Pharmaceutical Price Controls in OECD Countries

Implications for U.S. Consumers, Pricing, Research and Development, and Innovation

U.S. Department of Commerce
International Trade Administration

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Contents

Abbreviations and Acronyms

ANDA	Abbreviated New Drug Application
ANDS	Abbreviated New Drug Submission
ATC	Anatomical Therapeutic Chemical
ATP	actual transaction price
AUSFTA	Australia–U.S. Free Trade Agreement
BCG	Boston Consultancy Group
BPI	Biotechnology Industry Association
CMS	Center for Medicare & Medicaid Services
CMRI	Center for Medicines Research International
CRC	clinical research providers
CSIRO	Commonwealth Scientific and Industrial Research Organization
CTMs	Community Trade Marks
DDD	Defined Daily Dose
DMF	Drug Master File
EEA	European Economic Area
EMA	European Medicines Agency
EPC	European Patent Convention
FDA	Food and Drug Administration
GDP	gross domestic product
HHS	U.S. Department of Health and Human Services
IMF	International Monetary Fund
IPR	intellectual property rights
KFDA	Korean Food and Drug Administration
KG	kilogram
LTP	lowest transaction price
MHLW	Ministry of Health, Labor, and Welfare
MHRA	Medicines and Healthcare Products Regulatory Agency
MHW	Ministry of Health and Welfare
MIFs	Mutual Insurance Funds
NASs	New Active Substances
NDO	National Drug Organization
NFMI	National Federation of Medical Insurance
NHI	National Health Insurance
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NMEs	new molecular entities
OECD	Organization for Economic Cooperation and Development
OTC	over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
PhRMA	Pharmaceutical Research and Manufacturers of America
PMPRB	Patented Medicines Price Review Board
PPRS	Patented Price Regulation Scheme
PRS	Pharmaceutical Reimbursement Schedule
R&D	research and development
SHI	statutory health insurance
SMEs	small and medium-sized enterprises
SPC	Supplementary Protection Certificates
SU	standard units
TGA	Therapeutic Goods Administration
TPD	Therapeutic Products Directorate

TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
VRR	Vaccine Research Relief
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Executive Summary

Improvements in health care and life sciences are an important source of gains in health and longevity globally. The development of innovative pharmaceutical products plays a critical role in ensuring these continued gains. To encourage the continued development of new drugs, economic incentives are essential. These incentives are principally provided through direct and indirect government funding, intellectual property laws, and other policies that favor innovation. Without such incentives, private corporations, which bring to market the vast majority of new drugs, would be less able to assume the risks and costs necessary to continue their research and development (R&D).

In the United States, government action has focused on creating the environment that would best encourage further innovation and yield a constant flow of new and innovative medicines to the market. The goal has been to ensure that consumers would benefit both from technological breakthroughs and the competition that further innovation generates. The United States also relies on a strong generic pharmaceutical industry to create added competitive pressure to lower drug prices. Recent action by the Administration and Congress has accelerated the flow of generic medicines to the market for precisely that reason.

By contrast, in the Organization for Economic Cooperation and Development (OECD) countries studied in this report, governments have relied heavily on government fiat rather than competition to set prices, lowering drug spending through price controls applied to new and old drugs alike. Such controls, when applied to new drugs, reduce company compensation to levels closer to direct production costs, leaving less revenue for R&D. As OECD countries individually seek to reduce spending on drugs through price controls, their collective actions reduce R&D that would provide substantial health benefits to all.

The OECD countries examined in the study also employ a number of other regulatory practices that have the effect of limiting the competition that would otherwise accrue from generic pharmaceuticals. Perhaps the most glaring example is the bar imposed by a number of countries on the ability of generic pharmaceutical manufacturers to provide information on prices and therapeutic benefit directly to physicians and consumers. In short, the systems examined here rely heavily on government fiat to set prices rather than competition in the marketplace.

To examine the effect of such practices on prices, revenues, innovation and, ultimately, on consumers, Congress (in section 1123 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, P.L. 108-173) instructed the Secretary of Commerce—with the assistance and support of the U.S. International Trade Commission, the Department of Health and Human Services, and the Office of the U.S. Trade

Representative—to conduct a study on OECD drug price controls and the implications for U.S. consumers.

Specifically, the Conference Report (House Report 108-391) requested that the study include the following:

- Identification of the countries that use price controls or other such practices with respect to pharmaceutical trade.
- Assessment of the price controls and other such practices that the identified countries use.
- Estimates of additional costs to U.S. consumers because of such price controls, and the extent to which additional costs would be reduced for U.S. consumers if price controls and other such practices are reduced or eliminated.
- Estimates of the impact that price controls, intellectual property laws, and other such measures have on fair pricing, innovation, generic competition, and R&D in the United States and each identified country.

This report responds to Congress' request. It details the effect of price controls imposed by various U.S. trade partners on pharmaceutical prices, R&D, innovation, and U.S. consumers. The study examined the drug price regulatory systems of 11 OECD countries.[1] A quantitative analysis of prices, revenues, and R&D effects based on available data was also conducted for nine OECD countries.[2] For reasons explained in the report, two of these nine countries were excluded from further consideration. The results from the remaining six countries[3] were then extrapolated to the total patented markets of five additional OECD countries. Thus, the final estimates of the impact of price controls on R&D and innovation are based on an analysis of 11 OECD countries.[4]

Summary of the Report's Conclusions

Price Controls Are Widespread

The study examined the drug price regulatory systems of 11 OECD countries and found that all rely on some form of price controls to limit spending on pharmaceuticals. The principal methods these governments employ are reference pricing, approval delays and procedural barriers, restrictions on dispensing and prescribing, and reimbursement. These methods prevent companies from charging a market-based price for their products. They also tend to be nontransparent, as the criteria and rationale for certain pharmaceutical prices or reimbursement amounts are not fully disclosed even to the pharmaceutical companies seeking to market their drugs.

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[1] The overview of drug price regulatory systems corresponds to Australia, Canada, France, Germany, Greece, Japan, South Korea, Mexico, Poland, Switzerland, and the United Kingdom.
[2] The prices effects analysis corresponds to Australia, Canada, France, Germany, Greece, Japan, Poland, Switzerland, and the United Kingdom.
[3] Due to data limitations and methodology constraints, Poland, Greece, and Switzerland were excluded from the extrapolation.
[4] The final estimates of the impact of price controls on R&D and innovation correspond to France, Germany, Canada, the United Kingdom, Australia, Japan, Italy, Spain, Belgium, Netherlands, and Sweden.

The most direct method the OECD governments we examined use to control prices is to set the sales price and make sales at any other price illegal. Governments often are the dominant market participant and may negotiate favorable prices with manufacturers by leveraging this monopsonistic power. Such negotiations generally result in prices lower than they would be in a free market. Another method the OECD governments we examined use is to set the reimbursement price of a new drug at levels well below the free market price. Since any price above the regulated price is borne by consumers, the reimbursement price often functions as the de facto market price where such mechanisms are employed. Finally, some OECD governments regularly cut the prices of drugs already on the market.

Intellectual Property Rights Are Adequately Enforced

Intellectual property rights (IPR) confer on innovators certain exclusive rights over inventions, trademarks, and other works. In the case of patents, which provide the IPR protection for pharmaceutical innovations, rights exist for 20 years. After this time the invention falls into the public domain. In this way, a balance is struck between rewarding innovation and maximizing scientific progress and access to technologies.

This balance ensures that pharmaceutical companies can recoup their enormous R&D expenses and earn a return commensurate with the risks of their investment, while promoting generic competition after the expiration of the patent term. In short, intellectual property protection is a necessary prerequisite to ensure that innovative companies can continue to develop new drugs, which will eventually be available on the generic market. Conversely, poor enforcement or lack of intellectual property protection discourages the development of new medicines and results in a stagnant generic drug market.

The study did not find that a lack of intellectual property laws or enforcement of IPR in the selected countries (which generally have strong and effective intellectual property regimes) had a significant impact on prices. The existence of strong IPR and other incentives for innovation do not prevent robust generic competition. Indeed, the United States has the largest and most competitive generic market of the countries reviewed in this report.

Patented Drug Prices Are Below U.S. Levels

The study found that, for patented drugs that were best sellers in the United States, the prices in other OECD countries are below those in the United States. For the countries analyzed, the study showed that aggregate pharmaceutical prices were 18 to 67 percent less than U.S. prices, depending on the country. These results are consistent with recent academic research in this area.

It must be noted that since generic drugs account for more than half of all prescription drugs consumed in the United States, prices of patented and branded pharmaceuticals

cannot be used to draw a comprehensive picture of relative aggregate prices among the various countries examined in this study.

Importantly, this study does not incorporate the reductions in price expected as a result of implementing provisions of the Medicare Modernization Act (for example, drug discount cards). This Act, when fully implemented, could have the potential to significantly lower drug prices for seniors who are eligible for Medicare and lack insurance for drugs.

Without Price Controls, Revenues Available for R&D Could Be Significantly Higher

The study found that by depressing prices of patented pharmaceuticals, the price controls maintained by OECD countries yield lower revenues for patented products than would otherwise exist in a competitive market. The study estimates that, after extrapolating to a broader set of OECD countries, the diminished returns are in the range of $18 billion to $27 billion annually. This represents a 25 to 38 percent increase in revenues over actual 2003 revenues from sales of patented drugs in the OECD countries considered.

Higher Utilization Rates of Generic Drugs at Lower Prices in OECD Countries Offer Potential Savings

Analysis by the Department of Commerce and HHS found that higher utilization of generic drugs at lower prices could result in significant savings to OECD countries. The estimated savings, after extrapolating to a broader set of OECD countries, range from $5 billion to $30 billion annually. This range of potential savings suggests that if prices of on-patent drugs were to rise to competitive market levels, then the additional cost to OECD countries could be significantly or fully offset by a more competitive generic market.

Higher Revenues Would Mean More Research and Development and New Drugs

Based on published academic research, the study estimates the impact of increased revenues on pharmaceutical R&D. In limiting the return that would otherwise accrue to companies for undertaking the risk and expense of developing new drugs and bringing them to market, the price controls maintained by the OECD countries in the study also reduce the amount of global pharmaceutical R&D below what it would otherwise be under market conditions similar to those in the United States. The study estimates that this reduction falls in the range of $5 billion to $8 billion annually, once prices were fully adjusted. This represents between 11 and 16 percent of current private worldwide R&D, based on figures from the Center of Medicines Research (CMR) International Worldwide.

Based on an estimated cost of developing a new drug, an increase in R&D of $5 billion to $8 billion could lead to three or four new molecular entities annually once markets fully

adjust. The U.S. Food and Drug Administration approved, on average, 30 new molecular entities between 2000 and 2003.[5]

U.S. Consumers Would Benefit from the Elimination of Price Controls Abroad

The benefit to U.S. drug purchasers from the new drugs that would be developed and marketed if there were no price controls is in the range of $5 billion to $7 billion per year. In the short term, the deregulation of OECD prices is not likely to have any impact on U.S. drug prices. The "increased competition" in the U.S. market resulting from price deregulation abroad could have some effect on U.S. prices in the long term. Relaxation of foreign price controls, if coupled with appropriate reform of foreign generic markets, could potentially bring about much of these gains from the flow of new drugs, even without increasing foreign spending on prescription drugs.

How the Detailed Analysis of Prices and Revenues Was Conducted

In order to address the question of the impact of price controls, a detailed study of pharmaceutical prices for nine OECD countries was conducted, representing the largest OECD markets as well as OECD countries with a range of income levels. Price and related data for all products containing the active ingredient in the 60 best-selling products in the United States were purchased for each of the nine OECD countries from IMS Health, virtually the only source for detailed data on pharmaceutical prices and sales.

The analysis focused specifically on innovative pharmaceuticals, which are produced by research-based pharmaceutical companies and biotechnology companies. The study assumed that, in the absence of drug price controls, average prices in the OECD countries for innovative pharmaceuticals would be equal to U.S. prices adjusted for differences in per capita income. These adjusted prices were used to estimate revenues in the absence of drug price controls.

Constraints and Caveats

Given the resource and time constraints, it was necessary to make a number of significant simplifying assumptions that should be considered when reviewing the study's results, including:

- That subject to disparities in per capita income, U.S. prices could serve as a benchmark for deregulated prices;

[5]This estimate also includes FDA approvals of new biologics. See U.S. Food and Drug Administration, "Approval Times for Priority and Standard NMEs: Calendar Years 1993-2003" (created January 21, 2004), available at *www.fda.gov/cder/rdmt/NMEapps93-03.htm*; see also Pharmaceutical Research and Manufacturers of America, "New Drug Approvals In 2003" (January 2004), available at *www.phrma.org/newmedicines/resources/2004-01-22.123.pdf*.

- That the selected 54 molecules in the nine countries studied, as well as the United States (which represent 26 percent of world revenues in 2003[6]) are indicative of price differences for innovative drugs;
- That increased drug prices would not affect sales volumes;
- That funds would be available to pay the higher prices;
- That there would be no interplay between patented and generic drugs that might have affected the study's results.

Throughout this report, an effort has been made to use conservative assumptions regarding the effects of drug price regulations. Given the assumptions inherent in any analysis of this type, the results should necessarily be read with care and would not preclude other findings.

One further point bears emphasis. This assessment of the effects of foreign governments' policies regarding the pricing and use of drugs in their markets should not be construed to be an assessment of the impact of possible federal controls on the prices of drugs sold elsewhere, including the United States. This report does not address that question even indirectly. As the analysis reflects, both the economics of pharmaceutical production and the roles played by the private sector and government institutions in the United States vary significantly from those of its trading partners, rendering efforts to apply the results of this research to the U.S. context without merit.

[6] U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003 and IMS Health, *IMS World Review (*TM), Country Profiles, 2004.

1. INTRODUCTION

To examine the impact of foreign government policies on the incentives for further innovation and ultimately on consumers in the United States and abroad, section 1123 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (P.L. 108–173) called for a study and report on issues related to trade and pharmaceuticals. The subsequent conference agreement requested that the Secretary of Commerce, in consultation with the International Trade Commission, the Secretary of Health and Human Services, and the United States Trade Representative, conduct a study and report on the drug pricing practices of countries that are members of the OECD and examine whether those practices use non-tariff barriers with respect to trade in pharmaceuticals.

Specifically, the Conference Report requested that the study include the following:

- Identification of the countries that use price controls or other such practices with respect to pharmaceutical trade.
- Assessment of the price controls and other such practices that the identified countries use.
- Estimates of additional costs to U.S. consumers because of such price controls and the extent to which additional costs would be reduced for U.S. consumers if price controls and other such practices are reduced or eliminated.
- Estimates of the impact that price controls, intellectual property laws, and other such measures have on fair pricing, innovation, generic competition, and R&D in the United States and each country identified.

To fulfill this request, the Department of Commerce obtained information from a variety of sources. This was followed by a review of the relevant academic, industry, and government literature. In addition, the department solicited information pursuant to the study through two *Federal Register* notices. These notices were followed by a public hearing on August 3, 2004. A complete record of *Federal Register* submissions and testimony presented at the public hearing is available at *http://www.ita.doc.gov/drugpricingstudy*.[7]

In addition, the report benefited from the guidance and support of the Food and Drug Administration of the Department of Health and Human Services, the U.S. International Trade Commission, and the Office of the United States Trade Representative, as well as our embassies abroad. Nevertheless, the information and conclusions presented in this report are the responsibility of the U.S. Department of Commerce.

To estimate the impacts of foreign price controls on consumers, R&D, and innovation, an empirical analysis of drug sales and prices for nine OECD countries was undertaken. To conduct the study, the Commerce Department, in cooperation with the Food and Drug

[7] Appendix B lists and summarizes the responses to the Department's request for comments issued through two *Federal Register* notices.

Administration, purchased price data for all products containing the active ingredients in the 60 top-selling products in the United States from IMS Health, virtually the only source for such data.

Section 2 of this report presents an overview of drug and cost containment practices of OECD countries. Those practices reflect a deep intervention in the market, which can limit the ability of patients and their doctors to make appropriate medical decisions. They range from direct price controls to barring direct consumer access to information on alternative therapies to pricing mechanisms that limit competition. A country-specific review of these practices appears in Appendix C.[8]

Section 3 of the report presents the analysis and methodology used to estimate OECD prices and revenues in the absence of regulatory price controls. It is important to emphasize, at the outset, that this analysis necessarily models a purely hypothetical situation since all OECD countries studied use some form of price controls to set prices for pharmaceuticals. Developing an appropriate counterfactual necessarily required significant simplifying assumptions. Data limitations, as well as time and resource constraints, forced the analysis to focus on only a subset of OECD countries and drugs. A detailed explanation of the methodologies employed to estimate prices and revenues in the absence of controls are contained in Appendix A.

Section 4 of the report assesses the impact of deregulating prices among the OECD countries examined here on R&D, innovation, and, ultimately, on consumers. Specifically, this section estimates the impact of deregulating prices in 11 OECD countries on the propensity of innovative firms to finance additional R&D on new therapies, how changes in R&D spending would actually affect innovation delivered to the market, and, finally, the impact on consumers in the United States, both in terms of the effect on prices and the ultimate impact of greater competition from generic manufacturers and new and innovative therapies.

Given the constraints noted above with respect to the analysis, the results should necessarily be interpreted with some caution. They serve as useful indicators of the ultimate impact on innovation and consumer welfare, but make no pretense to offer more than estimates of the effects of the price controls imposed in other OECD countries or the benefits to U.S. consumers of lifting those controls. Given the limitations of such analysis, it is also important to caution against drawing general conclusions from these results and applying them to other countries. Such extrapolation would ignore the stated limitations of the model employed and would not be warranted, particularly in the case of countries with substantially different market structures, including the United States.

[8] This Appendix provides a general description of the pharmaceutical markets in 11 OECD countries: Australia, Canada, France, Germany, Greece, Japan, South Korea, Mexico, Poland, Switzerland, and the United Kingdom. The topics covered include R&D costs and expenditures, approval processes, health care coverage, and pricing. We will continue to monitor the topics outlined in Appendix as they evolve.

2. DRUG PRICE REGULATIONS IN SELECTED OECD COUNTRIES—AN OVERVIEW OF THE ISSUES

OECD[9] governments use a variety of strategies to control prices and contain costs related to pharmaceuticals. These include direct and indirect price controls, profit controls, reference pricing, physician budget constraints and prescribing guidelines, marketing approvals, and limits on promotion, among many others.[10] These strategies tend to have the most significant impact on the newest and most innovative medicines, because the controls usually focus on when drugs first enter the national health care systems.

The control strategies can be directed either at the supply of pharmaceuticals (the manufacturers) or at the demand (wholesalers, retailers, doctors, and patients). In either case, the purpose of these measures is to limit total government expenditure and (as in Canada and other nations) private expenditures on pharmaceuticals. These interventions can, however, produce a variety of negative consequences for the national health systems and reduce social welfare by depressing the number of new drugs added to the global pharmacopoeia. Such controls can also delay or reduce the availability of some innovative medicines in foreign countries, with the effect of limiting competition and requiring national health systems to forgo the benefits of those innovations in reducing health care costs.

Following is a review of the principal strategies employed by OECD governments to control pharmaceutical spending.

Government Price Control, Procurement, and Reimbursement

Price Controls

All OECD governments studied in this report rely on some form of price controls to manage spending on pharmaceuticals. The process is non-transparent in many countries as the criteria and rationale for price setting generally are not fully disclosed to companies. Price controls can be applied either at the manufacturing or the retailing level.

The most direct control method is for governments to set the sales price and prohibit sales at any other price. Alternatively, governments may negotiate favorable prices with manufacturers by leveraging their monopsonistic power to set prices below more liberalized prices. Another method governments use to control prices is to set the reimbursement price of a new drug at artificially low levels. Since any price above that is set by the government is borne by the consumer the reimbursement price functions as the

[9] OECD references in this report exclude the United States.
[10] The term "Drug price regulation" refers to all direct and indirect controls employed by OECD countries to limit government expenditure and private expenditure on pharmaceuticals.

de facto market price. Finally, governments may regularly cut the reimbursement price of drugs already on the market.

Canada, for example, controls prices of drugs sold through its government health care programs through reimbursement rates and price cuts. Canada's Patented Medicines Prices Review Board sets a maximum allowable price that pharmaceutical manufacturers may charge, and any attempt to impose higher prices can result in significant fines for the manufacturer. The Canadian provinces have used price cuts and price freezes to prevent manufacturers from raising prices to track inflation.[11]

While the mechanics of price-control regimes differ widely from country to country, the end result is the same. Pharmaceutical companies are prohibited from charging a market-based price for the products they manufacture. Reference pricing, approval delays and procedural barriers, restrictions on dispensing and prescribing, and reimbursement controls are the principal methods employed by OECD governments to control pharmaceutical prices and costs.

Reference Pricing

Reference pricing determines sales prices based on the prices in other countries or relative to existing therapies in the same country. Since reference pricing controls the reimbursement level and not the manufacturer's price, governments often view this method as less restrictive than price controls. Many countries that moved from a liberal approach to a regulated pharmaceutical market employ some form of reference pricing.[12]

"International" Reference Pricing

A common approach to reference pricing is to establish price based on a basket of prices from other countries. The comparison prices are often taken from a range of "peer" countries. Such comparisons are marred by the many difficulties inherent in cross-national pharmaceutical price comparison—lack of standardization regarding name, form, strength, and presentation. Such comparisons also fail to adjust for differences in per capita income between countries or other factors that would account for price differences. By taking comparison prices from other countries, the regulation of drug prices in one country can directly affect prices and revenues in another.

"Therapeutic" Class Reference Pricing

Therapeutic class reference pricing entails limiting reimbursement to the price of the average or lowest price of other drugs in its therapeutic class. Users of this approach

[11] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls,* Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 11.
[12] Patricia M. Danzon and Jonathan D. Ketcham, *Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, the Netherlands and New Zealand,* Working Paper 10007, National Bureau of Economic Research (September 2003), p. 2.

argue that it is intended to allow physicians, patients, and insurance companies to choose between similar products without concern for price.[13]

Others, particularly the research-based pharmaceutical companies, raise concerns that the process often undervalues additional therapeutic benefits of new drugs and assumes that all medicines within a category are appropriate for any patient with a specific illness. If generic and innovative drugs are grouped in the same therapeutic categories, this method of reference pricing forces prices for new drugs toward the level of existing generics, discouraging innovation by failing to adequately reward it. [14]

Volume Limitations

Governments may also impose volume limitations to control the quantity of a new drug that may be sold. A variation of the volume control is the "price-volume" agreement, which links a new drug's reimbursement price to a volume threshold. If the threshold is exceeded, the manufacturer must provide compensation through price reduction or cash payments to the government (depending on the country) or remove the product from the market. France and Australia both impose price-volume agreements on manufacturers of new medicines.[15]

Profit Controls

Some countries impose profit controls on pharmaceutical manufacturers. The controls limit the amount of profit a company may earn per product or within a specified period of time. If the limit is exceeded, the company may be required to either compensate the government for any excess profits or accept a price cut. In 1998, the European Union, in formulating single market legislation for pharmaceuticals, considered profit controls based on negotiations between the Member States and companies.[16] The United Kingdom currently places limits on the profit that a company can gain from sales to the U.K. National Health Service.[17]

Price Floors

Many countries impose price "floors" for pharmaceuticals following patent expiration in order to support the domestic generic manufacturing industry. The price floors are typically based on a percentage of the patented drug price. Maintaining high generic prices may lead to increases in the consumption of branded drugs. However, since countries maintain relatively fixed pharmaceutical budgets and are forced to pay

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[13] Ibid.
[14] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls*, Federal Register Notice Submission to the International Trade Commission, Investigation 332–419 (August 4, 2000), p. 4.
[15] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls*, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 12.
[16] European Commission, *http://europa.eu.int/scadplus/leg/en/lvb/l21227.htm*.
[17] Pharmaceutical Research and Manufacturers Association, Foreign Government Pharmaceutical Price and Access Controls, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 11.

relatively more for off-patent medicines, they may be left with less money to pay for new, innovative drugs. The ultimate impact of these floors on revenues to innovative firms is unclear. Consumers, meanwhile, are actually left with less money to pay for new, innovative drugs because they are forced to pay relatively more for off-patent medicines.

Approval Delays and Procedural Barriers

Marketing Approval

Marketing approval is required for the sale of all pharmaceuticals, regardless of whether they are over-the-counter or prescription drugs or whether they are reimbursable. While this requirement is designed to ensure the safety and effectiveness of medicines, marketing approval can be extremely difficult to attain due to time delays, cost of approval (both testing and fees), nature of regulations, and approval criteria. In many countries, the approval process suffers from non-transparency, lack of standardization, and unnecessary complexity. The process typically involves multiple stages of approval and multiple government and regulatory bodies. As a result bureaucratic delays tend to be the norm.

As an example, in June 2002, Korea implemented its Drug Master File (DMF) requirements. This regulation obligated manufacturers to submit significant quantities of proprietary manufacturing data to the Korean Food and Drug Administration as part of the drug approval process. While the Korean government maintains that the requirements are designed to assure product quality, U.S. industry has expressed concern that because the requirements apply only to new drugs, their impact is directed almost exclusively at the foreign manufacturers of innovative pharmaceuticals, not the domestic generic companies. U.S. industry has raised concerns that the requirements delay market access and may jeopardize intellectual property protection.[18]

Cost-effectiveness reviews, called the "fourth hurdle requirements" by industry, are defined as government consideration of "factors other than safety, efficacy, and quality in approving new drugs for marketing or reimbursement."[19] Although the schemes differ from country to country, the determination that a new medicine is not cost-effective or "medically necessary" can work much like price controls because the analysis can be performed in a way that makes clear that a price reduction will make the drug acceptable. The fact that approval criteria and procedures often lack transparency, combined with a near-prohibition on post-approval price increases, can cause cost-effectiveness requirements to create registration delays and increased costs for manufacturers, thus

[18] Untied States Trade Representative, "2004 National Trade Estimate Report on Foreign Trade Barriers: Korea" (2004), p. 296.
[19] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls*, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 13.

limiting the rewards for innovative drugs. The widespread occurrence of delay in approving and registering innovative drugs has been documented by academic experts.[20]

Pricing Approval

The pricing approval decision (or reimbursement decision) suffers from many of the same difficulties as the marketing approval decision. Manufacturers are typically required to submit scientific dossiers and economic reports and, in some cases, price data from other countries. Often the data required for reimbursement or pricing decisions is the same as the data required for marketing approval, a redundancy that introduces unnecessary cost and time delay to the process. The pricing decision may also be delayed by extensive negotiations, waiting periods, multiple decision-making stages, and lengthy bureaucratic delays. The lack of transparency contributes to costs and increases the risk to manufacturers. The EU Transparency Directive has mandated 90 days for reimbursement approval,[21] but some member states have not yet succeeded in meeting this mandate.[22] As noted earlier, the consequent delay in bringing innovative drugs to bear on health problems has been documented by academic experts.[23]

Barriers to Dispensing and Prescribing

Restrictive Formularies

A formulary is a selection of preferred drugs within a therapeutic class. A government body, hospital, third-party insurer, or other health plan determines the list. Some institutions or health plans impose closed (i.e., restricted) formularies, which prohibit the dispensing or reimbursement of drugs not listed on the formulary. Typically, drugs outside of the formulary are used only in rare, specific circumstances, and prior approval from the health plan or authority is usually required. Other formularies may have no restrictions (open formulary) or may have certain restrictions, such as higher patient cost-sharing requirements or co-payments for off-formulary drugs.

The type and choice of formularies available restrict manufacturers' access to pharmaceutical markets. In countries that impose a single, closed, national formulary, a

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[20] Patricia Danzon, Y. Richard Wang and Liang Wang, *The Impact of Price Regulation on the Launch Delay of New Drugs – Evidence from Twenty-Five Major Markets in the 1990s*, Working Paper 9874, National Bureau of Economic Research (July 2003).

[21] European Commission, Institute of Prospective Technological Studies, European Pharmaceutical Research, Development and Innovation: Assessment of the Socio-Economic Impact of New Drugs, Executive Summary (March 1997).

[22] In December 1988, the Council adopted a Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance schemes (Transparency Directive) acknowledged that the Directive was an initial step toward harmonization and that further measures should take place progressively. The Directive requires that the national authorities adopt transparent, objective, and verifiable criteria when deciding on price or profit regulation or set up limited and positive lists for drugs. It defines a time limit of 90 days on national authorities to agree or set a price on newly introduced products and requires that they state the reasons if they fix a price different than sought by the company.

[23] Danzon, Wang and Wang.

particular drug must be listed on the formulary in order to be prescribed. Even if off-formulary drugs can legally be prescribed, the fact that they are not reimbursed is a sufficient disincentive to effectively prevent or severely limit prescription, given current prohibition on manufacturers' communications to patients about the benefits of off-formulary or higher-priced brands. In countries with open formularies, access to the market depends on the range of formularies available, as well as the reimbursement rates specified.[24]

Prescribing Guidelines

Prescribing guidelines are intended to inform appropriate prescribing practices, serve as standards for determining the quality of care, and function as part of a wider process for improving the quality of care. Prescribing guidelines range from suggestions to requirements and can include brand substitution, limiting prescription of certain drugs to specialists, and recommending appropriate treatments.

With increasing frequency, guidelines are used as a tool to evaluate pharmaceutical standards rather than to assist physicians in the management of patients. When this occurs, the guidelines can dissuade doctors from prescribing treatments outside the guidelines. Similarly, when guidelines cover a large portion of clinical conditions, it is difficult for physicians to prescribe a drug or course of action not covered under the guidelines, even when the patient's specific circumstances warrant it. Certain countries require justification based on a "clear rationale" when prescribing outside the guidelines.

Prescribing Budgets

Prescribing budgets are often instituted by health care insurers or national agencies, such as in the United Kingdom, in the hope that economic incentives will induce physicians to reduce costs by choosing effective, low-cost therapies whenever possible and by reducing use of unnecessary medications without adversely affecting the health of their patients.[25]

Prescribing budgets assign a set "budget" for a given period from which to administer treatment. This limitation may control either the expenditure on or quantity of pharmaceuticals prescribed by a physician. In some cases, the national health care system sets a limit for pharmaceutical expenditure. When government spending exceeds the target, the government imposes a tax on either the pharmaceutical industry or on doctors.[26] In South Korea, the government evaluates physicians on the proportion of the "expensive drugs" they prescribe.[27] And, in some cases, doctors receive extra income for

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[24] Powers Pyles Sutter and Verville P.C., Attorneys at Law, *www.ppsv.com/issues/drug_glossary.htm* (2004).
[25] United Kingdom Department of Health, *U.S. Federal Register Notice: Drug Pricing Study*, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 2.
[26] Stephen B. Sournerai and Dennis Ross-Degnan, *Prescribing Budgets: Economic, Clinical and Ethical Perspectives*, Australian Prescriber 20, no. 2 (1997), p. 28–29.
[27] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls*, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p. 11.

under-spending. This arrangement can lead to agreements for rebates to the government or to volume limitations on sales.

Obstacles to Promotion

Some countries limit drug manufacturers' access to consumers and physicians. They contend that allowing promotion and direct-to-consumer advertising raises costs, promotes inappropriate drug use, and gives doctors ready access to information about new innovative drugs from other sources.

The innovative drug industry maintains that obstacles to promotion are designed to reduce demand for new drugs for which the government does not want to pay. It claims that governments are worried that if consumers were made aware of the "true" benefits of innovative drugs, they would demand that these drugs be reimbursed. Additionally, the industry asserts that marketing rights would provide drug companies with increased bargaining power in price negotiations because governments would fear public backlash if a desired drug were not made available in a country because the price was rejected. Finally, pharmaceutical manufacturers argue that these restrictions inhibit patients' access to life-saving cures.[28]

[28] Pharmaceutical Research and Manufacturers Association, *Foreign Government Pharmaceutical Price and Access Controls*, Federal Register Notice Submission, FR Doc. 04-12205, (July 1, 2004), p. 9.

