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Pharmaceutical Pricing Policies in a Global Market

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Foreword

This publication presents an analysis of the national and cross-national impacts of OECD countries' pharmaceutical pricing policies. It assesses how pharmaceutical pricing – and related policies – have helped countries achieve certain well-established health policy goals. And given the increasingly global scope of pharmaceutical markets, the broader impacts of these national policies on the availability and prices of pharmaceuticals in other countries are examined, as are their implications for the very important issue of pharmaceutical innovation.

The OECD Health Committee launched its work on pharmaceutical pricing policies in December 2005. The twin objectives of the project were: i) *to add to the base of information on pharmaceutical pricing policies and their effects within countries; and* ii) *to produce an assessment of the cross-national impacts of pharmaceutical pricing policies on the availability and prices of pharmaceuticals abroad, and on pharmaceutical research and development.*

The project has consisted of two complementary strands of work. Case studies of selected countries - Canada, Mexico, Switzerland, Sweden, the Slovak Republic and Germany - were the main focus of the first strand. The case studies were an integral input in the assessment of the national impacts of pharmaceutical pricing policies. The main focus of the second strand was to assess the global impacts of these policies

The project team conducted numerous interviews with officials, experts and stakeholders in the case-study countries, and beyond, to whom we are grateful for their insights and expertise. The OECD project also benefited from cooperation with the Pharmaceutical Pricing and Reimbursement Information (PPRI) project, managed by the Austrian Health Institute (ÖBIG) and the World Health Organization European Regional Office, and financed by the European Commission and the Austrian Ministry of Health, Family and Youth.

This report was prepared by Elizabeth Docteur, who served as project director, and Valérie Paris of the Health Division of the OECD Directorate for Employment, Labour and Social Affairs, and by Pierre Moïse, working in the Health Division on secondment from Health Canada. The report benefited from comments and suggestions from Martine Durand, John Martin, Peter Scherer and the project's experts group, which provided technical input and feedback on the work at three meetings convened during the course of the project. Statistical assistance was provided by Lihan Wei, and secretarial support by Marie-Christine Charlemagne and Gabrielle Luthy. Meghan McMahon and Johanneke Maenhout provided research assistance while at the OECD on student internships.

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Table of Contents

Executive Summary 9

Introduction 21

Chapter 1. **Key Characteristics of the Pharmaceutical Sector in OECD Economies** 23
Introduction 24
Pharmaceutical expenditures 24
Pharmaceutical consumption and relative price levels determine pharmaceutical expenditures 30
Financing 38
The pharmaceutical industry is important in the economies of several OECD countries 40
Conclusions 42
Notes 43
References 44
Annex 1.A1. Distribution Mark-ups and Value-added tax for Pharmaceuticals in OECD Countries 46

Chapter 2. **The Pharmaceutical Industry and its Activities** 51
Introduction 52
Concentration of the industry 52
Research and development 52
Pharmaceutical manufacturing 56
Pharmaceutical sales 58
Ex-manufacturer prices 62
Product life-cycle management 63
Profits of the pharmaceutical industry 70
Conclusions 70
Notes 71
References 73
Annex 2.A1. Price Comparisons at the Ex-manufacturer Level 78

Chapter 3. **Pharmaceutical Pricing and Reimbursement and the Broader Pharmaceutical Policy Environment** 85
Introduction 86
Coverage schemes 86
Pharmaceutical price regulation 97
Regulators, payers and purchasers use a mix of techniques for defining price levels 101

All components of the retail price of pharmaceuticals are subject to regulation . . 113
Many OECD countries regulate price increases and try to contain pharmaceutical expenditure growth 113
The stability, consistency and predictability of regulation 114
Other aspects of the pharmaceutical policy environment that affect the achievement of policy goals 115
Conclusions. 118

Notes 118
References 120

Annex 3.A1. Pharmaceuticals and Intellectual Property Rights in the European Union 125
Annex 3.A2. Marketing Authorisation in the European Economic Area 128

Chapter 4. **The Impact of Pharmaceutical Pricing Policies on Performance in Meeting Health Policy Goals** 131
Introduction 132
Promoting public health 132
The impact of pricing and reimbursement policies on pharmaceutical price levels . . 140
Pharmaceutical cost containment. 148
Pursuing good value for money in spending on pharmaceuticals 152
Conclusions. 155

Notes 156
References 157
Annex 4.A1. The Relationship between Retail Pharmaceutical Price Levels and Economy-wide Price Levels in OECD Countries 161

Chapter 5. **The Impact of National Pricing and Reimbursement Practices on Prices and Availability of Medicines in Other Countries** 167
Introduction 168
National pricing policies are likely to impact the availability and prices of drugs in foreign countries 168
Manufacturers use various strategies in order to maximise net revenues in the global market and counter spill-over effects of national policies 171
There is some evidence of market entry price convergence among OECD countries. . 174
Conclusions. 179

Notes 179
References 180

Chapter 6. **The Impact of Pharmaceutical Pricing Policies on Pharmaceutical Innovation** 183
Introduction 184
Pharmaceutical R&D investment. 184
Ways in which pricing and reimbursement practices contribute to trends in innovation 192
Conclusions. 198

Notes 199
References 200

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Conclusions 203

Glossary 207

List of Abbreviations 214

Boxes

1.1. Pharmaceutical expenditure: definition, deviations and sources 25
1.2. Purchasing power parities and comparative price levels for pharmaceuticals . . . 31
1.3. The role of retail price components in explaining relative pharmaceutical prices 34
2.1. Making a drug and getting it to market 57
2.2. Pharmaceutical pricing strategies in a competitive market 67
3.1. Formulary management in the US Veterans Health Administration 89
3.2. The use of reference pricing to define reimbursement amounts 92
3.3. Approaches used to influence physician prescribing behaviour 95
3.4. Pharmaceutical pricing in the US Medicaid programme 99
3.5. Approaches used in pharmaco-economic assessment 107
3.6. Risk-sharing arrangements for pharmaceuticals 109
3.7. The British Pharmaceutical Price Regulation Scheme 110
3.8. The French State – Industry agreements 112
3.9. Intellectual property rights (IPR) exhaustion regime 116
4.1. The price sensitivity of consumer demand for pharmaceuticals and potential consequences of increases in cost-sharing 138
4.2. Pharmaceutical cost containment and industry policy: conflicts between policy goals 141
5.1. Manufacturers strategies in a world of separable markets 172
6.1. Getting a drug to market 185
6.2. Private investment in pharmaceutical R&D benefits from public support 187

