8 countries. Moreover, bargaining for market access with the same governments that control every other aspect of commercial activity is not a fair bargain at all.

[13] Additional discussion of price differences is set forth in Appendix 1.

APPENDIX 1

Why Pharmaceutical Price Differences Exist

Why Pharmaceutical Price Differences Exist

As in the case of virtually all products, price differences exist for pharmaceuticals, within markets and across geographic boundaries. Pharmaceuticals, as opposed to steel or corn or cotton cloth, often are priced differently across the G-8 countries because governments, not the marketplace, dictate the price. This is done through a variety of mechanisms. In all cases, governments approve a medicine as safe and effective, dictate what can be said about it and to whom, and determine which products can reach patients by determining whether it will be reimbursed. Governments exert enormous power when they also set – directly or indirectly – a medicine's price.

Price Differences Across International Markets

Demand in different markets reflects not only different consumers, but important economic, social and political factors. The market for pharmaceutical products in any given country will depend on that country's income level, its disease patterns, drug prescribing practices, cultural patterns and preferences, availability and efficacy of alternative therapies, and whether patients and providers have information about available products.

Supply in different countries also reflects a variety economic, social and political factors. Manufacturing and selling pharmaceutical products in countries other than the United States involve different overall production and distribution costs. Tariffs and taxes, labor costs, transportation costs, customary wholesale and retail mark-ups, regulatory requirements, anticipated liability costs, levels of infrastructure, and quality standards all vary by country, resulting in different costs across borders.

In a deregulated world, these clusters of demand and supply factors will converge to determine market prices for every medicine offered to every patient group in each country. Unfortunately, only in the U.S. does this happen with sustainable regularity.[14] Pharmaceutical prices in most G-8 countries are artificially manipulated through government controls. Outside of the United States, most governments routinely choose to interfere in the market and set limits on pharmaceutical prices, particularly for newer innovative products, in an ill-conceived approach to containing expenditures. They do so because of their sovereign power. Unfortunately, such practices have not enabled countries to control health care expenditures. Moreover, these price controls have

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[14] This does not mean that a single medicine is sold throughout the U.S. at a single price. Within the U.S. patients pay different amounts depending upon, for example, whether they are part of a group such as an HMO, a union, or other private insurance group which may be able to negotiate lower prices through volume purchases or through the provision of other valuable services. Indeed, even for cash paying consumers, wide price differences can be found due to different pharmacy mark-ups, even within the same city. (Washington Consumer Checkbook, Spring/Summer 2000, Vol. 11, No. 3, at p. 42).

discouraged their local research-based pharmaceutical industry from investing in the continued discovery and development of innovative and life-saving drugs.

The Pitfalls of Making International Comparisons of Pharmaceutical Prices

As any reader of the newspaper is aware, snapshot cross-border comparisons of pharmaceutical prices have gained great popularity as "demonstrating" that prices charged in the U.S. are higher than those charged abroad. Like any still frame out of a movie, these snapshots often mislead and fail to tell the whole story.

Virtually all existing cross-national comparisons of drug prices have been flawed by faulty methodology. Professor Patricia Danzon of the Wharton School, and Fredrik Andersson and colleagues at the Battelle Medical Technology and Policy Research Centre, have published extensively on the shortcomings of different approaches for comparing drug prices internationally. They conclude that international price comparisons are misleading and generally based on flawed methodologies, and suggest that public policy is all too often influenced by price studies without an understanding of their technical limitations.[15]

One of the common flaws of many price comparisons – perhaps because it is easy to do – is comparing manufacturers' list prices for drugs in the U.S. with list prices in other countries. This practice leads to erroneous conclusions since the actual transaction price in the U.S. is often significantly lower than the list price, unlike in many other countries.

Another common flaw reflects the fact that price comparisons are also typically made on the basis of simple averages of the top-selling drugs in a given country for which matching products are available in other countries. This often results in the use of extremely small samples. The studies also typically make no attempt to include the most frequently used drugs in comparator countries, nor do they attempt to weight the prices based on the consumption of drugs in the countries examined.

Another major problem in many comparisons is that the sampled drugs are not always directly comparable. Differences in package size, dosage forms, strengths, indications, and dispensing methods need to be taken into account, but rarely are. In short, apples-to-apples comparisons are rare, so reported results must be viewed with care.

Converting foreign prices to local prices for comparison purposes produces another type of error, given that changes in exchange rates over time create considerable variability in price relationships. For example, the price of a

[15] See e.g. Danzon, P., Pharmaceutical Price Regulation: National Policies versus Global Interests. (AEI Press: Washington, DC, 1997).

drug introduced in the early 1990's at US$ 1 and CDN$ 1 would now be sold, all other things equal, at US$1 but the equivalent of US$0.70 in Canada solely due to depreciation of the Canadian dollar.

This phenomenon is exacerbated by foreign government price setting. When faced with a devaluation, U.S. exporters of most products try to raise their price in local currency to keep constant in U.S. dollars. All one needs to do is visit a local bookstore to see this phenomenon in action. A Twenty-five dollar book in the U.S. is actually priced on the jacket at CDN$33. Newspapers costing $1.50 are also listed as CDN$2. But in pharmaceuticals, the price ceiling imposed in Canada by the Patented Medicine Prices Review Board (PMPRB) – totally disconnected from exchange rates – has no mechanism which allows U.S. exporters of medicines to adjust their prices in Canada due to exchange rate fluctuations.

Many studies have focused on the final prices to patients or third-parties rather than revenue received by the manufacturers. However, in most countries, pharmaceutical wholesalers and retail pharmacies are reimbursed at fixed percentage mark-ups over the ex-manufacturer price. The margins are set by law and differ substantially from one country to another. Many countries also impose a value-added tax. Even if a manufacturer were to set a uniform wholesale price in all major industrialized countries, the final retail price to consumers would vary by as much as 90 percent due to these mark-ups. If hypothetically a manufacturer sold a product for $1.00 in North American and European markets, the final price to consumers would range from a low of $1.14 in the UK to a high of $2.08 in Finland. The U.S. price would be $1.43. Only the UK and Sweden would have a consumer price lower than that available to U.S. consumers.

Focusing on international comparisons at the ex-manufacturer level does not guarantee clarity, however. A recent study by Dr. Danzon focused on drug prices in nine countries, examining ex-manufacturer prices between 187 and 484 products, depending on the country studied.[18] She found that the results were extremely sensitive to the measure of price used, the sample of products selected, whether generics were included, and how prices were weighted. For example, if U.S. consumption baskets are used and generic products are included in the comparison, drug prices in Canada, Germany, Switzerland and Sweden were found to be higher than those in the U.S. But if the comparison countries' consumption baskets are used, then U.S. prices were found to be higher. These results imply that each country consumes higher quantities of products that are relatively inexpensive in that country, a pattern which is consistent with some degree of price sensitivity in the demand for pharmaceuticals.

[18] Danzon, P., and Chao, L., "Prices, Competition and Regulation in Pharmaceuticals: a Cross-National Comparison", Office of Health Economics, 2000.

In summary, there are numerous ways in which "simple" cross-border comparisons result in inaccurate conclusions. While these problems may be well known in academia, they are often missing from the public discourse. Finally, on top of the host of technical problems described, one must recall that in the U.S., for non-government purchases, market forces set the price. In other countries, governments, directly or indirectly, set the price and no government bureaucracy has ever been able to accurately mimic a market-based price for a large number of products on a sustainable basis.

APPENDIX 2

DESCRIPTION OF HEALTH CARE SYSTEMS AND HEALTH CARE FINANCING IN G-8 COUNTRIES AND MEXICO

Canada

Health Care Financing: Universal, public health care is available to all residents. Health care is administered provincially, and is financed through federal transfer payments to the provinces and provincial taxation.

Pharmaceutical Market: In 1997, the Canadian pharmaceutical market was valued at US$ 4,685 million, less than 2% of the global total. Private and public spending on pharmaceuticals comprised 13.8% of total health care expenditures in Canada in 1997.

Pricing and Reimbursement: Pharmaceutical companies are technically "free" to set their own prices for medicines. However, the suggested prices (both at launch and subsequently) of patented medicines must be reviewed by the Patented Medicine Prices Review Board (PMPRB) to determine their "reasonableness." In this way U.S. producers face a *de facto* system of government price controls in Canada. The PMPRB determines whether the price suggested is "reasonable" by placing the drug in one of three categories. The price of "breakthrough products" cannot be higher than the median price of the drug in the U.S., France, Germany, UK, Italy, Switzerland, and Sweden. The price of a line extension product must be in the range of the cost of therapy for existing drugs used to treat the same disease. Other products, deemed of "minor improvement", can have a price equal to but no higher than the highest price of the class in Canada at the time the product comes to market. In addition, products are not permitted to have price increases of greater than the Consumer Price Index. If the company prices a drug higher than the price determined by the PMPRB, it must reimburse the excess to the government.

Reimbursement for drugs in Canada is based on a mix of public, private, employer-based and private, out-of-pocket sources. About 12 percent of the population has no drug coverage at all. Once the price of the drug has been accepted by the PMPRB, individual provinces decide whether it will be placed on the provincial formulary for reimbursement. Each province has its own rules for how to determine who is covered under the provincial plan, what drugs will get onto the formulary, and at what reimbursement price.

Research and Development: In 1998, pharmaceutical sector R&D spending in Canada totaled CDN$ 879 million (approximately US$ 595 million). Until 1993, Canada had a compulsory licensing system for pharmaceuticals. Since 1993, when intellectual property protection in Canada was improved and its ability to resort to compulsory licensing limited, research spending has risen by 43 per cent although it remains proportionately far lower than in the U.S.