3. PRICE AND REVENUE EFFECTS

The Conference Report asked the Department of Commerce to estimate the impact of price controls maintained by OECD members on pricing, U.S. consumers, R&D, and innovation. Before turning to the actual analysis, the following discussion outlines the methodology employed to ensure an effective comparison of prices in order to analyze their impact on the factors cited in the Conference Report. This section details the approach used to estimate current prices of patented drugs, prices that would prevail in the absence of price controls, and adjusted revenues that would stem from allowing the market, rather than governments, to set prices.

To estimate the impact of price controls, it was necessary to make a number of significant, simplifying assumptions. The key assumption is that subject to disparities in per capita income, U.S. prices could serve as a benchmark for deregulated prices, at least for short-run impacts. Although it is true that even the U.S. market is regulated in a variety of ways, U.S. prices are undeniably more market-oriented and suffer from less direct government intervention than is true among its trading partners. Under the circumstances, U.S. prices offered the closest approximation of deregulated prices available for use as a benchmark for comparison with government-mandated prices among other OECD countries.

Based on this, aggregate price indices were estimated for patented pharmaceuticals in nine OECD countries relative to U.S. prices for the same medicines. The study then contrasted these aggregate relative price indices against relative levels of per capita income across the same group of countries. This exercise determined what, if any, adjustment factor should be employed to estimate what prices would be in each country without price controls. Adjusted revenues were then calculated based on the adjusted prices.

Given severe resource and time constraints, it was not possible to examine the many complex issues that would define a global, deregulated pharmaceutical market. In particular, the study did not explore the effect of free-market pricing on the interaction of generic and patented drugs, or how this interaction would shift demand, prices, or revenues. It was also necessary to make the assumption that consumption patterns would not change in the absence of price controls. While one might assume that higher prices brought on by the removal of price controls would reduce consumption, an empirical determination of this effect was outside the scope of the study.

The study finds evidence rejecting the suggestion that international price differences for patented drugs are in line with income differences. In some OECD countries the prices of patented drugs are low relative to their income levels, while other countries, notably Greece and Poland, have prices that are high relative to their income levels.

Overall, the price comparison suggests that for the molecules[29] studied, average ex-manufacturer prices of patented drugs in the nine OECD countries in 2003 were 18 to 67 percent lower than U.S. prices. That implies that, after adjusting the prices to simulate unregulated market conditions and extrapolating to other highly developed OECD countries, innovative drug companies lost an estimated $17.6 billion to $26.7 billion annually that would otherwise have accrued in the absence of price controls.

These estimates do not take into account the Medicare Modernization Act of 2003, which may result in significant savings to previously uninsured people eligible for Medicare. To the extent that such savings narrow the gap between U.S. and OECD prices, the revenue effects estimated in this report would be reduced accordingly.

International Price Comparisons

Developing the appropriate data set for purposes of answering the questions identified in the Conference Report presented a number of challenges. For example, since innovative drug manufacturers fund most private R&D spending to develop new pharmaceuticals, any attempt to analyze the effects of foreign drug price regulations on R&D requires an understanding of the effect of price regulation on the revenue of such firms. Because their revenue depends primarily on patented drugs, the study uses a set of the best-selling drugs with patented active ingredients (molecules) from the total IMS Health data set[30] to serve as the basis for price comparisons and the implications for revenue and R&D spending.

Defining the patented data set was also complicated by the fact that patent expiration dates vary across nations, and the patent expiration date itself can be an unreliable indicator of when generic competition begins. That date does not always coincide with the expiration of a patent. In the United States, the Hatch-Waxman Act[31] expedites the entry of generics into the marketplace, and this makes the patent expiration date a good proxy for when generic competition starts in the United States. Other countries do not employ similar incentives, and generic competition may occur much later as a result. This study defines the effective expiration of a patent to occur in the year when a generic manufacturer enters the market.

Ensuring that comparisons were based on similar products was further complicated by the fact that local brand names vary considerably across countries. Pfizer, for example,

[29] A list of the 54 molecules included in this study is presented in Appendix A.

[30] IMS Health is a leading provider of business intelligence services, strategic consulting services, and data for the pharmaceutical and health care industry.

[31] The Hatch-Waxman Act was designed, in part, to facilitate generic competition with brand-name products. Title I allowed generic drug companies to obtain Food and Drug Administration (FDA) approval for their products more rapidly and efficiently. If a new, innovative drug has been approved for at least five years, a generic manufacturer's product also can be approved, usually demonstrating that its drug is bioequivalent to the approved innovative drug. This saves a significant amount of time and money for the generic manufacturer because bioequivalence testing is much less expensive and time consuming than completing a full safety and efficacy clinical trial. The Hatch-Waxman Act also permits the generic manufacturers to begin bioequivalence tests prior to the expiration of the patent term of the innovative drug. This allows many generic manufacturers to be prepared to market the drug immediately following the expiration of the patent term and the exclusivity period of the innovator drug.

markets its cholesterol-reducing drug known as Lipitor in the United States, but sells the same product under the brand names of Tahor and Sortis, respectively, in France and Germany. Thus, proper comparisons required a definition of "product" by criteria that match across countries.

The challenges noted above led to a focus on the appropriate basis for comparison of prices that would address the fundamental questions posed by the Conference Report. That led to a review of the principal classification criteria for pharmaceutical data. Those criteria include molecule name, brand name, therapeutic use, dose form (tablets, capsules, injections), strength (milligrams), and package size (number of pills in a bottle).

Most studies have classified products at the molecule level, which is the broadest definition of a product. However, since each country's pharmaceutical basket is different, this approach produces comparisons of products that differ by dose form, strength, and/or package size. Conversely, matching products based on identical classification criteria yields the most accurate level of comparison but severely limits the data set available for analysis.

As a result, for the purposes of this study, a product is defined as a bilateral match between the United States and a partner country at the molecule level. For data on prices reported on that basis, the study relies on data for the year 2003 provided by IMS Health, IMS MIDAS (TM), Q4/2003.

The data provided was based on the top 60 prescription products in the United States, measured by 2002 sales. The molecular composition of each was determined, and combination products containing multiple molecules were removed from the data set, narrowing the data set to 54 molecules. The data set was then extended to include all single-molecule products made from these molecules. As a result, the data set includes on- and off-patent brand name products, generics, and products produced by licensees and offers as sound as possible a basis for price comparisons, given the variations between national markets. Sales data from the sample of 54 molecules represent 26 percent of total drug sales in 2003 across the ten OECD countries, including the United States, considered in this study.[32] Figures 1 and 2 show the coverage of the total and patented data sets resulting from the molecule-level product definition. From the descriptive statistics in Figure 1, it appears that the effective patent life of molecules in most OECD countries are shorter than in the United States. An analysis of the effective patent life for 46 molecules of the 54 molecules included in the data set shows that the effective patent life in the United States is two to two and half years longer than in the United Kingdom, Switzerland, Germany, and France and four to five years longer than in Poland and Greece.[33]

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[32]U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM),* Country Profiles, 2004.

[33] The information on effective patent lives for each OECD country in the IMS Health data set is based on an analysis completed by the Food and Drug Administration. Only 46 molecules out of the 54 molecules in the data set were analyzed because eight of the molecules were missing data to calculate the period of effective patent life for each molecule. The type of data used to compute the period of effective patent life included the molecule's launch date, patent expiration date, sales per year and volume per year.

IMS Health data are reported at the ex-manufacturer levels, before hospital or pharmacy markups or dispensing fees. Data at the manufacturing level offer a more reliable basis for comparison internationally than pharmacy or hospital prices, because they do not require further adjustment for differences across countries. IMS Health data for the United States do not include off-invoice manufacturing rebates given to managed-care and government buyers, which would make U.S. prices less expensive relative to foreign prices if taken into account. Previous studies of international drug prices discounted U.S. prices from IMS Health data to reflect off-invoice manufacturing rebates. The size of the off-invoice manufacturer discounts in these studies averaged between 8 and 11 percent.[34]

HHS recently completed an analysis of discounted U.S. pricing data from the Center for Medicare and Medicaid Services (CMS).[35] The analysis does not show a meaningful difference between the average manufacturers prices (AMP) for sales of brand-name drugs to non-Medicaid retail purchasers (CMS data) and the U.S. invoice prices collected by IMS Health. (Manufacturers' prices for sales to Medicaid are lower than the invoice prices in the IMS Health data set. This study does not use these prices, however, because it aims to quantify the difference between market-based prices in the United States and drug prices in other OECD countries, and the Medicaid program requires participating drug companies to pay mandatory rebates.) For the set of 29 off-patent molecules, the CMS average manufacturer prices for non-Medicaid transactions are approximately 24 percent lower than the IMS invoice prices.

Figure 1. Number of Molecules in Total and Patented Data Sets 2003

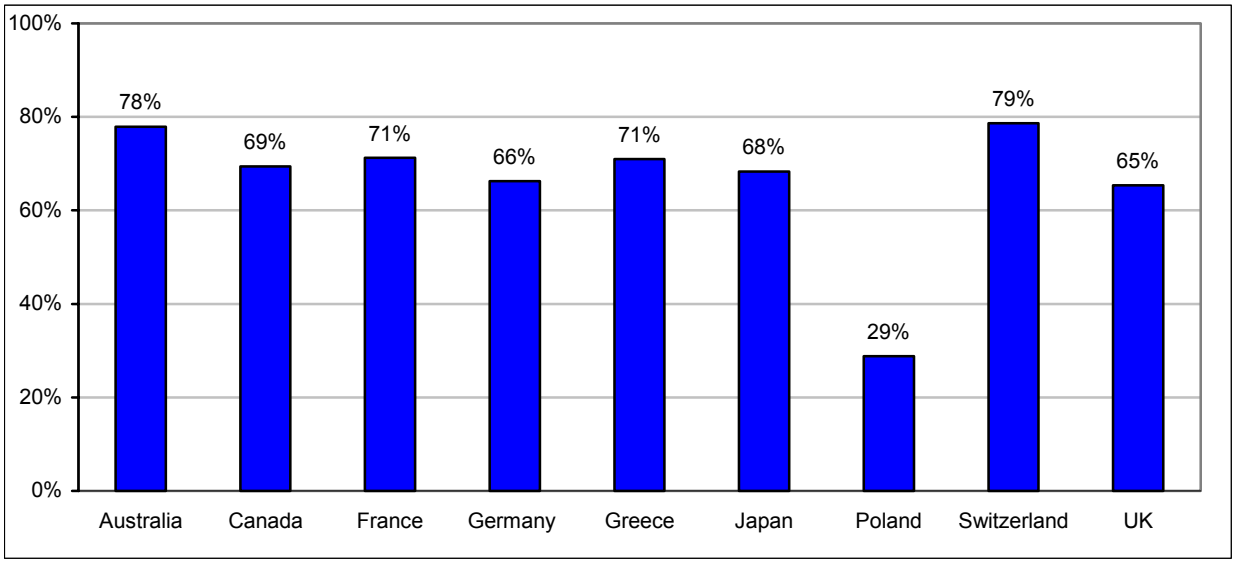
	AUS	CAN	FRA	GER	GRE	JAP	POL	SWIT	U.K.	U.S.
# of molecules in the IMS data set	52	52	53	53	51	38	50	53	54	54
# of molecules in the patented sample	33	34	36	37	36	25	26	40	34	41

Source: IMS Health, IMS MIDAS (TM), Q4/2003.

[34]See Patricia Danzon and Michael F. Furukawa, "Prices and Availability of Pharmaceuticals: Evidence From Nine Countries," *Health Affairs* (October 2003), p. 526. See also Pharmaceutical Research and Manufacturers Association (PhRMA), "Adverse Consequences of OECD Government Interventions in Pharmaceutical Markets on the U.S. Economy and the Consumer," Boston Consultancy Group White Paper, Federal Register Notice Submission, FR Doc. 04-12205 (July 1, 2004), p.11.

[35] CMS is a division of the Department of Health and Human Services that administers Medicare and Medicaid in cooperation with the states. CMS collects data from manufacturers on the prices they charge for drugs for distribution in pharmacies. These prices are after various adjustments, (such as discounts, rebates and chargebacks), including those that may be excluded from invoices.

Figure 2. Revenue from Patented Drugs as a Percent of Total Data Set Revenues in 2003



Source: U.S. Department of Commerce calculations are based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

The IMS Health data set does not include prices for each molecule. As a result, a molecule price is estimated by dividing revenues (current U.S. dollars) by volumes.[36] This study employs two different volume measures to estimate prices: standard units (SU) and kilograms (KG). We report results using both measures, although the differences are usually modest.[37] The results of this analysis, presented in Figure 3, indicate that prices in the United States are higher relative to each of the nine OECD countries. Relative price indices based on standard units range from 0.33 in Japan to 0.59 in Switzerland. Based on kilograms, relative price indices range from 0.40 in Poland (and Australia) to 0.82 in Japan.

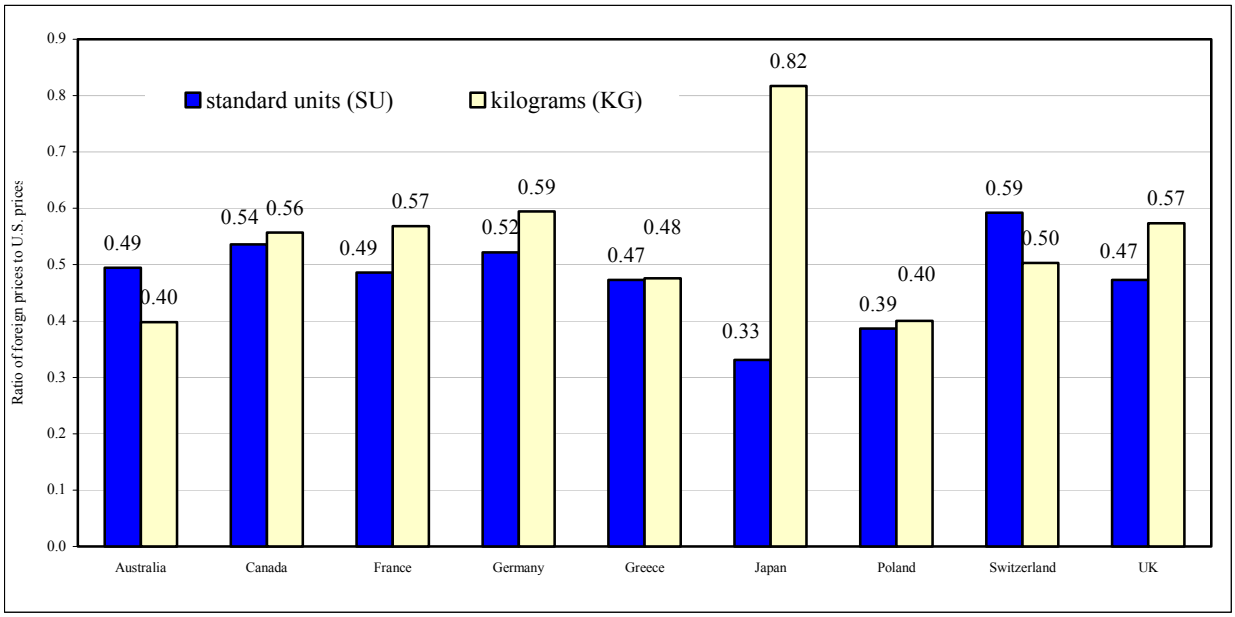
While price indices measured in standard units do not vary greatly by country compared to price indices measured in kilograms, Japanese prices are a notable exception. Japan's price index measured in standard units is 0.33, indicating that Japanese prices are 67

[36] This study was conducted using 2003 prices and exchange rates. Any fluctuations in exchanges rates can be expected to change the observed price differentials and revenue estimates. Given the continuing decline in the value of dollar relative to most OECD currencies and especially the Euro in 2004, there is a high probability that the price differences and related revenue effects reported in this study are larger than would currently be observed.

[37] "IMS Volume Measures" in Appendix A offers a definition of the different IMS Health volume measures. A standard unit is equivalent to a standard dose of medication, and is derived from other IMS Health volume measures. Kilograms are the amount of active ingredient in a molecule. There is no reason *a priori* to prefer standard units or kilograms. The drawback to using the standard unit measure is that it varies by dose across countries. The smallest common dose in one country is not necessarily the same as that of another. A second difficulty is that it implicitly assumes that all pills have the same value to the patient, independent of dose. The drawback to using the kilogram measure is that it can be sensitive to the sample of products because potency in molecules varies. This study calculates price based on both standard units and kilograms, providing a range of results. The price indices are weighted by a combination of U.S. and (bilaterally matched) foreign volume measures in order to avoid a result dependent on either domestic or foreign consumption pattern. The price indices in this study are Fisher price indices. A Fisher price index is the geometric mean of Laspeyres and Paasche indices. For a description of how each index is computed, see "Price Indices" in Appendix A.

percent lower than U.S. prices. However, Japan's price index measured in kilograms is 0.82, indicating that Japanese prices are only 18 percent lower than U.S. prices. This variation between the two price index measures for Japan results from the unique nature of Japanese prescribing habits.[38]

Figure 3. Patented Drug Data Set Prices in 2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.
Note: All prices are indexed to U.S. prices (1.0).

Pharmaceutical Prices in the Absence of Price Controls

Market forces, rather than government regulatory processes, would set pharmaceutical prices in the absence of price controls. The market for innovative pharmaceuticals is defined by several relatively unique characteristics that must be considered when estimating prices in the absence of price controls. First, the high cost of developing and testing a new drug means that no profit-maximizing firm would make the investment needed to bring new and innovative medicines to the market in the absence of patent protection. To overcome this obstacle, countries offer patent protection as a reward for innovation by conferring the right to use of the resulting chemical compound for a specific period of time. Such patent protection affords innovative pharmaceutical manufacturers significant pricing power.

[38] It has been noted in prior studies that the Japanese tend to prescribe relatively weaker doses compared to other countries. These studies suggest two reasons for the relatively weak doses prescribed in Japan. The first reason is that, due to physiological differences, the Japanese are said to require weaker doses to achieve a given therapeutic effect. The second reason is based on the fact that drug consumption in Japan is relatively high, in part because Japanese physicians profit from dispensing drugs. In such cases, weaker doses would provide some safeguard against adverse drug interactions. See Patricia M. Danzon and Jung D. Kim, "International Price Comparisons for Pharmaceuticals," *Pharmacoeconomics,* vol. 14 (1998), p. 124.

Second, trade in pharmaceuticals generally cannot take place except through authorized channels. Third, because direct manufacturing costs constitute a relatively small percentage of overall costs, prices can vary considerably and remain above the costs of production.[39] As a result, pharmaceutical firms can be expected to charge different profit-maximizing prices in different markets. That is, given the low cost of production and absence of trade, the profit-maximizing price will vary across countries because the patent holder will charge a price that reflects the demand factors in each market.

While a variety of factors affect demand for different drugs in different countries, one consistent factor influencing demand is income. It is assumed for this study that U.S. pharmaceutical prices are the benchmark for unregulated prices, and relative levels of per capita income determine variances in prices among developed countries. It is not assumed, however, that variances in prices for each molecule are determined solely by income levels, only that the aggregate prices would vary based on relative income levels.

Following this model, the methodology adopted in this study adjusts prices at the molecule level by a uniform adjustment multiplier for each country. As noted above, an aggregate price index for patented prescription products is calculated for each country relative to the United States. Then, the ratio of gross domestic product (GDP) per capita is computed for each country relative to the United States.[40] The difference between the ratio of the foreign price to the U.S. price and the ratio of foreign per capita income to U.S. per capita income is assumed to represent the effects of price regulation. The income ratio is then divided by each country's respective price index to produce the adjustment multiplier. Finally, this figure is multiplied by molecule level prices to estimate prices in an unregulated environment. Figure 4 displays the adjustment multipliers for the set of patented drugs in 2003.

Adjustment multipliers greater than one indicate that prices are below what would be expected in an unregulated market. Adjustment multipliers of less than one are not applied because there seems little reason to think that a relaxation of price ceilings would cause patented drug prices to fall. Applying this assumption to the adjustment multipliers in Figure 4, Greece, and Poland are excluded from further analysis because their adjustment multipliers in 2003 are below one. The rationale behind excluding Greece and Poland is based on the assumption that these countries' prices are reasonable relative to their income levels. If prices were reduced any further, some individual drug prices may even drop below the direct cost of production.

[39] Danzon estimates that direct manufacturing costs in the pharmaceutical industry are approximately 30 percent. See Patricia M. Danzon, "Price Discrimination for Pharmaceuticals: Welfare Effects in the US and EU," *International Journal of the Economics of Business,* vol. 4, no. 3 (1997), p. 303.

[40] GDP per capita is in current U.S. dollars. The source is the International Monetary Fund's International Financial Statistics.

Figure 4: 2003 Price Adjustment Multipliers

	AUS	CAN	FRA	GER	GRE	JAP	POL	SWI	U.K.	U.S.
GDP per capita (US$)	24,685	27,199	28,279	28,930	15,562	32,859	5,320	42,598	29,642	37,312
GDP per capita ratio to U.S.	0.66	0.73	0.76	0.78	0.42	0.88	0.14	1.14	0.79	1.00
Price index (SU)	0.49	0.54	0.49	0.52	0.47	0.33	0.39	0.59	0.47	1.00
Price index (KG)	0.40	0.56	0.57	0.59	0.48	0.82	0.40	0.50	0.57	1.00
Adjustment multiplier (SU)	1.34	1.36	1.56	1.49	0.88	2.66	0.37	1.93	1.68	1.00
Adjustment multiplier (KG)	1.66	1.31	1.33	1.30	0.88	1.08	0.36	2.27	1.39	1.00

Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.
GDP per capita in current dollars is from the International Monetary Fund's International Financial Statistics Manual.

Some drugs are unusually distinctive and face significantly less competition than other drugs. For example, when a drug has no therapeutic substitutes or is a member of a new and highly innovative class offering benefits to patients suffering from conditions largely untreatable by older methods, it tends to be priced higher and more in line with the U.S. prices than a drug that has many therapeutic substitutes. That is, such drugs appear to be relatively unconstrained by price controls. To control for these occurrences, all molecules with prices greater than or equal to equivalent U.S. molecule prices are held constant (i.e., not adjusted by the multiplier).

In some cases, the new price per dose (or kilogram) that results from application of the uniform adjustment multiplier is greater than the country's GDP ratio. This implies that in an unregulated market some foreign molecule prices would be higher than equivalent molecule prices in the United States. While it is conceivable that local demand conditions would allow relatively high foreign prices for certain drugs, determining which drugs would display such an outcome requires value judgments to be made about individual molecules in each foreign country. Therefore this study employs a conservative approach to price increases by assuming that in cases where the molecule price ratio exceeds the GDP ratio, the molecule price increases are capped at the level of relative GDP.[41]

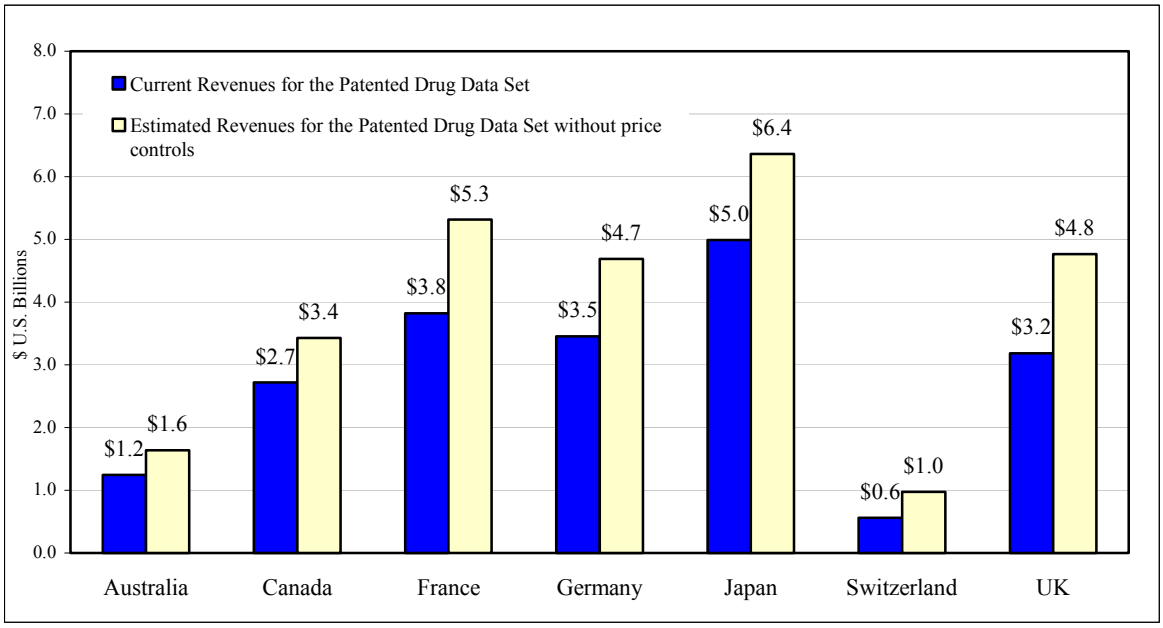
Estimated Revenues in the Absence of Price Controls

After adjusting prices, new foreign revenues are computed by multiplying adjusted prices and volume measures. Recall that this study makes the simplifying assumption that consumption patterns (i.e., volume) would not change in the absence of price controls. Figure 5 shows the difference between current revenues for the patented drug data set and

[41] For more information on the method used to cap individual molecule prices, see "Price Adjustment Method" in Appendix A. Imposing floors and ceilings on particular molecules, of course, imposes a somewhat artificial constraint on the extent to which markets would respond. Any further analysis of this sort would, if the data allowed, benefit from freeing the model from these constraints to ensure that any purely methodological bias (i.e., one built into the model by virtue of its assumptions) does not lean too much in one direction or the other.

estimated revenues for the patented drug data set without price controls in 2003 using standard units. Based on this study's calculations, estimates of revenues for the patented drug data set without price controls would range between 1.0 billion and 6.4 billion. Canada, France, Germany, Australia, and Japan all exhibit revenue increases between 25 and 40 percent for the drugs in this data set. The increase in adjusted revenues for Switzerland is the highest in the sample at 74 percent. This is explained by the previous finding that Swiss drug prices are low relative to their income levels, which results in a high adjustment multiplier. Switzerland's adjustment multiplier was the highest in the sample, 1.93.

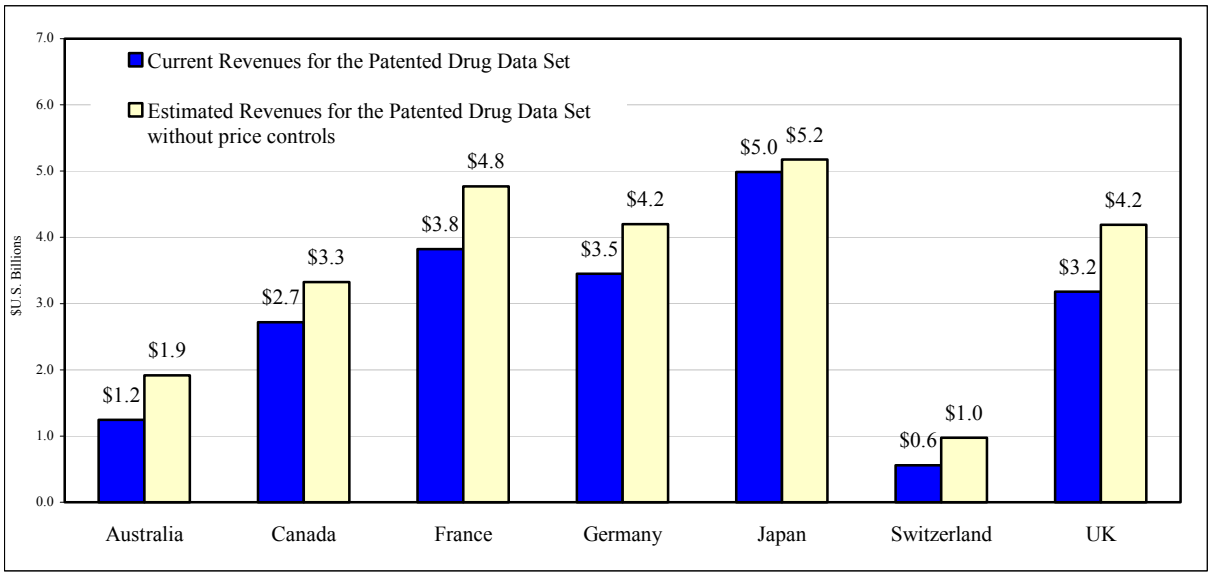
Figure 5: Current and Estimated Revenues for the Patented Drug Data Set Using Standard Units—2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

Figure 6 shows revenues for the patented drug data set in 2003 and revenues in the same year without price controls measuring volume as kilograms. Based on this study's calculations, estimates of revenue gains for the patented drug data set without price controls would range between $1.0 billion and $5.2 billion. In most cases, revenue adjustments based on kilograms are less dramatic than adjustments based on standard units because prices measured in kilograms tend to be higher and closer to relative income levels.

Figure 6. Current and Estimated Revenues for the Patented Drug Data Set Using Kilograms—2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

Estimated Global Revenue Changes in the Absence of Price Controls

In order to estimate the impact of foreign price controls on the global revenues of innovative pharmaceutical manufacturers, revenue changes from the patented data set are extrapolated[42] to the total patented market in 11 OECD countries: France, Germany, Canada, the United Kingdom, Japan, Australia, Italy, Spain, Belgium, the Netherlands, and Sweden. This subset of OECD countries was selected because each country exhibits relatively high per capita income, and collectively they represent a significant share (77 percent) of the pharmaceutical revenues generated in developed markets in 2003, excluding the United States and a group of lower income OECD countries.[43] Lower income OECD countries, such as Poland and Greece, were excluded because it is not clear if the drug prices in these countries relative to the United States can be explained by differences in per capita income relative to the United States.

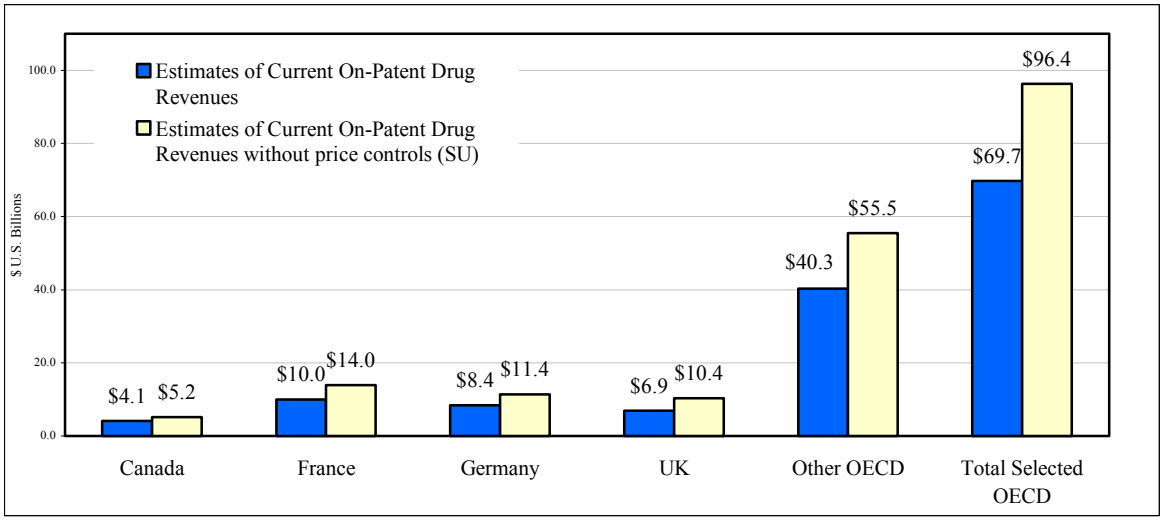
The results of the extrapolation based in kilograms and standard units are presented in Figures 7 and 8. This study estimates that, in the absence of price controls, total revenues from on-patent drug sales for these 11 OECD countries would increase by $17.6 billion to $26.7 billion in 2003, depending on the volume measure used to estimate prices. This

[42]For more information on the extrapolation method employed in this study, see "Revenue Extrapolation" in Appendix A.

[43] U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM),* Country Profiles, 2004 and IMS Health, *IMS World Review (TM)*, Generic, 2002. IMS Health market share data from the *IMS World Review (TM), Generic* report may contain sales for over-the counter (OTC) drugs whereas the patented sample data does not. This could lead to an overstatement of the actual level of total on-patent drug revenues in the absence of price controls but the size of this overstatement is not measurable due to data limitations.