Tables

1.1. Launch lags for 122 new molecules that were first marketed in 1986-1992 37
1.2. Private sector and out-of-pocket (OOP) expenditure as a percentage of total expenditure, by healthcare function, 2005 39
1.A1.1. Distribution mark-ups and VAT in OECD countries, 2007 or last available information 46
2.1. The level of innovation of new chemical entities (NCEs) launched between 1975 and 2002 55
2.2. Global pharmaceutical sales at ex-manufacturer prices, by region, 2006 58
2.A1.1. Bilateral comparisons of ex-manufacturer prices: review of recent studies . . . 81
3.1. The use of external price benchmarking in OECD countries, as of 2007 103
3.2. Categories used by pricing authorities to differentiate drugs according to therapeutic value 105
4.A1.1. Economy-wide price levels and retail price levels for pharmaceuticals, 2005 . . 162

Figures

1.1. Total expenditures on pharmaceuticals, 2005 25
1.2. Per capita spending on pharmaceuticals, 2005 26
1.3. Pharmaceutical expenditure per capita and GDP per capita, 2005 26

1.4. Share of prescription and over-the-counter (OTC) drugs in total pharmaceutical expenditures, 2005 . . . 27
1.5. Share of pharmaceutical expenditure in total health spending and in GDP, 2005 . 28
1.6. Real annual growth in pharmaceutical spending and total health expenditure (net of pharmaceutical expenditure), 1997-2005 . . . 29
1.7. Trend growth in pharmaceutical and total health expenditure for 15 OECD countries, and GDP, 1980-2005 . . . 30
1.8. Relative retail pharmaceutical price levels in OECD countries, 2005 . . . 32
1.9. Components of retail pharmaceutical prices, selected OECD countries, 2004 . . 33
1.10. Retail pharmaceutical price levels and GDP per capita, 2005 . . . 35
1.11. Real per capita spending on pharmaceuticals, 2005 . . . 35
1.12. Real per capita pharmaceutical expenditure and GDP per capita, 2005 . . . 38
1.13. Share of public expenditure in pharmaceutical and total health expenditure, 2005 . . . 39
1.14. Pharmaceutical industry trade balance in OECD countries, 2003 . . . 42
2.1. Global trend in market launch of new chemical entities, 1982-2006 . . . 54
2.2. Global pharmaceutical sales growth at ex-manufacturer prices, 1998-2006 . . . 59
2.3. Contribution to total world sales growth at ex-manufacturer prices, by region, 2001 and 2006 . . . 59
2.4. Top ten therapeutic classes by global sales at ex-manufacturer prices, 2006 . . 61
2.5. Market share of generics in terms of value and volume, 2004 . . . 62
2.6. Hypothetical cash-flow profile of a pharmaceutical . . . 63
2.7. Average time from first world application for marketing authorisation to application in market, 1999-2003 . . . 65
3.1. Average time from application for market authorisation to approval, 1999-2003 . . . 116
4.1. Average number of days from pricing and reimbursement application to decision, 1997-2001 . . . 133
4.2. Average number of months between first world application for marketing authorisation and launch in country, 1999-2003 . . . 134
4.3. Retail pharmaceutical price levels and economy-wide price levels, 2005 . . . 145
4.4. Original pharmaceutical price levels and economy-wide price levels, 2005 . . . 146
4.5. Generic pharmaceutical price levels and economy-wide price levels, 2005 . . . 147
4.6. Share of GDP spent on pharmaceuticals and income per capita, 2005 . . . 148
4.7. Share of GDP spent on health (net of pharmaceutical spending) and income per capita, 2005 . . . 149
4.A1.1. Retail price – economy-wide price level differentials for original and generic pharmaceuticals, 2005 . . . 164
5.1. Multilateral comparisons of UK pharmaceutical prices to comparator countries' prices, 1992-2004 . . . 175
5.2. Bilateral comparisons with Canada of ex-manufacturer prices for patented pharmaceuticals, 1997 and 1999-2004 . . . 176
5.3. Price convergence of market entry prices in the EU countries . . . 177
6.1. R&D expenditures and sales in the pharmaceutical industry, 2006 . . . 190
6.2. The R&D investment decision . . . 191
6.3. Retail pharmaceutical price levels and real per capita pharmaceutical expenditure, 2005 . . . 194

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Executive Summary

Variation in per capita expenditure on pharmaceuticals is relatively low across OECD countries…

The average OECD country spent 401 USD [measured in purchasing power parities (PPPs)] per person on pharmaceuticals in 2005, and half of OECD countries had per capita spending within 20% of the average. The United States had the highest level of per capita expenditure, at 792 USD PPP, and Mexico the lowest, at 144 USD PPP, just 18% of the US amount.

Variation in the volume of pharmaceutical consumption and in parmaceutical retail prices are similarly low

France and Spain had the greatest volume of pharmaceutical consumption (an estimate derived by adjusting pharmaceutical expenditures for cross-country differences in the average retail pharmaceutical price level) per person in 2005, followed by the United States and Australia. All of these countries had below-average retail pharmaceutical price levels in 2005, with the exception of the United States, which had retail prices about 30% above the OECD average. Canada and Germany had price levels similar to that of the United States, exceeded by Iceland (159%) and Switzerland (185%).

Mexico had the lowest volume of pharmaceutical consumption per capita – less than a quarter of the OECD average and less than half that of Poland, the second-lowest country – but was not among the countries with the lowest average retail pharmaceutical prices. The lowest-priced countries were Poland, Turkey, the Slovak Republic, the Czech Republic, Korea, Greece, Hungary, Spain and Australia, all of which had retail pharmaceutical price levels between 68% and 81% of the OECD average.