Implications: Canada's system of government price controls on pharmaceuticals does not serve to guarantee access to medicines to Canadians. Canadian

citizens suffer from a significant delay in access to innovative therapies due to inefficiency of the regulatory agency and since pharmaceutical companies require extra time to obtain a price for a new drug at the federal level followed by a second round of negotiations at the provincial level. Even clearing these hurdles is no guarantee of unfettered market access. In British Columbia, where there is a system of reference pricing in effect which results in year-to-year changes in the provincial formulary, in a 1997 survey physicians reported that 90 percent of their patients were forced to change medications as a result of reference pricing. The reported health implications of these shifts included adverse effects, worsened symptoms, and hospitalizations.[17] In addition, drug coverage is not a universal benefit, and the eligibility and level of benefit differs significantly from province to province. A person receiving a drug in one province may encounter difficulty accessing the same drug in another province. This means that the patient may have to undergo difficult, and possibly harmful, changes in medication if he or she moves.

[17] Canadian Association of Retired Persons, "CARP Survey: BC's New Drug Plan Hurts," Fifty Plus Net - CARP in Action, May 14, 1997.

France

Health Care Financing: France's health care system is financed through compulsory payroll taxes paid by employers and employees' contributions. Health is administered through sick funds which do not compete with each other since they are organized along occupational lines.

Pharmaceutical Market: In 1998, France's pharmaceutical market was valued at €14,950 million (approximately US$ 14 billion), of which U.S. research-based companies comprise 23% of the total turnover. Pharmaceuticals comprised 17.2% of total health care expenditures in France in 1997.

Pricing and Reimbursement: The prices of medicines which are reimbursed by Social Security, and which represent 77.3% of the pharmaceutical turnover in France, are subject to government regulation. Prices are either agreed to by the pharmaceutical company and the *Comité Economique du Médicament* (Economic Committee for Medicines, or "CEM") or are fixed by decree by the Ministries of Economics, Health, and Social Security. Drugs are placed into one of three reimbursement categories:

- 100% for "medicinal products acknowledged as irreplaceable and particularly expensive"
- 35% for "medicinal products primarily intended for the treatment of disorders and diseases that are generally not serious.
- 65% for other medicinal products.

Often, French employers will insure workers for the cost of co-payments, meaning that most people pay nothing at all for medicines. There are no controls on non-reimbursable drugs and those provided to patients in hospitals.

As part of a broader plan to reduce France's budget deficit, the Government fixes annual targets for spending on major categories of medicines. The growth of sales of reimbursable medicines dispensed by pharmacies is limited to 2% for the year 2000. In addition, limitations have also been placed on therapeutic categories, especially targeting those which experience high growth. In practical terms, all pharmaceutical companies must, in fact, enter into agreements with the CEM establishing individualized targets and refund obligations for their own products. A refund obligation is triggered if a company exceeds its individualized contractual growth rates. If a pharmaceutical company were to refuse to voluntarily enter into a CEM agreement, the French government has adopted a statutory "Safeguard clause" which automatically exacts rebates from companies which do not voluntarily enter into a volume/price contract. Manufacturers must also limit advertising costs, and inform doctors on a "rational use" of the drug in question. Finally, the French Social Security Financing Law also provides for the imposition of a levy on pharmaceutical companies of 1.3% on 1999 sales of reimbursable products in order to finance social security budget overruns.

Research and Development: In 1997, the pharmaceutical industry spent US$ 2 billion, or 14% of turnover on research and development activities in France.

A study by P. Etienne Barral shows that there is a direct correlation between the regulatory environment for innovation and the number of breakthrough products originating in a country.[18] France, with one of the strictest price control regimes in Europe, has been subject to a sharp decline as a source of new drug innovation, and has not been the original source for a breakthrough drug since 1985.[19]

Implications: The limit on the overall growth rate to 2%, which was determined in a non-transparent manner, harms the interests particularly of firms that invest heavily in R&D because sales of innovative products need to grow by more than 2% to allow these firms to recover their investments. Growth rates are also designed to hit those innovative products which experience high growth levels. Research-based firms are primarily non-French and thus the impact of this system on foreign firms is greater than the impact on domestic firms. Furthermore, companies determine their investments years in advance based on current projections of the market environment in the future. Arbitrarily capping the growth of the drug budget to 2% has severe competitive consequences which could also nullify and impair the value of the investments committed to by the U.S. industry under the previous system. Finally, the system favors older, less-expensive products, even if they are less effective or create greater public health risks or overall costs.

In large part because French employers tend to insure their employees for the cost of co-payments, France has one of the highest levels of drug utilization in the world. In addition, this practice tends to perpetuate the market life for old, less efficacious products. In November 1999, the Transparency Committee recommended that 262 of these older products be delisted from reimbursement as having little or no therapeutic value but action on the recommendation has been delayed for months due to political resistance from the manufacturers of these products, despite the argument that the delistings will free resources for reimbursement of newer medicines.

[18] P. Etienne Barral, "Twenty Years of Pharmaceutical Research Results Throughout the World: 1975-1994", Rhone-Poulenc Rorer Foundation, 1995.
[19] Id.

Germany

Health Care Financing: Health care is provided for over 90% of the population by non-profit sickfunds (*Krankenkassen*) funded by a compulsory payroll deduction. Those Germans with earnings above a set level may opt for private insurance.

Pharmaceutical Market: Germany is Europe's largest pharmaceutical market and the third largest market in the world after the U.S. and Japan, valued at €16,528 million (US$ 15.4 billion) in 1998. Of this, American research-based pharmaceutical companies represent 22% of the turnover. Pharmaceuticals comprised 12.3% of total health care expenditures in Germany in 1997.

Pricing and Reimbursement: For those products introduced onto the market after January 1, 1996, companies may price their products to reflect market conditions. All drugs prescribed by physicians are eligible for reimbursement as long as they are not included in a negative list. Patients have a modest variable co-payment. However, physicians operate under strict budgetary controls under which the amounts that they may prescribe for each patient are limited. If physicians exceed this limit by more than 25%, they must generally pay the difference. Germany maintains a reference price system for those patented products introduced onto the German market before December 31, 1995. The reference price system continues to regulate the prices of two-thirds of all prescribed pharmaceuticals although this declines with each passing year.

Research and Development: The imposition of reference pricing in Germany in 1989 had a significant and negative impact on investments in research and development. During the five-year period prior to reference pricing, R&D had grown at a rate of 54%. After the introduction of reference pricing, R&D fell by 13% over five years. In 1996, recognizing the negative impact of reference pricing on innovation, Germany amended its policy to exclude from the reference pricing system patented products registered after January 1, 1996. Since then, the investment climate for the research-based industry has improved and more research is taking place. Between 1996 and 1998, research and development expenditures in Germany rose by 12% and now total over DM 5.4 billion (US$ 2.5 billion).

Implications: Germany has recognized the adverse effect that its reference price system had on the climate for research and development, and took steps to correct this. However, the strict budgetary controls imposed upon German physicians mean that they may not always be in a position to prescribe the products that, in their professional opinion, would best suit their patients' needs. The impact of these budgets bias physicians' decision-making away from innovative therapies that are the most appropriate for them. This translates into a bias against many American pharmaceuticals.

In some cases only patients who specifically request innovative products may receive them, while those who do not are prescribed older, less effective medicines that do not improve their quality of life or medical condition as much as innovative medicines would – but do protect the physician against exceeding the allotted prescribing budget. However, because of restrictions on direct to consumer advertising, patients often lack the information required to request the innovative therapies best suited for their care. A recent study indicates that 12 percent of patients in the subsidized sickfund insurance system receive the newest innovative drugs, while 48 percent of patients in the private system obtain them. At the same time, in order to remain within their allotted budgets, physicians are often forced to transfer their patients to more expensive hospital and clinic-based care.

Italy

Health Care Financing: The Italian National Health Service guarantees universal coverage of the population. The system is financed through payroll taxes, general taxation, and through patient co-payment for some services. Italian citizens are permitted to obtain private insurance coverage, but must still pay taxes to support the public system.

Pharmaceutical Market: The Italian pharmaceutical market is valued at €9,662 million (US$ 9 billion), of which U.S. research-based pharmaceutical companies represent 26% of the total turnover. Pharmaceuticals comprised 19.4% of total health care expenditures in Italy in 1997.

Pricing and Reimbursement: The Italian National Health Service imposes cost-containment measures on pharmaceuticals. Pharmaceuticals which are included in the formulary determined by the Italian government are reimbursed at 100% or 50% levels. The positive list of the formulary covers approximately 48% of drugs, of which over 92% are 100% reimbursable. All drugs reimbursed by the National Health Service are subject to price regulations by the State. An interministerial committee determines prices. Under the current system, prices in Italy cannot be above the European Average Price (EAP) for drugs already on the market which were approved through the national registration procedure. The EAP is currently the weighted mean of the prices in twelve EU comparison countries. The prices of the three most frequently sold drugs (including generics) with the same active substance are compared, using the packs most similar to Italian trade packs. Since July, 1998 upward adjustments to the EAP have been made in six yearly tranches.

For new drugs that are approved through European registration routes, price and reimbursement status are negotiated by the pharmaceutical industry with government authorities. These agreements contain price-volume restrictions.

In addition, the Parliament has fixed the ceiling for public pharmaceutical spending for 2000 at ITL 14,421 billion (approximately US$ 7 billion). The pharmaceutical industry, wholesalers and pharmacists will have to jointly pay back 60% of any spending over budget for 1998 and 1999.

Research and Development: From 1996 to 1998, research and development expenditures in Italy rose from €753 million to €759 million (approximately US$ 702 million to US$ 707 million), a rate of 0.8%.

Implications: Italy's pricing system adds substantial administrative costs to the health care system because of its complexity, and has a negative impact on the quality of care for patients and on R&D investment. Furthermore by tying the Italian price to prices set by other European governments, the price faced by

innovative pharmaceutical manufacturers are twice removed from those arising from market conditions.

Japan

Health Care Financing: Health care insurance is mandatory in Japan. The entire population is covered by health insurance schemes, managed either by employers or by the Government. Regardless of the insurer, or whether treatment is in a public or private medical institution, a clinic or hospital, a common tariff rate, set for the National Health Insurance (NHI) scheme, applies. Only products in the NHI tariff lists can be prescribed, with reimbursement limited to listed tariff rates.