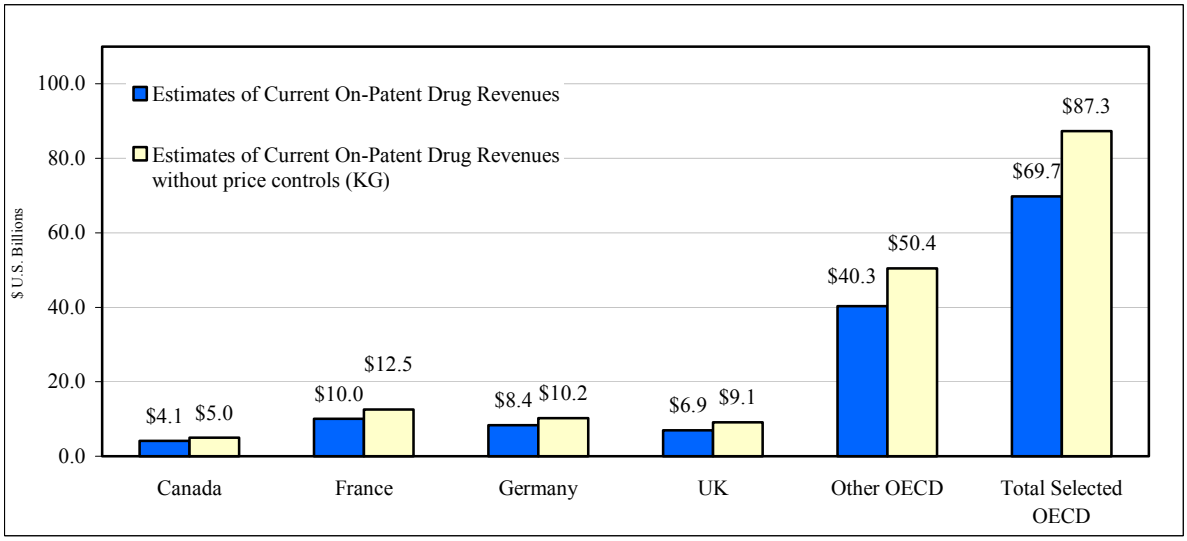
range represents a 25 to 38 percent increase over the original revenues from on-patent drug sales in 2003.[44]

Figure 7. Estimated Total On-Patent Drug Revenues for Selected OECD Countries Using Standard Units—2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

Figure 8. Estimated Total On-Patent Drug Revenues for Selected OECD Countries Using Kilograms—2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

[44]Estimates for Japan are included in the aggregate estimate, but due to various statistical and date issues there may be a higher degree of uncertainty regarding the Japanese estimates. While, Japan is the second largest pharmaceutical market in measured in U.S. dollars sales behind the United States, Japanese sales of the 54 molecules in the sample only accounts for 12 percent of the total Japanese market. In addition, data on the distribution of on and off-patent drug sales in Japan which is necessary for estimating the revenues effects for sales off all on-patent molecules in the Japanese market could not be located and had to be estimated. If Japan were to be excluded from the estimates of the effects of price controls, total revenues from on-patent drug sales for ten OECD countries, excluding Japan, would increase by $11.7 billion to $18.0 billion, depending on the volume measure used to estimate prices.

International Price and Utilization Comparisons of Generic Drugs

The United States employs a variety of regulatory tools to encourage the rapid development and marketing of generic versions of innovative drugs. Chief among these tools are the 1984 Hatch-Waxman Act and the Bolar Amendment to the Hatch-Waxman Act. The Hatch-Waxman Act, among other things, provides for FDA approval based upon clinical trials conducted on the original innovative drug. The Bolar Amendment permits generic firms to make use of originating firms' otherwise protected clinical data before the relevant patents have expired. In contrast, regulatory regimes and enabling legislation in many other developed nations are complex and tend to inhibit the rapid marketing of generic drugs.[45] In addition, complex price control regimes in these nations often keep generic prices artificially high, discouraging a competitive generic industry.[46] As a result, the prices of generic drugs in the United States tend to be lower than in other developed nations.

When considering the efficiency of a nation's pharmaceutical expenditures it is necessary to examine both the prices and utilization of generic drugs. This study classifies off patent drugs into two broad subcategories – off-patented branded and generic. Once a drug loses patent protection, it is common for several companies to manufacture competing versions. Typically the innovator company continues to manufacture and market its brand name product. Some companies, particularly licensees of the innovator company, attempt to brand and market their versions in the same manner as the original manufacturer. Others produce generic versions of drugs that are marketed under the molecular name rather than a brand name. Despite the fact that the competing off-patent branded and generic versions of drugs are usually identical products, the branded versions tend to command higher prices. Thus, consumption of off-patent branded drugs is an allocation of resources that raises drug spending. It follows that nations that consume a relatively high proportion of off-patent branded drugs may realize significant savings by utilizing a higher share of generics.

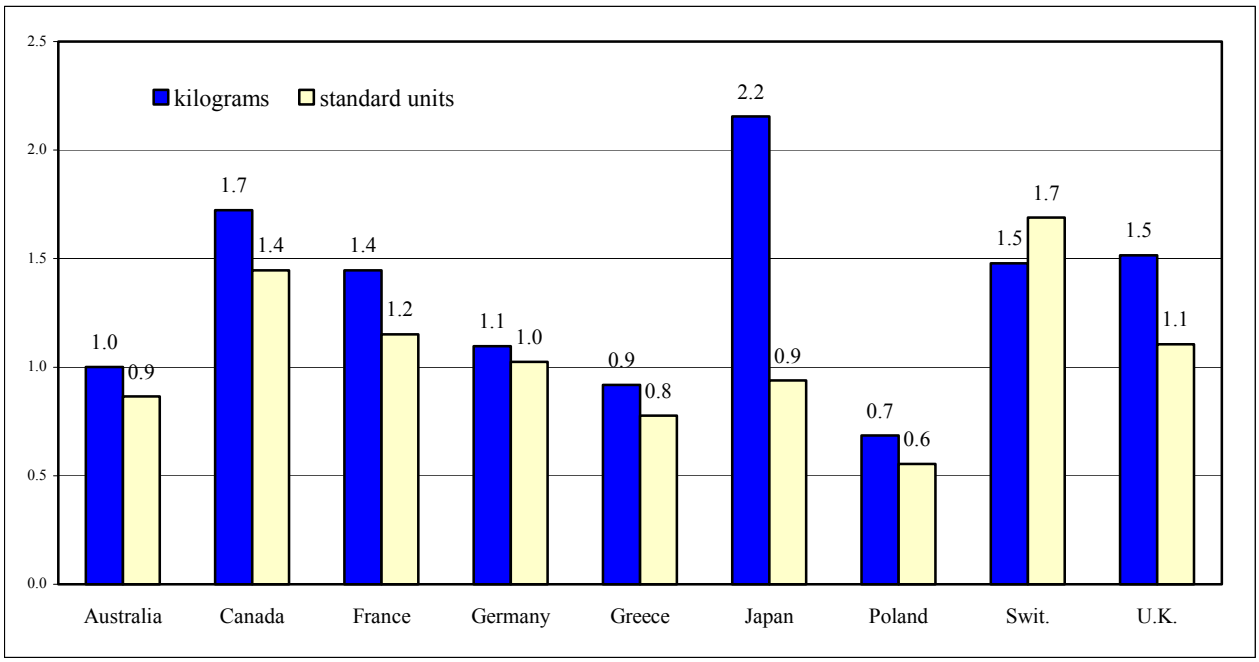
HHS, on behalf of the Department of Commerce, analyzed both the prices and utilization of generic drugs across the same nine OECD countries examined by the Department of Commerce in its empirical analysis of innovative drug prices.[47] Prices were calculated from IMS Health data for 29 widely used, internationally best-selling molecules generally lacking patent protection.[48] Generic drugs are defined within this dataset as those drugs not produced by an innovator or licensee company. All drugs using the same active ingredient are treated as one product. The quantity sold is measured as the total kilograms of the active ingredient or number of standard units. This approach, which includes in the analysis drugs with strengths, package sizes, or dosage forms that vary

[45] Edward Hore, "A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry," *Food and Drug Law Journal*, v. 55 n. 1 (2000), p. 373-388. See also Laura Magazzini, Fabio Pammolli, and Massimo Riccaboni, "Dynamic Competition in Pharmaceuticals: Patent Expiry, Generic Penetration, and Industry Structure," working paper (2003).
[46] Ibid.
[47] The FDA analysis of generics prices and utilization covered Australia, Canada, France, Germany, Greece, Japan, Poland, Switzerland, and the United Kingdom.
[48] IMS Health, IMS MIDAS (TM), Q4/2003.

internationally, permits full use of the dataset. U.S. prices in the IMS Health data set were discounted by approximately 24.2 percent.[49] Finally, Fisher price indices were constructed. Fisher price indices are an average of price indices using U.S. and foreign weights.

Figure 9 presents price estimates for generic drugs across nine OECD countries relative to the United States. When prices are measured in kilograms, Canada, France, Switzerland, and the United Kingdom have prices nearly 50 percent or more than U.S. prices. Japanese prices of generic drugs are more than double U.S. prices. Greece and Poland are the only countries that exhibit lower prices than the United States – not a surprising result given their relatively low-income levels and competitive generics markets. When prices are measured in standard units, Canada, France, Switzerland, and the United Kingdom have prices over 10 percent higher than U.S. prices. Other studies have also found that U.S. generic prices tend to be lower than in other countries.[50]

Figure 9. Prices of Generics in 2003



Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003 and the Center for Medicare and Medicaid Services (CMS).

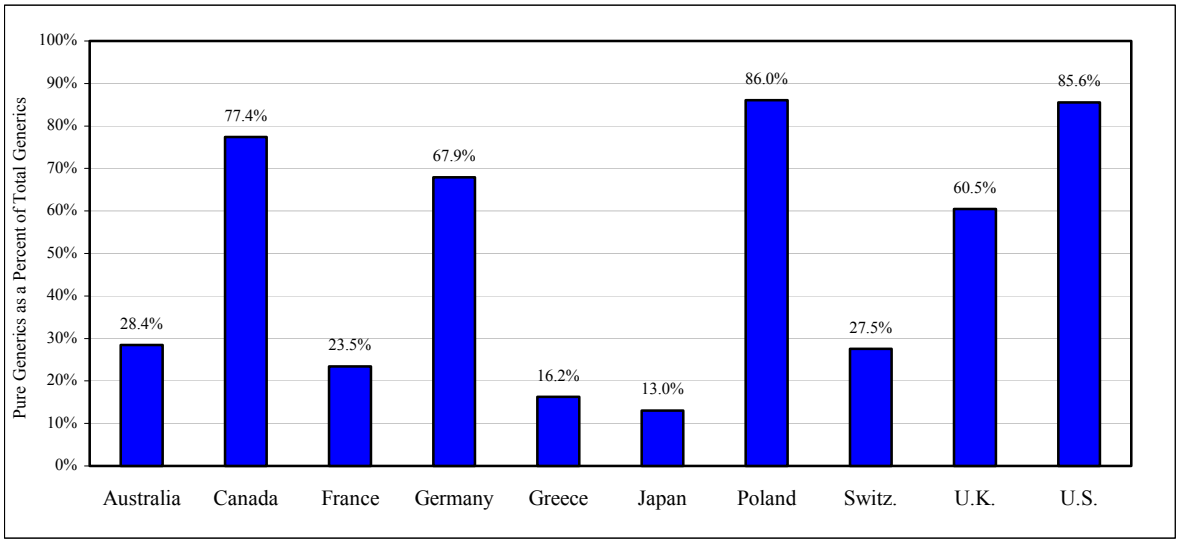
The analysis of generic drug utilization rates found that U.S. utilization rates of generic drugs tend to be significantly higher in the United States than in other developed countries. Figure 10 presents the quantity of generic drugs consumed across the nine OECD countries reviewed in this study as a percentage of total consumption of the 29

[49] This discount is based on a comparison of U.S. prices from IMS and average manufacturer prices (AMP) collected by the Center for Medicare and Medicaid Services (CMS). HHS found that the AMP collected by CMS were 24.2 percent lower than the prices in the IMS Health data set.

[50] Danzon and Furukawa, p. 527. See also Patented Medicine Prices Review Board (PMPRB), "A Study of the Prices of Top Selling Multiple Source Medicines in Canada" (2002).

off-patent molecules from IMS Health.[51] Australia, France, Greece, Japan, and Switzerland all show utilization rates below 30 percent, which contrasts with the U.S. rate of 86 percent. These figures are, of course, based on a sample that may not be completely representative of the utilization rates for all generics.

Figure 10. Utilization of Generic Drugs in 2003 as a percentage of Total Consumption



Source: U.S. Department of Commerce calculations based on the data set of 29 molecules from IMS Health, IMS MIDAS (TM), Q4/2003.

HHS went on to consider a scenario in which foreign countries shift their usage of generic drugs to match U.S. proportions and adopt policies that foster U.S. prices for generic drugs. HHS found that such a shift in generic drug prices and utilization would yield annual savings of $1.8 billion when prices were calculated as dollars per kilogram of active ingredient and $69 million when calculated as dollars per standard unit (dose), based on the molecules without patent protection[52] for the nine OECD countries studied.

In order to estimate the total annual savings from higher generic drug utilization at lower prices, the Department of Commerce extrapolated[53] the estimated savings from the data set of 29 molecules to the total generic market in 11 OECD countries[54] using market

[51] Utilization rates are measured in terms of standard units, not kilograms. Utilization rates based on kilograms would not be valid since the different molecule weights would skew the results.
[52]HHS estimate of potential savings from greater utilization of generic drugs at U.S. prices is based on 28 of the 29 unprotected molecules in the original IMS data set. One molecule was excluded from analysis because it was sold over-the-counter in the United States during 2003, and thus is not exclusively a prescription drug.
[53] The method used to extrapolate savings from generic drugs is the same method used to extrapolate revenues from the patented data set to total patented revenues. See "Generic Drugs: Savings Extrapolation" in Appendix A.
[54]The countries examined in the extrapolation are Australia, Belgium, Canada, France, Germany, Japan, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. These are the same 11 countries used to estimate total on-patent drug revenues without price controls.

share data from IMS Health.[55] This study estimates that total savings for these 11 OECD countries would have ranged between $5.2 billion and $29.6 billion in 2003, depending on the volume measure.[56] This range of potential savings suggests that if prices of on-patent drugs were to rise to competitive market levels, then the additional cost to OECD countries could be significantly or fully offset by a more competitive generic market.

[55] U.S. Department of Commerce calculations are based on IMS Health, *IMS World Review*, Generic (2002 edition).

[56] The extrapolation was conducted by applying the estimated savings from foreign generic spending at U.S. prices and utilization rates (based on the sample of 29 molecules) to total off-patent drug sales in each country. Figures on total off-patent drug sales are available only for Canada, France, Germany and the United Kingdom. Estimates of savings for other OECD countries are based on an average of off-patent drugs sales and potential savings for the four countries that had market share data readily available. These results should be interpreted with caution because 74 to 61 percent of the total potential savings (based on kilogram and standard unit measures, respectively) are accounted for by the countries for which market share data are not available. Excluding Japan, this study estimates that total savings from higher utilization rates of generic drugs at lower prices would have ranged between $3.0 billion and $19.3 billion in 2003.

4. IMPACT OF DEREGULATING PRICES ON RESEARCH & DEVELOPMENT, INNOVATION, AND CONSUMERS

The Conference Report asks how foreign price controls affect R&D, innovation, and consumers. The prior section examined the difference between prices in the United States and regulated prices among selected OECD countries, and estimated the effect of deregulating prices in 11 of those countries on pharmaceutical revenues.

This section draws on that analysis and takes it a step further to answer the questions posed by the Conference Report with regard to effects on R&D, innovation, and, ultimately, consumers. Here, the study estimates the impact of deregulating prices in 11 OECD countries[57] on the propensity of innovative firms to finance additional R&D on new therapies, how changes in R&D spending would actually affect innovation delivered to the market, and, finally, the impact on consumers in the United States, both in terms of the effect on prices and the ultimate impact of greater competition from generic manufacturers and new and innovative therapies.

The analysis below suggests that deregulating foreign prices would increase the flow of new molecular entities (NMEs) by three to four per year. It would likely increase access by foreign consumers to new therapies, potentially improving their health. By giving U.S. consumers greater choice among drugs, price deregulation would also provide health benefits to U.S. drug buyers that according to HHS analysis would range in value from $4.9 billion to $7.5 billion annually, after its full effects on the drug development pipeline are felt.

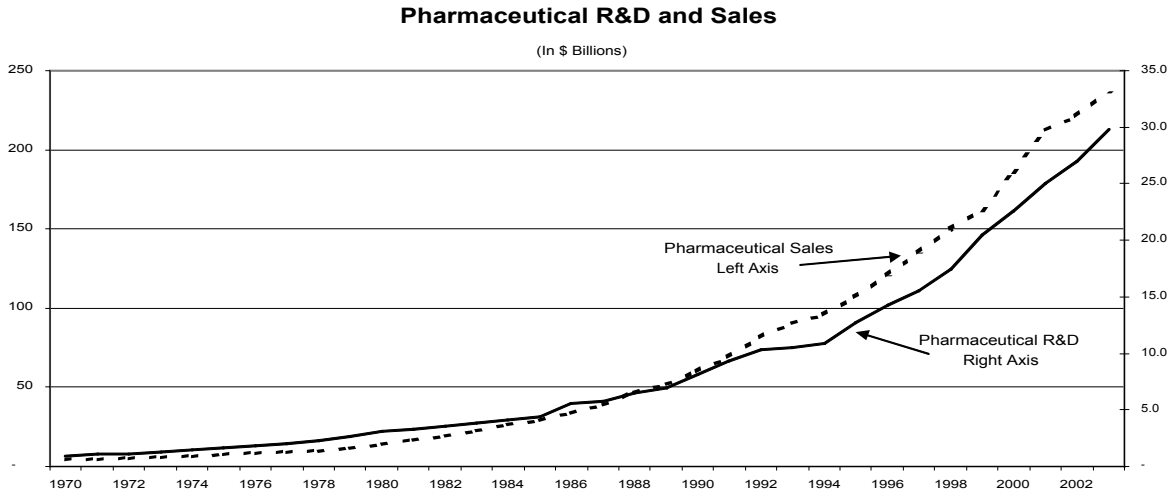
Effects of Eliminating Foreign Drug Price Controls on Research and Development

The long-term effects of higher revenues and prices on consumers are tied closely to the effects on R&D and innovation. Both economic theory and empirical evidence indicate a close correlation between revenues, cash flow, and profit margins on the one hand and R&D expenditures on the other. Figure 11 shows that R&D expenditures and revenues have tracked closely since 1970. Academic experts present data showing an even closer relationship between R&D and cash flow during the years 1962–1996.[58] In a submission sponsored by PhRMA, the Boston Consulting Group updated Scherer's data through 2003, again finding a strong relationship between cash flow and R&D expenditures. In general, the trend in R&D is less subject to annual fluctuations than is cash flow.

[57] The countries examined are Australia, Belgium, Canada, France, Germany, Japan, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. These are the same 11 countries used to estimate on-patent drug revenues without price controls at the end of Section 3.

[58] F.M. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs*, vol. 20, no.5 (September – October 2001).

Figure 11. Pharmaceutical Research and Development and Sales



Source: Pharmaceutical Research and Manufacturers of America (PhRMA).
Pharmaceutical Industry Profile 2004 (Washington, D.C. 2004)

Revenues and cash flow are related to R&D expenditures in two ways.[59] First, economic theory holds that a firm invests to the point where the marginal efficiency of capital (in effect, returns on the last dollar of investment) is equal to the cost of capital. In the case of the pharmaceutical industry, R&D is a major investment. Thus, profits and cash flow are both a measure of current and past returns and an indication of future rates of return. Other factors are, of course, important. One in particular is the productivity of R&D in generating NMEs. Over the years, there have been certain periods when the biological sciences appear to offer relatively more productive opportunities to develop NMEs.[60] In this study, it is assumed that this productivity factor is constant and thus does not enter into the calculations.

The second way revenues, profits, and cash flow are linked to investment is the cost of capital for the pharmaceutical industry. In practice it is not common for firms to borrow to finance new investments in R&D, especially for the large pharmaceutical firms. These firms typically depend upon retained earnings and depreciation to finance R&D

59 See, for example, F.M. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs*, vol. 20, no. 5 (September–October 2001), pp. 216–220; see also Henry Grabowski and John M. Vernon, "The Determinants of Pharmaceutical R&D Expenditures," *Journal of Evolutionary Economics*, vol. 10 (2001), pp. 201–215; see also John A. Vernon, "Examining the Link Between Price Regulation, Reimportation and Pharmaceutical R&D Investment," *Health Economics* (forthcoming in 2004).

60 Grabowksi, Vernon and DiMasi provide a good summary of the changing patterns of returns to pharmaceutical R&D in their March 2002 paper titled, "Returns on R&D for 1990s New Drug Introductions."

investments to develop new drugs. This result is not surprising because capital markets tend to be reluctant to make types of investments that are very risky, and the payoff can often take years. The net effect is to force innovative pharmaceutical firms to generate most of the funds for R&D from internal revenues—in short, profits.

The one exception to the basic rule that innovative pharmaceutical firms rely on internal cash flow and profits as their primary source of investment funds may be in the biotech area where venture capitalists frequently finance new risk start-ups. To date, however, the independent biotech sector appears to represent a relatively small proportion of pharmaceutical industry R&D.

The results suggested here are based on and consistent with other empirical research, which has confirmed the links between revenues, cash flow, profit margins, and R&D investments. While there are significant data problems in doing this work, all have found very high strong statistical relationships.[61]

There is one further point that bears some discussion—the enduring benefit of lasting deregulation relative to the short-term effect of temporary reforms. The benefits of price deregulation depend strongly on whether the industry expects deregulation to persist rather than succumb to reregulation. As is generally true of the response of market participants to changes in government policy, whether in the form of regulatory changes or the permanence of fiscal incentives like the R&D tax credit under the U.S. Internal Revenue Code, firms making long-term R&D investments must be able to rely on the deregulation of prices and the resulting higher cash flows as a permanent and continuing feature of the market.

In other words, to yield a permanent increase in R&D investment and the consequent flow of new and innovative medicines to the consumer market, governments need to ensure that firms can rely on the deregulation of prices for the long term. That will require a definitive break away from price regulation. If innovative pharmaceutical firms do not view the price changes as permanent, they would, all things being equal, be much less likely to respond by increasing R&D spending on a long-term basis.

Quantifying the Effects

The empirical work in explaining R&D investment decisions by industry has looked at several financial factors, separately and together. These included cash flow, profit margins, and prices as well as number of other nonfinancial factors. A number of studies that analyze effects of changes in cash flows and profits on U.S. pharmaceutical industry R&D intensity are most directly relevant to the questions posed by the Conference Report. The most recent of these are Grabowski and J.M. Vernon and J.A.Vernon.

J.M.Vernon and Grabowski examined cash flow and profit margins, as did J.A.Vernon. All reported very high correlations and statistically significant relationships. The

[61] See previously cited papers by Grabowski, J.M.Vernon, and J.A.Vernon.

parameters estimated by J.M.Vernon were employed in this report to make estimates of the R&D effects since his model most closely fit the scenarios examined in this report and his data are the most recent.[62]

To employ the methodology and parameters estimated by J.M. Vernon require a number of decisions and assumptions regarding the inputs. First, one must assume that pharmaceutical firms would treat the increased prices and revenues as permanent. If they did not view the price changes as permanent, but rather as a short-term windfall, there would be much less incentive to make long-term investments in increased R&D spending.

A second assumption is that the estimates of revenue increases made in the prior section are virtually entire additions to pretax profits. This is not unrealistic since no increase in production is assumed; hence, no additional production costs are incurred. Likewise the cost of distribution would be unchanged. The only possible increases in costs would be expanded marketing expenses, assuming that price controls were eliminated and firms had the incentive and ability to market more aggressively. Even with some increase in marketing expenses, most of the revenues would be profits or retained earnings. In addition, this study also assumed that firms would pay corporate taxes at the rate of 33 percent on the additional earnings.

Beyond these assumptions, there are a number of troublesome issues with regard to data. The basic problem is ensuring consistency between expenditures on pharmaceutical R&D and revenues. In order to calculate estimated changes in R&D from increased revenues, base case data on R&D and sales are needed. The most widely used source for R&D data is PhRMA. It provides data on R&D expenditures by all PhRMA members including non-U.S. firms within the United States. It also provides data on worldwide R&D levels but does not include R&D expenditures outside the U.S. by non-U.S. PhRMA members. Sales data are also provided on the same basis. This represents the most consistent data available.

A second source for R&D expenditures is the Centre for Medicines Research International (CMRI). While the CMRI data is more comprehensive than the PhRMA data, there are no revenue data consistent with this R&D spending. Because the PhRMA data was the most complete set of expenditure and revenue data, it was decided to use PhRMA's figure of $33 billion for R&D and expenditures for the base case.[63]

In addition, estimates of cash flows and profit margins were needed. These were estimated based on parameters developed by J.A Vernon for that purpose.

The study calculated R&D effects using both the low and high estimates of revenue effects from deregulation of pharmaceutical prices—$17.6 billion and $26.7 billion, respectively, on an annual basis. Based on the various assumptions described above, the

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[63] See "Research and Development Data Sources" in Appendix A for a more extensive discussion of R&D data.

deregulation of prices among the 10 OECD countries considered here and the resulting increase in revenues would yield an increase in R&D expenditures of between $5.3 billion and $8 billion on an annual basis (Figure 12). The estimated additional R&D expenditures would represent between 16.6 and 17.1 percent of current R&D annually. A test was made using the CMRI figure for R&D and an estimate of revenues on the same basis and it produced virtually identical results.[64]

Figure 12. Calculating Research and Development Effects of Increased Revenues

Vernon's regression equation is:

$$\Delta(RDS) = a + b_1 \cdot \left(P_2/R_2 - P_1/R_1 \right) + b_2 \cdot \left(C_2/R_2 - C_1/R_1 \right)$$

Where:

$R\&D_i$ = R&D expenditures for period i
RDS = Ratio of R&D to Revenues for period i, i = 1 to 2
P_i = Profits of pharmaceutical firms for period i, i = 1 to 2
C_i = Cash Flow of pharmaceutical firms for period i
R_i = Revenues of pharmaceutical firms for period i

To estimate the effect of changes in revenues Vernon's equation can be transformed as:

$$\Delta(R\&D) = [.073 \left(P_2/R_2 - P_1/R_1 \right) + .11 \cdot \left(C_2/R_2 - C_1/R_1 \right) \cdot R_2 + RDS_1 \cdot \Delta R$$

Data and Estimates

Scenario	Revenues	Profits	Cash Flow	R & D	Delta R&D
1 - Base	213	64	53	33	
2 - Low	231	76	65	38	5.3
2 - High	240	82	71	41	8

Sources: Base revenues and R&D—PhRMA ; other figures are U.S. Department of Commerce estimates.

[64] This occurs because the Vernon model is based on ratios of R&D to revenues and cost flow not absolute levels.

Impact of Higher Research and Development on Innovation

The Conference Report asked that the study examine the effect of deregulating prices among the OECD countries on innovation and the consumer. The higher level of R&D spending attributable to the deregulation of prices is one means of translating the effects of price deregulation into greater innovation and higher consumer welfare. This section addresses innovation, while the next addresses consumer welfare.

There is little if any econometric research on the direct benefits to consumer welfare from higher R&D spending. Rather, those benefits would flow from increased innovation, competition in the marketplace from new innovative medicines, and ultimately to the consumer in the form of lower costs, better value, or both. Here too, there is little to draw on from peer-reviewed literature regarding the rate of return (i.e., the actual number of new medicines) from increased R&D. Obviously, they are linked, but no quantification of that relationship over time is currently available, pointing to another possible topic for further research.

The impact of higher R&D spending on innovation may vary substantially with the nature of the spending. Indeed, not all R&D spending is for new molecular entities. Research by the Tufts Center for the Study of Drug Development suggests that only about two-thirds of total out-of-pocket R&D spending is associated with the development of new medicines (an average of $282 million per new drug).[65] Approximately one third is spent post-approval (an average of $140 million per approved drug) for long-term safety and efficacy studies in broader patient populations or specific patient groups, and for the development of new indications and/or new formulations.[66]

For the purposes of this analysis we assume that increased spending on R&D will be split between new active substances and other purposes in the same proportions as the current spending on R&D, i.e., approximately two-thirds, one-third. Thus elimination of foreign price controls in eight OECD countries could increase R&D spending on new drugs by between $3.5 billion ($5.3 billion x 0.67) and $5.4 billion ($8.0 billion x 0.67) annually.

A rough estimate of the effect of additional R&D on innovation could flow from what we know about the costs of developing new drugs. Various studies have been made regarding the cost of developing new drugs; the most recent and often cited is that by DiMasi, Hansen and Grabowski, who report that the total cost per new drug was $802 million in 2000.[67] The estimate reflects capitalization of the out-of-pocket costs to 10 multinational pharmaceutical firms of developing self-originated new molecular entities (NME) with a mean approval date of 1997, including losses on unsuccessful research. Assuming the same rate of growth in the inflation-adjusted capitalized costs of drug

[65] Tufts Center for the Study of Drug Development, "Therapeutic Class a Critical Determinant of Drug Development Time and Cost," *Impact Report*, vol. 6, no. 3 (May/June 2004).
[66] Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151–185.
[67] Ibid.

development between this most recent work and a comparable earlier work, the authors estimate that the capitalized cost for drugs approved in 2001 would be $1.1 billion. Applying these same assumptions suggests the cost of drugs approved in 2003 is about $1.3 billion in 2003 dollars.

This estimate may not be representative of all new drugs (NMEs and important biologics) approved by the Food and Drug Administration because it reflects the cost of developing self-originated NMEs marketed by multinational pharmaceutical companies and follow-on drugs. DiMasi's analysis excluded orphan drugs and/or drugs developed by relatively small entities. Orphan drugs, by definition, are used to treat very small patient populations and their clinical trials are generally much smaller and less expensive.

Put another way, if the real costs of R&D held constant, every $1.3 billion invested in R&D should, on average, yield one NME brought to market. This $1.3 billion figure represents the average cost, as opposed to the marginal or incremental cost of bringing one more NME to market and therefore may be an underestimate, but there are no data on the incremental cost.

Applying this figure suggests that the increased revenues from decontrolling drug prices in OECD countries would, all things being equal, yield on average 2.7 to 4.1 new drugs per year.[68] While somewhat speculative, the estimate suggests roughly what can be expected in the way of NMEs from the deregulation of prices in the OECD countries studied here.

Benefits of Deregulating Prices for Consumer Welfare

Deregulating prices will benefit residents of countries where prices are higher by bringing them faster access to more innovative medicines. It will also benefit Americans by increasing the flow of new therapies and treatments. We address each of these effects in turn.

Deregulating Prices Will Provide Greater Access to New Drugs

Deregulating drug prices abroad may significantly increase patients' access to new medicines in those countries. This conclusion follows both from systematic and anecdotal assessments of the timing of drug launches and from a comprehensive count of recently approved drugs available in different countries.

Earlier it was noted that recent research has suggested that foreign governments' price controls have delayed the launch of drugs in different markets, thereby adversely affecting patients' access to new medicines. Delays often are caused by the additional time it takes for companies and governments to agree on the prices at which a drug will be sold or reimbursed. In addition, Danzon, Wang, and Wang, using data on drug

[68] The additional NMEs may arrive with some delay because of the lags inherent in research and development.

launches between 1994 and 1998, find that countries with lower expected prices or smaller expected market size tend to experience longer delays in access to new drugs.[69]

They report that the average drug in their sample is launched in the United States only 4 months after the first launch in the world, while the launch delays in the United Kingdom Germany, and France are 7 months, 9 months, and 15 months respectively. This delay can have a direct impact on health outcomes by limiting early access to the most effective new drugs or slowing adoption of new medical advances.[70] A related issue is access to new active substances (NAS). The data indicate that significantly more NASs are available in the U.S. than in 10 other countries since 1993.[71]

While the available information suggests that consumers in countries with stringent price controls will benefit from improved access to new medicines as a result of price deregulation, consumers everywhere will likely benefit from an increased flow of new medicines.