Cross-country differences in retail prices reflect factors other than differences in the prices manufacturers charge. They also include distribution costs and – in many countries – value-added tax, which together can account from only a small share to more than one-half of the price paid by the end purchaser.

A country's income per head affects its pharmaceutical consumption, retail prices and expenditure levels, but other factors are at work

In general, income per capita is positively correlated across countries with the volume of pharmaceutical consumption and expenditure per capita. However, income is not the whole story. In fact, per capita income explains only one quarter of the variability observed in per capita volumes of consumption across OECD countries, and even less of the variability in expenditure and retail price levels. This is consistent with findings from research indicating that pharmaceutical demand varies across countries and is relatively income-inelastic – meaning that expenditure changes with income, but not as fast as income does.

Despite rapid growth, spending on pharmaceuticals accounts for a minor share of health expenditure in most OECD countries, though there are a few exceptions

Growth in pharmaceutical expenditures greatly exceeded the rate of growth in other types of health expenditures throughout the 1990s. Although pharmaceutical growth has since slowed while other health expenditures have increased more rapidly in recent years, growth in pharmaceutical expenditures continues to exceed the average growth of OECD economies. Nevertheless, the pharmaceutical sector accounts for a minor (average 17%) share of total health expenditure in most OECD countries. However, pharmaceutical expenditure accounted for about one third of health expenditure and more than 2% of GDP (compared with an OECD average of 1.5%) in Hungary and the Slovak Republic.

Out-of-pocket payments are relatively important sources of financing for pharmaceuticals

Private sources play a bigger role in financing of pharmaceutical expenditures – accounting for 40%, on average – than of other components of health spending, although the bulk of pharmaceutical spending is publicly financed in all but four OECD countries (the United States, Canada, Poland and Mexico). Out-of-pocket spending is generally more significant than private health insurance, which is an important source of financing for drug spending in only a handful of countries (the United States, Canada, the Netherlands and France).

The pharmaceutical industry plays an important role in the economies of several OECD countries

All of the top-15 firms in terms of global pharmaceutical sales have their headquarters in OECD countries, with about half in the United States and half in Europe (France, Germany, Switzerland and the United Kingdom). Production and R&D activities are undertaken in many countries, not only (or even primarily) in the country where the firm has its headquarters. The United States accounts for 39% of global pharmaceutical production, slightly more than the 36% European share. Pharmaceutical production accounts for a notable share of national income in Ireland (11% of GDP) and Switzerland (3% of GDP), the

two biggest net exporters of pharmaceuticals. Pharmaceutical industry R&D activities are relatively more important to the economies of Sweden and Switzerland, accounting for about 0.5% of GDP in those countries.

Parallel and cross-border trade accounts for only a small fraction of the value of the market

The practice of importing pharmaceutical products from a lower-priced country to a higher-priced one, either for sale (so-called "parallel trade") or for personal use (so-called "cross-border trade"), receives considerable policy attention. Parallel trade is most significant between EU countries, but even so only accounts for an estimated 2% of the EU market. Canadian cross-border trade with the United States peaked in 2004 at about 8% of total Canadian sales, which represented only 0.5% of the US market in terms of value.

The products of ten large firms account for much of the global pharmaceutical market

In 2006, the top ten pharmaceutical firms accounted for nearly half the value of global sales. The market for pharmaceutical products is increasingly a global one, with trade and policy practices making market segmentation and corresponding price differentiation by country difficult – particularly within Europe, where multinationals have encouraged their subsidiaries to set prices within narrow price corridors. New active ingredients are launched in an average of ten countries, although manufacturers often release multiple versions of their on-patent products in different markets to reflect consumer preferences and to reduce opportunities both for prospective buyers to make external price comparisons and for wholesalers to engage in parallel trade.

The United States is the predominant market in terms of pharmaceutical sales value

Nine OECD countries account for about 80% of the value of global sales of pharmaceuticals. The United States, with a 45% global share, is the world's largest market, followed by Japan, which accounts for 9% of global sales, France (6%), Germany (5%), the United Kingdom (4%) and Italy (4%).

Most sales revenues derive from on-patent products, rather than generics, with value concentrated in a relatively small number of therapeutic classes and successful products

Just ten therapeutic classes of drugs accounted for 36% of total global sales in 2006, a year in which approximately 105 original products were considered "blockbusters," *i.e.* each generating more than 1 billion USD in annual sales. By contrast, generic products accounted for just 14% of the global market in terms of value, although more than 40% of products sold in several large markets, including the United States, Germany and the United Kingdom, are generics. Generics have less than a 10% share of the market in terms of both volume and value in Italy, Belgium, Spain and Portugal.

The prices manufacturers receive for their products vary across countries, although there is less variation in prices for the most innovative products

Japan, Switzerland and the United States have been identified in the research literature as countries with particularly high ex-manufacturer prices for patented medicines. Japan and Switzerland also have high ex-manufacturer prices for generic products. Studies have found that ex-manufacturer prices vary according to national income per capita, although there were important exceptions. In particular, such prices were higher than expected in some low-income countries, including Mexico. Another study found that there is less cross-country variation in ex-manufacturer prices for those products representing significant innovation.

In spite of continuously increasing R&D investment, output of new drugs has declined and most pharmaceutical innovation has been incremental

Because most R&D initiatives are unsuccessful in bringing a new product to market, the total amount of investment per successful drug – an indication of the "productivity" of R&D spending in the pharmaceutical industry – is very large. A decline in productivity has been evident since the mid-1990s, as increased R&D investment has coincided with a decline in the number of new chemical entities approved for marketing.

As is true in other industries, most pharmaceutical innovation has been incremental, rather than radical. Most such innovation has little or no added therapeutic value over existing treatments.