Pharmaceutical Market: Annual per capita consumption is the highest in the world. Drug costs (US$ 65 billion in 1999) at the NHI level constituted 21.2% of the total cost of health care. Japan is the world's second largest national pharmaceutical market after the United States. U.S. companies account for 12% of sales in the Japanese market. If licensed-in products are included in this mix, the U.S. companies enjoyed a 19% share of the Japanese market in 1999. Doctors and hospitals receive a margin on the difference between the fixed reimbursement fee and the ex-wholesaler price. The Japanese Government has made efforts to eliminate that margin but difficulties remain.

Pricing and Reimbursement: The Ministry of Health & Welfare (MHW) fixes the introductory price of every new prescription brand-name drug through negotiation with its manufacturer. In principle, a new product receives the same National Health Insurance price as a similar "comparator" product already established on the market. For a variety of administrative/regulatory reasons, so there are very few opportunities for the new product to receive a "premium" price over the existing "comparator" drug. Since 1997, 47 new drugs have been introduced and none has received the top – or "innovation" – premium.

Drugs with changes in principal indications, efficacy, dosage levels, or market size are subject to special price revisions. MHW attempts, in annual price revisions, to reduce tariff prices closer to market levels, through a survey of the current market in specific drug categories. A new Drug Price Organization, which will advise MHW on comparators and premiums, will be established in October 2000. MHW is also evaluating other components of the current NHI drug price system, and is aiming at significant reform of this system by April 2002.

Research & Development: The introduction of innovative drugs has been delayed in Japan. Of 230 global products launched since 1985, 130 were not available in Japan by 1997.

Implications: The impact of various price controls in Japan has been to deny or delay Japanese patient access to innovative medicines that are normally made available to patients in the U.S. and Europe; reduce overall incentives for innovation; complicate business planning by pharmaceutical company

executives in Japan; delay the introduction and launching of New Chemical Entities and make most Japanese companies less competitive and less able to invest in overseas markets.

Mexico

Health Care Financing: Health care in Mexico is financed through a mix of public and private sources. One-half of the population is covered by insurance, either through the social security system, or through private insurance funded by employers. Private insurance in the private sector is relied on as an alternative or complement to the social security system. The Government finances and provides care directly for many of the remainder of the population, including the poorest citizens and those living in the most geographically remote sectors of the country. For these services, patients must pay a co-payment.

Pharmaceutical Market: In 1995, total expenditure at ex-wholesaler prices was about 20,000 million pesos, or approximately US$ 3 billion. U.S. companies enjoy a market share of 37.12%.

Pricing and Reimbursement: It is important to distinguish between the public and private markets for pharmaceuticals. Providers of pharmaceuticals to the public market must follow specific bidding procedures which, in effect, set the price in the public sphere. In this market, low-priced copy products which have not been authorized by the Health Department as "exchangeable generic products" often appear. Doctors who prescribe in the public sector must limit their prescriptions to a formulary of approximately 600 unbranded (copy or generic) products. Doctors are required to include the generic name of a medication, but they are permitted to write a branded name as well. The pharmacist is then prohibited from filling the prescription with a generic drug.

In the private market, innovative patented products are sold. Although prices in the private market must be approved by the Mexican Government, this requirement has been significantly relaxed recently, and price requests are generally granted readily. The de facto result is that pharmaceuticals are priced according to market condition. Manufacturers are allowed to increase prices when they choose.

Research and Development: The pharmaceutical industry spends 5 percent of revenue on research and development in Mexico nearly exclusively in the form of clinical research done in cooperation with organizations such as medical schools and clinics. Although Mexico has an intellectual property rights law that provides full patent protection to pharmaceuticals, the ability of the research-based industry to capitalize on its protections is hampered by lax administration and enforcement.

Implications: Important divisions exist between the treatment of the insured and uninsured populations. Because lowest-price, rather than cost-effectiveness criteria are used in purchasing decisions, patients outside the social security and private health care systems have decreased access to innovative medicines.

Indeed, seven of the top twenty drugs prescribed are over 40 years old. Additionally, in some cases patients may receive copy products of the therapies that are best suited for their care. These copy products may pose important health risks to the patient, as it is impossible to trace their origin, or to state with certainty that they were manufactured in accordance with minimum standards.

Russia

Health Care Financing: Russia has a compulsory health insurance scheme. A private insurance system is still under-developed and does not cover the reimbursement of pharmaceuticals. Local health care funds derive their income from a tax on employees' monthly salaries, and provide revenue for health care services included in regional health programs. The services are paid for according to fixed tariffs. The federal fund also derives its income from a tax on employee wages, and supplements the low local fund income in less wealthy regions. The self-employed must make their own contributions.

Pharmaceutical Market: In 1997, the pharmaceutical market was estimated at about US$ 5.9 billion. Approximately one-third of the pharmaceutical companies operating in Russia are of Western origin. In 2000, the pharmaceutical market will reach US$ 2 billion at ex-manufacturer prices, and from now on will slowly recover to pre-crisis levels.

Pricing and Reimbursement: Pharmaceutical prices are not regulated at a federal level in Russia. Customs duties introduced in 1994 raised prices by 10-15 percent, and import duties introduced in 1998 raised prices a further 10 percent for imported products for which local versions are available. In addition, there are significant (100-120%) pharmacy mark-ups on the prices of imported products. Many pharmaceuticals are reimbursed from the regional government budgets. The reimbursement scheme, however, operates separately in each region due to lack of coordination.

Research and Development: Due to economic conditions including large budget deficits, Russia is unable to sustain research in the Western sense.

Implications: Currently, there is inconsistency throughout the country and even within cities. Prices differ considerably from pharmacy to pharmacy and city to city. Consumers suffer and the government suffers as inflation makes it difficult for the government to meet its drug purchasing requirements. Although the bulk of public expenditure is dedicated to purchasing medicines, due to high retail prices caused by retail mark-ups and budget cuts, hospitals are experiencing a shortage of drugs. As a result, patients are responsible for the cost of their treatment. A large sector of the population is unable to afford this, and must go without treatment. Finally, the U.S. research-based pharmaceutical industry in Russia experiences many of the same bureaucratic and other business impediments experienced by other industrial sectors.

United Kingdom

Health Care Financing: Public health care is available to all residents through the government-managed National Health Service (NHS). The NHS is funded primarily through taxation, but also derives funds from national insurance contributions and patient co-payments. Private insurance schemes are available, and usually provide supplementary coverage.

Pharmaceutical Market: The UK pharmaceutical market was valued at €11,601 million (approximately US$ 10.8 billion) in 1998. U.S. research based companies represent 33% of the total pharmaceutical turnover. Pharmaceuticals comprised 16.9% of total health care expenditure in 1997.

Pricing and Reimbursement: Manufacturers are free to determine the price of a product. All prescription-only medicines are reimbursed by the NHS, unless they are on the "Selected List Scheme" (SLS), a negative list which includes 2000 products in 17 categories. For those products reimbursed by the NHS, pricing is subject to the Pharmaceutical Price Regulation System (PPRS), and any increase must be authorized by the Department of Health (DOH). For prescription only medicines, patients face a co-payment of £5.90 (US$ 8.80) for each item dispensed. Nevertheless, few actually pay the co-payment as most of the population qualifies for exemptions. The PPRS' profit framework is fixed for each individual manufacturer based on their level of investment in the UK. If profits exceed the target level, excess profits must be repaid to the NHS, or prices will be lowered for the next period.

The National Institute for Clinical Excellence (NICE) develops guidelines on clinical and cost-effectiveness of new treatments for the guidance of health care professionals. Following a NICE appraisal, products are categorized as recommended for routine use in the NHS, recommended only for use in the clinical trials to help answer specific questions about cost-effectiveness, or not recommended for use.

Research and Development: From 1994 to 1998, research expenditures grew from US$ 3.1 billion to US$ 4 billion, a rate of 22.5%. Over the same period in the U.S., research expenditures grew from US$ 13.4 billion to US$ 21 billion, a rate of 36.1%.

Implications: Under the NICE guidelines, patient choice and clinical freedom are limited. Access to innovative therapies may be restricted or denied. In some cases it is not possible for the doctor to provide the best possible care to the patient, since doctors are not able to interpret the guidelines in the context of the particular circumstances of each individual patient. The PPRS' profit control scheme dampens innovation and efficiency by introducing non-market considerations into investment decisions.

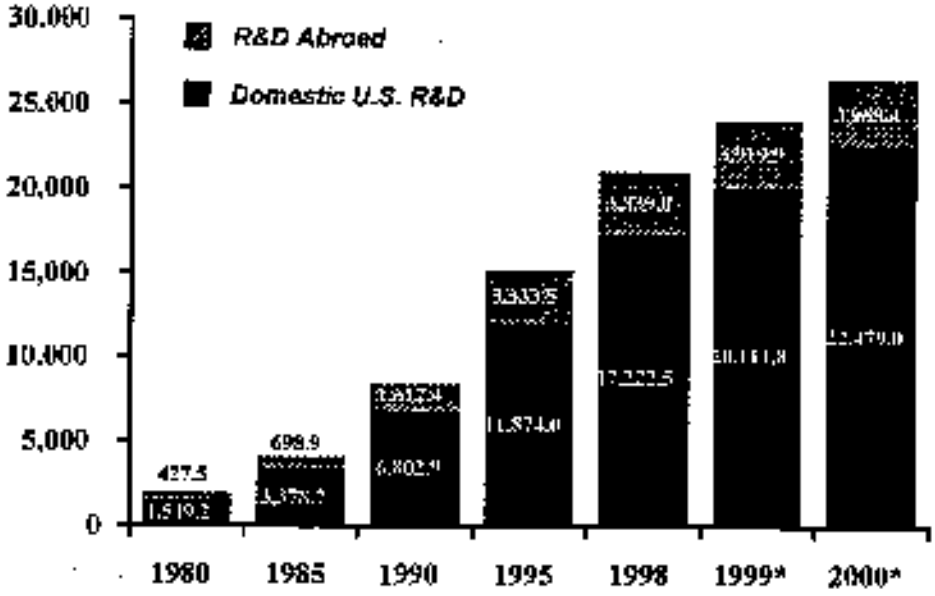
APPENDIX 3

Pharmaceutical Industry Expenditures on Research and Development

Figure 2.1

R&D Expenditures, Ethical Pharmaceuticals, Research-based Pharmaceutical Companies, 1980–2000