Deregulating Prices Will Help U.S. Consumers

From a U.S. perspective the primary benefits from foreign deregulation of prices will derive from the higher levels of R&D and new drugs. There is a considerable literature on the benefits on new drugs on health as well as on reducing other medical costs such as hospitalization.[72] In addition, there is some recent research that suggests that there are benefits as well from "follow-on" drugs in terms of increasing competition and reducing prices. Clearly, the development and marketing of those new drugs will be of benefit not just to American people but also to consumers worldwide.

In short, the analysis above strongly suggests that consumer benefits will flow from stronger competition from the introduction of "follow-on" drugs and from the higher flow of new innovative medicines to the market. The magnitude of these benefits clearly varies according to what the new drugs might be, whether they are the first antiretrovirals used to treat AIDS, SSRIs used to treat depression, or various statins, a class of drugs used to lower cholesterol levels.

Conventional approaches to valuing new products use economic measures of the benefits to consumers and producers. Berndt et al. (2004) show that, under plausible assumptions, total drug sales provide a lower bound estimate of total social surplus, i.e., the gains to

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[69] Patricia M. Danzon, Richard Y. Wang and Liang Wang, "The Impact of Price Regulation on the Launch Delay of New Drugs—Evidence from Twenty-Five Major Markets in the 1990's," National Bureau of Economic Research Working Paper, no. 9874 (2003). To locate this paper, use the following link: *http://www.nber.org/papers/w9874*.

[70] See "Cancer Care: A Case Study" in Appendix A.

[71] See "New Active Substances" in Appendix A.

[72] For more information, see Frank Lichtenberg, "Are the Benefits of Newer Drugs Worth Their Costs? Evidence from the 1996 MEPS," *Health Affairs*, vol. 20, no. 5 (September/October 2001); see also Frank Lichtenberg, "Benefits and Cost of New Drugs: An Update," National Bureau of Economic Research Working Paper, no. 8996 (2002).

both producers and consumers.[73] In addition, they show that one-third of this amount provides an approximate measure of the surplus to drug buyers associated with a new drug.

Implementing the insights of Berndt et al. suggests that about $1.8 billion is a reasonable estimate of the value to drug buyers of a representative additional NME. This figure is a third of the present discounted value of sales of an innovative new drug—$5.4 billion—according to a published FDA analysis of IMS Health data.[74] If deregulating foreign prices increases the flow of NMEs by three to four per year, then the benefits to U.S. drug buyers, including households, government agencies, and private third-party payers would amount to between $4.9 billion and $7.5 billion per year.

These estimated benefits, of course, would occur in the future, after prices had adjusted, and not as an immediate response to foreign deregulation of prices. The full effect of price deregulation would be observed only after drugs in the development pipeline were in the market, or abandoned.

Short-Term Effects in the United States

Given the current structure of the U.S. market for both innovative medicines and for generic pharmaceuticals, deregulating prices overseas is unlikely to reduce prices in the United States in the short term. The rationale for this conclusion is relatively straightforward and lies in the basic characteristics of the industry. Prices, expected revenues, and profits are critical factors in making investment decisions to launch new R&D efforts as was discussed above; but, once a new drug is launched on the market, the nature of pharmaceutical markets and economic theory suggest that prices in one market will behave relatively independent of prices in other markets, absent the more fundamental changes in the competitive forces operating in those markets.

Patents give manufacturers very significant pricing power. The market exclusivity conferred by patent protection enables pharmaceutical companies to recoup their extraordinary R&D costs by charging a price that exceeds the marginal cost of production. Normally trade in pharmaceuticals would tend to lead to price arbitrage, but patent restrictions limit trade to authorized channels. As a result, pharmaceutical manufacturers can segment and price discriminate among markets so as to charge profit-maximizing prices in each market.

The written comments and oral testimony submitted to the Commerce Department in response to the agency's request for comments on the questions raised in the Conference Report also suggested that a positive impact on U.S. prices would flow from the longer-

[73] E. Berndt, A. Gottschalk, T. Philipson, and M. Strobeck, " The Prescription Drug User Fee Acts: Towards an Economic Evaluation," MIT mimeo (June 2004).
[74] DHHS, FDA, "The Pediatric Exclusivity Provision: Status Report to Congress," (Jan. 2001), pp. 48–49. The cited data were reformatted to better reflect annual sales since initial marketing date and converted from 1999 to current (2003) dollars using the GDP deflator before estimating the present value using a 5 percent discount rate.

term effects of increased competition, both from follow-on drugs as well as NMEs, rather than an immediate impact on U.S. prices flowing from the deregulation of prices alone in the OECD countries studied here.

Deregulation of foreign drug prices would not be expected to lead to an immediate reduction in prices in the U.S. market. Over the longer term, the benefits for consumers in the United States from deregulation of foreign drug prices and increased R&D would be expected to rise as a result of savings from hospitalization, fewer missed work days, and other medical cost savings. Obviously, aggressive reforms among the OECD countries would accelerate this effect.

Location of Research and Development

The Conference Report requested information as to effects on R&D in the United States and in OECD countries. There are many factors determining where firms conduct research. These can include, in addition to where they can generate the highest return on investment, the availability of skilled staff, relative costs, ability to run clinical tests, and other factors, including the general fiscal environment (e.g., the availability of a permanent R&D tax credit).

That said, there is some evidence to suggest that lower prices and rates of return can influence the location of R&D activities. According to the European Federation of Pharmaceutical Industries and Associations, R&D in the United States quadrupled between 1990 and 2003, while R&D in Europe grew by only 2.6 times.[75] One of the factors that may be contributing to this relative decline is the regulatory and competitive environment for pharmaceuticals in Europe.[76]

While correlation does not necessarily imply causation, the phenomenon does suggest that the United States has benefited from market prices in terms of the level of investment already in place in the United States, which benefits both those employed in those operations and U.S. consumers who, all things being equal, would benefit first from the innovations they produce. This also suggests that a more competitive environment for pharmaceutical prices in Europe and elsewhere would encourage increased R&D in those regions, especially by locally based firms.

[75] European Federation of Pharmaceutical Industries and Associations, "The Pharmaceutical Industry in Facts and Figures, 2004 Edition," (2004).
[76] F. Pammolli et al., "Global Competitiveness in Pharmaceuticals: A European Perspective," prepared for the DG Enterprise of the European Commission (November 2000).

Appendix A

Technical Methodology

IMS Health Data Set

Figure A-1 provides a list of the 54 molecules included in this study. These 54 molecules are the top-selling U.S. molecules based on 2002 sales. Figure A-1 includes information on the U.S. patent status (on or off) in 2003. Patent status is not based on the year of patent expiration, but the year when the first generic competitor enters the market. The molecules that are designated as "on" patent in the United States are included in the 2003 patented drug data set.

Figure A-1. List of Molecules from the IMS Data Set

Molecule Name	U.S. Patent Status in 2003 (On or Off)
ALENDRONIC ACID	ON
AMLODIPINE WBENAZEPRIL	ON
ATORVASTATIN	ON
AZITHROMYCIN	ON
BUPROPION	OFF
CELECOXIB	ON
CETIRIZINE	OFF
CIPROFLOXACIN	OFF
CITALOPRAM	ON
CLOPIDOGREL	ON
DOCETAXEL	ON
DONEPEZIL	ON
ENOXAPARIN SODIUM	ON
EPOETIN ALFA	ON
ESOMEPRAZOLE	ON
ESTROGENIC SUBSTANCES,CONJUGATED	OFF
ETANERCEPT	ON
FENTANYL	OFF
FEXOFENADINE	ON
FILGRASTIM	ON
FLUCONAZOLE	OFF
FLUTICASONE WSALMETEROL	ON
GABAPENTIN	ON
INFLIXIMAB	ON
INTERFERON BETA 1A	ON
LANSOPRAZOLE	ON
LEVOFLOXACIN	ON
LEVOTHYROXINE SODIUM	OFF
LORATADINE	OFF
METOPROLOL	OFF

Molecule Name	U.S. Patent Status in 2003 (On or Off)
MONTELUKAST	ON
OLANZAPINE	ON
OMEPRAZOLE	OFF
ONDANSETRON	ON
OXYCODONE	OFF
PANTOPRAZOLE	ON
PAROXETINE	OFF
PIOGLITAZONE	ON
PRAVASTATIN	ON
QUETIAPINE	ON
RABEPRAZOLE	ON
RIBAVIRIN	ON
RISPERIDONE	ON
RITUXIMAB	ON
ROFECOXIB	ON
ROSIGLITAZONE	ON
SERTRALINE	ON
SILDENAFIL	ON
SIMVASTATIN	ON
SUMATRIPTAN	ON
TOPIRAMATE	ON
VALPROATE SEMISODIUM	OFF
VENLAFAXINE	ON
ZOLPIDEM	ON

Source: IMS Health, IMS MIDAS (TM), Q4/2002 and Q4/2003. Patent information for 2003 is based on the U.S. Department of Commerce's analysis of IMS Health data.

IMS Volume Measures

IMS provides three different measures of volume: counting units, standard units, or kilograms of active ingredient.[1]

Counting units are the number of tablets of a product sold.[2] They are determined by multiplying the number of packages sold by the number of pills in the package. By definition, counting units are only appropriate to use when the packs or products being compared are in similar form (i.e., tablets must be compared to tablets, capsules to capsules, etc.). Since this study will not be performed at the pack size, counting units are not used to estimate prices.

Standard units are the number of standard "dose" units sold. The measure is determined by taking the number of counting units sold divided by the standard unit factor.[3] The use of standard

[1] Kilograms refer only to drugs in solid form. This study treats international units (IU) as a liquid equivalent of a kilogram.
[2] Depending on the form of the product, counting units can be milliliters of liquid or grams of ointment.
[3] A standard unit factor is the smallest common dose of a product as defined by IMS Health.

units is widespread in the literature. One potential drawback is that dosing practices can vary across countries. The smallest common dose in one country is not necessarily the same as that of another. For example, Japan tends to have much weaker doses.[4] Price per standard unit allows for aggregation over all dosage forms, strengths, and package sizes.

Using the number of kilograms of active ingredient as a measure of volume avoids the dosage problem found with standard units and the form problem of counting units. As with standard units, aggregation can be performed over dose forms, strengths, and package sizes. This measure, however, can be sensitive to the sample of products included because potency in molecules varies.[5] This measure of volume also receives considerable attention in the literature.

Price Indices

To compare prices across countries, a price index must be calculated. There are three generally accepted methods for such a process: Laspeyres, Paasche, and Fisher indices. In this study, a Laspeyres index uses U.S. quantities as weights, and a Paasche index uses each foreign country's quantities as weights. The Fisher index is the geometric mean of Laspeyres and Paasche. For completeness, an index will be constructed using each method.

Each index is calculated in the following manner. Let $\sum$ be the sum over all molecules, M = 1, …, 54. P_M is the price for molecule *M*. *C* represents the foreign country and *USA* represents the United States. *Q* is the quantity as measured in standard units or in kilograms.

Laspeyres: Country C's index number = $$\frac{\Sigma (Q_{M,USA})(P_{M,C})}{\Sigma (Q_{M,USA})(P_{M,USA})}$$

Paasche: Country C's index number = $$\frac{\Sigma (Q_{M,C})(P_{M,C})}{\Sigma (Q_{M,C})(P_{M,USA})}$$

Fisher: Geometric mean of Laspeyres and Paasche indices

Figure A-2 displays this study's estimates of Laspeyres, Paasche, and Fisher price indices for the 2003 patented set of drugs using standard units and kilograms as quantity weights.

[4] Patricia M. Danzon and Jung D. Kim, "International Price Comparisons for Pharmaceuticals," *Pharmacoeconomics,* vol. 14 (1998), p. 124.
[5] Ibid., p. 121.

Figure A-2. Price Indices Relative to the United States in 2003

Patented Set of Drugs	Australia	Canada	France	Germany	Greece	Japan	Poland	Switzerland	U.K.	U.S.
Laspeyres su	0.65	0.57	0.55	0.55	0.53	0.54	0.52	0.63	0.53	1.00
Laspeyres kg	0.44	0.59	0.63	0.67	0.54	0.96	0.68	0.71	0.60	1.00
Paasche su	0.38	0.51	0.43	0.49	0.43	0.20	0.29	0.56	0.43	1.00
Paasche kg	0.36	0.53	0.51	0.53	0.42	0.70	0.24	0.35	0.54	1.00
Fisher su	0.49	0.54	0.49	0.52	0.47	0.33	0.39	0.59	0.47	1.00
Fisher kg	0.40	0.56	0.57	0.59	0.48	0.82	0.40	0.50	0.57	1.00

Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.
Notes: SU indicates standard units and KG indicates kilograms of active ingredient. All prices are indexed to U.S. prices (1.0).

Price Adjustment Method

The method used to compute a price adjustment multiplier for each country is presented below.

Step 1. Compute the ratio of Country X's GDP per capita in current dollars to U.S. GDP per capita in current dollars (Figure A-4).

Step 2. Then, compute a Fisher price index for Country X.

Step 3. Divide the GDP per capita ratio by the Fisher price index to derive the price adjustment multiplier for Country X.

For example, in 2003, the relative GDP per capita (local GDP per capita relative to U.S. GDP per capita) for Canada is 0.73, and the Fisher price index using standard units for Canada is 0.54 (Figure A-3). Dividing 0.73 by 0.54 yields 1.36, which is Canada's price adjustment multiplier measured in standard units (Figure A-4).

Figure A-3. GDP Per Capita Ratios and Price Indices, 2003

	Australia	Canada	France	Germany	Japan	Switzerland	U.K.	U.S.
GDP per capita ratio to U.S.	0.66	0.73	0.76	0.78	0.88	1.14	0.79	1.00
Fisher Price index-SU	0.49	0.54	0.49	0.52	0.33	0.59	0.47	1.00
Fisher Price index-KG	0.40	0.56	0.57	0.59	0.82	0.50	0.57	1.00

Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003. GDP per capita data in current dollars is from the International Monetary Fund's International Financial Statistics Manual.

Figure A-4. Adjustment Multipliers, 2003

	Australia	Canada	France	Germany	Japan	Switzerland	U.K.	U.S.
Adjustment multiplier-SU	1.34	1.36	1.56	1.49	2.66	1.93	1.68	1.00
Adjustment multiplier-KG	1.66	1.31	1.33	1.30	1.08	2.27	1.39	1.00

Source: U.S. Department of Commerce calculations based on data from IMS Health, IMS MIDAS (TM), Q4/2003.

The price adjustment multiplier is multiplied by all molecule prices in a particular country to estimate new molecule prices in the absence of price controls. In order to control for drugs with prices that already correspond to U.S. drug prices, molecule prices are compared on an individual basis. Foreign molecules with prices in line with U.S. drug prices are excluded from the application of the adjustment multiplier. The box below outlines the steps used to identify these molecules.

Step 1. Compute a molecule price ratio by dividing Country X's molecule price by the equivalent U.S. molecule price.

Step 2. Compare the molecule price ratio to GDP per capita ratio:

a. If the molecule price ratio is greater than the GDP per capita ratio, then hold that the molecule price in Country X is excluded from all adjustments. OR

b. If the molecule price ratio is less than the GDP per capita ratio, then adjust the foreign molecule price with Country X's adjustment multiplier.

Step 3. Adjust all molecule level prices in Country X that meet criterion 2b.

For example, the price of a standard unit of Molecule X in Australia is $5.20, and the price of a standard unit of Molecule X in the United States is $6.34. Molecule X's relative price (price in Australia divided by the price in the United States) is 0.82. Because the molecule price ratio is higher than the income ratio (0.66) for Australia (Figure A-3), Molecule X's price will not be adjusted. On the other hand, if Molecule X's relative price is less than the relative GDP per capita in Australia, then Molecule X's price would be increased by Australia's price adjustment multiplier (Figure A-4).

After applying the price adjustment multiplier, the new molecule price ratios in the absence of price controls are reviewed. If the new molecule price ratio exceeds the GDP ratio, then the molecule price will be capped to the income ratio. This study takes a conservative approach in analyzing molecule price increases by assuming that no molecule price in the absence of price controls should exceed a country's relative income ratio. The box below describes the capping process employed in this study.

Step 1. Compute a new molecule price ratio by dividing Country X's newly adjusted molecule price by the equivalent U.S. molecule price.

Step 2. Compare the new molecule price ratio for Country X to Country X's GDP per capita ratio:

a. If the new molecule price ratio is less than the GDP per capita ratio, then do not cap. OR

b. If the new molecule price ratio is greater than the GDP per capita ratio, then the new molecule price needs to be adjusted downward.

Step 3. Those molecules that meet criterion 2b are capped so that the new molecule price is equal to the income ratio; that is, the new molecule price ratio equals Country X's GDP per capita (income) ratio.

For example, the price of a standard unit of Molecule Y in France is $0.30, and the price of Molecule Y in the United States is $0.60. Molecule Y's price ratio (Y's price in France divided by Y's price in the United States) is 0.50, which is below the 0.76 income ratio for France (Figure A-3). Since the price ratio is less than the income ratio, the price of Molecule Y is adjusted upward by the price adjustment multiplier in France, which is 1.56 (Figure A-4). After applying the adjustment multiplier, Molecule Y's new price in the absence of price controls is $0.50, and Molecule Y's new price ratio (Y's adjusted price in France divided by Y's price in the United States) increases to $0.84. This new price ratio exceeds France's income ratio of 0.76. Since this study assumes the new molecule price should not exceed the income ratio, Molecule Y's price will be adjusted downward to $0.46. This adjustment yields a new price ratio for Molecule Y that equals France's income ratio of 0.76 and ensures that Molecule Y's price in the absence of price controls does not exceed France's income ratio.

Revenue Extrapolation

In order to extrapolate revenue changes from the patented drug sample to total revenues from patented drugs in 11 OECD countries (Canada, France, Germany, United Kingdom, Australia, Japan, Italy, Spain, Sweden, Belgium, and the Netherlands), this study estimated the proportion of total revenues represented by sales of on-patent drugs. Source data for total on- and off-patent drug sales are from IMS Health, *IMS World Review (TM),* Country Profiles, 2004. Source data for on and off patent drug market shares are from IMS Health, *IMS World Review (TM),* Generic, 2002 edition. This study had to use two data sources to estimate total drug sales and market shares because a single source that was reliable and comprehensive could not be found. Estimates were made for Canada, France, Germany, and the United Kingdom using market share data for the year 2001 (Figure A-5).

Figure A-5. 2001 Pharmaceutical Market Shares by Country
% U.S. dollar revenues

Country	Off-Patent	On-Patent
Canada	54.9%	41.1%
France	51.5%	41.5%
Germany	60.9%	31.8%
United Kingdom	53.1%	42.2%
Other OECD	55.1%	39.1%

Source: U.S. Department of Commerce calculations based on data from *IMS Health, IMS World Review (TM),* Generic, 2002 edition. The sum of the on and off patent market shares do not equal 100 percent because some of the IMS Health data could not be categorized as on or off patent. IMS Health market share data from the *IMS World Review (TM), Generic* report may contain sales for over-the counter (OTC) drugs whereas the patented sample data does not. This could lead to an overstatement of the actual level of total on-patent drug revenues in the absence of price controls but the size of this overstatement is not measurable due to data limitations.

In the absence of data for the remaining seven OECD countries, this study uses an average of on-patent market shares from Canada, France, Germany, and the United Kingdom (Figure A-5). These four European OECD countries can arguably be used as a proxy for the other five European countries and Australia. The problem lies in extending estimates from these European countries to Japan. Japan, as identified in the main body of this paper, is the second largest pharmaceutical market behind the United States measured in U.S. dollars sales and has been identified as having unique prescribing practices, setting it apart from most other markets. Based on the uniqueness of the Japanese market, this study presents an estimate of total revenues from on-patent drug sales in the absence of price controls with and without Japan.

Multiplying the 2001 on-patent market share percentages from Figure A-5 and the total on- and off-patent revenues in 2003 results in an estimate of current on-patent drug revenues (Figure A-6).

Figure A-6. Total and On-Patent Drug Revenues for Selected OECD Countries
Billions of U.S. dollars

Country	Total On- and Off-Patent Drug Revenues	Of Which: Current On-Patent Drug Revenues
Canada	$10.0	$4.1
France	$24.2	$10.0
Germany	$26.4	$8.4
United Kingdom	$16.4	$6.9
Other OECD including Japan	$102.9	$40.3
excluding Japan	$44.0	$17.2

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition.

Current estimates of on-patent drug revenues (from Figure A-6) are adjusted by the percent increases in revenues estimated for the patented drug sample. This results in an estimate of current on-patent revenues without price controls in 2003. Estimates of current on-patent drug

revenues without price controls for select OECD countries (including Japan) would range between $87.3 billion and $96.4 billion in 2003 (Figure A-7). For all countries, revenue gains measured in dollars per kilogram are more conservative than those measured in dollars per standard unit.

Figure A-7. Estimates of Total On-Patent Drug Revenues for Selected OECD Countries in 2003, including Japan

Billions of U.S. dollars

Country	Estimates of Current On-Patent Drug Revenues	Estimates of Current On-Patent Drug Revenues Without Price Controls		Change in U.S. Dollars		Percent Change	
		SU	KG	SU	KG	SU	KG
Canada	$4.1	$5.2	$5.0	$1.1	$0.9	26%	22%
France	$10.0	$14.0	$12.5	$3.9	$2.5	39%	25%
Germany	$8.4	$11.4	$10.2	$3.0	$1.8	36%	22%
United Kingdom	$6.9	$10.4	$9.1	$3.4	$2.2	50%	32%
Other OECD including Japan	$40.3	$55.5	$50.4	$15.2	$10.1	38%	25%
Total	**$69.7**	**$96.4**	**$87.3**	**$26.7**	**$17.6**	**38%**	**25%**

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition.
Notes: SU indicates standard units and KG indicates kilograms of active ingredient.

Estimates of current on-patent drug revenues without price controls for select OECD countries (excluding Japan) would range between $58.4 billion and $64.6 billion in 2003 (Figure A-8).

Figure A-8. Estimates of Total On-Patent Drug Revenues for Selected OECD Countries in 2003, excluding Japan

Billions of U.S. dollars

Country	Estimates of Current On-Patent Drug Revenues	Estimates of Current On-Patent Drug Revenues Without Price Controls		Change in U.S. Dollars		Percent Change	
		SU	KG	SU	KG	SU	KG
Canada	$4.1	$5.2	$5.0	$1.1	$0.9	26%	22%
France	$10.0	$14.0	$12.5	$3.9	$2.5	39%	25%
Germany	$8.4	$11.4	$10.2	$3.0	$1.8	36%	22%
United Kingdom	$6.9	$10.4	$9.1	$3.4	$2.2	50%	32%
Other OECD excluding Japan	$17.2	$23.7	$21.6	$6.5	$4.3	38%	25%
Total	**$46.7**	**$64.6**	**$58.4**	**$17.9**	**$11.7**	**38%**	**25%**

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition.
Notes: SU indicates standard units and KG indicates kilograms of active ingredient.

Generic Drugs: Savings Extrapolation

The potential savings estimates from greater utilization of generic drugs at lower prices were extrapolated from the data set of 29 molecules to the total generic market in 11 OECD countries by estimating the proportion of total revenues represented by off-patent drug sales in 2003. Source data for total on-and off patent drug sales are from IMS Health, *IMS World Review (TM),* Country Profiles, 2004. Source data for on and off patent drug market shares are from IMS Health, *IMS World Review (TM),* Generic, 2002 edition. This study had to use two data sources to estimate total drug sales and market shares because a single source that was reliable and comprehensive could not be found. Estimates were made for Canada, France, Germany, and the United Kingdom using market share data for the year 2001 (Figure A-5). In the absence of data for the remaining seven OECD countries, this study uses an average of off-patent market shares from Canada, France, Germany, and the United Kingdom. The data problems associated with the Japanese pharmaceutical market continue to be a problem when analyzing off-patent drugs. Thus, this study estimates total potential savings from greater generic drug utilization at lower prices for a select group of OECD countries with and without Japan.

Multiplying the 2001 off-patent market share percentages from Figure A-5 and total on- and off-patent revenues in 2003 results in an estimate of current off-patent drug revenues (Figure A-9).

Figure A-9. Total and Off-Patent Drug Revenues for Selected OECD Countries
Billions of U.S. dollars

Country	Total On- and Off-Patent Drug Revenues	Of Which: Current Off-Patent Drug Revenues
Canada	$10.0	$5.5
France	$24.2	$12.4
Germany	$26.4	$16.0
United Kingdom	$16.4	$8.7
Other OECD including. Japan	$102.9	$56.7
excluding Japan	$44.0	$24.3

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition. IMS Health market share data from the *IMS World Review (TM), Generic* report may contain sales for over-the counter (OTC) drugs whereas the generic sample data does not.

Current estimates of off-patent drug revenues (from Figure A-9) are adjusted by the percent change in revenues estimated by the FDA for the sample of 29 molecules. This adjustment results in a savings estimate between $5.1 billion and $29.6 billion dollars, depending on the volume measure (Figure A-10). For all countries, including Japan, estimated savings using standard units tend to be lower than those estimated with kilograms. This is largely due to the fact that generic drug prices per standard unit tend to be closer to U.S. generic drug prices, which decreases the amount of potential savings from moving to lower U.S. prices.

Figure A-10. Estimates of Total Savings from Generic Drugs in 2003, including Japan
Billions of U.S. dollars

Country	Estimates of Current Off-Patent Drug Revenues	Estimated savings from greater utilization of generic drugs at lower prices (Sample Estimates)		Total Potential Savings 2003	
		SU	KG	SU	KG
Canada	$5.5	20.5%	37.8%	**$1.1**	**$2.1**
France	$12.4	14.3%	33.6%	**$1.8**	**$4.2**
Germany	$16.0	-11.9%	7.7%	**-$1.9**	**$1.2**
United Kingdom	$8.7	4.1%	47.5%	**$0.4**	**$4.1**
Other OECD including Japan	$56.7	6.8%	31.6%	**$3.8**	**$17.9**
Total	**$99.4**			**$5.2**	**$29.6**

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition.
Notes: SU indicates standard units and KG indicates kilograms of active ingredient.

Excluding Japan, estimated total savings for the 10 remaining countries ranges between $3.0 billion and $19.3 billion, depending on the volume measure (Figure A-11).

Figure A-11. Estimates of Total Savings from Generic Drugs in 2003, excluding Japan
Billions of U.S. dollars

Country	Estimates of Current Off-Patent Drug Revenues	Estimated savings from greater utilization of generic drugs at lower prices (Sample Estimates)		Total Potential Savings 2003	
		SU	KG	SU	KG
Canada	$5.5	20.5%	37.8%	**$1.1**	**$2.1**
France	$12.4	14.3%	33.6%	**$1.8**	**$4.2**
Germany	$16.0	-11.9%	7.7%	**-$1.9**	**$1.2**
United Kingdom	$8.7	4.1%	47.5%	**$0.4**	**$4.1**
Other OECD excluding Japan	$24.3	6.8%	31.6%	**$1.6**	**$7.7**
Total	**$66.9**			**$3.0**	**$19.3**

Source: U.S. Department of Commerce calculations based on data from IMS Health, *IMS World Review (TM)*, Country Profiles, 2004 and IMS Health, *IMS World Review (TM),* Generic, 2002 edition.
Notes: SU indicates standard units and KG indicates kilograms of active ingredient.

Research and Development (R&D) Data Sources

Pharmaceutical Research and Manufacturers Association (PhRMA)

PhRMA publishes a regular series on R&D expenditures by PhRMA members. There are two data sets: one covering R&D expenditures in the United States and the other covering R&D expenditures abroad. The association writes, "R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies."[6] R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies is excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member countries. PhRMA figures do not include non-PhRMA member pharmaceutical companies and any non-PhRMA member biotechnology companies.

Center for Medicines Research (CMR) International Worldwide

CMR International Worldwide produces data on global pharmaceutical spending on research and development. This group reports that global R&D reached $50 billion in 2003. This figure is based on R&D expenditures of 'traditional' global pharmaceutical companies, and as such their contribution to biotechnology expenditures will be captured in the estimate. However, expenditures by specialized biotechnology companies are not included in the data.[7] These figures differ from PhRMA figures, most importantly because they include R&D performed outside the United States by non-U.S. pharmaceutical companies.

Cancer Care: A Case Study

The case of cancer care illustrates how delays in access to new medicines can hurt patients. According to a study published in the European Journal of Cancer in 2001, European cancer patients waited longer than their American counterparts for cancer drugs to be reviewed and approved by the European Medical Evaluation Agency (EMEA). "This means that European cancer patients are deprived of potentially effective treatments which are available for use in other parts of the world," wrote Kathy Redmond, author of the study. This, she says, is exemplified by the approval times of the anti-cancer drug Gleevec: 72 days in the USA compared with eight months in Europe.[8]

An analysis of 15 cancer drugs approved in both Europe and the United States between 1995 and 2001 found that the European approvals averaged 468 days, versus 273 days in the United

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[6] Pharmaceutical Research and Manufacturers of America (PhRMA), The Pharmaceutical Industry Profile 2004 (Washington, D.C.: PhRMA, 2004).
[7] See CMR International, "R&D Pharmaceutical Innovation and Output Survey 2003" (2003); see also "Trends in Worldwide R&D Expenditure: Global R&D Expenditure: Global Pharmaceutical and Biopharmaceutical R&D Expenditure, 1991–2001," *PAREXEL's Pharmaceutical R&D Statistical Sourcebook* (2002/2003), p. 18.
[8] Vicki Brower, EMBO Reports 3, 1, 14–16 (2002), *www.nature.com/cgi-taf/DynaPage.taf?file=/embor/journal/v3/n1/full/embor239.html*.

States.[9] The drug Herceptin, used for the treatment of certain forms of breast cancer, was under review by the EMEA for about 550 days; in the United States it was approved in 120 days. The drug bexarotene, used for the treatment of certain forms of skin cancer, was under review in Europe for more than 450 days; in the United States it was approved in less than 200 days. The drug Campath, for the treatment of B-cell lymphoma, was under review in Europe for more than 450 days; in the United States it was approved in less than 175 days. The time from EMEA's approval of docetaxel (Taxotere), an important member of the taxane class (a common and effective breast cancer drug), to its eventual approval by U.K. authorities for reimbursement was four and a half years.

These delays may affect patient health. In Germany, 41 percent of German physicians are treating early-stage breast cancer with taxanes, compared with 60 percent adoption in the United States in similar patients. German breast cancer mortality decreased by 9 percent from 1990 to 1998, while in the United States mortality dropped more than twice as much, 19 percent, over the same period.[10]

A 2002 study by the U.S. consulting firm Lewin Group, Inc., examining prescribing patterns between 1996 and 1998, found that while 99.9 percent of patients with advanced breast cancer in the United States received treatment with a taxane, the comparable figures were 48 percent for the Netherlands and only 25 percent for Britain. A study done in 2003 for the U.K. National Health Service found that more than 1,000 eligible breast cancer patients across the United Kingdom were still not receiving Herceptin, even after its approval.

The impact of these delays was cited in some explanations for the disappointing results from EUROCARE-3,[11] a study that reported on the survival of cancer patients across Europe. EUROCARE-3 found that survival rates for U.K. cancer patients remained below the European average. The study examined five-year survival after diagnosis during 1990–1994 in 22 European countries, covering 42 types of cancers, and followed patients for nine years.[12]

New Active Substances

An assessment of the number of recently approved drugs available in different countries offers a complementary insight into this issue. Of all the new active substances (NASs) launched in the world since 1993, significantly more are available in the United States than in 10 other countries. This conclusion follows from an analysis of NASs launched between January 1, 1994 and December 31, 2003, using data from IMS Health's Chemindex (TM) 2003.