The pharmaceutical industry uses a range of techniques to maximise profits over a product's life cycle

Since marginal production costs are relatively low, maximising profits translates into maximising cash flows during the life of a product. In each market where sales would be expected to enhance a product's global profitability, pharmaceutical firms endeavour to launch products quickly at the price that maximises prospective profits. Firms try to extend the period of market exclusivity and to engage in promotional activities that aim both to capture as large a market share as possible and to increase the potential market.

By some estimates, pharmaceutical marketing expenditures account for a share of firms' outlays that exceeds that of R&D expenditures. Furthermore, the costs of doing business in different countries vary, depending on factors such as the burden imposed by regulatory compliance, the types of marketing and/or advertising activities permitted and the exposure to liability for safety or quality problems.

Prices are not the only factor determining profits

Because marginal costs of producing most pharmaceuticals are very low relative to the cost of research, development and bringing a product to market, firms can make volume-price trade-offs that result in equivalent sales revenue and profits for the industry, provided spillover to other markets can be prevented. Pharmaceutical firms have therefore made with public and private purchasers and third-party payers confidential agreements that provide discounts and rebates linked to the level of product sales.

Widespread health insurance coverage distorts the market for pharmaceuticals

The coverage schemes that subsidise the amount individuals spend on pharmaceuticals and protect them against the risk of incurring high out-of-pocket costs also distort the pharmaceutical market, affecting both prices and volumes of consumption. They define the degree to which the pharmaceutical market is subsidised, with greater subsidies resulting in relatively lower consumer price elasticity of demand. While there is great cross-country variation in cost-sharing requirements, individuals in OECD countries typically bear much less than half the cost of their pharmaceutical consumption, resulting in consumption that is greater than it otherwise would be if individuals paid the full cost. Beyond this, coverage schemes differ importantly in the extent to which they seek to manage the volume and mix of pharmaceutical consumption, with many coverage schemes having few restrictions on choice by physicians and patients while others are active in efforts to affect physician, pharmacist and/or patient decision-making.

The global market for original medicines is competitive

Unlike sellers of most health services in OECD countries, research-based pharmaceutical firms operate globally and thus do not face a single purchaser wielding monopsony power. Firms can and do choose not to launch their products in countries where doing so is not profitable. On the other hand, the manufacturer of an on-patent medicine normally has a monopoly on sales of a particular product in a particular market, although the product may be subject to competition from therapeutic alternatives.

Specific characteristics of the pharmaceutical market have given rise to pharmaceutical price regulation in most countries

The perceived potential for manufacturers to exploit a monopoly position when facing relatively inelastic demand for medicines has led many countries to regulate prices for at least some portion of the pharmaceutical market. Two countries with pluralistic coverage schemes – Canada and Mexico – have established price regulation for on-patent pharmaceuticals intended to assure that prices paid by any part of the population, insured or not, are not excessive. In most other OECD countries, coverage schemes require manufacturers to accept price limits in exchange for subsidisation through reimbursement schemes, which

act as *de facto* regulation for that part of the market covered by reimbursement. Even in the United States, manufacturers must submit to price regulation if they wish to be reimbursed under Medicaid and the Veterans Health Administration, the public schemes providing coverage to 19% and 2.6% of the US population, respectively.

Market-based or "free" pricing is common for products not subsidised by coverage schemes

Except in Mexico and Canada, where the prices of all on-patent medicines are subject to regulation, over-the-counter (OTC) products are normally not subject to price regulation unless their purchase is reimbursed by a coverage scheme. In a minority of OECD countries, including Denmark, Germany, the United Kingdom and the United States, firms are not constrained in setting either OTC or prescription drug prices at market entry, irrespective of the product's reimbursement status.

Several types of practices are used to limit prices and define reimbursement amounts

Regulatory authorities use a common set of tools to limit the prices charged by pharmaceutical firms. The most commonly used methods involve comparing proposed prices for new products against those prices paid by other payers, a practice known as external price referencing, or against those prices already paid for products judged to be similar, a practice known as internal price referencing. Pharmaco-economic assessment is used by some schemes as a means of making a formal judgment as to value provided, in terms of benefits and costs. There are a limited number of other approaches used, including profit controls, which serve as an indirect form of price regulation. Pricing policies are not limited in focus to the payment received by pharmaceutical firms; regulation of the distribution chain is undertaken in many systems.

With the exception of profit controls, public and private payers and purchasers of pharmaceuticals use the very same approaches to define the acceptable payment or reimbursement price. In the context of reimbursement, so-called reference price systems are often used to set common reimbursement amounts for products judged to be equivalent or similar, leaving patients to pay any price difference out-of-pocket. In cases where generic substitutes or therapeutic alternatives are acceptable, purchasers in some markets obtain low prices using tendering processes that require sellers to bid for an agreed volume of sales.

Pharmaceutical prices are determined by the respective market powers of the parties involved

In the case of the pharmaceutical firm, market power is determined by the perceived value of the product and the extent of competition from alternative therapies on the market.

In the case of the buyer (or payer), market power is determined by the size of the market represented – as measured in terms of the number of persons and their willingness and ability to pay – provided that the payer has the ability to act in ways that influence the

volume of a product consumed. While most OECD countries have a universal scheme that maximises market power by representing all or nearly all of the country's consumers, a few countries, such as the United States, have pluralistic schemes. Several large publicly financed coverage schemes and private insurers in the United States have enrolments that exceed the populations of some OECD countries.

The extent to which prospective buyers or third-party payers have the power to walk away from a transaction varies. Either regulation or competition to provide comprehensive coverage can limit their ability to deny patients reimbursement for a product that is categorically eligible for coverage. In particular, the power to walk away from a transaction is limited when a drug is in a monopoly position in a therapeutic area and is used in the treatment of a life-threatening disease. In such cases, both public and private payers experience public pressure to cover the drug. Thus, the ability to obtain price concessions often rests instead with the ability to influence the volume of the product consumed, by limiting reimbursement to particular circumstances or identifying preferred products.