R&D Expenditures in $Millions

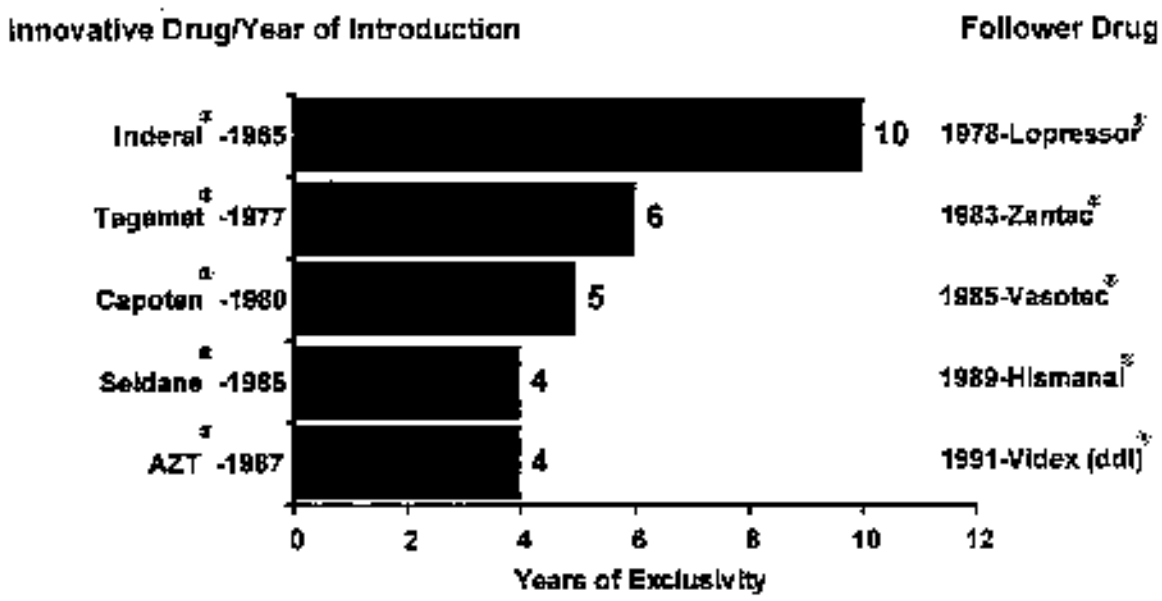


Source: PhRMA Annual Survey, 2000.

**estimated*

Figure 5.5

Shrinking Period of Market Exclusivity Between Introduction of Breakthrough Medicine and Competing Innovators



Inderal (beta blocker for cardiovascular disease); Tagamet (H_2 antagonist for ulcers); Capoten (ACE inhibitor for cardiovascular disease); Seldane (antihistamine for allergies); AZT (antiviral for HIV/AIDS).

Source: The Wilkerson Group, 1995.

APPENDIX 4

Growth of Biotechnology in the U.S.

Growth of Biotechnology in the U.S.

In the health field, biotechnology is creating new knowledge at a remarkable rate. It has already enabled researchers to:

- provide new tools for manufacturing medicinal products as well as for therapy and diagnosis.
- enable better identification of new disease-causing agents such as viruses,
- facilitate understanding of the mechanisms of diseases through the identification of genes and their effect on diseases.

Approximately one-fifth of new molecular entities launched on the world market each year are now biotechnology derived. The application of human genomics knowledge to clinical practice and drug development will allow us to prevent the development of disease, predict a patient's response to treatment and create new personalized medicines according to genetic variations.

The U.S. biotechnology sector is the most highly developed in the world, while Europe is lagging far behind. The latest data on the location of biopharmaceutical development work show that 63 percent of biotechnology-derived medicines are currently under development in the U.S., compared with 25 percent in Europe. Seventy percent of gene therapy medicines are under development in the U.S., compared with 22 percent in Europe. For biotechnology patents filed in Europe in 1997, 59.6 percent were of U.S. origin, and 27.1 percent of European origin. In the U.S., of 150 biotechnology patents filed in 1995, 122 were of U.S. origin and 11 were of European origin.

This discrepancy is not accidental. Biopharmaceutical companies are founded and flourish in economic environments that favor innovation – and in particular those that are free from price controls on medicines. In the U.S., the general attitude towards innovation and biotechnology and the overall climate in which research and innovation takes place are such that these new technologies can thrive. The U.S. market for pharmaceutical products has not been subject to extensive government price controls, and the venture capital market is highly developed.

Whereas in Europe, pharmaceutical companies are directly affected by the many constraints that EC legislation imposes on biotechnology, taking little notice of existing pharmaceutical legislation. U.S. legislators, on the other hand, adapt sector-specific legislation to biotechnology. In addition, biotechnology research is not restricted to major global companies, but is often carried out through research alliances and arrangements with smaller companies and start-ups. Cumbersome regulations, (such as co-marketing rules, single trademark requirements, and GMO directives) and policy interpretations fail

disproportionately hard on these smaller companies that have limited initial resources.

Policy makers in Europe have agreed that biotechnology is a key factor for enhancing the competitiveness of the pharmaceutical industry in Europe. Biotechnology in the U.S. operates in an environment of optimism, where one success leads to another. Europe will not be able to catch up to the U.S. until actions are taken to restore investment confidence and give predictability by adapting regulatory requirements to research needs. Only then will Europe be able to compete with the U.S. in fostering innovative research and new technologies.

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
DEPARTMENT OF INTERNATIONAL COOPERATION

101431, Moscow, Rakhmanovsky per. 3. Fax: 200 0212; E-mail: Saveliev@Health.msk.su; Tel. 925 1140/921 4672

September 15, 2000 No. 519

Mr. T. Quilter
Specialist in International Trade Affairs
U.S. International Trade Commission
Washington, USA

Fax: 202-205-2217

Dear Mr. Quilter,

I have the honor of confirming receipt of your letter of July 24 of this year regarding matters of price determination for pharmaceuticals, and I can report that for the purpose of reducing prices for vitally essential and most important pharmaceuticals and rational use of budget funds at all levels, the Government of the Russian Federation passed a resolution on March 29, 1999 No. 347 "On Measures of Government Control of Prices of Pharmaceuticals." This resolution introduced government registration of manufacturers' prices for vitally essential and most important pharmaceuticals, which is carried out by the Ministry of Health of Russia after preliminary agreement of the manufacturers with the Ministry of Economics of Russia on the level of prices.

The above-mentioned resolution determines the delimitation of authority between the federal and territorial organs of administrative power in matters of price regulation.

As of August 10, 2000, the Ministry of Health of Russia, taking into account the medicinal forms, dosages, and packaging, had registered prices on 5699 pharmaceuticals from 343 manufacturers (of which 162 were native and 181 foreign).

Along with the work carried out by the Ministry of Health and the Ministry of Economics of Russia on registration of prices for vitally essential and most important pharmaceuticals, the organs of the administrative power over the subjects of the Russian Federation have been charged with analysis of the size of price increases established for these pharmaceuticals, and to take the necessary decisions on their level.

The wholesale and retail increases approved by the organs of administrative power over the subjects of the Russian Federation must be applied to the registered prices for pharmaceuticals. The level of these wholesale and retail increases established by the organs of administrative power over the subjects of the Russian Federation averages 25% and 40%, respectively (except for the regions of the Far North and those on an equal footing with them).

Knowing the level of the registered selling price and the limit of wholesale and retail increases approved in the region, each participant in the pharmaceutical market can calculate the maximum prices for concrete pharmaceuticals, which enables realization of control over them.

Therefore, the envisioned mechanism for price formation for pharmaceuticals is directed toward providing price transparency at all levels of its formation as the goods move from the manufacturer to the ultimate consumer.

The procedure for government registration of selling prices of vitally essential and most important pharmaceuticals should be followed by all manufacturers that are licensed for production and are holders of registration certificates from the Ministry of Health of Russia for a concrete type of consumer package.

It must be recognized that the introduction of price registration only for vitally essential and most important pharmaceuticals does not completely solve the problem of reducing prices for medications as a whole, inasmuch as for other pharmaceuticals the operating procedure allows the first wholesaler to establish a free price.

Therefore, with the Federal Law of January 2, 2000, No. 5 FZ "On Implementation" supplemental to the Federal Law "On Pharmaceuticals," the functions of the government in government regulation of prices of all pharmaceuticals are strengthened.

On the basis of this law, the Ministry of Health of Russia in conjunction with the Ministry of Economic Development of Russia and the Ministry of the Science Industry of Russia should develop a mechanism for regulation of the prices of pharmaceuticals.

Please excuse the delay in responding to you, which was connected to the vacation period. I hope that this information will be useful for carrying out an analysis of the state of the pharmaceutical industry.

Yours respectfully,

Chief, Department of International Cooperation — /signature/ — N. N. FETISOV

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ
УПРАВЛЕНИЕ МЕЖДУНАРОДНОГО СОТРУДНИЧЕСТВА

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
DEPARTMENT OF INTERNATIONAL COOPERATION

[illegible]

15 09 2000 г. № 519

Г-ну Т. КИЛТЕР

Специалисту по вопросам
международной торговли
Комиссии США по между-
народной торговле

Вашингтон, С Ш А

ф. 202 205 22 17

Уважаемый г-н Киллер,

Имею честь подтвердить получение Вашего письма от 24 июля с.г. относительно вопросов ценообразования на лекарственные средства и сообщаю, что в целях снижения цен на жизненно необходимые и важнейшие лекарственные средства и рационального использования средств бюджетов всех уровней, Правительство Российской Федерации приняло постановление от 29 марта 1999 г. № 347 «О мерах государственного контроля за ценами на лекарственные средства». Данным постановлением введена государственная регистрация цен производителей на жизненно необходимые и важнейшие лекарственные средства, которая осуществляется Минздравом России после предварительного согласования производителями уровня цен с Минэкономики России.