[9] K. Redmond, "A Comparison of Cancer Drug Approval Between Europe and the United States and Between Cancer Drugs and HIV Drugs in Europe," poster presented at ECCO 11: The European Cancer Conference (October 23, 2001), Lisbon, Portugal.
[10] World Health Organization Cancer Mortality Databank.
[11] Ludger Wess, BioCentury (November 3, 2003), p. A15.
[12] P. Roazzi, et al., "Electronic Availability of EUROCARE-3 Data," *Annals of Oncology*, supplement 5 (2003), pp. 150–155.

While U.S. residents had access to 63 percent of all NASs launched anywhere in the world during this period, with one exception (the United Kingdom), residents of all of the other countries in this sample had access to less than 55 percent. Figure A-13 presents the number of NASs launched in the different countries and information on the overlap in drug availability. The rightmost column shows the ratio of the number of NASs launched in each country to the 360 NASs launched worldwide. An independent source of information states that 360 NASs were launched in at least one country during the period in question.[13] Thus the United States has 63 percent of all NASs launched worldwide since 1994. The United Kingdom has 58 percent, Australia has 46 percent, and Canada has 48 percent.

The estimates in Figure A-12 represent launched NASs, i.e., those that were marketed, even if they were subsequently withdrawn for safety reasons. If a NAS was withdrawn for non-safety reasons, it might not be included in Figure A-12 because products withdrawn more than five years ago are not included in IMS Chemindex (TM) 2003. Taking into account non-safety withdrawals might slightly change the estimates of the number of NASs available in different countries, but it would probably not appreciably affect the general results or the conclusion that Americans have access to significantly more NASs than residents of other countries.

Figure A-12. Launches of New Active Substances (NASs) and Drug Availability

Countries	NASs Launched Since 1994	NASs Available in United States and Comparison Country	NASs Available in United States but NOT in Comparison Country	NASs Available in Comparison Country but NOT in United States	Drug Availability Index*
Worldwide	360	Not applicable			1.00
United States	227	Not applicable			.63
Australia	167	152	75	15	.46
Canada	174	163	64	11	.48
France	190	168	59	22	.53
Germany	203	175	52	28	.56
Greece	162	139	88	23	.45
Italy	185	157	70	28	.51
Japan	151	77	150	74	.42
Poland	110	97	130	13	.31
Switzerland	189	164	63	25	.53
United Kingdom	207	177	50	30	.58

Source: IMS Health, IMS Chemindex (TM) 2003.
*The Drug Availability Index is computed by dividing the number of NASs launched in each country by 360, which is the number of NASs launched worldwide.

[13] "New Drug Sources," *Scrip Magazine,* PJB Publications Ltd. (January 1994–1999 and February 2000–2003).

Appendix B

Drug Pricing Study — *Federal Register* Notice Responses

The Department of Commerce solicited information pursuant to the study through *Federal Register* notices issued on June 1 and July 18, 2004. A summary of each response to this request for comments follows. The *Federal Register* notices begin after page B-6. A complete record of *Federal Register* submissions and testimony presented at the public hearing is available at *www.ita.doc.gov/td/chemicals/submissions.html*.

U.K. Department of Health

The response of the U.K. Department of Health (DOH) describes the types of regulations used to control drug prices and manufacturing profits. In the United Kingdom, prices of branded medicines and manufacturer profits on sales to the National Health Service (NHS) are regulated by the Pharmaceutical Price Regulation Scheme (PPRS). According to the DOH, the PPRS gives companies the freedom to price all new chemical entities but requires that the companies make an agreement with the DOH for any price increases. Price increases are only granted if a company's application meets the criteria outlined in the agreement. Companies with NHS sales of more than £25 million per year are required to submit annual data on sales, costs, assets, and profitability. These companies must repay any excess profits in cases where profits exceed the agreed return-on-capital threshold.

The DOH acknowledges that the operation of the pharmaceutical market has been affected by PPRS. However, a study published in 2002 was unable to find consistent volume responses to price changes. Over half of price changes triggered no response from competitors. In the majority of cases, the launch of a new product provoked no price response from competitor products. The U.K. government believes that the abolition of price controls would lead to higher prices in the United Kingdom, but that neither the extent of price increases in the United Kingdom nor the impact on the U.S. market is predictable. Furthermore, the DOH argues that the pricing policy on pharmaceuticals in the United Kingdom is not a non-tariff barrier, as pricing mechanisms do not distinguish between U.K.-based and non-U.K.-based companies.

The Amyotrophic Lateral Sclerosis Association

The Amyotrophic Lateral Sclerosis Association's (ALSA) response includes studies that demonstrate the negative impact foreign pharmaceutical price controls have on R&D investment in those countries. The studies also showed how price controls negatively impact patient access to, and use of, new medicines. Because research, drug development, and innovation are key for people with amyotrophic lateral sclerosis, ALSA "wants innovative companies to have the desire

to apply their skills to ALS drug development and their business considerations to be protected so ALS drugs can be worthwhile to bring to the market."

Pharmaceutical Research and Manufacturers of America (PhRMA)

PhRMA submitted five documents in their response to the Department's Federal Register notice: "Foreign Government Pharmaceutical and Price Controls"; "Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries"; a presentation titled "PhRMA Project on Government Interventions in Pharmaceutical Markets in OECD Countries: Overview of Government Interventions in OECD Countries"; a paper by Daniel P. Kessler of Stanford University, Hoover Institution and the National Bureau of Economic Research titled, "The Effects of Pharmaceutical Price Controls on the Cost and Quality of Medical Care: A Review of the Empirical Literature"; and a White Paper from the Boston Consulting Group titled "Adverse Consequences of OECD Government Interventions in Pharmaceutical Markets on the U.S. Economy and Consumer."

PhRMA's "Foreign Government Pharmaceutical and Price Controls" provides an overview of the pharmaceutical industry in the United States and abroad. It also addresses how foreign price controls and other market access barriers impact the pharmaceutical industry, patients and the U.S. economy (i.e., jobs). This section is tied closely with the study by the Boston Consulting Group (BCG), which will be discussed shortly.

"Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries" provides an overview of the health insurance systems, pharmaceutical markets, and pricing and reimbursement regimes used in twenty-eight foreign countries. The countries included in the overview are Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

"The Effects of Pharmaceutical Price Controls on the Cost and Quality of Medical Care: A Review of the Empirical Literature" summarizes the various empirical approaches that have been used to measure the impact of government regulations on the pharmaceutical industry (prices and innovation) and the quality of medical care.

The Boston Consulting Group (BCG) White Paper titled "Adverse Consequences of OECD Government Interventions in Pharmaceutical Markets on the U.S. Economy and Consumer" estimates the impact of foreign price and market access controls on the pharmaceutical industry, patients, and the U.S. economy. The study focused on seven OECD countries: Canada, France, Germany, Japan, Poland, Spain, and the United Kingdom. After controlling for price and consumption levels, BCG found that "global revenues would increase by 35 to 35 percent" in the absence of price controls. BCG estimated that absent price controls an additional 10 to 13 new drugs would have been launched over the past decade. BCG estimated that higher revenues and R&D spending would have created 20–30 thousand extra R&D jobs (with even greater increases overseas), and 15–20 thousand additional pharmaceutical jobs.

Novartis Corporation (Tracy Haller, Executive Director, International and Public Affairs)

Novartis Corporation is a global health care company whose businesses include research-based pharmaceuticals, generic pharmaceuticals, consumer health care products, medical and infant nutrition products, animal health products, and vision care. Novartis argues that drug-pricing policies that do not take into account the high cost of R&D will inevitably decrease the number of innovative drugs and thus lead to deterioration in health care. Faced with the inability to recoup R&D costs in certain markets, companies will divert their R&D activities to locations where they can recover the costs associated with innovation. Novartis argues that under the current approach to drug pricing outside of the United States, OECD governments get a "free ride" by imposing artificially low drug prices at home, while assuming that the U.S. market will continue to underwrite the development of new drugs.

Mexican Pharmaceuticals Analysis, Jesús González, ITA Commercial Specialist

This document provides an analysis of the Mexican pharmaceutical industry, including a discussion of market trends, imports, competition, end users, sales prospects, and market access. Regarding drug prices, the report notes that "although the Mexican pharmaceutical industry is a good example of the new global economy, traces of protectionism still exist; the government of Mexico still controls the price of medicines for the private market. Even though the prices of medicines in the private market have increased significantly in the past four years, the average Mexican retail price is about one-fourth to one-third of that in the U.S."

Manhattan Institute for Policy Research, Center for Medical Progress

The Manhattan Institute for Policy Research's Center for Medical Progress submitted studies that address the relationship between market access barriers and price controls vis-à-vis drug innovation. These studies argue that foreign pharmaceutical price controls have led to reduced R&D investment and impede patient access to new medicines.

Kevin Outterson, West Virginia University College of Law

The author, an associate professor of law, submitted four documents in his response to the Department of Commerce's *Federal Register* notice: "Pharmaceutical Arbitrage," "Reference Pricing Subcommittee Report," "The Transparency Revolution in PhRMA Pricing," and "The U.S.-Australia FTA's Unfortunate Attack on Good Healthcare Policy."

"Pharmaceutical Arbitrage," a draft paper written by Outterson in 2004, explores the key functions of pharmaceutical arbitrage, including its impact on the cost-quality access dynamic and implications for the WTO Agreement on Trade-Related Intellectual Property Rights (TRIPS) and related government interventions. Part 1 establishes a theoretical framework for

understanding pharmaceutical markets and innovation. Part 2 applies the framework from Part 1 in two case studies on anti-retroviral pricing in sub-Saharan Africa and Canadian-U.S. pharmaceutical arbitrage.

"Reference Subcommittee Pricing Report" is a draft report written in 2004 by the West Virginia Pharmaceutical Cost Management Council. It argues that West Virginians pay more for their most prescribed drugs than consumers in other advanced countries such as Australia or Canada, and that West Virginia's drug cost burden is 59 percent above the U.S. national average. The report posits that if all West Virginians paid Australian prices for drugs, their annual savings would exceed $500 million per year. The West Virginia Pharmaceutical Cost Management Council proposes three legislative steps to reduce drug prices in West Virginia: (1) permit West Virginia to act as a virtual wholesaler of drugs (which would be purchased both domestically and abroad), (2) permit an appropriate state agency to issue a state license for certain patented drugs if the manufacturer refuses to negotiate a "reasonable price," and (3) regulate pharmaceutical marketing within the state.

"The Transparency Revolution in PhRMA Pricing," a paper written by Outterson in 2004, argues that conflicts of interest, information disparities, and non-transparent pricing characterize the current pharmaceutical pricing system, which enable drug companies to price discriminate on a global scale. Recent developments have made foreign drug prices more visible to U.S. consumers and policymakers, threatening this system of price discrimination. The author notes that for all other major sectors of Medicare, reimbursements began at market prices but eventually succumbed to prices set by the government. He argues that if innovation is the pharmaceutical industry's defense for why drugs are different from other medical services, the industry must provide accurate and detailed data to the public to support the argument. Outterson believes that transparency is key to preventing price controls in the United States.

"The U.S.-Australia FTA's Unfortunate Attack on Good Healthcare Policy" comprises comments submitted by Outterson to the House Ways and Means Committee on June 22, 2004. He argues, "undermining Australia's Pharmaceutical Benefits Scheme (PBS) is an inappropriate topic for a free trade agreement." Outterson contends that the PBS allows pharmaceutical companies to request higher reimbursement levels if data establish the greater cost effectiveness of the drug. Outterson argues that Australia is not "free-riding" on U.S.-funded innovation, since companies are given ample opportunity to seek higher reimbursement for truly innovative drugs. He expects the Australia-U.S. Free Trade Agreement to raise drug prices in Australia but possibly not to decrease drug prices in the United States.

Jana Thompson, U.S. Citizen

The author, a disabled single parent, estimates she spends $400 to $500 a month on prescriptions. Because she has difficulty affording her medication, she has turned to Canadian prescription orders and pharmaceutical physician samples. She has recently given up Medicaid to qualify for indigent patient programs for all but two of her prescriptions. Having worked at the University of Louisville, Section of Infectious Diseases, she has seen the marketing techniques that pharmaceutical companies employ at hospitals and finds them extravagant. She questions why pharmaceutical companies advertise on television, when doctors write prescriptions and

know what is available and best for patients. She pleads that the U.S. government "not let the pharmaceutical companies lobby for their own interest, at the cost of Americans, and also allow price fixation from countries, twice financially disabling Americans."

Generic Pharmaceutical Association

The GPhA represents manufacturers and distributors of finished, generic pharmaceutical products and bulk, active pharmaceutical chemicals, as well as suppliers of other goods and services to the generic pharmaceutical industry. The GPhA argues that if countries with strict price regulations were to liberalize their regulations and provide incentives to encourage a competitive generic drug market, the savings from the use of generics would provide access to quality medicine and also yield significant financial headroom to fund new, innovative medicines. The GPhA warns that if trade agreements contain certain provisions that promote innovation, yet are devoid of other provisions that foster access to generics, America's access to affordable medicines could be severely harmed as a result of future harmonization measures.

Czech Republic Local PhRMA

The Czech Republic's local PhRMA argues that the Czech system for determining reimbursement levels for pharmaceutical products constitutes a significant barrier to trade and will restrict patient access to innovative medical treatments in the Czech Republic. Since 1997, the Czech Republic has used a therapeutic reference pricing system to determine the reimbursement levels for new and existing drugs. The Czech PhRMA argues that this reimbursement process is protectionist in nature because the Czech Republic has no innovation-based pharmaceutical companies, and the domestic, generic pharmaceutical industry frequently benefits from relaxation in prescription restrictions coupled with the entry of new generic products. Furthermore, the Czech PhRMA believes that with the accession of the Czech Republic to the European Union, "the amount of future damages will likely increase substantially, and could run into hundreds of millions of dollars if artificially low priced patented products from U.S. manufacturers are re-imported to higher priced EU markets."

Consumer Project on Technology

CPTech is a nonprofit organization that represents consumer interests in policies designed to promote innovation in medicines. Its response to the *Federal Register* notice includes a letter addressing the Department of Commerce's drug pricing study and an article that provides more detail about CPTech's proposed R&D-plus trade framework. CPTech argues that U.S. residents pay more than those of other OECD countries for global pharmaceutical R&D. It argues further that despite the patent system, private sector R&D in the United States is not very innovative or productive. CPTech believes that the rules the United States is asking for in bilateral trade agreements will prevent both foreign trading partners and the United States from effectively addressing abuses of patent rights or excessive pricing of pharmaceutical products. The new "TRIPS Plus" trade agreements seek to increase investment in R&D, but only by increasing prices. CPTech proposes a new trade framework, "R&D-plus," which focuses directly on R&D rather than on patent rights and drug prices and aims at sharing the burden of paying for R&D. In an ambitious, multilateral setting, the R&D-plus approach would involve

setting targets for R&D that are reasonably related to incomes and stages of development, such as 10 to 15 basis points of GDP. Countries could choose among several options in order to meet such targets. For bilateral, regional, or more limited multilateral negotiations, the R&D-plus approach could supplement or co-exist with traditional intellectual property rights agreements. CPTech believes trading partners would be more receptive to R&D-plus.

Biotechnology Industry Organization

The Biotechnology Industry Organization (BIO) argues that innovative accomplishments in the biotechnology industry are the result of the disproportionate contribution of patients residing in the United States, because more than 80 percent of R&D costs is absorbed by patients in the United States as a result of certain international pricing policies. BIO finds this model unsustainable and strongly supports efforts to remove artificial price controls in other countries, so that prices reflect the true value of medicines and OECD members "contribute their fair share to R&D costs." Additionally, BIO argues "if the United States does not sustain a free market approach—if companies are repressed by inadequate intellectual property laws and restricted by price controls—financing of biotechnology R&D will fade to less risky and resource-intensive endeavors, choking the development of next-generation miracle cures."

Aidan Hollis, Department of Economics, University of Calgary

The author submitted "An Efficient Reward System for Pharmaceutical Innovation," which he wrote in 2004, arguing that the patent system functions poorly for pharmaceuticals. He believes the patent system leads to misdirected innovation and advertising, inefficiently high prices, high volumes of counterfeit drugs, parallel imports, and, indirectly, price controls. Hollis proposes a new system in which the government rewards drug innovations based on their therapeutic value through a central Pharmaceutical Innovation Fund. A "new type of patent reward" would replace the "patent reward." According to the author, benefits of the proposed system include better-directed research expenditures, lower prices and the elimination of "deadweight loss," reduction of counterfeit drugs, elimination of price control regimes, more efficient advertising, and a reduction of total costs.

Advanced Medical Technology Association (AdvaMed)

AdvaMed represents more than 1,200 of the world's leading medical technology innovators and manufacturers of medical devices, diagnostic products, and medical information systems. It supports the U.S. government's efforts to assess pharmaceutical price controls outside of the United States and their impact on innovation, trade, and patient access. In addition, AdvaMed draws attention to similar price controls that the medical technology industry faces in Europe, Japan, and Asia. AdvaMed claims that these controls lead to a distortion of trade in medical technologies, discrimination against U.S. exports of medical technology, disruption of the rapid innovation process that characterizes the medical technology sector, delays in patient access to new technologies, and denial of patient access to the most innovative medical technologies. To the extent that the Department of Commerce's drug pricing study results in specific actions to tackle pharmaceutical price controls outside the United States, AdvaMed would like to work

with the U.S. government to discuss and identify ways that these actions might be tailored to address similar price control concerns in their industry.

Appendix C

Report on Pharmaceutical Markets in 11 OECD Countries*

* This appendix provides a general description of the pharmaceutical markets in 11 OECD countries. We will continue to monitor the issues outlined in the appendix as new information becomes available and as policy developments occur.

Australia

In 2002, the Australian pharmaceutical market (consumption of domestic production and imports) totaled approximately US$5.5 billion and accounted for about 1 percent of the world pharmaceutical market.[1] International trade is an important component of the country's pharmaceutical industry; imports amounted to approximately US$3.2 billion, and exports, US$1.2 billion.[2] In 1999–2000, the primary markets for Australian pharmaceutical exports were Asia, Europe, and New Zealand, and Pacific; Australia's primary source of imports was Europe (primarily the United Kingdom, Germany, and Switzerland), accounting for approximately 75 percent, with North America accounting for approximately 15 percent.[3, 4]

Ranked by sales, Australia was the 18th largest pharmaceutical market in the world; by population, it was the 50th largest market.[5] The country has comprehensive markets for all categories of pharmaceutical products, including over-the-counter medicines, complementary drugs (vitamins, minerals, and supplements), and generic and patented prescription products (including biopharmaceutical products). The entire population has prescription drug coverage under its national health care system and pays only a modest co-payment per prescription.

The public can purchase any pharmaceutical that has been determined safe either on the open market or from the government set "formulary"—the Pharmaceutical Benefits Scheme (PBS). In fact, about 95 percent of drugs are purchased through the PBS. Consequently, the government has considerable market power. In 1998, per capita spending on drugs was $123, and prescription drug spending accounted for 7.3 percent of national health spending.[6]

The Australian pharmaceutical industry is composed of about 120 domestic and foreign-owned companies. These companies include "international companies with headquarters in the United States, United Kingdom, or Europe, Australian-owned companies, companies who concentrate on a niche market, companies who manufacture products under license for other companies and companies who have entered into co-marketing agreements. There are domestically-owned companies involved in all aspect of production and marketing, however, the

[1]All money figures in this section are in Australian dollars, unless otherwise stated.
[2]International Business Strategies, "Pharmaceutical Industry in Australia" (October 2003), pp. 1–3, found at *www.internationalbusinesstrategies.com,* retrieved June 5, 2004.
[3]Australian Pharmaceutical Manufacturers Association, Inc., *1999–2000 APMA Facts Book: Pharmaceutical and Health Industry Information* (2002), pp. 9–12.
[4]Based on U.S. Department of Commerce statistics, including both bulk active ingredients and finished products. In 2003, Australia exported some US$17.2 million to the United States and imported approximately US$510 million from the United States.
[5]This ranking is based on a total of 187 markets. International Business Strategies, "Pharmaceutical Industry in Australia" (October 2003), p. 5.
[6]AARP Public Policy Institute, "Australia: Key Facts About the Health Care System and Prescription Drugs" (June 2003).

subsidiaries of multinational enterprises (mainly based in the United States and the United Kingdom) provide approximately 90 percent of the values of prescriptions."[7]

R&D Costs and Expenditures

Australia both participates in and benefits from the worldwide surge in collaborative R&D between basic research institutions, the academic community, and the pharmaceutical industry. Approximately 90 percent of the pharmaceutical companies operating in Australia engage in R&D activity, amounting annually to about $200 million. The Australian government also supports basic biomedical research, spending over $325 million annually in support of biomedical research projects, most of which are conducted at public universities, hospitals, and public research centers, such as the Australian Nuclear Science and Technology Organization and Commonwealth Scientific and Industrial Research Organization (CSIRO).

Clinical trials activity makes up a large portion of R&D expenditure in Australia, approximately 42 percent of the total. New requirements for marketing drugs in Australia have resulted in a steady increase in the number of clinical trials undertaken in the past ten years.

Drug Approval Process

Before any pharmaceutical product can be considered for inclusion in the Pharmaceutical Benefits Scheme, it must be approved for safety and efficacy by the Therapeutic Goods Administration (TGA), a national regulatory authority similar to the U.S. Food and Drug Administration. The TGA conducts a range of assessments to ensure the products are acceptable.

Any product, whether manufactured, imported, exported, or modified, must be "sponsored" by an Australian entity. Australian manufacturers must themselves be licensed and prove that they engage in good manufacturing practices. Australian sponsors, applying for registration of an imported product, must supply evidence that the overseas production facilities comply with good manufacturing practices.

Health Care Coverage

In Australia, the federal government participates in the regulation, availability, and funding of pharmaceutical and health care services.[8] "The federal government, through the department of Health and Ageing, sets national health policies and funds the provision of health services by state and territory governments and the private sector."[9] Australia has universal,

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[7]International Business Strategies, "Pharmaceutical Industry in Australia," pp. 5–7.
[8]See AARP Public Policy Institute, "Australia: Key Facts About the Health Care System and Prescription Drugs" (June 2003); Melissa Hilless and Judith Healy, "Health Care Systems in Transition—Australia," *European Observatory on Health Systems* (2001), found at *www.health.gov.au/pubs/hit/hit.htm,* retrieved June 20, 2004; Australian Department of Health and Ageing, "Australia Now: Health Care in Australia" (2002).
[9] Australian Department of Health and Ageing, "Australia Now: Health Care in Australia."

compulsory, health care coverage provided by the Australian Medicare system. This national health system covers inpatient and outpatient hospital care, physician services, inpatient and outpatient medicines, mental health care, some preventive services, and rehabilitation. It is also a major financial source for medical research. The program is funded by a 1.5 percent tax on income, additional federal and state revenues, and patient fees. High-income patients who do not have private health insurance may be required to pay a Medical Levy Surcharge.[10] In 2000, 71 percent of funds were from the government, the consumer paid 16 percent out of pocket, 7 percent was from private insurance, and 5 percent was designated "other."[11]

Private insurance is provided primarily by not-for-profit mutual insurers. About 44 percent of the population has private insurance, which covers the gap between Medicare benefits and scheduled fees for inpatient services.

Pricing

Pharmaceutical Benefits Scheme

Approximately 95 percent of prescriptions issued in Australia are subsidized by the government under the PBS.[12] The remaining 5 percent of prescriptions were those that cost less than the patient co-pay or were private prescriptions. The PBS covered about 80 percent of the cost of the approximately 128 million prescriptions filled in Australia (or about eight prescriptions per year per person). In 2003, this included approximately 600 different pharmaceuticals (many of which were generic brands), presented in some 1,500 forms (e.g., tablet, gel cap, liquid) and 2,500 brands.[13] The price paid included the manufacturer's negotiated price, a 10 percent wholesaler's margin, and a 10 percent markup for the pharmacist, plus the pharmacist's professional fee ($4.39 per script as of August 1999).[14] Annual inflation adjustments are provided to those at every stage of distribution, except to manufacturers.

The PBS has created two categories for recipients of PBS-subsidized medicines: "general" patients and "concession" patients. The latter are typically low-income workers, the unemployed, the disabled, and senior citizens. As of January 4, 2004, general consumers pay up to $23.70 for most medicines listed on the PBS, while people with concession cards pay $3.80.[15]

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[10] AARP Public Policy Institute.
[11] Hilless and Healy," Health Care Systems in Transition—Australia," p. 32.
[12] Kim Sweeny, "Price and Quantity Trends in the PBS," Centre for Strategic Economic Studies, Draft Working Paper No. 14 (August 2003), found at *www.cfses.com/pharma/documents/14-Price_and_Quantity_Trends.pdf.*
[13] Amanda Biggs, "Pharmaceutical Benefits Scheme—An Overview," Department of Parliamentary Library: Canberra (January 2003), p. 8; see also International Business Strategies, "Pharmaceutical Industry in Australia," p. 19.
[14] APMA, *1999—2000 APMA Facts Book*, p. 25.
[15] As of January 2005, the general public will pay up to $28.60 for a medicine, and a concession card holder will pay up to $4.60. See *www.health.gov.au/pbs/pharm/Index.html,* retrieved June 15, 2004.

"Currently the majority of government expenditure on PBS prescriptions is directed towards concession cardholders (79.8 percent of the total)."[16]

Pharmaceutical Benefits Scheme (PBS) Process

The PBS submission process is complex. A pharmaceutical company seeking to list a drug on the PBS selects a comparator drug, usually the drug that it is seeking to replace. The company must prove that its drug is more cost effective or at least as cost effective than that comparator drug in order to be listed on the PBS. To prove cost effectiveness, a company must provide data showing incremental cost in dollars of its drug compared with the comparator, and incremental outcomes of its drug compared with the comparator drug. What factors a company is permitted to use when calculating outcomes significantly influences the determination of incremental cost effectiveness.

Sponsors submit their applications to the Pharmaceutical Benefits Advisory Committee (PBAC) and the submission is reviewed by external evaluators and then provided to the PBAC and its economic subcommittee, which analyze the cost effectiveness of the pharmaceutical based on a comparator drug. The PBAC makes a recommendation whether to list, defer or reject a drug. If the recommendation is to list, the recommendation goes to the Pharmaceutical Benefits Pricing Authority (PBPA). The PBPA determines the price at which the government will purchase the drug, taking into consideration a number of factors, most importantly the PBAC's advice on clinical and cost effectiveness. The PBPA then offers a price to the manufacturer and often also seeks price/volume arrangements and limits on the specific indications that will be covered. If no agreement is reached between the PBPA and the drug sponsor, the product will not be listed. If the price is accepted, the PBPA makes a recommendation to the Federal Minister of Health, who has final approval over all PBS listings. The agency also annually reviews the prices of all products listed as pharmaceutical benefits and can seek price reductions or allow price increases, virtually always the former.

The U.S.-Australian Free Trade Agreement included provisions on pharmaceuticals and specific steps to improve the transparency and accountability of the PBS process. The Australian Government agreed to an independent review of listing decisions, which will enhance the accountability of the process.

[16]Amanda Biggs, "The Pharmaceutical Benefits Scheme—An Overview," p. 8.

Japan

The Japanese pharmaceutical market is the second largest in the world after the United States and totaled $52.4 billion in 2003 (Table C-1).[17] Japanese sales expanded at an average compound annual growth rate of only 1 percent, and the Japanese market, as a percentage of the world market, slipped from 17 percent to 11 percent during the period of 1999-2003. Japanese sales are expected to continue growing more slowly than worldwide sales.

During 1991–2000, Japan consistently ran a trade deficit in pharmaceutical trade.[18] In 2000 (the last year for which data are available), the pharmaceutical trade deficit was approximately $2 billion, and imports of pharmaceuticals accounted for approximately 9 percent of total pharmaceutical sales in Japan.[19] In 2001, foreign firms accounted for about 30 percent of all Japanese drug sales, and foreign drugs manufactured under license by Japanese companies accounted for an additional 28 percent.[20] In 2000, the United States was both the largest market for Japanese pharmaceuticals, accounting for over 46 percent of Japanese exports, and the largest supplier of pharmaceuticals, accounting for almost 20 percent of Japanese imports of pharmaceuticals.[21]

Table C-1. Japanese Pharmaceutical Sales, 1999–2003

Year	*World*	*Japan*	*Percent*
		—Billions of U.S. dollars—	
1999	295.9	50.0	16.9
2000	317.2	51.5	16.2
2001	364.2	47.6	13.1
2002	400.6	46.9	11.7
2003	466.3	52.4	11.2

Source: IMS Health Press Releases, *www.imshealth.com.*

In 1999, there were 471 manufacturers of prescription pharmaceuticals in Japan,[22] most of which were small compared with global competitors. Table C-2 shows the top-ranked

[17]PhRMA, "Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries" (2004), p. 32.
[18]Japanese Pharmaceutical Manufacturers Association, "Pharmaceutical Trade," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/017.html,* retrieved on June 2, 2004.
[19] Ibid.
[20]David Pilling, "Pharmaceuticals 2001/Japanese Focus Global Firms Sell Direct," *Financial Times* (April 26, 2001), found at *http://specials.ft.com/pharmaceuticals2001/FT32JUM0MC.html*, retrieved on June 2, 2004.
[21]Japanese Pharmaceutical Manufacturers Association, "Pharmaceutical Trade of Japan by Country," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/018.html*, retrieved on June 2, 2004.
[22]Japanese Pharmaceutical Manufacturers Association, "Number of Pharmaceutical Manufacturers," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/004.html*, retrieved on June 2, 2004.

Japanese pharmaceutical firms along with their world ranking in 2001 and 2002. In 2001, the largest Japanese pharmaceutical firm, Takeda, had a reported market capitalization of about $50 billion (one-fifth the size of Pfizer, the largest drug company in the world)[23] and was the 15th largest pharmaceutical firm in the world.

Table C-2. Top Japanese Pharmaceutical Companies World Ranking, 2002

	Global Ranking	
Company	*2001*	*2002*
Takeda	15	15
Eisai	21	21
Sankyo	22	24
Fujisawa	27	29
Yamanouchi	28	30
Otsuka	30	33
Daiichi	31	36
Shionogi	39	41
Tanabe	44	47
Ono	48	50

Source: Lisa Jarvis, "Biotechs begin to look to Japan for partnerships," *Chemical Market Reporter,* July 21, 2003.

Table C-3 shows the top-ranked pharmaceutical firms in Japan based on 2003 sales. IMS estimates that the market share of U.S. and European pharmaceutical firms in Japan increased from 32 percent in 2000 to 38 percent in 2002.[24]

Table C-3. Top 10 Pharmaceutical Firms in Japan, 2003

Company	*Nationality*	*Global Rank*
Takeda	Japan	15
Pfizer	USA	1
Sankyo	Japan	26
Roche	Switzerland	9
Otsuka	Japan	24
Novartis	Switzerland	5
Daiichi	Japan	36
Eisai	Japan	20
Yamanouchi	Japan	33
Merck (Banyu)	USA	3

Source: "Western Sumos Wrestle into Japan" found at *www.ims.global.com,* retrieved on June 17, 2004.

[23]Pilling, "Pharmaceuticals 2001."
[24]IMS Health, "Multinationals Seek Growth in Japan."