Price regulation does not necessarily result in lower prices

While private insurers universally face pressure to extract the best possible price which their relative market power will permit, regulators and public schemes seek to balance cost-containment objectives with others, such as public health improvement, as well as industry policy goals and considerations of support for future pharmaceutical innovation, which may mean that they fail to push their market power as far as they might to obtain the lowest possible price. For this reason, it is not necessarily the case that price regulation will always result in lower pharmaceutical prices than would be obtained in an environment characterised by competing private insurers.

Many other types of policies, other than those directly related to pricing, affect the pharmaceutical market

While pricing policies have been the focus of attention in terms of their impact on pharmaceutical markets, other types of policies are important in their prospective impact on the timely availability of products in the market, the adoption and diffusion of those products, and the level of consumption of the product over its life cycle. Chief among these policies are those that affect market authorisation and those that set standards for enforcement of intellectual property rights. In addition, coverage schemes routinely employ policies aimed at modifying patient demand (in particular, cost-sharing requirements), often employ policies aimed at influencing pharmacists' dispensing (such as policies to promote use of generic alternatives to off-patent original medicines), and occasionally employ policies aimed at altering physician prescribing (*e.g.*, prescribing budgets).

Policy makers hold common objectives, but may weight them differently when trade-offs are required

Policy makers intervene in pharmaceutical markets to promote public health by fostering prompt, affordable access to effective medical treatments. But subsidising individuals' pharmaceutical consumption often results in pressure to contain overall costs. And payers are increasingly concerned with being able to demonstrate that they attain good value for money in their pharmaceutical expenditures. Trade-offs across these goals are required when conflicts arise among them and with industrial policy goals, as may occur depending on the economic significance of the pharmaceutical industry in the country in question.

There are shortfalls in access to effective medicines, even in OECD countries

Although the availability of medicines on the market varies considerably across countries, the implications for accessibility are unclear, since countries often grant exceptional access to drugs that have not (yet) been launched in a market. Heavy subsidies for pharmaceuticals provided by public coverage and private insurance, reasonable cost-sharing arrangements, exemptions of vulnerable patients and caps on out-of-pocket spending serve to limit the likelihood of access being threatened on affordability grounds in most OECD countries. More serious risks come from gaps in coverage, given that a few countries still have populations without adequate coverage to ensure affordable access to prescription medicines. Furthermore, access can be limited by decisions not to subsidise expensive drugs that are judged not to be affordable or cost-effective at the offered price.

Policy makers seek to restrain the rate of growth in pharmaceutical expenditures, although the optimal expenditure level is undefined

The variation in pharmaceutical expenditures across countries raises questions about whether and which countries may be over- or under-spending, although there are no agreed international benchmarks for making such assessments. Policy makers in OECD countries attempt to control pharmaceutical expenditures using a range of tools, including control of prices and/or volumes (*e.g.*, benefits management strategies directed at physicians or pharmacists). Some countries use policies to control the level of spending for particular products (*e.g.*, product-specific rebates) or for pharmaceuticals generally (*e.g.*, claw-backs, patient cost-sharing).

Payers are experimenting with sophisticated approaches to purchasing and payment arrangements

There may well be scope to move to cost-control mechanisms, such as price-volume agreements, that focus on achieving the desired level of expenditure on pharmaceuticals. In France, for example, specific agreements are signed for some products with high risk of overuse or misuse, under which the pharmaceutical company will pay rebates when the

agreed volume of consumption is exceeded or when drugs have been misused. Risk-sharing arrangements, under which the price may be retroactively adjusted as information about utilisation and outcomes under normal use become available, have the potential to reduce the need to make a trade-off between the objectives of ensuring prompt access and getting good value for money, when faced with incomplete information about the relative efficacy and cost-effectiveness of a new product.

Improvement in meeting public health objectives may well be possible without sacrificing cost control

Efforts to improve value for money in public spending on pharmaceuticals could help free up resources that could be better spent enhancing the availability, accessibility and appropriate use of effective medicines. Many, if not all, countries have some room for improvement in this respect. They could get better value for their money by maximising the use of generic alternatives to off-patent original products, fostering erosion of the prices of off-patent products through greater competition, ensuring efficient distribution systems for prescription and OTC products, and becoming more sophisticated in their reimbursement pricing strategies.

Reference pricing is a practice by which payers seek to get good value for money in pharmaceutical expenditure

Under normal market conditions, informed consumers compare products to determine if added benefits are worth added cost. This is difficult in the case of pharmaceuticals, not only because information on relative benefits may not always be fully available at the time of decision making, but also because patients rely heavily on physicians to act as their agents in choosing appropriate medicines. The practice of setting a common reimbursement amount for similar products, leaving patients to pay the difference out-of-pocket if they use more expensive alternatives – a practice that is somewhat misleadingly known as "reference pricing" – is attractive in the sense that, theoretically, only those products valued by patients and their physicians should receive a premium price. In practice, however, manufacturers often prefer to price at the reference point rather than risk losing market share in imperfectly operating markets.

Pharmaco-economic assessment can help to ensure good value for money in pharmaceutical expenditure

A tool for evaluating a product's benefits relative to its costs, pharmaco-economic assessment can help achieve good value for money when incorporated into pricing and reimbursement decisions. Since its introduction into pricing and reimbursement processes by Australia and Canada in the 1990s, pharmaco-economic assessment has been incorporated in the pricing and reimbursement practices of many OECD countries in ways ranging from asking manufacturers to provide information on relative cost-effectiveness in support of applications for reimbursement to conducting original assessments of the

benefits that would be derived from use of a product and expected costs to payers or society generally. Experience from these countries demonstrates that pharmaco-economic assessment can be technically and politically feasible when employed in different types of health systems. It remains, however, a technically challenging and value-laden exercise, particularly when judgments about the value of a product for which there is no therapeutic alternative must be made.

Pharmaceutical pricing policies have an impact outside national borders

External price referencing (or international benchmarking) stands to affect the prices and availability of medicines outside the country undertaking the benchmarking practice by reducing manufacturers' willingness to set prices according to national market conditions. This may have a negative effect on affordability and availability of medicines in smaller markets and lower-income countries, including lower-income countries in the OECD. The practice of agreeing to confidential rebates can also have an external effect, in that other countries using external benchmarking may reference artificially high prices, resulting in list-price inflation. Claw-backs have a similar impact in that they mean the price is effectively changed post-purchase (after the list price has already affected the global price through external benchmarking). The convergence in list prices of pharmaceuticals that has been observed in Europe (including Switzerland) and between European countries and Canada is consistent with what would be expected in a market characterised by such practices.