Вышеназванное постановление определяет разграничение полномочий между федеральными и территориальными органами исполнительной власти в вопросах регулирования цен.

По состоянию на 30 августа 2000 г. Минздравом России с учетом лекарственных форм, дозировок, расфасовок зарегистрированы цены на 5699 лекарственных средств от 941 производителей (из них 162 отечественных и 181 зарубежный).

Наряду с проводимой Минздравом и Минэкономики России работой по регистрации цен на жизненно необходимые и важнейшие лекарственные средства органам исполнительной власти субъектов Российской Федерации поручено проводить анализ размеров торговых надбавок, устанавливаемых на эти лекарственные средства, и принимать необходимые решения по их уровню.

Утвержденные органами исполнительной власти субъектов Российской Федерации оптовые и торговые надбавки должны применяться к зарегистрированным ценам на лекарственные средства. Уровень этих оптовых и торговых надбавок, установленный органами исполнительной власти субъектов Российской Федерации, составляет в среднем 25% и 40% соответственно (кроме районов Крайнего Севера и приравненных к ним).

Зная размер зарегистрированной отпускной цены и предельный уровень оптовой и торговой надбавок, утвержденных в регионе, каждый участник фармацевтического рынка может рассчитывать максимальные цены на конкретные лекарственные средства, что позволяет осуществлять контроль за ними.

Таким образом, предусмотренный механизм формирования цен на лекарственные средства нацелен на обеспечение прозрачности цены на всех этапах ее формирования при прохождении товара от производителя до конечного потребителя.

Процедуру государственной регистрации отпускных цен на жизненно необходимые и важнейшие лекарственные средства должны пройти все производители, имеющие лицензию на производство и удостоившиеся держателями регистрационного удостоверения Минздрава России на конкретный вид потребительской упаковки.

Следует признать, что введение регистрации цен только на жизненно необходимые и важнейшие лекарственные средства не в полной мере решит проблему снижения цен на медикаменты в целом, поскольку на другие лекарственные средства действующий порядок разрешает первому оптовику устанавливать свободную цену.

Поэтому Федеральным законом от 2 января 2000 г. № 5-ФЗ «О внесении дополнений в Федеральный закон «О лекарственных средствах» закреплены функции государства по государственному регулированию цен на все лекарственные средства.

На основании этого закона Минздравом России совместно с Минэкономразвития России и Минпромнауки России должен быть разработан механизм регулирования цен на лекарственные средства.

Прошу извинить за задержку ответа, которая связана с отпускным периодом. Надеюсь, что указанная информация будет полезна для проведения анализа состояния фармацевтической промышленности.

С уважением.

Начальник Управления
международного сотрудничества — Н.Н. ФЕТИСОВ

Appendix H
More Patent Information by Country

PATENT PROTECTION SYSTEMS

Patents are one of the most important forms of statutory intellectual property for the pharmaceutical industry.[1] Information about the terms of patents in each of the countries under consideration, as well as information about working the patent and compulsory licensing in each country, is provided in chapter 3. The following addresses, on a country-by-country basis, methods of obtaining a patent and information regarding infringement and noninfringement.[2] As in chapter 3, points of specific applicability to the pharmaceutical industry are noted in the text.

Overview

The patent protection systems in Canada, France, Germany, Italy, Japan, Mexico, Russia, and the United Kingdom are similar to the system in the United States and similar to each other in regard to obtaining a patent. The United States and each foreign country covered by the investigation issue patents on the basis of an application and apply essentially the same criteria for patentability.

Also like the United States, each foreign country provides civil remedies for infringement. For example, as in the United States, the United Kingdom provides the option of litigating the issue of infringement in an administrative forum. Unlike the United States, the laws of Mexico and Germany make infringement a criminal offense punishable by fine and/or imprisonment. The countries vary with respect to acts that are considered noninfringing. However, the United States and each country allow the use of patented inventions for at least some of the following purposes: private or domestic uses; noncommercial purposes; research or experimental use; the development of information required by law; and the filling of prescriptions for patented medicines by a pharmacy. Canada, Germany, Mexico, Russia, and the United Kingdom also permit certain prior uses of an invention to continue after the issuance of a patent for the invention and without liability for infringement.

The United States

Obtaining a Patent

The Patent and Trademark Office of the United States Department of Commerce (PTO) will issue a utility patent for an invention consisting of a process, machine, manufacture, or composition of matter, or an improvement thereof.[3] In order to be patentable, the invention must be new, non-obvious, and useful.

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[1] USITC, *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals*, USITC Publication 2437, September 1991, p. 3-11.

[2] Owing to the limited focus of this investigation, this discussion does not summarize the patent provisions of international conventions, agreements, or treaties to which the United States or the other countries adhere, nor does it discuss European or Eurasian patents.

[3] The PTO also issues design patents and plant patents. Utility patents, however, are by far the most common and most important patents for the pharmaceutical industry. See *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharmaceuticals*, p. 3-11. The discussion of U.S. patents in the present report accordingly focuses on utility patents.

A patent is granted on the basis of an application that is given formal examination by the PTO. The application must be filed by a person who believes himself to be the original and first inventor of the invention, or by a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter.

The application for patent must be accompanied by a prescribed fee. An additional fee is charged for each claim, in excess of a specified number of claims, that the applicant files at any other time.[4] The applicant also may incur miscellaneous, processing, or other fees and charges during processing of the application for patent.

The PTO can ask the U.S. Department of Health and Human Services to furnish information with respect to questions relating to drugs as the PTO may submit concerning any application for patent. The PTO also can ask the Department to conduct such research as may be required.

On average, the PTO takes 1½ to 2 years to process an application for patent for a pharmaceutical product or process.[5] Decisions on various issues may be appealed to the PTO's Board of Patent Appeals and Interferences or to the U.S. Court of Appeals for the Federal Circuit. Further appeal is possible by way of a petition for a writ of certiorari to the U.S. Supreme Court. The applicant also may initiate a civil action to obtain a patent.

If it appears that the applicant is entitled to a patent under the law, the applicant must pay a fee in order for the patent to be issued.

Infringement and Noninfringement

A U.S. patent gives the patent owner the right to exclude others from making, using, offering for sale, or selling the patented invention throughout the United States, or from importing the invention into the United States, during the term of the patent. If the invention is a process, the patent owner may exclude others from using, offering for sale, or selling throughout the United States, or from importing into the United States products made by the patented process.

Infringement generally consists of taking any of the aforementioned actions without permission from the patent holder. Infringement can be literal or equivalent.[6] Liability also attaches for inducement of infringement and contributory infringement.

It is not infringement to make, use, sell, or offer to sell a patented invention (other than a new animal drug or certain veterinary biological products) within the United States, or to import the invention into the United States, solely for uses reasonably related to the development and submission of information under Federal law which regulates the manufacture, use, or sale of drugs (or veterinary biological products). Also, no remedy may be granted for infringement of a process patent based on

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[4] The amount of the additional fee also depends on whether the additional claim is in independent form or dependent form and whether the applicant is a small entity.

[5] Commission staff conversation with a representative of the PTO on Aug. 1, 2000.

[6] Under U.S. law, infringement under the doctrine of equivalents means that an accused device may be found to infringe even if it does not precisely meet the terms of a patent claim, as long as the patent holder can show that the accused device performs substantially the same function in substantially the same way to achieve substantially the same result as the patented device.

noncommercial use or retail sale of a product, unless there is no adequate remedy for infringement under the patent law on account of the importation or other use, offer to sell, or sale of that product. Finally, a product made by a patented process will not be considered to be so made after it is materially changed by subsequent processes or becomes a trivial and nonessential component of another product.

Civil actions for patent infringement must be filed in U.S. District Courts, with appeal to the U.S. Court of Appeals for the Federal Circuit. Further appeal, to the U.S. Supreme Court, is possible. Judicial remedies for infringement include injunctions and damages. In exceptional cases, a court may award reasonable attorney fees to the prevailing party.

To obtain relief for infringement by imported articles, a patent owner also may request an investigation by the U.S. International Trade Commission under section 337 of the Tariff Act of 1930. Possible remedies include exclusion of the infringing articles from entry into the United States and/or a cease and desist order. Infringing articles also can be seized and forfeited to the United States provided that certain conditions are met.

Canada

Obtaining a Patent

The Canadian Intellectual Property Office will issue a patent for an invention that is new, non-obvious, and useful. A patent is granted on the basis of an application, but the application will be examined only if formally requested. The patent is granted to the inventor of the invention, or the inventor's legal representative, who first files an application. Any person who invents an improvement on a patented invention may obtain a patent for the improvement, but does not thereby obtain the right of making, vending, or using the original invention; nor does the patent for the original invention confer the right of making, vending, or using the patented invention.

The application for patent must be accompanied by a prescribed fee. The amount of the fee depends on whether the applicant is a small entity or a large entity. A maintenance fee must be paid on a pending application in order to keep it in good standing. The applicant also may have to pay other fees and charges during processing of the application for patent, such as an examination fee.

On average, the Canadian Intellectual Property Office takes 2½ to 3 years to issue a patent.[7] The Office's decisions on various issues, including the refusal to grant a patent for a particular application, may be appealed to Canada's Federal Court.

If it appears that the applicant is entitled to a patent under the law, the applicant must pay a fee in order for the patent to be issued.

Infringement and Noninfringement

Actions for patent infringement must be filed in court. The orders and judgments in such actions may be appealed to a higher court. Judicial remedies for infringement include injunctions, an inspection and accounting, and/or damages. In an action for infringement of a patent covering a process for obtaining a

[7] Commission staff conversation with a representative of the Canadian Intellectual Property Office on Aug. 8, 2000.

new product, any product that is the same as the new product will, in the absence of proof to the contrary, be considered to have been produced by the patented process.

The Canadian patent law also imposes liability for damage before a patent is granted. A person is liable for reasonable compensation for any damage sustained by the patentee or persons claiming under the patentee, by reason of any act by that person, after the application for patent became open to public inspection and before the patent was granted, that would have constituted infringement if the patent had been granted on the day that the application became open to public inspection.