Japanese pharmaceutical wholesalers have been consolidating in recent years. During 2000–2004, the number of members of the Japan Pharmaceutical Wholesalers Association decreased by 33 percent from 217 to 146.[25] However, annual sales by Japanese wholesalers have increased steadily. In 2002, sales of prescription pharmaceuticals were over 93 percent of total sales by Japanese pharmaceutical wholesalers.[26]

Traditionally, Japanese pharmaceutical firms have focused on the domestic market. Products of Japanese origin have consistently accounted for about 60 percent of that market,[27] and a substantial share of the new drugs introduced in Japan were so-called "follow-on" products.[28] Nonetheless, despite adverse economic conditions, a complex regulatory environment, and limited international marketing infrastructure, Japanese companies have been relatively prolific in creating new drugs.[29] Many are successful in international markets, such as mevalotin (Pravastatin) by Sankyo and famotidine (Pepcid) by Yamanouchi.[30] In 2002, Takeda joined the list of companies with blockbuster drugs as the firm's drug, pioglitazone (Actos), topped $1 billion in annual sales.[31] Lansoprazole (Ogastro/Prevacid), a product of TAP Pharmaceutical (a joint venture of Abbott and Takeda), was the seventh best selling drug in 2002 with global sales of $3.6 billion.[32]

Some Japanese pharmaceutical firms (e.g., Takeda, Daiichi, Yamanouchi, Eisai, Sankyo) have large operations outside of Japan, which account for a significant part of their profits.[33] During 1996–2000, the number of foreign manufacturing plants owned by Japanese pharmaceutical companies increased steadily from 71 in 1996 to 101 in 2000, an increase of 42 percent.[34] The Japan Pharmaceuticals Manufacturers Association (JPMA) reports that overseas

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[25]"Who Are our Members? " found at *www.jpwa.or.jp/jpwa/members-e.html,* retrieved on June 16, 2004.
[26]Wholesaler annual sales found at *www.jpwa.or.jp/jpwa/graph2-e.html*, retrieved on June 16, 2004.
[27]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation No. 332-419), USITC publication 3333, 2000, p. 3-34.
[28]Brian Woodall and Aki Yoshikawa, "Japan's Failure in Pharmaceuticals: Why is the World Saying 'No' to Japanese Drugs?," March 1997, found at *www.ciber.gatech.edu/workingpaper/1997/woodall.html,* retrieved on June 3, 2004.
[29]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation No. 332-419), USITC publication 3333, 2000, p. 3-34.
[30]David Pilling, "Pharmaceuticals 2001/Japanese Focus Global firms sell direct," *Financial Times*, Apr. 26, 2001, found at *http://specials.ft.com/pharmaceuticals2001/FT32JUM0MC.html*, retrieved on June 2, 2004.
[31]Blockbuster drugs are those that achieve annual sales of $1 billion or more. Patricia Van Arnum, "Boom and Bust for Blockbuster Drugs: As Reliance on Blockbuster Drug Revenue Increases, Weaker Pipelines and Generic Competition Create Strategic Challenges for Pharmaceutical CEOs," *Chemical Market Reporter* (September 29, 2003), found at *http://articles.findarticles.com,* retrieved on June 3, 2004.
[32]Patricia Van Arnum, "Top Active Pharmaceutical Ingredients, 2002," *Chemical Market Reporter*, found at *http://articles/findarticles.com,* retrieved on June 3, 2004.
[33]Lisa Jarvis, "Biotechs Begin to Look to Japan for Partnerships," *Chemical Market Reporter* (July 21, 2003).
[34]"Foreign Business of Japanese Pharmaceutical Companies," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/020.html,* retrieved on June 2, 2004.

sales accounted for an average of 21 percent of consolidated sales for the 31 JPMA member firms reporting overseas sales in 2000.[35]

R&D Costs and Expenditures

In 2002, total R&D expenditures for prescription pharmaceuticals in Japan were approximately $6.4 billion,[36] up from $5.2 billion in 1998.[37] In 2000 (the last year for which company data are available), R&D expenditures for the 20 leading Japanese firms averaged over 11 percent of sales.[38]

A study of Japanese pharmaceutical firms indicated that average drug development cost in Japan ranged from $268 to $517 million (1995 dollars), and that average development time from the start of preclinical trials to marketing was 11.5 years.[39]

Drug Approval Process

The Ministry of Health, Labor, and Welfare (MHLW) is responsible for pharmaceutical regulatory affairs in Japan. Japan has committed to reduce the average approval period to 12 months,[40] and recent data suggest that progress has been made toward that goal. The average approval time decreased from 34 months in 1999 to 17 months in 2001.[41] The pharmaceutical industry associations reports that, although Japan has committed to accept foreign clinical trials, the narrow MHLW interpretation of the guideline on ethnic factors continues to force firms to redo trials and thereby continues to delay drug approvals.[42]

Japan accepted Good Clinical Practice (GCP) standards as a part of the International Conference on Harmonization (ICH).[43] Medical service providers that conducted clinical trials

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[35]In 1997, 13 JPMA firms reported that overseas sales averaged 11 percent of consolidated sales. "Advances into Overseas Markets by JPMA Member Companies," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/017.html*, retrieved on June 2, 2004.

[36]"Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries," PhRMA, 2004, p. 32.

[37]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation No. 332-419), USITC publication 3333 (2000), p. 3-35.

[38]"R&D Expenditures of 20 Leading Manufacturers," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/035.html,* retrieved on June 2, 2004.

[39]Included in those figures are the costs of development for those drugs not reaching the market. Yoshindo Takahashi "Time Frames and Costs of New Drug Development: Analysis of Survey Results," found at *www.jpma.or.jp/12english/publications/pub022e_time/index.html,* retrieved on June 2, 2004.

[40]Information on Japan found at *http://phrma.org/international/asia/japan.cfm,* retrieved on June 2, 2004.

[41]"The impact of the changing regulatory environment on review times," found at *www.cmr.org/pdfs/r_d35.pdf,* retrieved on June 3, 2004.

[42]Information on Japan found at *http://phrma.org/international/asia/japan.cfm,* retrieved on June 2, 2004, and EFPIA-EBC position paper on Japan found at *www.efpic.org/4_pos/economic/Japan.pdf*, retrieved on June 3, 2004.

[43]U.S. International Trade Commission (USITC), *Pricing of Prescription Drugs,* Investigation No. 332-419, (USITC publication 3333, 2000), p. 3-36.

have had difficulty meeting the new standards and are now required to hire and train the clinical research coordinators (CRC) and technical staff needed to conduct trials that meet the new standard.[44] Drug development time in Japan is about 12 years, and the costs for late-stage clinical trials are two to four times higher in Japan than abroad.[45] Reacting to the higher cost, Japanese pharmaceutical firms have increasingly moved drug development operations overseas.[46] One result of the MHLW "Pharmaceutical Industry Vision" is a plan to establish a large-scale clinical trial network intended to reverse the decline in the number of clinical trials conducted in Japan.[47] Released in April 2003,[48] the plan calls for an additional 2,500 CRCs to be hired and trained in the next three years.[49]

The Medical Device and Pharmaceutical Working Group of the U.S.-Japan Economic Partnership for Growth's Regulatory Reform Initiative has continued to focus on reform in the Japanese system for health care, drug approvals, and pharmaceutical pricing.[50] Japan has implemented some of these recommended reforms. In May 2003, the MHLW issued a report entitled "Pharmaceutical Industry Vision: Progress of Action Plans for International Competitiveness."[51] The report identified 37 action plans pertaining to research, development, production, and marketing of pharmaceuticals.[52]

Health Care Coverage

The Japanese National Health Insurance system (NHI) has provided universal coverage since 1961.[53] It provides a comprehensive set of uniform benefits.[54] It is financed by employer-employee contributions to either private employer-based or government insurance plans but also

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[44]USITC, *Pricing of Prescription Drugs*, p. 3-37.
[45]Ibid.
[46]By 2003, the number of applications for clinical trials in Japan had dropped to one third of that a decade ago. See Obayashi, "Japan Drug Makers Take Drug Development Abroad."
[47]Yasuhisa Takeda, "Interim review of progress in the action plans of Pharmaceutical Industry Vision," found at *www.jpma.or.jp/12english/topics/031002/031002_1.html,* retrieved on June 2, 2004.
[48]Obayashi, "Japan Drug Makers Take Drug Development Abroad."
[49]"Towards Internationally Attractive Environment for Drug Discovery," found at *www.jpma.or.jp/12english/topics/topics030820_2.html,* retrieved on June 2, 2004.
[50]Information on Japan found at *http://phrma.org/international/asia/japan.cfm,* retrieved on June 2, 2004.
[51]Yasuhisa Takeda, "Interim review of progress in the action plans of Pharmaceutical Industry Vision," found at *www.jpma.or.jp/12english/topics/031002/031002_1.html,* retrieved on June 2, 2004.
[52]Yasuhisa Takeda, "Interim review of progress in the action plans of Pharmaceutical Industry Vision," found at *www.jpma.or.jp/12english/topics/031002/031002_1.html,* retrieved on June 2, 2004.
[53]The origin of the National Health Insurance program was the Health Insurance Law of 1922, which provided insurance coverage for major occupational groups. Gradual revisions 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. See USITC, *Pricing of Prescription Drugs*, p. 4-31.
[54]Ibid.

by government subsidies for certain groups.[55] A persistent deficit has plagued the system, which is largely attributable to two factors: a rapidly aging population and stagnant revenues.

The basic structure of health care delivery in Japan is weighted toward outpatient care; Japan has the highest rate of physician visits and the lowest rate of hospital admissions among industrialized nations.[56] However, most institutional care for the elderly is provided in hospitals (i.e., social hospitalization) rather than nursing homes.[57] In general, the quantity of drugs per patient has increased,[58] and a study of 26 OECD countries showed that Japan ranked as the eighth highest in spending per capita on pharmaceuticals and other medical nondurables ($301 based on purchasing power parity) in 1999.[59] Between 1980 and 1998, Japanese national health care expenditures increased about 5 percent per year. During 1998–2002, however, they remained relatively flat at $227 billion (¥29.8 trillion at 131 yen per dollar) in 1998[60] and $240 billion (¥30 trillion at 125 yen per dollar) in 2002.[61] It is reported that national medical expenditures decreased in fiscal year 2002 for the first time in history.[62] A study of 30 OECD countries showed that in 1999, Japanese annual health care spending per capita of $1,796 ranked 15th among the countries studied based on purchasing power parity.[63]

The Health Insurance Law was revised on August 2, 2002.[64] Key provisions of the revision are listed below.

- The co-pay for social health insurance holders was increased from 20 to 30 percent,[65] and

[55]Approximately one-third of total health care expenditures come from government revenue, and additional funds are transferred from employment-related insurance plans (e.g., SMHI, MAA, and GMHI) to pooling funds for the elderly. See Naoki Ikegami and John Creighton Campbell, "Health Care Reform In Japan: The Virtues Of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[56]An OECD study reported that in 1998, per capita annual doctor consultations was 16 in Japan compared with 6.6, which is the average for OECD countries. Yutaka Imai, "Health Care Reform in Japan," found at *www.olis.oecd.org/olis/2002doc.nsf/linkto/eco-wkp%282002%297/$file/JT00120719.pdf*, retrieved on June 3, 2004, and Naoki Ikegami and John Creighton Campbell, "Health Care Reform In Japan: The Virtues Of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[57]Naoki Ikegami and John Creighton Campbell, "Health Care Reform In Japan: The Virtues Of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[58]Ibid.
[59]Uwe E. Reinhardt, Peter S. Hussey, and Gerald F. Anderson, "Cross-National Comparisons Of Health Systems Using OECD Data, 1999," *Health Affairs*, Vol. 21, No. 3, May/June 2002, pp. 169–181.
[60]"Pharmaceutical Market in Japan," International Business Strategies, Sept. 2002, p. 9.
[61]Osamu Kido, "Trends in the Japanese Pharmaceutical Market," found at *www.jpma.or.jp/12english/publications/pub021a_trends/index.html*, retrieved on June 2, 2004.
[62]Health care expenditures were 6.5 percent of GDP in 2002, up from 6 percent in 1999. Naoki Ikegami and John Creighton Campbell, "Japan's Health Care System: Containing Costs and Attempting Reform," *Health Affairs*, Vol. 23, No. 3 (May/June 2004), pp. 26–36.
[63]Uwe E. Reinhardt, Peter S. Hussey, and Gerald F. Anderson, "Cross-National Comparisons Of Health Systems Using OECD Data, 1999," *Health Affairs*, Vol. 21, No. 3 (May/June 2002), pp. 169–181.
[64]Shinichi Kaburagi, "Amendment of the Health Insurance Law," found at *www.jpma.or.jp/12english/publications/pub023c_amendment/index.html,* retrieved on June 2, 2004.
[65]EFPIA-EBC position paper on Japan found at *www.efpic.org/4_pos/economic/Japan1102.pdf*, retrieved on June 3, 2004.

coverage for the insured and dependents was unified at 70 percent, except that coverage for children less than three years of age was set at 80 percent.[66]

- The age threshold for eligibility for geriatric health care was increased from 70 to 75 years of age.[67] Also, the co-pay for the elderly covered by old-age insurance increased to at least 10 percent[68] and 20 percent for elderly with income in excess of a certain level.[69]
- The co-pay for outpatient drugs was abolished.[70]
- Premiums were changed to 8.2 percent of total annual income including bonuses.[71]
- The limit on co-pay for high cost treatments was raised.[72]

In addition to hiking co-payments, suggestions for NHI reform by the Ministry of Health and Welfare include: 1) the introduction of balance billing; 2) the creation of an independent insurance plan for the elderly; and 3) the introduction of inclusive payments (i.e., diagnosis-related groups) for acute inpatient care.[73] The MHLW proposed two alternative reforms: 1) cross-funding across all plans and the eventual merging of all plans into a uniform financing system within each prefecture; and 2) creating an independent health plan for everyone age 75 and older, with higher premiums than people now pay.[74] In March 2003, a hybrid plan including elements from both alternatives was adopted. A new independent insurance plan for people 75 years and older is to be created, and cross funding among various plans will cover people age 65–74.[75]

Pricing

The MHLW, through the Special Committee on Drug Prices (part of the Central Social Insurance Medical Council or Chuikyo),[76] establishes the introductory price of every new

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[66]Shinichi Kaburagi, "Amendment of the Health Insurance Law," found at *www.jpma.or.jp/12english/publications/pub023c_amendment/index.html*, retrieved on June 2, 2004.
[67]Ibid.
[68]Naoki Ikegami and John Creighton Campbell, "Japan's Health Care System: Containing Costs and Attempting Reform," *Health Affairs*, Vol. 23, No. 3 (May/June 2004), pp. 26–36.
[69]EFPIA-EBC position paper on Japan found at *www.efpic.org/4_pos/economic/Japan1102.pdf,* retrieved on June 3, 2004.
[70]Shinichi Kaburagi, "Amendment of the Health Insurance Law," found at *www.jpma.or.jp/12english/publications/pub023c_amendment/index.html*, retrieved on June 2, 2004.
[71]"Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries," PhRMA, 2004, p. 32, and Shinichi Kaburagi, "Amendment of the Health Insurance Law," found at *www.jpma.or.jp/12english/publications/pub023c_amendment/index.html,* retrieved on June 2, 2004.
[72]Shinichi Kaburagi, "Amendment of the Health Insurance Law," found at *www.jpma.or.jp/12english/publications/pub023c_amendment/index.html,* retrieved on June 2, 2004.
[73]Naoki Ikegami and John Creighton Campbell, "Health Care Reform In Japan: The Virtues Of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[74]Naoki Ikegami and John Creighton Campbell, "Japan's Health Care System: Containing Costs and Attempting Reform," *Health Affairs*, Vol. 23, No. 3 (May/June 2004), pp. 26–36.
[75]Ibid.
[76]The Chuikyo is comprised of 20 members, 8 representatives each from payers and providers and 4 members from public-interest groups. Naoki Ikegami and John Creighton Campbell, "Health Care Reform In Japan: The Virtues Of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.

prescription brand name drug through negotiation with the manufacturer.[77] Generally, the price of a "comparator" product, which is already on the market, is considered, and overseas prices in four countries (United States, United Kingdom, Germany, and France) are also taken into account.[78] The Drug Price Organization, which was established in October 2000, is intended to provide the MHLW with advice on the appropriate comparators and premiums.[79] If a comparable product does not exist or if the manufacturer chooses to avoid the comparator-based system, a price can be determined by a cost calculation, but MHLW makes the final decision regarding the actual method used.[80] Drugs are also classified by usefulness and market size. (The criteria in each of the categories are summarized in Table C-4.) The "usefulness" categories allow price premiums to be awarded to the new drug. Drugs containing NCEs are added to the NHI drug price list four times annually: March; May; August; and November.[81]

Table C-4. Classification and Rate of Drug Pricing Premiums

1. Classification Based on Usefulness
• Innovative (standard 40 percent; range 40–100 percent) • Useful I (standard 15 percent; range 15–30 percent) • Useful II (standard 5 percent; range 5–10 percent) • Other new drugs (no premium)
2. Classification Based on Market Size
• Designated as orphan and pharmacologically new (standard 10 percent; range 5–15 percent) • Small market and pharmacologically new (standard 3 percent; range 1.5–4.5 percent) • Other new drugs (no premium)
Sources: "Pharmaceutical Administration and Regulations in Japan," found at *http://jpma.or.jp/12english/guide-jpma/index.html,* retrieved on June 2, 2004; "NHI Drug Price System," found at *www.jpma.or.jp/12english/guide_industry/nhi.nhi.html,* retrieved on June 3, 2004.

MHLW reviews procurement prices and purchase prices approximately every other year and revises reimbursement prices to minimize the price gaps, taking into consideration the commercial practice in which medical institutions buy drugs at prices below official NHI prices.[82] In spite of the fact that there were almost 12,000 drugs on the NHI price list in 2000,[83] prices are altered individually rather than making across-the-board adjustments for inflation or

[77]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation No. 332-419), USITC publication 3333, 2000, p. 4-32.
[78]Ibid.
[79]Ibid.
[80]Ibid.
[81]"NHI Drug Price System," found at *www.jpma.or.jp/12english/guide_industry/nhi.nhi.html,* retrieved on June 3, 2004.
[82]"NHI Drug Price System," found at *www.jpma.or.jp/12english/guide_industry/nhi.nhi.html,* retrieved on June 3, 2004.
[83]"Number of NHI Price Listed Pharmaceuticals in Japan," found at *www.jpma.or.jp/12english/publications/databook/databook2002/14DATA/whtml/031.html,* retrieved on June 2, 2004.

other factors.[84] Revised reimbursement prices are determined using a formula developed by the Chuikyo.[85] Drugs are subject to repricing if principal indications, efficacy, dosage levels, or market size change or if the wholesale discount for a drug is more than the difference between the price of the drug and its reimbursement price (yakkasa).[86] The Japanese pharmaceutical industry contends that research on innovative drugs has been discouraged because prices are likely to be cut before the large investment in development can be recovered.[87] In the regular biennial review of 2000, prices were lowered by an average of 7 percent.[88] In the 2002 review prices were cut again by an average of 6.3 percent.[89] Also in 2002, additional reductions were implemented on long-listed drugs for which generic substitutes are available. MHLW said the potential price premiums (Table C-4) were increased so as to value innovative and effective new drugs more highly than before.[90]

The generic share of the Japanese pharmaceutical market is small, at about 7 percent. Three factors have limited the use of generic drugs in Japan: 1) doctors are brand conscious and uncertain of the quality of generic drugs; 2) pharmacists are not allowed to substitute generic drugs; and 3) because of NHI, patients are not sensitive to the cost of drugs.[91] In April 2004, generic drug prices were listed on the NHI price list at 70 percent (decreased from 80 percent) of the price of the original drug unless another generic has already been listed.[92]

[84]Naoki Ikegami and John Creighton Campbell, "Health Care Reform in Japan: The Virtues of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[85]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation No. 332-419), USITC publication 3333 (2000), p. 4-33.
[86]Ibid.
[87]Naoki Ikegami and John Creighton Campbell, "Health Care Reform in Japan: The Virtues of Muddling Through," *Health Affairs*, Vol. 18, No. 3 (May/June 1999), pp. 56–75.
[88]Osamu Kido, "Trends in the Japanese Economy and Pharmaceutical Industry in 2000," found at *www.jpma.or.jp/12english/publications/pub019a_trends2000/index.html,* retrieved on June 2, 2004.
[89]EFPIA-EBC position paper on Japan found at *www.efpic.org/4_pos/economic/Japan1102.pdf*, retrieved on June 3, 2004.
[90]Ibid.
[91]U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation no. 332-419), USITC publication 3333 (2000), p. 4-33.
[92]If another generic has already been listed, the price is set at that of the cheapest existing generic drug. U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation no. 332-419), USITC publication 3333 (2000), p. 4-33 and "Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries," PhRMA (2004), p. 32.

Republic of Korea

In 1999, there were approximately 200 pharmaceutical firms operating in the Republic of Korea. The largest firms accounted for approximately 5 percent of total annual production.[93] These local companies together supplied 78 percent of the South Korean pharmaceutical market in 1999, compared with 12 percent for European suppliers and 9 percent for U.S. companies.[94] Prior to 1999, the South Korean government did not allow foreign pharmaceuticals to be marketed or sold in South Korea.

With a population of 48 million, South Korea directs approximately 6 percent of the country's annual GDP into health care, compared to an average of about 8 percent for other OECD countries.

In 2000, the latest year for which data are available, the total South Korean pharmaceutical market was estimated at U.S. $6.5 billion. Spending on pharmaceuticals in South Korea constitutes approximately one third of total annual health care expenditures, compared to approximately 7 percent in the United States, 11 percent in Canada, and 14 percent in France.

R&D Costs and Expenditures

A number of pharmaceutical firms in South Korea are actively involved in joint R&D collaborations with foreign and domestic manufacturers, generally to conduct preclinical tests and postclinical trials needed for the regulatory approval of new chemical entities in South Korea.[95] Other South Korean companies have entered into co-marketing agreements with foreign firms in order to acquire the marketing rights to specific drugs and to participate in new drug R&D projects.[96]

In 1999, the R&D expenditures of the top five South Korean pharmaceutical companies ranged from 2.6 to 5.7 percent of gross sales.[97]

Drug Approval Process

The Korea Food and Drug Administration (KFDA) grants new drug approvals based on a review of data submitted by the applicant, including the basic screening research data, research

[93] Organization for Economic Co-operation and Development, Directorate for Financial, Fiscal, and Enterprise Affairs, Committee on Competition Law and Policy, *Competition and Regulation Issues in the Pharmaceutical Industry* (February 6, 2001), p. 229.
[94] European Federation of Pharmaceutical Industries and Associations, Position Statement, "Korea: Trade Barriers to International Pharmaceuticals" (June 1999), p. 1.
[95] OECD, *Competition and Regulation Issues*, p. 229.
[96] Ibid.
[97] Ibid., p. 229.

data, efficacy data, preclinical data, and clinical data.[98] The data submitted in connection with the approval are in principle protected from disclosure, except when such disclosure is deemed to be necessary in the public interest.[99]

The KFDA seeks to render its decisions within 95 days, allocating 70 days to screen the safety and efficacy data and 25 days for the license review.[100]

Generic manufacturers are discouraged from relying on the same data submitted by the original manufacturer. Nonetheless, imported drugs containing the same ingredients, as local drugs, which have already been approved and which are classified as over-the-counter products, do not need a separate review for safety and efficacy in order to receive marketing approval.[101]

Health Care Coverage

South Korea has a compulsory public health insurance system covering the entire population and administered by the Ministry of Health and Welfare (MHW). This nationwide plan was established in 1989. Different plans within this system cover different classes of individuals (e.g., self-employed, private-sector employees, public-sector employees, and the unemployed). Private companies are not permitted to provide comprehensive health insurance.[102]

South Korea's insurance system was initially set up to pay approximately 80 percent of the cost of inpatient hospital care or treatment for certain chronic diseases, with the patient absorbing the remaining 20 percent. Nevertheless, the increased incidence of medical technologies that are not routinely covered under the national system has risen to the extent that by 1996 patients were paying for nearly 60 percent of total health care expenditures.[103]

The medical payment schedule in South Korea is a fee-for-service plan that creates incentives for doctors and hospitals to encourage more frequent visits by patients and greater use of pharmaceuticals and other medical supplies. The resulting rapid rise in health care expenditures has prompted South Korea's National Federation of Medical Insurance (NFMI), which reviews all reimbursement claims, to vigorously review individual claims. This, in turn, has created an acrimonious relationship between NFMI and doctors. South Korean hospitals are thus hesitant to provide treatment that may be viewed as "uncommon" by NFMI.[104]

The South Korean medical insurance scheme typically covers only those drugs (including over-the-counter products) that are listed on the Pharmaceutical Reimbursement Schedule maintained by MHW.[105] Drugs the South Korean government views as used for non-therapeutic

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[98] Ibid., p. 230.
[99] Ibid., p. 230.
[100] Ibid.
[101] Ibid.
[102] U.S. Department of State, U.S. and Foreign Commercial Service, *Industry Sector Analysis: Health Care Insurance, South Korea*, found at *www.buyusainfo.net/info.cfm?id=96209&keyx=,* retrieved June 29, 2004.
[103] U.S. Department of State, Health Care Insurance, *South Korea*.
[104] Ibid.
[105] OECD, *Competition and Regulation Issues,* p. 231.

purposes or diseases (such as tonics, preventive vaccines, and acne drugs) are normally excluded from insurance coverage.[106]

The standard co-payment for covered pharmaceuticals dispensed by doctors or hospitals is 20 percent. When the pharmaceuticals are obtained from pharmacists with a doctor's prescription, the co-pay is roughly 30 percent, while drugs prescribed and dispensed by pharmacies typically involve co-pays of approximately 40 percent.[107]

Although South Korean law distinguishes the roles of pharmacists and doctors in prescribing and dispensing drugs in South Korea, the legal distinctions are not rigorously enforced and there is an ongoing dispute between the two groups over the right to dispense and administer certain types of drugs and which drugs need prescriptions and which can be sold without a doctor's prescription or over the counter. This controversy is seen as contributing to certain patterns in pharmaceutical sales in South Korea. For example, pharmacists who are dispensing an antibiotic without a doctor's prescription are more likely to dispense a generic product because the typical South Korean pharmacy is too small to stock a large inventory of specific or expensive brand-name drugs. At the same time, the use of injected drugs is reported to be unusually high because they can only be administered by doctors and medical staff (because the use of injected drug commands high reimbursement rates within the South Korean health care system).[108]

Pricing

After obtaining a product license from the KFDA, the drug manufacturer/importer must request that MHW list its drug on the Pharmaceutical Reimbursement Schedule (PRS). The PRS lists the ceiling prices for each product as determined by consultations between the MHW and South Korea's Pharmaceutical Reimbursement Prices Review Committee. Industry, especially U.S. and other foreign manufacturers of innovative drugs, has lodged numerous complaints about transparency of this process, as well as the methodologies for setting prices.

In January 2002, a U.S.-South Korean bilateral working group was formed with the goal of increasing transparency in drug policy and facilitating consultation on a broad range of health care issues. The group is composed of South Korean and U.S. drug companies and South Korean government officials with U.S. government participation. The first meeting was held in May 2002, and additional meetings have been held annually.

Attempts to Introduce New Pricing Formulas

Actual Transaction Price. Following discussions in 1999 with the United States, South Korea agreed to allow foreign pharmaceutical products to be sold in the South Korean market. It agreed to set the initial reimbursement prices of innovative drugs at the average ex-factory price

[106] Ibid.
[107] U.S. Department of State, Health Care Insurance, *South Korea*.
[108] Ibid.

of the A-7 countries.[109] In subsequent quarters, reimbursement prices were to be determined based on a sales-weighted average of the actual transaction price (ATP) from the previous quarter. This ATP system was designed to discourage hospitals from demanding discounts when buying drugs and then pocketing the difference between the discounted price and the larger reimbursement price provided by the government-operated health insurance system. However, South Korea's poor enforcement of the ATP system prevented reimbursement prices from settling at levels reflecting the reality of the South Korean market.

Triennial Repricing. In effort to further reduce prices, South Korea adopted the Triennial Repricing system effective on January 1, 2003. Under this system, all registered drugs are subject to repricing every three years. It covers all drugs registered on the national reimbursement list at the end of 1999. The system reduced prices for 2,732 products by an average of 7.2 percent in its first year. U.S. industry has raised concerns that the repricing formula appears to disproportionately reduce the price of innovative drugs compared to the price of generics. In addition, the repricing system does not allow for price increases when data supports such action.

Reference Pricing. The South Korean government has been considering implementation of a reference pricing system since 2001. Such a system faces considerable opposition from doctors, hospitals, patient's associations, and other domestic stakeholders, as well as foreign pharmaceutical companies. The South Korean government shelved the proposal.

Study on Managing Drug Expenditures

The NHI Reform Commission commissioned a study on ways to manage drug expenditures. In August 2004, details of the study became public. They include the following:

1. Establishing a positive list to evaluate the cost effectiveness of a new drug to determine whether reimbursement will be allowed; and
2. Establishing price-volume agreements, which would allow the South Korean government to reduce price reimbursements when sales exceed an estimated level.

[109]The A-7 countries include the United States, the United Kingdom, Germany, France, Italy, Switzerland, and Japan.

Overview of European Union vs. Member States' Roles

While applicable EU pharmaceutical legislation focuses on some aspects of marketing, safety, and transparency and authorization procedures, two other key issues, namely pricing and reimbursement levels, remain entirely with the member states and vary considerably. Consequently, pharmaceutical prices are not subject to free market forces, and vary significantly between countries as a result of their differing national health care programs and policies.

Pricing remains an issue. Unlike other goods, pharmaceuticals are often either purchased by governments or reimbursed by governments that consequently have an incentive to keep prices low. These price differentials have resulted in significant parallel trade. The Netherlands, Denmark, and the United Kingdom are the largest parallel importers.

Legislation establishing the European Medicines Agency (EMA) and the Directive on the Community Code relating to Medicinal Products for Human Use was passed on March 31, 2004. The EMA, located in London, will coordinate the scientific evaluation of pharmaceuticals and provide scientific advice to member states and technical support on questions relating to quality, safety, and efficacy. EMA will also disseminate information on adverse reactions to medicines and assist member states with pharmacovigilance.

Certain medicines—those derived from biotechnology or designed for AIDS, cancer, neurodegenerative disorders, diabetes, or orphan medicinal products—must be registered through EMA, the latter three by November 10, 2005. The regulation establishing EMA (No. 726/2004) stipulates that by 2008, medicines for viral or autoimmune diseases and other immune dysfunctions must also be registered through the EMA. Medicines not derived from biotech or not pertaining to the diseases listed above will have the option of being registered through the EMA or through the member state. Title 1, art. 1 of the regulation states that the regulation "shall not affect the powers of the member states' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes."

A separate directive (2004/27) sets out registration requirements and IPR protection for EU member states. It provides data protection of eight years for files and ten years for marketing, which must be implemented before October 30, 2005. The G-10 Medicines Group was established as an advisory group to focus on competitiveness and health issues. It consists of health and industry ministers from five member states, representatives from different sectors of the industry and of mutual health funds, and a specialist in patient issues. The group has been influential in making recommendations for the pharmaceuticals legislation in the European Union.

France

France is one of the major players in the European pharmaceutical industry and since 1995, has been the leading drug-producing nation in the European Union (EU).[110] The French market for pharmaceuticals increased by 2.2 percent in 2002 to $21.2 billion.[111] France is one of the highest per-capita (US$382) consumers of pharmaceuticals in the world and more than twice that of the United Kingdom (UK).

The French national health system covers virtually the entire French population for at least part of medical costs.[112] Because of the high level of the state coverage of drug spending, doctors and patients have little incentive to limit the amount of drugs consumed by French patients.[113] The French government recently cut compensations and put pressure on doctors to prescribe fewer or cheaper drugs to patients in an effort to control costs, which has cut government spending to about 2 percent compared to 10 percent in the mid-90s.[114] These changes have lead to an expansion of the share of the generic market in France, which remains relatively low.

France was the world's third largest producer of pharmaceuticals in 2001, employing approximately 96,300 persons.[115] The industry is comprised of major publicly owned multinationals and several privately owned companies. Many of the industry's small firms, however, are struggling to survive in an increasingly competitive environment.[116] The French company, Aventis, continued to lead in terms of market share in 2000, accounting for 16 percent of the market, followed by Sanofi Synthelabo with 12 percent, and GlaxoSmithKline with 8 percent. Other major French companies include Roussel Uclaf, Pierre Fabre, Laboratories Fournier, and Beaufour Ipsen. The industry is becoming more concentrated with the four leading companies now accounting for nearly 43 percent of the market. In 2004, Aventis and Sanofi-Synthelabo merged.[117] There were 300 companies in 2002 that marketed at least one pharmaceutical product in France, compared with 350 a decade ago, and 1,000 in the 1950s.[118] Nevertheless, of the 300 pharmaceutical companies in France, less than 40 percent have a majority of French capital. The remaining share was accounted for by multinational subsidiaries.[119]

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[110] Faiz Kermani, *France Fights for Its Pharma Future*, Chiltern International (May 20, 2004), found at *www.inpharm.com* and retrieved on June 2, 2004.
[111] Euromonitor International, *Pharmaceuticals in France* (June 1, 2002), p. 1, found at *www.marketresearch.com,* retrieved (ordered) on June 10, 2004.
[112] WPM Espicom Business Intelligence, *World Pharmaceutical Markets, France* (September 2000), p. 1, found at *http://news.investinfrance-nordic.org/1/txt/Pharma%20in%20France.pdf*, retrieved on June 22, 2004.
[113] Euromonitor International, *Pharmaceuticals in France*, p. 1.
[114] Ibid.
[115] European Federation of Pharmaceutical Industries and Associations (EFPIA) member associations (official figures). EFPIA is essentially Europe's pharmaceutical association, the equivalent of PhRMA in the United States.
[116] Ibid.
[117] Ben Hirschler, "Pfizer Sees More M&A in Tough Europe Drug Market," *Reuters News Article (*July 12, 2004).
[118] Euromonitor International, *Pharmaceuticals in France*, p. 1.
[119] WPM Espicom Business Intelligence, *World Pharmaceutical Markets, France*, p. 1.