Manufacturers have developed strategies to maximise profits in an increasingly global market

Even as globalisation has reduced opportunities to maximise profits through market segmentation and differential pricing, manufacturers have responded to the increasingly global market for their products in a strategic way. In response to external price referencing, they launch their products first in countries where they can set prices freely or can negotiate relatively high prices (often in the country where they have their headquarters), delay or refrain from launching in relatively lower-price countries and maintain artificially high list prices, even when they are willing to consent to confidential rebates. They use strategies to inhibit parallel trade, such as supply-chain management, litigation, lobbying and product proliferation (*e.g.*, release of products with different formulations, strengths and package sizes). The latter technique also serves to limit opportunities for international price referencing. The success of these strategies is evident in that the pharmaceutical industry continues to be one of the more profitable industries in the global economy.

Profits reward past investment in pharmaceutical R&D and serve as an incentive for future investment

As in other industries, private R&D investment in the pharmaceutical industry is motivated primarily by expected returns on the investments, given scientific opportunities

(the state of the art in a therapeutic area or in a mode of production) and the comparative advantages of firms. The pharmaceutical products that make it to market are those that are viewed by the pharmaceutical industry as most likely to be profitable in terms of the conditions they target and the level of innovation they represent over existing alternatives.

R&D investment incentives are distorted by characteristics of the pharmaceutical market

Important characteristics of the pharmaceutical market call into question whether it is possible to obtain a socially optimum level and direction of R&D investment. In the case of prescription medicines, the combined impact of insulating patients from the cost of the medicines they consume and providing firms that produce innovative medicines with the exclusive rights to sell their products distorts market signals, creating a risk of over-investment in the development of new products. On the other hand, cost-containment pressures may lead regulators, payers and purchasers to make pricing and reimbursement decisions that establish profit signals for under-investment.

Beyond this, purchasing decisions made in the absence of full information may well distort the incentives firms face as to how to direct their R&D investments. Information on the effectiveness of new medicines, relative to therapeutic alternatives, is often not available to patients and the physicians who act as decision-making agents, and neither may have incentives to consider whether any added benefits are worth the cost differential.

Pharmaceutical pricing policies are among several policy variables that influence the expected returns on investment in R&D that in turn serve as an incentive to finance new investment

Methods used to establish relative price levels, particularly techniques by which products are differentiated for price premia, provide market signals that steer investment towards particular types of innovation. The most commonly used practice, external benchmarking, encourages firms to differentiate their products across countries so as to limit price comparisons. Such practices yield no therapeutic benefit and may come at the expense of other types of innovation. The practice of referencing prices or reimbursement amounts to therapeutic comparators, on the other hand, provides incentives for innovation that offers demonstrably more value than existing therapies and acts as a disincentive for incremental innovation that offers little or no improvement over existing therapies. However, therapeutic referencing only provides an indication of the new product's value if the price of the comparator product is reasonably reflective of its own value. This is not necessarily the case in the current pharmaceutical market environment, where third-party payers and regulators predominantly use external benchmarking of prices paid elsewhere to limit or define the prices of products that have no therapeutic comparators.

Pharmaceutical pricing and reimbursement approaches using pharmaco-economic assessment establish incentives for investment in valued innovation

In the interest of encouraging valuable innovation, efforts to link the level of expenditure for a given pharmaceutical product to the value of the benefits offered by the new product are attractive in that they can be used by manufacturers to assess willingness to pay for future innovations and should thus provide incentives for investment in R&D leading to valued innovation. Pharmaco-economic assessment can be used to reward and foster innovation with the greatest value to patients and society. To the extent that pharmaceutical producers profit more from innovations that have the greatest value to patients and society, they will face incentives to invest more in R&D to produce such therapies.

Each country's policies will have only a marginal impact on future pharmaceutical innovation, except when there are spill-over effects

Pharmaceutical R&D investment decisions reflect the industry's assessment of the future market with a global perspective. Therefore, the marginal impact of any one country's policies will be proportional to market size and thus minor (with the important exception of that of the United States). Nevertheless, features of national markets and national policy practices may encourage firms to invest in R&D in order to differentiate products and segment markets, especially when national policy impacts have spill-over effects on other countries' price levels. The practice of external price benchmarking means that early-launch countries in particular (and those that are most often selected by other countries for price references) are likely to have an impact on incentives for investment that is disproportionate to the size of the market. This suggests that it is particularly important that the prices established in those countries present an accurate reflection of the product's value, both in absolute terms and relative to other products on the market.

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Introduction

At the first OECD meeting of Health Ministers in May 2004, pharmaceutical pricing policy was not explicitly on the agenda. Yet the issue was raised by a number of Ministers. A particular concern they voiced related to the impact of pricing policies on the reward to private investment in pharmaceutical R&D and on the incentives for future innovation. On the one hand, countries whose policies restrict the prices pharmaceutical firms can charge for their products were, it was suggested, potentially free-riding on the rewards and incentives for innovation provided by others. On the other hand, Ministers from the former countries highlighted the strong profitability record of the pharmaceutical industry and argued that their policies gave greater weight to public health objectives than to industrial policy objectives. Ministers called on the OECD to take up work on these difficult and contentious questions to provide a basis for more informed policy making. The goal would be to document the facts about pharmaceutical pricing and reimbursement policies in different countries and the links to innovation in order to help arrive at appropriate policies and cooperative initiatives to achieve common cross-national policy goals.