In some cases (depending on when the patent was issued), the patent rights do not affect previous purchasers. In such cases, every person who, before the claim date in a patent, has purchased, constructed, or acquired the subject matter defined in the claim, has the right to use and sell to others the specific article, machine, manufacture, or composition of matter patented and so purchased, constructed, or acquired, without being liable to the patentee (or his legal representative) for doing so.

It is not an infringement for any person to make, construct, use, sell the patented invention solely for uses reasonably related to the development and submission of information required under any law of Canada, a Province, or a country other than Canada that regulates the manufacture, construction, use, or sale of any product. It also is not an infringement to engage in the aforesaid actions, during the period specified in regulations promulgated by the Governor in Council, for the manufacture and storage of articles intended for sale after the patent expires.[8]

It also appears that exceptions to the exclusive rights and privileges conferred by a patent exist with respect to acts done privately and on a noncommercial scale or for a noncommercial purpose or in respect of any use, manufacture, construction, or sale of the patented invention solely for the purpose of experiments relating to the subject matter of the patent.

France

Obtaining a Patent

The National Institute of Industrial Property (the French Patent Office) will issue a patent for any invention that is a product, a process, an application, or a combination of means.[9] To be patentable, the invention must be new, involve an inventive step, and be capable of industrial application. The patent belongs to the inventor or his successor in right. If two or more persons have made the invention independently of each other, rights to the patent will belong to the person who is able to show that he was the first to file an application for patent.

A patent is granted on the basis of an application that is given formal examination to determine whether it complies with the requirements of law. The application can be rejected if the applicant does not pay a prescribed fee within one month of the date of filing. The applicant also must pay an annual renewal fee for maintaining the patent application. The applicant may incur other fees as well during processing of the application.

[8] The period specified in the regulations promulgated by the Governor in Council must terminate immediately before the expiration date of the patent.

[9] The French Patent Office also issues certificates of utility.

On average, the French Patent Office takes 3 to 3½ years to process an application for patent.[10] Decisions of the French Patent Office may be appealed to the Court of Appeals of Paris.

If it appears that the applicant is entitled to a patent under the law, the applicant must pay a fee for the granting and printing of the patent.

Infringement and Noninfringement

If the patented invention is a product, a French patent gives the patent owner the right to forbid any third party to manufacture, offer, dispose of commercially, use, or import the patented product, or be in possession of it for the aforesaid purposes, without consent from the patent owner. If the invention is a process, the patent owner may forbid any third party to take the following actions: (1) use the patented process or offer to use it in French territory when the third party is aware or it is obvious under the circumstances that use of the process is forbidden without the consent of the patent owner; and (2) offer, dispose of commercially, use, or import a product directly obtained by the patented process; or be in possession of such a product for the aforesaid purposes; without consent from the patent owner.

A patent also gives the patent owner the right to forbid any third party from supplying or offering to supply to a person on French territory (other than one entitled to work the patented invention) means for carrying out the invention on French territory and which relate to an essential element of the invention, when the third party knows or it is obvious from the circumstances that these means are suitable and intended for carrying out the invention.[11]

The rights conferred by the patent do not extend to: (1) acts done privately for noncommercial purposes; (2) acts done for experimental purposes relating to the subject matter of the patented invention; and (3) the extemporaneous and individual preparation of medicines in chemists' dispensaries in accordance with medical prescriptions or relating to the medicines so prepared. Patent rights also do not extend to acts relating to the patented product that are accomplished on French territory after the product has been disposed of commercially in France by the patent owner or with his express consent.

With certain limitations, French patent law also grants, in territory where that law is applicable, a personal right to work a patented invention despite the existence of the patent, if the person was in good faith possession of the patented invention on the filing date or priority date of the patent.

Actions for patent infringement are handled by District Courts and the Courts of Appeal. Possible remedies for infringement include injunctions, confiscation of infringing articles, and damages.

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[10] Commission staff conversation with a representative of the French Patent Office on Aug. 11, 2000.

[11] This rule of law does not apply when the means for carrying out the invention are staple commercial products, unless the third party induces the person to whom he is delivering the product to commit acts forbidden by this rule of law.

Germany

Obtaining a Patent

The German Patent Office will issue a patent for an invention that is new, susceptible of industrial application, and involves an inventive step.[12] The right to the patent belongs to the inventor or his successor in title. If two or more persons have jointly made an invention, the right to the patent belongs to them jointly. If two or more persons have made the invention independently of each other, the right belongs to the person who is the first to file an application for patent with the Patent Office.

A patent is granted on the basis of an application that is given formal examination by the German Patent Office. The application for patent must be accompanied by a prescribed fee. The applicant also may incur other fees during processing of the application for patent, such as the fee for a request for a search for publications to be taken into consideration in determining whether to grant or deny the patent. An applicant may be eligible for legal aid, funded by the Federal Treasury, in proceedings before the Patent Office, if there are adequate prospects that the patent will be granted.[13]

The German Patent Office takes about 2 to 2½ years to process an application for patent. If the Office determines to grant a patent, the applicant must pay a fee. If the Patent Office determines to reject an application for patent or makes other decisions adverse to the applicant (such as limiting the patent in some respect), the applicant may appeal to the Patent Court. Further appeal to the Federal Court of Justice may be possible, depending on the issue for which further review is desired. The applicant may be eligible for legal aid in the proceedings before the Patent Court and the Federal Court of Justice.[14]

Infringement and Noninfringement

After the German Patent Office publishes notice of a patent application in the Patent Journal, the applicant may request reasonable compensation from any person who has used the invention that is the subject of the application provided that person knew or should have known that the invention was the subject of an application

The grant of a German patent gives the patent holder the exclusive right to use the patent. Third parties are prohibited from engaging in the following acts without the patent holder's consent: making, offering, putting on the market, or using the patented product, or importing or stocking the product for those purposes. If the patented invention is a process, third parties are prohibited from using it, or if the third party knows or it is obvious from the circumstances that use of the process is prohibited without consent from the patentee, the third party is prohibited from offering the patented process for use within the jurisdiction of the German patent law. Third parties also cannot offer, put on the market, use, import, or stock for the aforesaid purposes the product directly obtained from the patented process. It is also unlawful for third parties to supply or offer to supply, within the jurisdiction of the German patent law, to any person other than one entitled to exploit the patent, the means, relating to an essential element of the

[12] The German Patent Office also issues patents for utility models and patents of addition (i.e., a patent that covers an improvement on or a further development of a prior patented invention and expires at the same time as the patent for the prior invention).

[13] Nationals of foreign States, with the exception of the countries in the European Union, can obtain legal aid only insofar as reciprocity is guaranteed.

[14] Ibid.

patented invention, for putting it into effect when the third party knows or it is obvious in the circumstances that these means are suitable and intended for putting the patented invention into effect. This rule of law does not apply when the means are staple commercial products, unless the third party induces the person supplied with the means to commit an act of infringement.

Patent rights do not extend to the following acts (among others): (1) acts done privately and for noncommercial purposes; (2) acts done for experimental purposes relating to the subject matter of the patented invention; and (3) the extemporaneous preparation of a medicine in a pharmacy, for individual cases, in accordance with a medical prescription, or acts concerning the medicine so prepared. A patent also has no effect against a person who, at the time that the application for patent was filed, had already used the invention in Germany, or had made the necessary arrangements for doing so. That person is entitled to use the invention for the needs of his own business in his own plant or workshops or the plant or workshops of others.

Actions for patent infringement must be filed in court. Possible remedies include injunctions, compensatory damages, indemnity to the injured party and the profit that has accrued to the infringer, destruction of the infringing articles or the articles made from an infringing process, and/or requiring persons who use an infringing product or a product made by an infringing process to furnish information about the source and distribution channel of the product.

In addition, it is a crime, punishable by fine or imprisonment, to do the following without consent from the patent holder: (1) make, offer, put on the market, or use a patented product or a product obtained from a patented process, or import or stock the product for those purposes; or (2) use or offer to use a patented process within the jurisdiction of German patent law.

Italy

Obtaining a Patent

The Italian Patent and Trademark Office will issue a patent for an industrial product or process invention that is novel, involves an inventive step, and is capable of industrial application.[15] The right to a patent generally belongs to the author of the invention or to his assignees or legal representatives or, depending on the circumstances, to his employer.

The Italian Patent and Trademark Office gives each application for patent a formal examination and a technical examination, but not an examination of novelty. Also, the application must be rejected when the Minister of Health expresses the opinion that the invention may be harmful to health, or if any doubts exist in that regard. The application for patent generally must be accompanied by a certificate of payment of the prescribed fees, namely, the application and power of attorney fees, the annual fee for the first year, and the printing fee. It reportedly takes the Italian Patent and Trademark Office roughly three years after the filing date to issue a patent.[16] Decisions on various issues may be appealed to the Commission of Patent Appeals.

[15] The Italian Patent and Trademark Office also issues patents for new plant varieties, utility models, and industrial designs. Registrations are issued for semiconductor products topographies.

[16] Notes regarding patents in Italy provided by Avvocato Ghidini (furnished to the Commission by the American Embassy in Rome).

Infringement and Noninfringement

An Italian patent gives the patent owner the exclusive right to work the invention and the profit from it in the territory of Italy, within the limits set by law. This exclusive right extends to the trade of patented products but is exhausted as soon as the product has been commercialized by the patent holder or with his consent in the territory of Italy. If the patented invention is a new industrial method or process, the patent holder has the exclusive use of it. Such use includes also commercializing the product directly obtained by the patented method or process. If the product is a new one, every identical product is presumed to have been obtained by the patented method or process, unless there is evidence to the contrary.

The exclusive rights conferred by the patent do not extend to acts performed in the private sphere and for noncommercial or experimental purposes or to the extemporaneous preparation, per unit, of pharmaceutical products on medical prescription and to the pharmaceuticals thus prepared in pharmacies. In addition, whenever the holder of a patent for a new industrial method or process places at the disposal of others the means clearly destined to work the patented method or process, the law presumes that the patent holder also conferred a license to use that method or process, in the absence of stipulations to the contrary. In addition, persons who used the patented invention in their business during the 12 months preceding the filing date of the application for patent or the priority date may continue to use the invention within the limits of the prior use.