France is one of the largest exporters of pharmaceuticals in the world. In 2002, the total French pharmaceutical exports were valued at US$17 billion. Due to its low, state-controlled prices, France is a prime source for inexpensive drugs. The major buyers are Germany, the United Kingdom, Belgium, Italy, Spain, and the Netherlands. In 2002, France imported pharmaceuticals valued at US$9.7 billion, an increase of 6 percent annually.[120]

R&D Costs and Expenditures

The pharmaceutical industry in France has experienced a succession of mergers giving way to huge multinationals with very large R&D budgets. The French pharmaceutical industry invested approximately 15 percent of its profits, approximately €4 billion, in R&D in 2001.[121] R&D activity represented 70 percent of total spending, approximately the European average. However, the larger predominantly French-owned companies have much higher levels of R&D investment. An increasing percentage of this research is being carried out abroad. According to a survey by the Ministry of Research, French pharmaceutical groups conduct nearly 45 percent of their research activities outside of France.

Three major firms[122] account for about 60 percent of the total pharmaceutical R&D spending in France; subsidiaries of foreign multinationals account for another 30 percent, and smaller independent French firms contribute the remainder.[123] Virtually all R&D in France is privately financed by private pharmaceuticals companies. Less than 1 percent comes from public funds.[124]

The French government is attempting to improve the R&D environment for its pharmaceutical industry and prevent any further decline without changing its price control regime. In 2003, the French government launched several programs to sustain innovation, including reforming the R&D tax credit scheme and creating a new fiscal status for emerging innovative companies. In January 2004, the French Minister for the Economy, Finance, and Industry commissioned a fact-finding report, entitled *PharmaFrance 2004*, detailing measures that could improve France's R&D position.[125]

Drug Approval Process

The French pharmaceutical industry typically identifies about 100,000 drugs a year that are submitted for preliminary testing. From those drugs initially screened, about 10 will apply for a patent application, and only one may come through all tests and clinical trials. The cycle from innovation to use in actual patients is 12 years on average. The cost of developing a new

[120] A Levy, "Industrial Analysis: Pharmaceutical-France" (draft. ITA-Paris, August 2004).
[121] Euromonitor International, *Pharmaceuticals in France*, p. 1.
[122] Aventis Pharma, Sanofi-Synthelabo, and Sevier.
[123] Pierre Fabre, Beaufour-Ipsen, and Fournier.
[124] WPM Espicom Business Intelligence, *World Pharmaceutical Markets, France*, p. 139.
[125] Kermani, *France Fights for Its Pharma Future*.

drug is approximately €800 million. After obtaining a patent, a company must apply for marketing authorization, and approval by the Transparency Commission.[126]

Health Care Coverage

Health costs are covered by the central government, by patients' out-of-pocket payments, and by Mutual Insurance Funds (MIFs). MIFs provide supplemental and voluntary private insurance to cover cost-sharing arrangements and extra billings. MIFs account for 6 percent of health expenditures. The French health care system, funded by the Social Security program, is administered by the Ministry of Health, followed by 21 regional health offices that administer programs in each of the 95 provinces.[127]

The system of health insurance funding was changed in January 2000 with the replacement of employee health contributions to occupational funds by a new tax (deductible from income) known as the Universal Health Charge (Cotisation Maladie Universelle or CMU), and the extension of health insurance to all French citizens. Since the introduction of the CMU, people with low income who are not covered by complementary insurance have access to doctors and hospitals free of charge.[128]

Pricing

France has one of the strictest pricing systems in Europe. Data from the French pharmaceutical trade association indicate that although the cost of living more than doubled between 1980 and 2000, the retail price of pharmaceutical products increased by only 34 percent over the same period. Overall, French prices are close to the European average. Nonetheless, French patients spend relatively more on pharmaceuticals than other OECD countries and successive governments have pursued cost containment policies as a means to drive down drug spending.[129]

The government regulates the prices of reimbursable drugs. The Social Security Code provides the procedures and criteria for pricing and reimbursement listing. Pricing decisions are jointly agreed between the Ministry of Social Affairs and the Ministry of Economy.[130]

To encourage further generic substitution, the French government implemented a new pharmaceutical distribution margin system. The generic market is currently estimated to account for only 4 to 6 percent of the total prescription market, with sales valued at €800 to €1,000 million.

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[126] LEEM, "The Life Cycle of Drugs," *The French Pharmaceutical Industry: Facts and Figures 2002*, p. 13.
[127] PNHP, Physicians For a National Health Program, *International Health Systems* (March 27, 2003), found at *www.pnhp.org/facts/international_health_systems.php?page=all*, and retrieved on June 24, 2004.
[128] WPM Espicom Business Intelligence, *World Pharmaceutical Markets, France*, p. 44.
[129] Kermani, *France Fights for its Pharma Future*.
[130] WPM Espicom Business Intelligence, *World Pharmaceutical Markets, France*, pp. 20–22.

Germany

Germany is one of the largest pharmaceutical markets in Europe. Pharmaceuticals produced in Germany account for approximately 6 percent of global production total. The country remains among the top five producers in terms of value and is the world's third largest consumer of pharmaceuticals after the United States and Japan.[131] The German Pharmaceutical and Biotechnology Industry Association (BPI) reports that exports of drugs from Germany were €16.3 billion in 2002 and €14.7 billion in 2003.[132] BPI also puts imports at €18.8 billion in 2002 and 2003. In 2002, the pharmaceutical industry employed nearly 115,000 people.[133]

Germany's share of the world's pharmaceutical output has declined from 9 percent in 1990 to 6 percent in 2000.[134] Moreover, German market share of global pharmaceutical sales declined from 5 percent in 1997 to 4 percent in 2002.[135] Of all prescription pharmaceutical sales in 2002, 73 percent were brand name compounds, down 7 percent since 2001.[136] The market share of imports has increased from €49 million (3.1 percent) in 2000 to €1.3 billion (7.1 percent) in 2002.[137]

R&D Costs and Expenditures

The German pharmaceutical industry's expenditures on R&D rank among the highest in Europe. R&D spending in Germany grew during 1985–1999, although the rate of increase slowed over the period. R&D expenditures increased by about 22 percent during 1996–1999 compared with a fourfold increase in R&D spending during 1985–1994. Pharmaceutical R&D spending averaged about 50 percent more than that in other German industry sectors.

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.

Member companies of the German Research Pharmaceutical Association, Verband Forschender Arzneimittelhersteller (VFA), increased R&D expenditures in 2002 by 6.9 percent to €3.59 billion from 2001. On average, these companies spent 16 percent of their German sales on R&D.[138] VFA states that in 2002, "27 innovative pharmaceuticals received marketing authorization in the German pharmaceutical market."[139]

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[131] Invest In Germany, "Germany's Pharmaceutical Industry" (March 2004), p. 9, found at *www.invest-in-germany.de/upload_files/20040319184616_pharma_brochure_english_2004.pdf*, retrieved June 7, 2004.
[132] German Pharmaceutical and Biotechnology Industry Association, found at *www.bio-pro.de/.*
[133] Invest In Germany, "Germany's Pharmaceutical Industry," p. 10.
[134] Ibid.
[135] Ibid.
[136] Ibid.
[137] Ibid. These imports are principally patented innovative pharmaceuticals.
[138] VFA, *Statistics 2003: The Pharmaceutical Industry in Germany*, p. 24.
[139] Ibid. p. 4.

Drug Approval Process

Pharmaceutical companies must apply for initial marketing authorization at the Federal Institute for Drugs and Medicinal Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)). BfArM must approve pharmaceutical products for use before they can be placed on the market in Germany.[140] 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 system of pharmaceutical approval is considered to be one of the most efficient in the EU, leading many drug manufacturers who wish to pursue mutual recognition within the European Union to try to seek initial approval in Germany.[141]

Health Care Coverage

The German health care system provides universal health care. Currently, apart from capital investment in the inpatient hospital and clinic settings, it is reportedly financed through 290 sickness funds under the statutory health insurance (SHI) system and approximately 60 private health insurers.[142] The statutory or public sickness funds are self-governing, nonprofit insurance funds organized on a regional, company, occupational, or national basis and funded by employee/employer contributions, as well as pension funds and unemployment funds. Germany's system differs from the U.S. in that premiums are assessed as a percentage of wages, putting great pressure on the SHI revenue side.

The 10 largest statutory sickness funds have an average premium rate of 14.4 percent.[143] 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 private insurance instead, and about 8 percent do so. The density of primary care doctors is below the EU average.[144]

Germany also provides universal access to inpatient prescription drugs for citizens over age 65. Senior citizens in Germany have outpatient drugs included in their overall health care premiums; there is no deductible, and co-payments are limited to pack size as in the reference price system. Maximum co-payments are no more than 2 percent of patient annual income. Those with chronic disease are limited to 1 percent of total income.[145]

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[140] Germany's Federal Institute for Drugs and Medicinal Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)), found at *www.bfarm.de.en/drugs/index.php*, retrieved June 9, 2004.
[141] USITC, inv. No. 332-419, "Pricing of Prescription Drugs," p. 3-25.
[142] Betriebskankenkassen Bundesverband, found at *www.bkk.de/bkk/pressemitteilungen/powerslave,id,i3,nodeid,15.html*.
[143] Ibid.
[144] Ibid, p. 4-20.
[145] Ibid, p. 4-20.

The German government has faced growing pressure financing the costly SHI system. Germany's economic stagnation in recent years, and especially high unemployment, mean there are fewer people paying into the system. In addition, the government has exacerbated the financial problems of health care funds by limiting payments to health care funds from the pension and unemployment contributions, in response to shortfalls in those social funds. Costs are increasing as well, in part because of increased life expectancy, which is rising more rapidly in Germany than in other industrialized nations, but also from increases in costs for hospitals, doctors, and pharmaceuticals. In 2002, the top four areas of SHI expenditures were hospital visits (34 percent), doctor's treatment (17 percent), other health services (17 percent), and prescription drugs (16 percent).[146]

Over the past few years, the SHI has faced many issues resulting in what Germany's Federal Ministry of Health and Social Security, the Bundesministerium für Gesundheit und Soziale Sicherung (BMGS), calls a "problematic revenue and spending trend in statutory health insurance."[147] In October 2003, the German government passed the Act on the Modernization of Statutory Health Insurance (referred to as the GMG in Germany), which went into effect on January 1, 2004. Its goal was to reduce the general contribution rate to 13.6 percent while relieving the SHI by approximately €9.8 billion.[148] The German federal government asserts that "a balanced distribution of the costs is necessary to reduce average health insurance contributions to 13 percent for the long term, cut add-on costs, and provide more employment."[149] This effort to reduce non-wage benefit costs is part of an overall economic structural reform plan to reduce Germany's high unit labor costs and increase the competitiveness and attractiveness for investment of the German economy. Discussion continues on how to address long-term decline in premium revenue.

Co-payments

In 2004, the co-payment levels were changed under the GMG reform of the SHI, with a minimum of €5 and maximum of €10 for pharmaceuticals not subject to reference prices. As before, patients must pay 100 percent of the difference over reference price.[150]

Pricing

Germany implemented a reference price system as part of the Health Care Reform Act implemented on January 1, 1989. Reference prices are fixed by the sickness funds for groupings

[146] *Invest in Germany,* "German Health Care Market" (September 2003), p. 15.
[147] Bundesministerium für Gesundheit und Soziale Sicherung (BMGS), "Modernization of the Health Service," found at *www.bmgs.bund.de/downloads/DieReformenglish.pdf*, retrieved Jul. 1, 2004.
[148] BVMed, "Annual Report 2003/2004," p. 5.
[149] Bundesregierung, "Agenda 2010, Health," found at *www.bundesregierung.de/en/News-by-subject/Agenda-2010,11317/Health-care.htm*, retrieved Jul. 9, 2004.
[150] Ibid., p. 7.

of drugs established by a federal committee of representatives of physicians' associations and the sickness funds.

If prices exceed the reference price, the patient is required to pay the difference. In practice, however, it has reportedly not been feasible for suppliers to set prices higher than the reference price because the insured patients were generally not willing to pay the out-of-pocket expenses, and doctors have been reluctant to prescribe drugs priced above the reference price. Thus, reference prices in practice typically represent the *de facto* upper limit of prices.

The system, which covered patent and non-patented pharmaceutical products, had a negative impact on the German pharmaceutical industry. The German government revised the system in 1996. Key changes included removal of patented drugs from reference pricing, cessation of mandatory dispensing of drugs brought into Germany by parallel imports, and the encouragement of biotechnology investment.

Seeking to contain growing budgetary pressures, the Germany government revised the system again in 2004. Certain patented pharmaceuticals were again subject to reference pricing. An independent federal committee is currently developing the reference price groups, and the reference pricing including patented pharmaceuticals is to take effect in January 2005. On July 20, 2004, the independent federal committee charged with setting up reference pricing groups, established a pricing group combining generics and patented pharmaceuticals (generally known as "jumbo groups") for statins (cholesterol control drugs). It intends to announce other jumbo groups in the coming months.

The health care reform included an "innovation clause," which allows pharmaceuticals with special therapeutical qualities to be exempted from reference pricing. However, the criteria for determining whether a drug meets these qualities needs to be clarified further.

In addition, since 2003, the German government has required pharmaceutical companies to pay a 6 percent mandatory rebate to statutory health funds. To provide immediate savings to the health fund system while reference pricing is being developed, this rebate was increased to 16 percent in January 2004. The government has stated it intends the rebate to revert to 6 percent once reference pricing is introduced.

Greece

The pharmaceutical market in Greece is estimated to total $2 billion, the majority of which was supplied by imports and is expected to grow at an annual rate of around 8 percent a year for the next five years.[151] The import share totaled 68 percent in 2002, locally produced and packaged medicinal products were 21 percent and 11 percent of the market, respectively. The import market is expected to grow between 15 to 20 percent annually.

Greece's health expenditure totaled $16.28 billion (or 9.5 percent of GDP) in 2002.[152] Pharmaceutical expenditures comprised 15.3 percent of the total health expenditure in 2002.[153] Generics account for 10.6 percent of the total market value in Greece in 2002.[154]

The Greek pharmaceutical industry is comprised of 66 pharmaceutical companies. These companies accounted for 90 percent of Greece's pharmaceutical market for 2001, with 54.9 percent of this market represented by only 10 companies.[155]

R&D Costs and Expenditures

The Department of Drugs and Drugstores in the Ministry of Health and Welfare promotes research and development in the Greek health care sector. However, there is no significant pharmaceutical research in Greece; most research is done by multinationals in other countries.[156]

Drug Approval Process

The Ministry of Health and Welfare is responsible for licensing pharmaceuticals and regulating the industry through its National Drug Organization (NDO). A working group called the Moutsopoulos Group oversees the drug approval process onto Greece's positive list. The group is composed of seven members: two professors from a Faculty of Health Sciences, one National Health System (ESY) registrar, one pharmacist with five years of work experience in ESY, and one doctor/pharmacist from NDO, Institute of Social Insurance (IKA) and Organization of Agricultural Insurance (OGA).[157]

The application procedure follows the EU Directive 89/105. Products must satisfy several criteria in order to be listed on Greece's positive list: efficacy, tolerance, safety of the product

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[151] U.S. and Foreign Commercial Service and U.S. Department of State, *Industry Sector Analysis: The Greek Market for Drugs and Pharmaceuticals* (April 2004).
[152] PhRMA, "FRN Submission Appendix A: Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries" (July 1, 2004), p. 21.
[153] Ibid.
[154] PhRMA, p. 22.
[155] Ibid.
[156] PhRMA, p. 22.
[157] V. Kontozamanis, *Greece: Pharmaceutical Pricing and Reimbursement Policies*, p. 8, *http://pharmacos.eudra.org/F3/g10/docs/tse/Greece.pdf*.

compared to other similar products, and reimbursement amount from European countries.[158] Health economic evaluations are being considered as one of the factors in eligibility, but the country has not taken any actions to implement it.[159] The drug will not be approved unless it has been first granted a market authorization in other EU countries.[160] Not unlike other countries, pharmaceutical manufacturers seeking approval for sale in Greece must provide specific information with the application for approval: the drug's complete quantitative composition; preparation process; therapeutic indications; contraindications and side effects; mode of administration; previous test results; and drafts of information sheets for doctors, pharmacists, and users. Once the procedure is done, the list is published in the press and in the Greek Government Official Gazette; the list goes into effect the minute it is published.[161]

Pharmaceutical imports require special approval from the NDO. New product licenses officially require seven months for approval, but in practice the time is much longer (usually around two years). Marketing licenses are valid for five years. The same registration procedure applies to both over-the-counter and prescription-only medicinal products.

Health Care Coverage

The Ministry of Health is responsible for provision of health care and development of health policy. Ninety-nine percent of the population is covered by health insurance. The ESY, established in 1983, is funded by taxation, social insurance (employer and employee contributions), and private insurance schemes. Social insurance covered 53 percent of total expenditures in 2000.[162] Payments from private health insurance account for 2.3 percent of the funding and patients' out-of-pocket payments account for the remaining 41.4 percent.[163] Ninety-five percent of the population has supplemental health insurance,[164] and 90 percent of the population is insured under three insurance schemes:

1. Institute of Social Insurance (IKA): covers 55 percent of the population[165]
2. Organization of Agricultural Insurance (OGA): covers 23 percent of the population[166]
3. Fund for Merchants, Manufacturers, and Small Businessmen (TEVE)

All the funds have primary, secondary, pharmaceutical, and dental care reimbursement plans. Forty of 300 social insurance organizations provide coverage against sickness; the funds are allocated by occupation.[167] The uninsured and the needy have free access to public hospital

[158] PhRMA, p. 22.
[159] P. Kanavos, *Overview of Pharmaceutical Pricing and Reimbursement Regulation in Europe,* p. 12, *http://pharmacos.eudra.org/F3/g10/docs/synthesis.pdf*.
[160] Kontozamnais, *Greece*, p. 8.
[161] Ibid.
[162] PhRMA, p. 21.
[163] Ibid.
[164] Ibid.
[165] Kontozamanis, *Greece,* p. 2.
[166] Ibid.
[167] Ibid.

outpatient departments in health centers in rural areas.[168] Patients' co-payment rates for drugs are the same for all insurance funds and set at 0 , 10, or 25 percent. Co-payment rates depend on the type of illness and population group.[169] Generally, rates of co-payment for prescription drugs are set at 25 percent for all funds.[170] Some drugs are permitted to be dispensed only by public hospitals.

Pricing

The Directorate of Prices and Medicinal Products in the Ministry of Development sets pharmaceutical prices. The pricing committee in the Ministry of Development consists of nine members and is responsible for giving expert, nonbinding opinion on pharmaceutical prices.[171] The committee operates under the General Secretariat of Commerce and consists of three representatives from the General Secretariat, a representative from the NDO, a representative from the Ministry of Finance, two pharmaceutical industry representatives, and a pharmacist.[172]

Greece follows the EU Directive 89/105, in which drug-pricing decisions must be granted within a 90-day period.[173] However, in practice, these deadlines have not always been met. Prices are published in a Price Bulletin, which is published in the press and the Greek Government Official Gazette.

Separate pricing procedures apply to imported and domestically produced pharmaceuticals.[174] The lowest ex-factory European price applies toward imported products, while production and distribution cost factors are taken into account for domestic products.[175] Greece uses the basic cost formula for locally produced pharmaceuticals; the country will not grant a price unless a product is marketed in one European country.[176] A three-year monitoring period applies after a price is set for a specific product, and the maximum price of the product in Greece is reduced if a lower price is recorded in Europe during that period.[177] Basically, the product's maximum retail price is relative to the price of the same product in neighboring countries.[178] The price is reexamined annually, and the Management of Prices and Industrial Products and Pharmaceutical Products—General Division of Interior Commerce—General Secretariat of Commerce investigates whether the reference prices have fallen in order to readjust.[179] If the Ministry of Health or the National Drug Organization deems the

[168] Ibid.
[169] PhRMA, p. 22.
[170] Kontozamanis, *Greece*, p. 10.
[171] Ibid., p. 4.
[172] Ibid.
[173] Ibid.
[174] Ibid., p. 21.
[175] Ibid.
[176] Kanavos, *Overview,* p. 5.
[177] PhRMA, p. 22.
[178] Kanavos, *Overview,* p. 9.
[179] Kontozamanis, *Greece,* p. 5.

pharmaceutical as a necessity to the public's well-being, the procedure is exempted for the drug.[180]

Generic prices are set at 80 percent of the original product's price, but generic products are not actively promoted by health insurance organizations.[181] Prices of over-the-counter (OTC) products are also regulated and can only be sold by pharmacies.[182]

[180] PhRMA, p. 22.
[181] Kanavos, *Overview,* p. 22.
[182] Kontonzamanis, *Greece,* p. 8.

Poland

The Polish pharmaceutical market has grown rapidly in the last few years. Poland's pharmaceutical market value was at $3.6 billion in 2003[183] and health spending per capita totaled $246 in 2000. Total health care expenditure as a percentage of GDP equaled 6 percent.[184] Forecasts predict the pharmaceutical market will be $4.5 billion in 2005.[185] There are approximately 200 pharmaceutical firms active in Poland, most of them relatively small, and overall, employing around 20,000 people.[186]

Prior to the fall of communism, and due to the lack of patent protection for drugs before 1993, the state owned the Polish drug companies and focused mainly on generic drugs. The prevalence of generic drugs continued after 1989, mainly due to the low purchasing power of the society and the limited budgets of the state refund system.[187] According to industry, generic drugs now account for 65–70 percent of pharmaceutical consumption by volume and 30 percent by value.[188] Foreign investments in the Polish pharmaceutical industry are estimated to be in excess of $600 million.[189]

R&D Costs and Expenditures

Currently, innovative drug research is scarce in Poland. There is a relative abundance of educated scientists and the internal market is sizable, yet the country lacks innovative research and development due to the dearth of necessary capital and facilities.[190] Researchers active in Poland must travel periodically to other countries to use laboratories to support their research.[191] Cooperation is being sought between academia and industry to encourage new product development.[192] The shortage of venture capital funds specializing in biotech and pharmaceutical companies is also likely to slow the growth of the native Polish biotech industry.

Drug Approval Process

Registration of a new drug is based on effectiveness, quality, safety, price, and availability of similar drugs. Since 1989, applications for registration have rapidly increased to

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[183] PhRMA, "FRN Submission Appendix A: Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries" (July 1, 2004), p. 47.
[184] Ibid.
[185] W. Rzycki, "The Polish Pharmaceutical Industry—Dynamic Growth in a Challenging Legal Environment," *www.samedanltd.com/members/archives/PMPS/Summer2002/WladyslawRzicki.htm*.
[186] Ibid.
[187] Ibid.
[188] PhRMA, p. 47.
[189] Rzycki, "The Polish Pharmaceutical Industry."
[190] Ibid.
[191] Ibid.
[192] World Health Organization, Regional Office for Europe, *Country Profiles:* Poland, available at http://www.euro.who.int/pharmaceuticals/Topics/Overview/20020415_1.

3,000 per year. Many applications of new drugs are herbal medications, vitamins, and galenic drugs.

To have a pharmaceutical product admitted for sale in Poland, the Ministry of Health and Social Welfare must issue a registration certificate in accordance with the Pharmaceutical Products, Medical Materials, Pharmacies, Wholesalers, and Pharmacy Inspection Law. Applicants must cover the cost of laboratory tests of pharmaceutical products carried out by appropriate analytical departments on request in addition to the registration fees.[193] Applications for the registration of drugs, vaccines, allergens, and diagnostic kits are submitted to the Bureau of Drugs in the Institute of Drugs in Warsaw. The Ministry of Health issues registration certificates after the Drug Registration Committee, a subset of the Institute of Drugs, approves the pharmaceutical product.[194] The Pharmaceutical and Medical Materials Registration Office was established to assist the registration committee in speeding up the process. The Institute of Hygiene evaluates vaccines.

In general, it takes about two years to register a product in Poland.[195] Products of Polish origin have priority in the registration process.[196] On the other hand, Poland is one of the 10 Central and Eastern European countries that signed the Collaboration of Drug Regulatory Authorities in European Union Associated Countries (CADREAC) procedure agreement, which, since January 1999, has given fast-track registration to products approved under the European Union system,[197] thus pharmaceutical products approved under the European Union are approved in Poland in about three months.[198]

The Drug registration committee (the Bureau of Drugs and Medical Materials Registration) is composed of 18 members who serve five-year terms and meet monthly to grant approvals.[199] Companies must submit details of proposed prices, samples for analytical testing and a free sales certificate from the country of origin of the manufacturer.[200]

Recently, Poland's accession to the European Union compelled it to initiate a new set of pharmaceutical laws and the government negotiated a transition period in order to allow Polish producers to supplement and upgrade their registration files to meet the new standards during such periods.[201] The expiration date for the transition period is December 31, 2008. With respect to any product registered after January 1, 2004, but prior to the expiration of the transition period, the registrant will need to comply with the new, more stringent registration rules.[202]

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[193] Ibid.
[194] Ibid.
[195] Ibid.
[196] Ibid.
[197] Z. Sobiepanek, "Pharmaceutical Sales," (2001), available (in Polish) at *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr-77132e.html* and *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/fr/gr-74193f.html.*
[198] Ibid.
[199] Ibid.
[200] Ibid.
[201] W. Rzycki, "The Polish Pharmaceutical Industry—Dynamic Growth in a Challenging Legal Environment," available at *www.samedanltd.com/members/archives/PMPS/Summer2002/WladyslawRzicki.htm*.
[202] Ibid.

Under the new pharmaceutical law, the Office of Registration was set up in October 2002 to replace the Bureau of Drug Registration,[203] but the office is not independent and the Drug Commission still has an advisory role. In addition, increased power has been given to the Minister of Health in granting marketing authorizations.[204]

Health Care Coverage

Poland's communist era health care system offered universal coverage with a comprehensive program of health care benefits distributed through facilities owned and run by the state, but it was costly and inefficient. In 1990, the government implemented significant reforms to change the system from a centrally controlled, budget-based system to a decentralized insurance-based system. In January 1999, a new general obligatory health insurance system entered into force, giving patients more choice and decentralizing the health services.[205] The government deducts 7.5 percent of gross wages from each Pole's earnings and put in patients' funds. Poland is now divided into 16 provinces, each of which has its own patients' fund that is administered independently of the local government. All health care services provided by physicians and institutions, both private and publicly owned, are covered by these funds.[206]

Reimbursement from the Ministry of Health and Social Welfare depends on the type of drug on the basic and supplementary list, and the type of patients. Drugs on the basic list are available at a flat fee equivalent to 0.05 percent of the minimum hourly wage. On average, the government spent approximately $30 per patient on medicine in 1998, the total spending on medicine was actually around $58, meaning that patients pay a proportion, usually 30–50 percent of the cost of drugs on the supplementary list.[207] Pharmacists are required to dispense the cheapest drugs, and the state only reimburses the cost of the cheapest drugs, leaving patients to pay the difference.

Committees of medical and pharmaceutical experts issue guidelines on cost-effective prescribing, which the Chamber of Physicians publishes in regular bulletins along with the reimbursement regulations. The Ministry of Health and Social Welfare plans to influence prescription behavior by forming a computerized database on practitioner prescribing habits and associated costs. This information feeds back to doctors to enable them to compare their own prescribing pattern and costs to the average pattern and cost and to the guidelines.

The level of reimbursement depends on the Drug Registration Committee's determination of the product efficacy. Essential drugs receive 100 percent reimbursement, while second tier

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[203] IMS Health, *Poland Moves Towards EU Membership*, available at *www.ims-global.com/insight/news_story/0303/news_story_030327.htm.*
[204] Ibid.
[205] C. Gray,"Polish health care morphs into new system at breakneck speed," *Features Chroniques* in CMAJ (September 21, 1999) p. 1. Available at *http://collection.nlc-bnc.ca/100/201/300/cdn_medical_association/cmaj/vol-161/issue-6/pdf/pg739.pdf.*
[206] Ibid.
[207] European Commission, Enterprise Directorate-General, "Poland: Health Care, Pharmaceutical Pricing and Reimbursement," p. 13. Available at *http://pharmacos.eudra.org/F3/g10/docs/tse/Poland.pdf.*

drugs receive 70 percent, and third tier receive 50 percent. Drugs that do not qualify for reimbursement can be purchased with private funds.[208]

In addition, there are prescribing controls in Poland. The Sick Funds are responsible for monitoring and controlling the issuing and dispensing of prescriptions. Inspectors are stationed at pharmacies to monitor prescriptions and pharmacies are responsible for repayment of unjustified reimbursement.[209]

Pricing

Poland operates a reference pricing system of reimbursement.[210] The reimbursement list is operated under the Health Insurance Fund.[211] If the therapeutic group to which the new drugs belong is included on the reimbursement list, the new drug can be added to the same list, but the reimbursement price will be set at the lowest price in the group. Prices of imported generics are set at the level of the cheapest generic equivalent.[212]

As of 2000, Poland used a three drug-pricing system:

1. Locally produced reimbursed drugs: The Ministry of Finance set prices for domestically manufactured prescription medicine. The average prices are usually 20–50 percent of their equivalent in the European Union market. The prices are calculated based on a "cost-plus" formula.[213] Prices are usually revised once a year; price increases are kept below inflation rates.[214]
2. Imported reimbursed drugs: The Ministry of Health negotiates imported pharmaceuticals. On average, prices are 20–30 percent lower than in the country of origin. Negotiated prices are set in foreign currencies.[215]
3. Non-reimbursed drugs: These pharmaceuticals are not under any price control.

The price setting mechanism has resulted in a wide price differential between imported branded products and domestic generic products,[216] but changes are being made due to Poland's accession into the European Union.[217]

Foreign pharmaceutical companies have raised concerns that the criteria for determining reimbursement pricing are nontransparent.[218] In establishing reimbursement prices, the Polish

[208] Ibid.
[209] Sobiepanek, "Pharmaceutical Sales."
[210] Ibid.
[211] PhRMA, p. 47.
[212] Sobiepanek, "Pharmaceutical Sales."
[213] European Commission, "Poland," p. 13.
[214] Ibid.
[215] Ibid.
[216] Sobiepanek, "Pharmaceutical Sales."
[217] European Commission, "Poland," p. 13.
[218] Sobiepanek, "Pharmaceutical Sales."

government takes into account prices in relative low-priced EU markets such as France, Greece, Portugal, Spain, the Czech Republic, Hungary, Slovakia, and Lithuania,[219] but different reference countries are used for different cases.[220]

Under the Ministry of Health, the reimbursements are determined based upon the recommendation of a Drug Management Team.[221] The members of the team include three representatives from each of the Ministries of Health, Finance, and Economy and may include representatives from the regional branches of the Health Insurance Fund.[222] The pharmaceutical industry has raised serious concerns about the fairness, transparency, and accountability of this process. The team is obliged to notify the applicant if the application is rejected.[223]

Moreover, the industry has raised concerns about the slowness of the process. A price law, implemented in 2001, aimed at ensuring compliance with the EU Transparency Directives (Directive 89/105/EEC),[224] was supposed to ensure that the decision process did not take longer than 90 days from a price submission, or 180 days if both pricing and reimbursement submissions are made simultaneously.[225] However, these time frames are frequently exceeded.