In subsequent discussion of the scope of OECD work in this area, delegates from several OECD countries observed that pharmaceutical policy making serves multiple objectives that must be balanced with one another to arrive at the policy mix that best reflects national priorities. Considering the impact of policies in terms of only one objective would therefore be unsatisfactory. The objective of ensuring affordable access to effective medicines runs up against strong pressures for public sector cost-containment in recent years when pharmaceutical expenditure growth has exceeded both economic growth and growth in the health sector as a whole. There is also a tension in several OECD countries which have, or aspire to have, a significant domestic pharmaceutical industry presence and activity, between health-system performance objectives and those pertaining to industry policy.

But perhaps the most difficult trade-off in pharmaceutical policy is the seemingly inherent trade-off between *static efficiency* – in which consumer welfare is maximised by getting the most health value from today's expenditures, as constrained by the limits of present technological capability – and *dynamic efficiency*, in which the R&D incentives serve to generate growth in the capacity to prevent health conditions and cure diseases in the future. Getting the best possible price or lowest possible expenditures for pharmaceutical products in the market today may mean having fewer and less innovative alternatives for the future.

Even if it is recognised that short-term efficiency is in potential conflict with the prospect of future gains, the way forward is not clear. On the one hand, few would doubt that patients have derived significant health gains from innovative pharmaceutical products. On the other, there are many policy makers and the citizens and patients whose interests they serve, who believe that incentives in the pharmaceutical market have

yielded sub-optimal outcomes – not enough new treatments focused on the most important health concerns, too many products to treat conditions not formerly recognised as requiring treatment, not enough breakthrough innovations, and too many so-called "me-too" products introduced in therapeutic classes already amply stocked. Furthermore, national policies stand to affect not only innovation, but also the prices and availability of medicines in other countries, giving countries a rationale for strong interest in the policies of their peers.

The OECD project on pharmaceutical pricing policy was launched in December 2005. It included research to describe and evaluate the pharmaceutical market and policy environment in six OECD countries – Canada, Germany, Mexico, the Slovak Republic, Sweden and Switzerland – selected to represent a range of policy and market characteristics seen within the OECD, development of an analytic framework and indicators for assessing the impact of pharmaceutical pricing policies, and application of that framework to produce a report assessing policies. Findings from the case studies, supplemented by material from the health economics and health policy research literature and results of other ongoing work, were used as inputs to the policy analysis presented in this final report from the project.

The report is organised in two parts, with *Part 1* (Chapters 1-3) providing background information for policy makers and setting the stage for the analysis of pharmaceutical policies and their impact that is presented in *Part 2* (Chapters 4-6).

Chapter 1 provides an overview of the role of the pharmaceutical sector within the health systems and the economies of OECD countries. The second chapter is complementary in that it provides an overview of the global market for pharmaceuticals and of the activities of the pharmaceutical industry. Chapter 3 describes the range of practices used by public and private payers or purchasers and by regulators, in their efforts to define pharmaceutical prices and reimbursement amounts. Chapter 4 considers the impact of those pricing practices and closely related policies on commonly held policy goals such as promotion of public health, cost-containment and pursuit of maximum value for money. The report's final chapters consider the external impact of pricing policies, first on foreign availability and prices of medicines (Chapter 5), and second on future pharmaceutical innovation (Chapter 6). The main conclusions from the study are presented in a short final section.

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Chapter 1

Key Characteristics of the Pharmaceutical Sector in OECD Economies

This chapter serves to provide context for the analysis of pharmaceutical pricing policy presented in later chapters of this report. It provides an overview of the pharmaceutical sector in OECD countries, identifying key cross-country differences and similarities. The chapter begins by describing pharmaceutical expenditure levels and cross-country differences in the value of consumption and in retail prices paid. It then assesses the role of the pharmaceutical industry in OECD economies, in terms of the levels of production, R&D and trade.

Introduction

Policy makers' interest in pharmaceutical expenditures goes beyond its level and price and volume components; the rapid growth of pharmaceutical spending and the significant portion paid out-of-pocket by individuals also generate attention. Beyond this, the pharmaceutical industry plays an important role in the economy of several OECD countries. These varying conditions are likely to influence the relative weight policy makers apply to common policy goals such as access to effective treatments, cost containment and value, and how they seek to resolve conflicts that may arise among these goals and with industrial policy goals.

Pharmaceutical expenditures

The United States accounts for more than 40% of OECD expenditure on pharmaceuticals

OECD countries spent USD 569 billion on pharmaceuticals (excluding pharmaceuticals for in-patients) in 2005. The predominance of the United States is striking (Figure 1.1). US pharmaceutical expenditure amounted to USD 235 billion, accounting for 41% of total expenditure on pharmaceuticals in the OECD, a figure which exceeds its share of total OECD GDP (36%). Next to the United States, Japan spent USD 71 billion. Rounding out the top five were Germany (USD 45 billion), France (USD 39 billion), and Italy (USD 32 billion). The bottom five countries in terms of total pharmaceutical expenditures are the OECD countries with the smallest populations.

Variation in per capita expenditure on pharmaceuticals is not very great, except for outliers

OECD countries spent an average of USD PPP 404[1] per person on pharmaceuticals in 2005 (Figure 1.2). The modest degree of deviation from the average is notable–half of all OECD countries have spending that deviates by less than 20% of the average–although three countries are outliers in this respect. Per capita pharmaceutical expenditures were much higher in the United States (USD PPP 792) than they were in the next highest spending country, Canada, which spent USD 589 per capita. At the other extreme, Mexico spent only USD PPP 144 per capita, about USD PPP 100 less per capita than Poland, the next lowest-spending country, and just 18% of the US spending level. Turkey's expenditure appears comparable to that of Mexico, but was calculated at ex-manufacturer prices, thus resulting in an underestimate of spending.