Italian patent law does not authorize the unlicensed use of a dependent patent owned by another patent holder. In other words, if practicing an industrial invention patent necessarily involves practicing the invention of a prior patent that is still in force, the newer invention cannot be practiced or utilized without permission from the owner of the prior patent to use the invention of the prior patent.

Legal proceedings concerning industrial invention patents are considered commercial or personal proceedings and must be brought before the appropriate Judicial Authorities of the Country. Possible remedies for infringement include (but are not limited to) the judicial seizing of infringing articles, injunctive relief, assignment of the infringing articles or the means used to infringe a patented process to the owner of the patent, and/or damages. However, the removal, destruction, or prohibition against the use of infringing articles cannot be ordered when they are owned by a person who makes only good faith personal or domestic use of the articles.

Japan

Obtaining a Patent

The Japanese Patent Office Patent will issue a patent for an invention that is industrially applicable, novel, and non-obvious.[17] A patent is granted on the basis of an application that is given formal examination. When two or more patent applications for the same invention are filed on different dates, only the first applicant may obtain a patent for the invention. If two or more applications for the same invention are filed on the same day, only one applicant may obtain a patent for the invention, by mutual agreement among all applicants. If no agreement is reached, none of the applicants will be granted a patent for the invention. The person who files an application for patent must pay a prescribed fee. The applicant also may have to pay other charges during processing of the application.

[17] The Japanese Patent Office also issues registrations for utility models.

On average, the Japanese Patent Office takes 3-5 years from the filing date to process an application for patent.[18] If the examiner who reviews the application determines that the application should be denied, the applicant can obtain a trial before a collegial body of examiners who will make decisions by a majority vote. An applicant dissatisfied by the outcome of the trial may be able to demand a retrial. The Tokyo High Court has exclusive jurisdiction over any action to contest a trial decision or an action pertaining to a demand for retrial.

If it appears that the applicant is entitled to a patent under the law, the applicant usually must pay the annual fee for the first year of the patent term in order for the patent to be issued, i.e., in order for the patent to come into force upon registration of its establishment. The fee can be waived or deferred, however.

Infringement and Noninfringement

If the patented invention is a product, it is infringement to manufacture, assign, lease, import, or offer for assignment or lease, in the course of trade, articles to be used exclusively in the manufacture of the patented product. If the patented invention is a process, infringement consists of the act of manufacturing, assigning, leasing, importing, or offering for assignment or lease, in the course of trade, articles to be used exclusively in the working of the patented invention. When a patented invention would utilize another person's patented invention under an application filed prior to the filing of the application concerned, the patentee or licensee cannot commercially work the patented invention.

A patentee's rights do not apply to another person's working of an invention for the purposes of experiment or research or products existing in Japan prior to the filing of the application for patent. The patent rights for inventions of medicines, i.e., products used for the diagnosis, cure, medical treatment, or prevention of human diseases, that are manufactured by mixing two or more medicines, or for inventions of a process for manufacturing medicines by mixing two or more medicines, do not extend to the act of preparing medicines in accordance with the prescriptions of physicians or dentists or to medicines prepared in accordance with the prescriptions of physicians or dentists.

Possible judicial remedies for infringement include injunctions, an order to destroy the infringing articles or the articles made by an infringing process, an order to remove the facilities used for infringement, or other measures to prevent infringement, damages, and/or an order requiring the infringer to take the measures necessary for the recovery of the business reputation of the patentee or exclusive license holder, if that reputation was injured.

The applicant who is granted the patent also can collect compensation for certain acts that occurred before the patent was granted. If a person commercially worked the applicant's invention after the application for patent was "laid open" for public inspection (i.e., described in a notice published in the Japanese Patent Gazette), and if the applicant provided written warning to that person about the content of the invention claimed in the application, the applicant may, after the patent is granted, claim compensation from that person in an amount equivalent to what the applicant would have received for working the invention if it had been patented at that time. Even if the applicant did not issue a written warning, the applicant may still claim compensation if the person commercially worked the invention with knowledge that it had been claimed in a patent application laid open for public inspection.

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[18] Information obtained by Commission staff via e-mail, dated Aug. 25, 2000, from representatives of Baker & McKenzie in Japan.

Mexico

Obtaining a Patent

The Mexican Institute of Industrial Property will issue a patent to any individual who makes an invention that is novel, the result of inventive activity, and susceptible of industrial application.[19] An invention is defined as a human creation that allows matter or energy existing in nature to be transformed for exploitation by man, through immediate satisfaction of a specific need. This includes products or processes for industrial application.

A patent is granted on the basis of an application that is given formal examination by the Institute. The application must be filed by the inventor, his assignee, or a representative of the inventor or assignee. When several inventors, independently of each other, have made the same invention, the right to the patent will belong to the one who has the application with the earliest filing date or recognized priority date, provided that the application was not rejected or abandoned.

The application must be accompanied by a prescribed fee. The applicant also may incur other fees and charges during processing of the application for patent. The Institute generally takes about 30 months to process an application. If the application is denied, the applicant can request reconsideration. If it appears that the applicant is entitled to a patent under the law, the applicant must pay government fees in order for the patent to be issued.

Infringement and Noninfringement

A Mexican patent gives the patent owner the exclusive right of exploiting the patented invention to his benefit, either by himself or by third parties who have his consent. However, the right conferred by a patent has no effect at all on the following persons (among others):

(1) a third party, who in the private or academic field, performs, for noncommercial purposes, purely experimental, scientific or technological research, testing, or teaching activities, and for this purpose produces or uses a product or process equal to the patented one;
(2) anyone who trades with, acquires or uses the patented product or a product obtained by the patented process, after such product has been legally introduced into trade;
(3) anyone who prior to the filing date of the patent application, or the recognized priority date, uses the patented process, manufactures the patented product, or takes the preparatory measures required to carry out such use or manufacture;
(4) a third party who, in the case of patents related to living matter, uses the patented product as an initial source of variation or propagation to obtain other products, unless such use is repetitive; and
(5) a third party who, in the case of patents related to products that consist of living matter, uses, puts into circulation or trades with the patented products, for purposes other than multiplication or propagation, after they have been legally introduced into trade by the patentee or a voluntary licensee.

Each action enumerated above will not constitute administrative infringement or a criminal offense under Mexican law.

[19] The Institute also issues registrations for utility models and industrial designs.

It is a criminal offense to do the following: (1) manufacture or make products covered by a patent of invention without consent from the patent holder or the respective licensee; (2) offer for sale or place in circulation the products covered by a patent, knowing that they were manufactured or made without the consent of the patent holder; (3) use a patented process, without consent of the patent holder; or (4) offer for sale or place in circulation products that result from the use of a patented process, knowing that the process was used without permission from the patent holder or the person having license to exploit the patented invention. A person who commits any of those offenses is subject to two to six years in prison and a fine in the amount of one hundred to ten thousand times the general minimum wage prevailing in the Mexican Federal District.

In addition, any person adversely affected by any of the aforesaid criminal offenses may bring an action for the payment of damages. The courts of the Mexican Federation will have jurisdiction over the criminal offenses, as well as over any commercial or civil controversies that arise as a result of the application of the Mexican law for the protection and promotion of intellectual property. But when a controversy affects only particular interests, a court of common pleas may hear the case, at the option of the plaintiff.

The patent holder also may bring an action for damages against third parties who may have worked the patented process or product, without his permission, prior to the grant of the patent, when such working took place after the effective publication date of notice of the application for patent.

Russia

Obtaining a Patent

The State Patent Agency of Russia (Rospatent), a division of Russia's Federal Institute of Industrial Property, will issue an invention patent for a device, method, substance, microorganism strain, plant or animal cell culture or the use of a previously known device, method, substance, or microorganism strain for a new purpose.[20] To be patentable, the invention must be novel, possess an inventive level, and be industrially applicable.[21]

Each application for patent undergoes expert examination by Rospatent. The application must be filed by the author of the invention, the employer, or the author or the employer's respective successor(s) in law. The application for an invention patent must be accompanied by a document confirming that the applicant has paid the established duty for the application or stating grounds upon which payment can be waived or the amount of the duty reduced.

The invention is given temporary legal protection from the date that Rospatent publishes information about the application for patent to the date of publication of information about the granting of the patent. Persons who use the invention during that period of temporary protection will have to pay monetary compensation to the patent holder after the patent is granted. The amount will be determined by mutual agreement of the parties.

[20] Rospatent also issues useful model certificates and industrial design patents.

[21] An invention is industrially applicable if can be used in health service (or other specified industries and sectors).

A decision to reject an application for patent may be appealed to the Appeal Chamber of Rospatent. An applicant dissatisfied with a ruling of the Appeal Chamber may file a complaint with the Supreme Patent Chamber. Consideration by courts of law, including arbitration courts, also may be possible. If a patent is granted, the applicant must pay a duty. Thereafter, the patent holder must pay duties to keep the patent in force for the duration of its term.

Infringement and Noninfringement

An invention patent gives the patent holder the right to use the patented invention at his own discretion, provided that such use does not infringe the rights of other patent holders. The patent holder also has the right to prohibit use of the patented invention by others, except where such use is legally noninfringing.

Infringement is recognized as the unsanctioned manufacture, use, importation, offer to sell, sale or other "introduction into economic turnover," or storage, a with these aims, of a product containing the patented invention. If the invention is a process, infringement constitutes use of the patented process or introduction into the economic turnover, or storage with these aims, of a product manufactured directly by the patented process. In such a case, the new product will deemed to have been made by the patented process in absence of evidence to the contrary. Infringement can be literal or equivalent.

Certain prior users are not considered infringers. Any person or legal entity who, before the priority date of the patented invention, has fairly used an independently created identical invention, or made preparation for such use, in Russia is entitled to pursue that use as long as the scope of the use remains unchanged.