Price increases for compulsory priced drugs have normally been below inflation rates. Prices of domestically produced drugs remain lower than those of equivalent imported drugs. However, the import of foreign drugs has risen, and more drugs are being prescribed. The 1991 Act of Payment for Drugs and Medical Materials limited the cost increase by reducing the numbers of people entitled to state reimbursement.[226] Furthermore, Poland's accession into the European Union may introduce parallel trading into the market, and off-patent drugs and drugs fully protected by patents in the accession countries will be potential legal candidates for parallel trade.[227] Multinational pharmaceutical companies worry that the outcome will be an influx of cheap products into the European Union from Poland due to the low drug prices in Poland.[228] This is a misconception because, in general, the price of local products and branded generics in Poland are more inexpensive, but prices of leading branded products (targets of parallel trade) are actually higher in Poland than many other EU countries. Many of these products, in fact, are not reimbursed and sale volumes are low.[229]

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[219] PhRMA, p. 47.
[220] Ibid.
[221] Ibid.
[222] Ibid.
[223] Jan Rolinski, "Pharmaceutical and the Law," *Warsaw Voice* (April 27, 2004), available at *www.warsawvoice.pl/view/5403*.
[224] Ibid.
[225] Ibid.; see also PhRMA, p. 48.
[226] WHO, *Country Profiles: Poland*.
[227] IMS Health.
[228] Ibid.
[229] Ibid.

United Kingdom

The production of pharmaceuticals in the United Kingdom in 2001 (the latest year for which data are available) was estimated at €22.3 billion, or about $27.6 billion.[230] The U.K. pharmaceutical industry is the fifth largest in the world by total sales after the United States, Japan, Germany, and France.

In 2003, the United Kingdom imported £8.3 billion, or about $13.6 billion, in pharmaceuticals and exported £11.9 billion ($19.5 billion).[231]

Nonetheless, U.K. spending on new medicines is relatively low. In 2002, less than 16 percent of expenditures on medicines went to products launched during the previous five years, compared with 20 to 25 percent elsewhere in Europe and over 29 percent in the United States.[232] At the same time, penetration by generic medicines (those for which patent protection has expired) is higher at 20 percent than in any other European country, except Germany.[233]

As a member of the European Union, the United Kingdom applies the principle of "Community exhaustion," which provides that a patent holder's rights are exhausted once the goods have been put on the market for the first time anywhere in the European Union.[234] As a result, parallel imports of drugs from other EU members account for around 20 percent of the U.K. market.[235]

R&D Costs and Expenditures

In 2002, U.K. R&D expenditures on pharmaceuticals were an estimated £3.2 billion, or about $5.9 billion, with clinical development accounting for almost two-thirds of companies' expenditures.[236] The United Kingdom is estimated to receive a third of the total European investment in pharmaceutical R&D.[237]

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[230]European Federation of Pharmaceutical Industries and Associations (EFPIA), "The Pharmaceutical Industry in Figures: 2003 Update," found at *www.efpia.org/6_publ/Infigures2003.pdf*.
[231]Association of British Pharmaceutical Industry (ABPI) Press Release, "Pharmaceutical Industry Trade Surplus Higher than Expected" (May 19, 2004), found at *www.abpi.org.uk/press/press_releases_04/040519.asp*, retrieved June 30, 2004.
[232]Pharmaceutical Industry Competitiveness Task Force, "Competitiveness and Performance Indicators, 2003," found at *www.abpi.org.uk/publications/pdfs/78324-DoH-PICTF-Indicators.pdf*.
[233]Pharmaceutical Industry Competitiveness Task Force, "Competitiveness and Performance Indicators, 2003," found at *www.abpi.org.uk/publications/pdfs/78324-DoH-PICTF-Indicators.pdf* .
[234]Euractiv, Parallel trade in Medicines, available at *www.euractiv.com/cgi-bin/cgint.exe?204&OIDN=2000574*.
[235]Economic & Social Research Council, "UK Industry Is the Loser from Parallel Trade in Pharmaceuticals" (March 22, 2004), found at *www.esrc.ac.uk/esrccontent/news/mar04-2.asp*.
[236]ABPI, "Facts and Statistics from the Pharmaceutical Industry: Pharmaceutical R&D expenditure in the UK," found at *www.abpi.org.uk/statistics/intro.asp*.
[237]ABPI Press Release, "UK Sees Healthy Growth in Investment, but European Levels Decline" (January 29, 2003), found at *www.abpi.org.uk/press/press%20releases_03/030129.asp*.

The U.K. government has introduced three tax relief programs to encourage pharmaceutical R&D. The first two programs cover R&D generally, while the third specifically targets the pharmaceutical industry.[238] Small to medium-sized enterprises (SMEs), for example, may claim 50 percent of the qualifying costs of R&D against its taxable profits.[239] For SMEs that are incurring losses, claims can be made for cash refund of 16 percent of the loss.[240] A large company can claim 25 percent of the qualifying costs of R&D against its taxable profits.[241] Capital expenditures are not eligible for the relief, but can be eligible for immediate deduction against taxable profits under the Research and Development Capital Allowances rules.[242]

The Vaccine Research Relief (VRR), launched in April 2003, benefits companies who perform R&D for vaccines and medicines for tuberculosis, malaria, and HIV/AIDS. VRR is intended to encourage R&D in diseases that primarily affect developing countries. The relief allows companies to claim an additional 50 percent of the qualifying costs of R&D against taxable profits. SMEs incurring losses can claim cash back, as above, while large companies may use the additional deductions in the normal way, but cannot claim any cash back.[243]

Drug Approval Process

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the pharmaceutical licensing body.[244] In cooperation with the Committee on the Safety of Medicines, the MHRA commissions and oversees clinical trials and ultimately grants product licenses. Pharmaceutical approval practices are considered to be relatively efficient compared to other EU countries. Median approval time for new pharmaceuticals (including clinical trials) decreased from a median of 18 years in 1995 to a median of 15 years in 1997. 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 United Kingdom.

Section 118 of the Medicines Act 1968 prevents authorities from disclosing any information about the process, and thus less information about the clinical trial histories of approved drugs is available than in other countries, including the United States. Although there is

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[238]John Moore, "Effective Relief?" Pharmafocus (September 3, 2003), found at *www.pharmafocus.com/cda/focusH/1,2109,22-0-0-SEP_2003-focus_feature_detail-0-72871,00.html*, retrieved June 25, 2004.

[239]Inland Revenue Service, *IR179 - Research and Development (R&D) Tax Credit* (August 2002), found at *www.inlandrevenue.gov.uk/pdfs/ir179.htm*.

[240]Moore, "Effective Relief?"

[241]Ibid.

[242]European Commission, Commission Recommendation of May 6th, 2003, concerning the definition of micro, small and medium-sized Enterprises, (2003/361/ec). A small enterprise is defined as one which employs fewer than 50 persons and whose annual turnover and/or annual balance sheet total, does not exceed €10 million (about $12.4 million). A medium-sized enterprise is one that employs 50 or more but fewer than 250 persons and which has an annual turnover exceeding €10 million but not exceeding €50 million (about $61.8 million), and/or an annual balance sheet total not exceeding €43 million (about $53.2 million).

[243] Moore, "Effective Relief?"

[244] U.S. International Trade Commission, *Pricing of Prescription Drugs* (investigation no. 332–419), USITC publication 3333 (2000), p. 3–30.

no proof that doctors prescribe certain drugs less because they lack this information, the strict confidentiality of the United Kingdom's system remains controversial.[245]

Health Care Coverage

The National Health Service (NHS) provides comprehensive health care, free to all at the point of delivery. In 2003, the NHS's total budget was £74.3 billion.[246] NHS expenditures per person in the United Kingdom are steadily increasing. The total NHS cost per person in the United Kingdom in 2003 is estimated to have been £1,257, an increase of £104 per person from £1,153 in 2002.[247] Nearly 750 million prescriptions are dispensed every year.[248]

The NHS pays for most drugs prescribed in the United Kingdom.[249] As such, it is in the government's interest to strictly control the cost of pharmaceuticals. Costs are contained in a number of ways including the following:

1. Price and profit controls;
2. Encouragement for the use of generics and patient co-payments;
3. Publication of "negative lists" of inefficient drugs;
4. Publication of a "Selected List" of minor drugs that are not paid for by the NHS; and
5. Campaigns to encourage doctors to control drug expenditures.

Some patients pay either a standard fee for prescribed drugs or a yearly fee for a "Prescription Pre-Payment Certificate" of $168 that covers unlimited prescription costs. The co-payment for prescribed drugs since April 2004 is $11.75. This favors patients who are prescribed expensive or large amounts of pharmaceuticals. Approximately 90 percent of patients, however, are exempt from paying the prescription charge.

Use of drugs is also influenced by the recommendations of the National Institute for Clinical Excellence (NICE). NICE is an independent organization responsible for providing national guidance on treatments and care for those using the NHS in England and Wales. Its main responsibilities are to assess the cost-effectiveness of treatments and to make recommendations about whether or not these treatments should be provided by the NHS.

Pricing

The Pharmaceutical Price Regulation Scheme (PPRS) regulates the prices of branded medicines and profits that manufacturers are allowed to make on their sales to the NHS. The

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[245] Ibid., p.3-31.
[246] The Association of the British Pharmaceutical Industry, "Facts and Statistics from the pharmaceutical industry: 4 Medicines and the NHS," found at *www.abpi.org.uk/statistics/section.asp?sect=4* .
[247] Ibid.
[248] Ibid.
[249] USITC, "Pricing of Prescription Drugs," p. 4-28.

PPRS uses voluntary agreements negotiated between the pharmaceutical industry—represented by the Association of the British Pharmaceutical Industry—and the Department of Health. This scheme covers 80 percent by value of the medicines used in the NHS in both primary and secondary care ($12 billion). The current scheme was negotiated in 1999 and will expire in the last quarter of 2004. A new scheme is currently being negotiated.

Initial launch prices of pharmaceuticals are not controlled, but once manufacturers set an initial price, they must obtain official permission to raise it. If a company's total profit on branded sales to the NHS exceeds the PPRS limit, a company can be forced to reduce prices. If profit falls below an approved level, the company may be allowed to increase product prices. If companies exceed allowed profit, they must either repay the excess profit directly to the PPRS, or lower existing and future prices. Promotional spending is limited to 6 percent of the sales to the NHS or £464,000, whichever is less.[250]

The PPRS does not cover generic pharmaceuticals. The increased use of generic medicines in the United Kingdom has led to rapid price increases and increasing medical costs. In response, the United Kingdom established a maximum price scheme for generic pharmaceuticals in August 2000. The maximum prices are recalculated monthly by the Prescription Pricing Authority.[251]

[250]ABPI and DHS, "The Pharmaceutical Price Regulation Scheme."
[251]United Kingdom Parliament, "First Report: the Cost and Availability of Generic Drugs to the NHS" (December 9, 1999), found at *www.parliament.the-stationery-office.co.uk/pa/cm199900/cmselect/cmhealth/105/10507.htm.* retrieved June 24, 2004.

Switzerland

Pharmaceuticals, the second most important sector in Switzerland, accounts for about 25 percent of all exports of goods from Switzerland.[252] The country is the largest exporter of pharmaceutical products worldwide—more than 90 percent of the drugs produced in Switzerland are destined for export, mainly to Europe, America, and Asia.[253]

Domestically, 28 percent of the drugs sold in Switzerland are produced in country.[254] In 2003, the pharmaceutical market was valued at $2.9 billion. The generic drug industry accounted for 3.6 percent of the market.[255] Patent-protected original brand-name drugs accounted for 59.8 percent of the market.[256] More than a quarter of the market is covered by drugs whose patents have expired but have no generic substitutes.[257]

R&D Costs and Expenditures

Switzerland leads in biological, immunological, and microbiological research. The country is ranked second in molecular biology/genetics, and is ranked third out of all research nations, preceded by the United States and the Netherlands.[258]

Switzerland's three largest pharmaceutical companies—Novartis, Roche, and Serono—alone were responsible for 30 percent of the country's $8.13 billion spent on R&D in 2002.[259] The pharmaceutical industry finances its research activities from risk capital.[260] Novartis, Roche, and Serono alone spent $5.5 billion on R&D worldwide in 2001, equivalent to 17.3 percent of their total pharmaceutical sales, but they sold only $390 million of drugs in their home country.[261] The three companies, on average, develop three new active substances each year to submit for registration.[262]

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[252] E. Mbitha-Schmid, *Pharmaceutical Outlook: Switzerland* (January 29, 2004), available at *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr122993e.html.*
[253] E. Mbitha-Schmid, *Pharmaceutical Market: Switzerland* (May 23, 2003), available at *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr116356e.html.*
[254] Ibid.
[255] PhRMA, "FRN Submission Appendix A: Pharmaceutical Price Controls and Other Market Access Barriers in Developed Countries" (July 1, 2004), p. 58.
[256] Mbitha-Schmid, *Pharmaceutical Market*.
[257] Mbitha-Schmid, *Pharmaceutical Outlook*.
[258] Ibid.
[259] Ibid.
[260] E. Mbitha-Schmid, *Drug research and Development — Switzerland* (May 23, 2003), available at *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr116372e.html.*
[261] Ibid.
[262] Ibid.

Drug Approval Process

The Swiss Federal Law on Medicinal Product and Medical Devices (Law on Therapeutic Products) lays out the rules for the authorization, production, quality control and market supervision of therapeutic products, including pharmaceuticals, and for national and international cooperation between the authorities working the therapeutic product sector.

Swissmedic, the Swiss Agency for Therapeutic Products, is responsible for authorizations, review, and enforcement of all therapeutic products; it monitors all advertising of medical products and, in conjunction with cantonal health authorities, monitors production and trade of medical products.[263]

An application assessment typically takes six to seven months. The process is characterized by five stages:

1. Check the application for completeness.
2. Evaluate the quality, efficacy, and safety of the drug, including assessing the risk-benefit ratio.
3. Analyze the quality of the drug based on clinical and laboratory results.
4. Make a decision. (The authorization announcement is not public.)
5. Perform periodic reviews with the requirement that any negative side effects be reported. (The authorization process must be renewed every five years.)[264]

A fast-track procedure was introduced to ensure the quick availability of particular innovative medicines used for life-threatening or debilitating diseases such as Alzheimer's. The accelerated procedure takes three to four months.[265]

Health Care Coverage

Switzerland requires all of their citizens to have health insurance.[266] Management, delivery, and financing of health services is operated at the canton level, and each canton operates differently, depending on its population, size, etc.[267] Sixty-five percent of all health funds are financed by mandatory private insurance; government contributions, general taxation, and patient co-payments provides the rest.[268] The total health care spending is about 11.2 percent of the GDP.[269]

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[263] E. Mbitha-Schmid, "New Federal Law on Medicinal Products and Medical Devices" (April 3, 2002), available at *http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr111705e.html.*
[264] WPM Espicom Business Intelligence, World Pharmaceutical Markets, Switzerland, "Switzerland — Pharmaceutical Market" (March 15, 2002).
[265] Ibid.
[266] PhRMA, p. 58.
[267] Ibid.
[268] Ibid.
[269] Ibid.

Switzerland's health insurance system has three components: compulsory basic health insurance; voluntary supplementary insurance; and sickness, old age and disability insurance. The Federal Law on Sickness Insurance regulates the basic insurance and daily allowance insurance. It requires that every individual have basic insurance, which covers medical and pharmaceutical care. Basic insurance is not proportional to the insured person's income or other parameters such as age or health, and insurers are required to accept every individual desiring coverage. There are various types of insurance plans with different premiums, but, in most cases, the insured must pay, in addition to the premium, a deductible, as well as a co-payment of 10 percent of the public price of the pharmaceutical up to a given maximum, varying by insurance plans.[270]

Daily allowance insurance and supplemental insurance are optional. Supplemental insurance includes dental care and packages that improve the comfort of the patients, such as better accommodations in a hospital.

The compulsory insurance and the sickness, old age and disability insurance are funded through mandatory income-based employer and employee contributions. Insurance premiums vary by insurance companies, deductible level, residential location, and degree of supplementary benefit coverage chosen.[271] The premiums are federally regulated but not fixed and independent of income; the cost of insurance is around $2,358 per person annually.[272] The government subsidizes the premium for the elderly, disabled, and low-income persons, specifically those whose premium comprises more than 8 to 10 percent of their income.[273]

The Federal Office for Social Insurance draws up a positive list of pharmaceuticals for which the compulsory health insurance system will pay.[274] One third of Swiss pharmaceuticals are on a positive list. The Swiss Federal Office of Public Health oversees the health insurance and maintains the list of medical products covered by sickness insurance benefits according to the health insurance legislation.[275]

The Federal Department of Home Affairs decides which medicines are covered by the compulsory insurance, at what price they should be sold, and determines which laboratory analysis, investigation, medical devices, and medical aids are covered by the compulsory insurance.[276] In its decision, the department consults five different specialist commissions, including the Federal Commission for Pharmaceuticals and the Federal Commission for Fundamental Questions of Health Insurance.[277] The Commission for Fundamental Questions of Health Insurance consists of 17 member representatives from the Federal Office for Public

[270] Ibid, p. 59.
[271] Ibid.
[272] Ibid.
[273] Ibid.
[274] Swiss Federal Office of Public Health, "Benefits under the compulsory basic health insurance scheme," available at *www.bag.admin.ch/kv/grundlag/e/leist.htm*, last update June 2004.
[275] There are essentially two relevant bodies of legislation relating to the pharmaceutical market in Switzerland: the Law on Therapeutic Products and the health insurance legislation.
[276] Ibid.
[277] Ibid.

Health, the Data Protection Agency, Intercantonal Office for the Control of Medicines and the Swiss Competition Commission, and the canton.

Pricing

The Swiss Federal Office of Public Health manages the pricing and reimbursement of pharmaceuticals. The maximum price for a reimbursed pharmaceutical is based on three criteria:[278]

1. Average price of the product in a group of reference countries (Germany, the United Kingdom, Denmark, and Netherlands).

2. Product's therapeutic and economic value compared to older products of the same therapeutic group.

3. If neither of the two above criteria applies, the manufacturer's suggested price is considered as the maximum price.

New generics are priced at 30 percent below the branded products.[279] Price revisions are conducted every two years after the granting of the initial reimbursement price, and after a patent expires, or after 15 years of reimbursement; factors considered in revision include sales volume and price comparison.[280] Sales of reimbursed drugs account for over two thirds of the country's pharmaceutical expenditure.[281]

In an attempt to prevent price fixing, the Swiss Parliament adopted a revised competition bill, effected on April 1, 2004, that includes the possibility of sanctioning anticompetitive behavior without prior warning.[282] Switzerland is planning to adopt the French's latest initiative on drug pricing, where health insurers will only pay for drugs up to the price of the generic alternative.[283]

[278] PhRMA, p. 58.
[279] Ibid.
[280] Ibid.
[281] ESPICOM.
[282] United States Trade Representative, 2004 *National Trade Estimate Report on Foreign Trade Barriers*, "Switzerland," p. 449.
[283] Mbitha-Schmid, *Pharmaceutical Outlook*.

Canada

In 2001, Canadian spending on prescription drugs reached $13.2 billion, while non-prescription spending reached $3.5 billion.[284] The average annual growth rate in drug expenditure during 1997–1999 was 8.7 percent, rising to 11.6 percent in 2000. In 2001, public funds paid for 46 percent of prescription drugs, while insurance companies and out of pocket expenditures accounted for the remainder. The Canadian Institute for Health Information forecasted 2003 total prescription drug expenditures would reach $16 billion, with 47 percent paid for out of public funds and 53 percent from private funds.[285]

R&D Costs and Expenditures

Companies with active Canadian pharmaceutical patents must file their R&D expenditures on an annual basis with the Patented Medicine Prices Review Board (PMPRB).[286] Private pharmaceutical research spending in Canada increased steadily from $626 million in 1995[287] to $1.1 billion in 2001.[288] Canadian R&D to GDP ratio was 0.08 percent in 2000.[289]

In 2001, the ratio of Canadian pharmaceutical research spending to domestic sales was estimated to be about 9.9 percent for all producers. By contrast, the ratio of domestic sales to R&D expenditures for U.S. companies was 17.7 percent.[290] Moreover, the ratio of R&D spending relative to sales has been falling steadily for Canada's Research-Based Pharmaceutical Companies (Rx&D)—slipping to 10 percent in 2002 and 9.1 percent in 2003.[291] Canada ranks sixth among the C-7 countries (Canada, France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) in such spending.[292]

Venture capital is an important component in Canadian pharmaceutical R&D funding. Canadian biopharmaceutical and other life sciences firms led other sectors in venture capital disbursements in 2003, receiving a total of $392 million. This money was invested in 110 life

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[284] All dollar figures in this section are in Canadian currency, unless otherwise stated.
[285] Ibid., table A.1-part 1, p. 54.
[286] *A Comparison of Pharmaceutical Research and Development Spending in Canada and Selected Countries (2002)* (Ottawa: Patented Medicine Prices Review Board, 2002), PMPRB Study series S-0217, p. 7.
[287] Ibid., p. 11.
[288] John Stewart, "Message from the Chair," *Information Guide,* 2nd ed. (Ottawa: Canada's Research-Based Pharmaceutical Companies, May 2003), p. 7.
[289] Ibid., table 7, p. 17; table 8, p. 18.
[290] See PMPRB, *Annual Report, 2001*, table 7; see also Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Membership Survey 2002.* In 2000, with similar sales to R&D investment ratios, only Italy provided less money per capita for pharmaceutical research and development than Canada. See The Canadian Generic Pharmaceutical Industry, *The Facts About Canada's Generic Pharmaceutical Industry* (2003), found at *www.cdma-acfpp.org/en/resource_facts.html*, retrieved June 5, 2004.
[291] "New PMPRB R&D Figures Confirm Need for an Invigorating Innovation Agenda," press release issued by the Rx&D, July 28, 2004. Available at *www.canadapharma.org/Internet_Pharmacy/EN_New_PMPRB_Figures.pdf.*
[292] These seven countries are used by the Patented Medicine Prices Review Board to establish Canadian benchmark prices for drug sales. Patented Medicine Prices Review Board (PMPRB), *A Comparison of Pharmaceutical Research and Development Spending*, (Ottawa: PMPRB, Dec. 2002), PMPRB Study Series S-0217, executive summary.

sciences companies, and represented 26 percent of all Canadian venture capital disbursements for the year.[293]

Drug Approval Process

The current process for evaluating drug products has been in place for almost 30 years and applies equally to all drugs.[294, 295] Applications for approval of new drugs are reviewed by scientists in the Therapeutic Products Directorate (TPD) of Health Canada (and, on occasion, by outside experts) to assess the safety, efficacy, and quality of a drug.[296] If the preclinical benefits of a new compound appear to outweigh the side effects, the manufacturer may request approval from the TPD for clinical studies. The TPD reviews the information (including the results of some preclinical testing) provided by the new drug's sponsor before agreeing to clinical trials performed by a group of clinical investigators named in the application.

After successful clinical trials, the drug's sponsor must file a New Drug Submission form with the TPD, in order to have the compound and the findings of these trials more thoroughly reviewed. In 2002, this process took an average of 24 months.[297] During this review, TPD looks at both preclinical and clinical results, weighs the benefits against the risks of the drug, whether or not these risks can be mitigated, and decides if outside experts should be contacted. Should the drug be suitable for public sale, the sponsor is issued a Notice of Compliance and a Drug Identification Number, allowing the marketing of the compound.

Canada has mutual recognition agreements with other countries, which allow each country to mutually accept to some degree test results, thereby potentially reducing the development time and costs for such products. Canada, however, does not have such an agreement with the United States.[298]

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[293]2003 Annual Statistical Review, *2003 Key Observations*, (Toronto: Canadian Venture Capital and Private Equity Association, Feb. 2004), found at *www.cvca.ca/statistical_review/index.html*, retrieved June 18, 2004, p. 3.
[294]This section derived principally from: "How Drugs Are Reviewed in Canada," Therapeutic Products Directorate, Health Canada, Aug. 1, 2001, found at *www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/fact_drug_e.html.* retrieved May 27, 2004. The Therapeutic Products Directorate is the national authority that regulates, evaluates, and monitors the safety, efficacy, and quality of therapeutic and diagnostic products and vaccines available in Canada.
[295]Health Canada, *The Safety and Effectiveness of Generic Drugs* (November 20, 2002), found at *www.hc-sc.gc.ca/english/iyh/medical/gen_drugs.html*, retrieved June 9, 2004.
[296]A drug is defined by the Food and Drugs Act as "any substance or mixture of substances manufactured, sold or represented for use in a.) the diagnosis, treatment, mitigation, or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals; b.) restoring, correcting or modifying organic functions in human beings or animals; or, c.) disinfection in premises in which food is manufactured, prepared or kept." See Ibid; see also Department of Justice Canada, *Food and Drugs Act: Consolidated Statutes and Regulations*, found at *http://laws.justice.gc.ca/en/F-27/C.R.C.-c.870/section-C.08.002.html*, retrieved June 9, 2004.
[297]See Health Canada, Therapeutic Products Directorate, "How Drugs are Reviewed in Canada" (August 1, 2001), p. 3, found at *www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/fact_drug_e.html*; see also Canada's Research-Based Pharmaceutical Companies (Rx&D), *Information Guide*, 2nd ed. (Ottawa: Rx&D, May 2003) p. 19.
[298]Health Products and Food Branch Inspectorate, MRAs Updates (Ottawa: Health Canada, Oct. 1, 2003), found at *www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/mrasupdate_new_e.html*, retrieved June 25, 2004.

Health Care Coverage

Because the Canadian provinces share the financial burden of paying for health care with the central government, provincial authorities are allowed discretion to construct and fund health care plans as they see fit. Consequently, there is a wide variety of public health care plans, as well as prescription drug plans, often designed to target specific subgroups within a province. The provinces also use a diverse range of cost-containment measures, including generic substitution, limits on the products for which reimbursement is provided (as detailed in provincial formularies), deductibles, co-payments, reimbursements, and maximum limits on professional fees.

Pricing

The pricing system in Canada is a two-tiered system that relies on negotiated prices.[299] The PMPRB first negotiates a final price for new (or "breakthrough") prescription drugs, which acts as a price cap for the prices negotiated by each individual province or territory. 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). Subsequently, prices are allowed to increase in step with the rate of inflation according to the Consumer Price Index.

For drugs with minor or no innovative therapeutic effect, as deemed by the PMPRB, prices are tied to those of existing drugs with similar effects.

Federal prices act as a ceiling on prices nationally and further discounts are negotiated by the provincial and territorial governments. The British Columbian provincial government sets a reimbursement 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.

[299]Ibid., pp. 4–10.

Mexico

The Mexican pharmaceutical market is among the top 15 in the world and the largest in Latin America, recently overtaking Brazil. Current health regulations limit the importation of pharmaceuticals to local manufacturers holding a health license for such products. Imports of raw material are thus more abundant than imports of finished products.

Production is concentrated in the private sector, while the public sector is the principal purchaser of drugs. Mexico had 390 private-sector pharmaceutical manufacturers in 2003, including subsidiaries of foreign companies. Typically the subsidiaries of multinational companies focus on branded products, whereas the local companies concentrate on generics. Private companies hold about 80 percent of the Mexican market, with the public sector accounting for the remaining 20 percent.[300]

The estimated value of the Mexican market for pharmaceutical products was $6.5 billion in 2002, equal to approximately 1.3 percent of GDP.[301]

R&D Costs and Expenditures

There is little information available regarding R&D costs and expenditures by pharmaceutical firms in Mexico. However, U.S. industry sources indicate that the Mexican pharmaceutical industry spends on average 5 percent of revenue on R&D in Mexico. Typically this R&D consists of clinical research done in cooperation with organizations, such as medical schools and clinics. Combined with minimal government incentive for domestic firms to invest heavily in R&D, the relatively low prices of pharmaceuticals in Mexico provides little encouragement for domestic firms to conduct R&D. Multinational firms active in Mexico generally conduct their new drug research elsewhere in the world.

Thus, the Mexican pharmaceutical industry depends on product innovation that has been developed and imported by multinational firms. Mexican firms typically specialize in the production of "copy products"[302] and generic pharmaceuticals. Generic drugs account, however, for less than 3 percent of the total market.[303]

Drug Approval Process

The Secretariat of Health awards health registrations to products imported or manufactured by holders of health licenses. Pharmaceutical companies must apply for the

[300] Jesus Gonzalez, *Industry Sector Analysis (Mexico),* U.S. & Foreign Commercial Service (June 2002).
[301] "Pharmaceutical Sector Outlook," *Latin American Monitor*, vol. 20, issue 9 (September 2003), p. 6.
[302] A copy product is one in which the original innovative product is still under patent in Mexico. Copy products are an important part of the domestic market, particularly in the public sector. Copy products will continue to be an important issue in the Mexican pharmaceutical market until 2011 (20 years after the introduction of the 1991 Patent Laws or *Leyes de Patentes).*
[303] International Business Strategies, *Drugs and Pharmaceuticals in Mexico* (July 2002), p. 3.

approval of a new drug or pharmaceutical input. Upon approval, such products are included in the Pharmacopeia of Mexico[304] or in the corresponding standards.

Application for registration must be filed with the Secretariat of Health. For well-known generic drugs not protected by patents, decisions must be issued within 40 working days. For drugs already approved in other countries, the approval period is 60 working days. For new drugs not approved in other countries, the deadline is 90 working days. These approval periods compare favorably with those of many other countries but oftentimes are exceeded for different reasons. Registration is generally issued for indeterminate periods.[305]

Health Care Coverage

Since 2000, Mexico has undertaken substantial reforms to decentralize its health care system and significantly expand coverage. As part of this effort, established social security programs have been joined by a large-scale pilot program called Popular Health Insurance (SPS). In the SPS program, funding is drawn from the federal and state governments, as well as participating families. Enrolled families have access to a predetermined and relatively restricted health package, including some pharmaceutical coverage. Restrictions differ by individual Mexican state, but generally patients are not covered or reimbursed if they go to a private hospital or clinic.[306]

In addition to the SPS system, the Mexican government provides health care services to about 60 to 70 percent of the population. The majority of health care services are provided through social security institutions financed by compulsory contributions from employees, employers, and the government.

Private medical insurance is available for purchase in Mexico; however, it is not widely purchased. The Mexican Association of Insurance Companies (AMIS) reports that in 2002 there were 3.6 million Mexicans with medical insurance plans. This accounts for only three percent of the total population but represents an 80 percent increase over the insurance figures for 2000.

It is estimated that about 10 to 15 percent of the population are not covered by any program and use private health care services that they pay for out of pocket.

Pricing

The pharmaceutical industry is one of a small number of Mexican industry sectors that is still subject to government price controls, but in recent years the government has loosened price controls to give the industry greater flexibility. Maximum prices are set in consultation with the

[304] The pharmacopeia is a legal document in which general methods of analysis are established and the requirements to guarantee the identity, purity, and quality of medicines and pharmaceutical inputs.
[305] Directorate for Finance, Fiscal, and Enterprise Affairs, Committee on Competition Law and Policy, Organization for Economic Co-Operation and Development (OECD), "Competition and Regulation Issues in the Pharmaceutical Industry" (February 6, 2001), p. 24.
[306] Organization for Economic Cooperation and Development, "*Health Data 2000: A Comparative Analysis of 29 Countries,"* CD-ROM (Paris: OECD, 2000).

Secretariats of Health and Economy, as well as Mexico's National Chamber for the Pharmaceutical Industry (Canifarma), the primary industry trade association.[307]

Wholesale and retail margins are subject to negotiation between the government of Mexico and the individual manufacturer. The final retail price requires government approval. The prices to the public sector are much lower than those in the private market.

In the public market, Mexico's system of price controls mandates that the lowest price criteria be used in purchasing decisions, which may reduce a patient's access to innovative medicines. Seven of the top 20 drugs purchased by the government of Mexico are over 40 years old. In a few cases, patients may receive copy products of the therapies that are best suited for their care.

In 2003, the government of Mexico proposed the establishment of a reference pricing system for patented medicines. The details of this system are still under review, but over-the-counter and generic drugs will be exempt from it.

[307] "Pharmaceutical Sector Outlook in Mexico," *Latin American Monitor* (May 2004), p. 6.