The manufacture of medicines in pharmacies, one time only and pursuant to a physician's prescription, also does not constitute infringement. The following are other examples of noninfringing acts: (1) research or experiments on the patented invention; (2) use of the patented invention in force majeure circumstances (natural calamities, disasters, and/or major accidents) with subsequent payment of commensurate compensation to the patent holder; (3) use of the patented invention for personal, nonprofit-making purposes; and (4) use of the patented invention if it has been introduced legally into economic turnover.

Disputes about infringement may be considered by courts of law, including arbitration courts.

The United Kingdom

Obtaining a Patent

The Patent Office of the United Kingdom will issue a patent for an invention that is new, involves an inventive step, and is capable of industrial application. A patent is granted on the basis of an application that is given substantive examination. The application must be filed by the inventor of the invention, any other person entitled to rights at the time the invention was made, or the successor in interest to the inventor or the other person. An application for a U.K. patent must be accompanied by a filing fee. The applicant also may incur other fees during processing of the application, such as the fee for a preliminary examination and search report, if requested by the applicant, and the fee for the substantive examination of the application. On average, the U.K. Patent Office takes about 4 ½ years to process an application for

patent.[22] Decisions on various issues may be appealed to the Patents Court with the possibility of further appeal to a Court of Appeal.

Infringement and Noninfringement

If the patented invention is a product, infringement consists of taking any of the following actions during the term of the patent without the patent proprietor's consent: making, disposing of, offering to dispose of, using, or importing the product or keeping it for disposal or another purpose. If the invention is a process, it is infringement for a person to use the process or offer it for use in the United Kingdom when he knows, or it would be obvious to a reasonable person in the circumstances, that its use there without the consent of the proprietor would infringe the patent. It would also be infringement for the person to dispose of, offer to dispose of, use, or import any product obtained directly by means of the patented process or to keep any such product for disposal or another purpose.

It is an infringement for a person to supply or offer to supply in the United Kingdom another person (other than the proprietor, a licensee, or other person entitled to work the patent) with any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows or should know, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom.[23]

Each of the aforesaid definitions of infringement are subject, however, to certain limitations under provisions of the European Community Patent Convention.

An act that would otherwise constitute infringement is not considered infringement if: (1) it is done privately and for noncommercial purposes; (2) it is done for experimental purposes relating to the subject matter of the invention; or (3) it consists of the extemporaneous preparation in a pharmacy of a medicine for an individual in accordance with a prescription given by a registered medical or dental practitioner or consists of dealing with a medicine so prepared. Certain other acts are exempted as well. With certain limitations, the law also grants the right to continue a use that would otherwise constitute infringement but was begun before the priority date of the invention.

Civil proceedings for patent infringement must be brought in Court. The possible remedies include a declaration that the patent is valid and infringed, an injunction, an order to deliver up or destroy infringing articles or articles made by an infringing process, damages, or an accounting of the profits accrued from the infringement. A person aggrieved by groundless threats of infringement proceedings can obtain a declaration that the threats were unjustified, injunctive relief, or damages.

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[22] Commission staff conversation with a representative of the U.K. Patent Office on Aug. 11, 2000.

[23] This rule does not apply to the supply or offer of a staple commercial product unless the supply or the offer is made for the purpose of inducing the person supplied, or the person to whom the offer is made, to commit an act constituting infringement of the patent.

By agreement between the proprietor of the patent and the accused infringer, the questions of whether the patent is valid and infringed and if so, what damages should be paid, can be referred to the Comptroller at the Patent Office.[24] But if the Comptroller decides that the aforesaid questions would more properly be determined by the Court, he may decline to deal with them and leave the matter for the Court.

[24] The Comptroller also can award reasonable costs to any party.

Appendix I
Glossary

Active ingredient–the specific chemical in a formulated drug that exhibits the desired medical result.

Abbreviated New Drug Application (ANDA)–a simplified submission permitted for a duplicate of an already approved drug.

Association of the British Pharmaceutical Industry (ABPI)–the trade association representing research-based pharmaceutical companies operating in the United Kingdom.

Association of International Pharmaceutical Manufacturers (AIPM)–the trade association representing international research-based and medical equipment companies operating in Russia.

Associazone Nazionale dell'Industria Farmaceutica (Farmindustria)–the trade association representing research-based pharmaceutical companies operating in Italy.

Blockbuster drug–defined by Lehman Brothers as a product with annual sales over $1 billion.

Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medicinal Devices (BfArM))–the German agency responsible for approval of finished medicinal drugs marketed for human use.

Bundesverband der Pharmazeutischen Industrie (BPI)–a trade organization representing research-based and generic pharmaceutical companies operating in Germany.

Canada's Research-Based Pharmaceutical Companies (Rx&D)–the trade association representing the research-based pharmaceutical companies operating in Canada.

Committee on Proprietary Medicinal Products (CPMP)–A committee established in the EU to examine matters relating to the granting, suspension, or revocation of marketing authorities for pharmaceuticals.

Compulsory licensing– defined as "permission to use intellectual property, compelled by the Government in order to accomplish some political or social objective. Compulsory licensing forces an intellectual property owner to allow others to use that property at a fee set by the Government."

Drug pipeline–the progress of new drugs through the discovery, development, and marketing phases. A drug may fail at any stage in the pipeline and be eliminated from the firm's portfolio of potential new products. Several drugs can be in the pipeline simultaneously.

Drug Price Competition and Patent Reform Term Restoration Act (Hatch Waxman Act)–Legislation enacted in 1984 that contained provisions to allow partial restoration of an innovative drug's patent term up to five years, depending on the amount of time lost during regulatory review. It also amended the FDCA to provide for ANDAs for generic versions of previously approved innovative drugs.

Enhanced Initiative (the U.S.-Japan Enhanced Initiative for Deregulation and Competition)–a bilateral process begun in 1997 to address regulatory and anti-competitive barriers for both foreign and domestic firms in Japan.

European Federation of Pharmaceutical Industry Associations (EFPIA)–the federation of the national pharmaceutical industry associations. EFPIA's members include 18 national pharmaceutical industry associations and 45 innovative companies operating in Europe.

FDCA–Federal Food, Drug and Cosmetic Act (21 USC 301 et seq.).

Formulary–a listing of medicinal substances and formulas.

Generic products–non-patented products.

Global joint cost–defined as a case in which the fixed cost is the same regardless of the number of users served worldwide, and hence cannot be rationally allocated to individual users.

Health Maintenance Organization (HMO)–the generic name for a type of U.S. private health plan.

International reference pricing–when prices in one country are controlled in a way that makes them equal or proportional to prices in another country or the average price in a set of countries. In an economic sense, reference pricing is somewhat analogous to "100 percent parallel trade" because of similar effects it can have on prices in two countries.

Investigational New Drug Application (INDA)–an application that a drug sponsor must submit to the FDA before beginning tests of a new drug on humans.

Innovative firm–a drug manufacturer which invents, develops, and, in most cases, markets a new product. Such firms dedicate a significant share of sales to primary research and development activities.

Japanese Pharmaceutical Manufacturers Association (JPMA)–the trade association representing innovative companies operating in Japan.

Market Oriented Sector Specific (MOSS)–Intergovernmental talks between the United States and Japan concerning a variety of trade issues that transpired during the 1980s.

Market segmentation–the grouping of consumers by unique demand characteristics.

Megabrand–defined by AstraZeneca as a product that (1) by the second year of its launch has already reached $1 billion in annual sales and will likely earn several billion dollars in its lifetime; (2) will be introduced and marketed in as many as 60 countries during the first two years of its lifetime; and (3) significant marketing expenditures are required.

Me-too products–defined broadly as a product that is therapeutically similar to an existing pharmaceutical product. Some "me-too" products are also chemically similar to the existing product.

Ministry of Health and Welfare (MHW)–a Japanese Government agency.

National Chamber of Pharmaceutical Industry (Canifarma)–a non-profit autonomous organization that represents and protects the interests of pharmaceutical companies operating in Mexico.

New chemical entity (NCE)–a term used to refer to a chemical that is being tested or marketed as a potential drug. The compound can be at any stage in the development process from discovery to initial marketing.

New drug application (NDA)–an application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from clinical studies for FDA review.

National Health Service (NHS)–the United Kingdom's national health program.

National Institutes of Health (NIH)–the U.S. Federal Agency responsible for, among other things, coordinating Federal research activities.

Over-the-counter (OTC)–products generally not requiring a prescription (in contrast, OTC ethical products are OTC products that are primarily promoted to healthcare professionals).

Pack size–generally defined as the number of units dispensed under a prescription that combine the same level of active ingredient. If pills were dispensed, for example, the number of pills would determine the size of the "pack"for copayment purposes. A "large" pack would contain more pills than a "medium" pack which, in turn, would contain more than a "small" pack.

Parallel trade–the importation of products from countries with low cost by countries with higher costs.

Pharmaceutical Research and Manufacturers of America (PhRMA)–the U.S. trade association representing companies operating in the U.S. pharmaceutical industry.

Price discrimination–charging different prices in different market segments.

Priority drugs–defined by the FDA as those products considered to be an important therapeutic gain over existing products.

Pharmaceutical Price Regulation Scheme (PPRS)–the name, since 1978, of the UK's national system to maintain price levels that allow for a "reasonable return on capital."

Reference pricing–defined as "a system for determining the maximum reimbursement amount for approved categories of pharmaceutical products prescribed by physicians." "Reimbursable products are placed in clusters or groups of drugs that have 'interchangeable" chemical characteristics or are considered to be "therapeutically equivalent' when prescribed for a particular medical condition. Each group of products is given a single 'reference' price which then becomes the mandated average or maximum price at which all products in the group are reimbursed." (see ***International Reference Pricing***)

Statutory health insurance (SHI) system–self-governing non-profit insurance funds in Germany organized on a local, company, occupational or national basis and funded by employee/employer contributions and general taxation

Strategic alliances–specific arrangements, ranging from marketing agreements to agreements to share the products of research in specified areas, that allow both sides to benefit. Individual companies may enter into multiple strategic alliances.

Syndicat National de l'Industrie Pharmaceutique (SNIP)–the trade association that represents research-based pharmaceutical companies in France.

Verband Forschender Arzneimittel-hersteller (VFA)–a trade association representing research-based pharmaceutical companies operating in Germany.