A weak, positive relationship between per capita income and per capita pharmaceutical expenditure

The finding, presented in Figure 1.3, that there is a weak, positive relationship between per capita income and per capita pharmaceutical expenditure, is consistent with recent research. Okunade and Suraratdecha (2006) estimated the income elasticity of pharmaceutical expenditure for 12 OECD countries.[2] They found that the income elasticity

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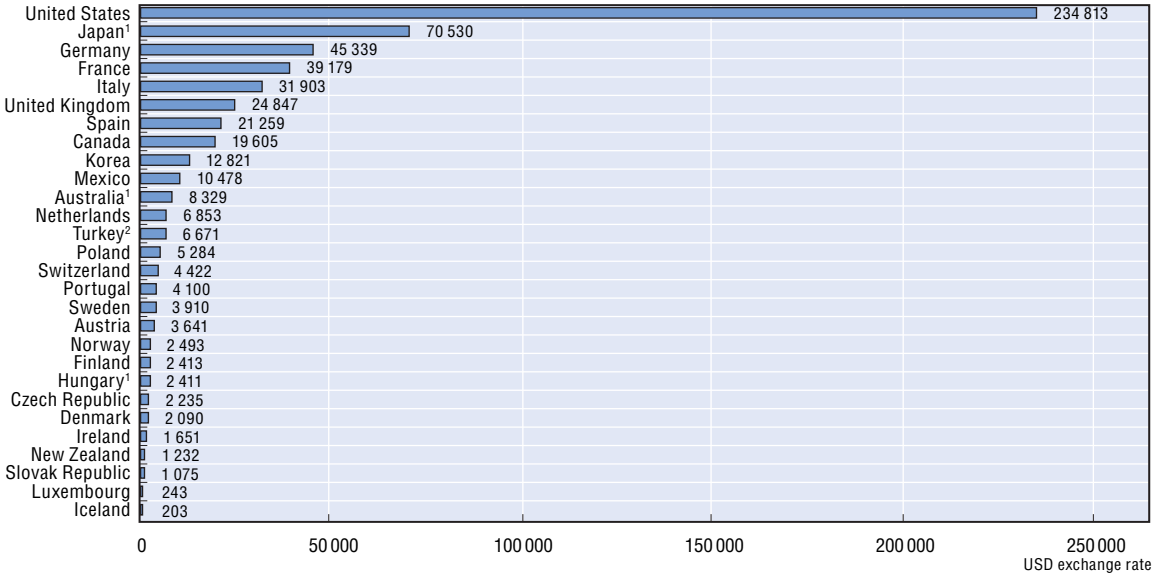
Figure 1.1. **Total expenditures on pharmaceuticals, 2005**

In million USD



Note: Expenditures were converted from national currency units to US dollars at 2005 average exchange rates. See Box 1.1 for more notes.

1. 2004 (Japan and Hungary) and 2004/05 fiscal year (Australia).
2. Data reported are 2005 pharmaceutical sales at ex-manufacturer prices, which underestimate total health expenditure.

Source: *OECD Health Data 2007* and authors' estimates. See Box 1.1 for more sources.

Box 1.1. **Pharmaceutical expenditure: definition, deviations and sources**

Definition

Pharmaceutical expenditure corresponds to item HC.5.1 in the International Classification of Health Accounts-health care functional classification; it includes spending on prescription medicines and over-the-counter products, as well as other medical non-durable goods. It includes wholesale and retail margins and value-added tax. It also includes pharmacists' remuneration when the latter is separate from the price of medicines. Pharmaceuticals consumed by hospital inpatients are excluded.

Deviations

Expenditure for Australia is reported for the Australian fiscal year (1 July to 30 June). Expenditure for Luxembourg does not include over-the-counter medicines and is therefore underestimated. Pharmaceutical expenditures for Denmark, Hungary and Poland are estimates. Pharmaceutical expenditure data for Belgium and Greece were not available.

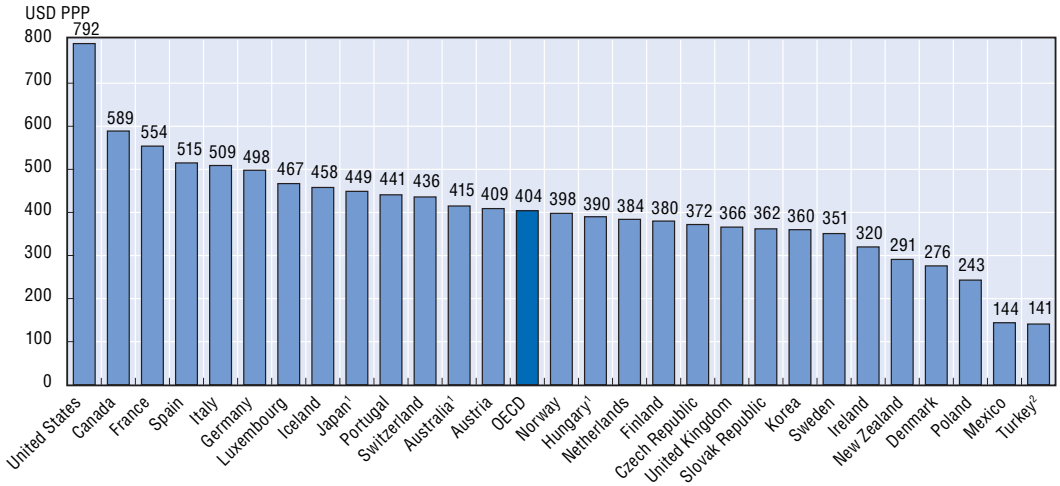
Sources

Except for the United Kingdom and the Netherlands, data are drawn from *OECD Health Data 2007*. For the United Kingdom the data are derived from authors' calculations based on an estimate of total NHS costs for prescription medicines from data compiled by the Office for Health Economics,[1] plus households' final consumption expenditures for pharmaceuticals from the UK National Statistics Office.[2] For the Netherlands the data are drawn from the Centraal Bureau voor de Statistiek (CBS, Statistics Netherlands),[3] except for Figure 1.5 and Figure 1.13 where *OECD Health Data* were used.

1. OHE (2007), *Compendium of Health Statistics: 18th edition 2007*, Office for Health Statistics, London.
2. *www.statistics.gov.uk*, updated 15 June 2007.
3. CBS Persbericht PB07-041 and CBS StatLine databank (*www.cbs.nl/en-GB/menu/cijfers/statline/default.htm?Languageswitch=on*, accessed 7 January 2008).

Figure 1.2. **Per capita spending on pharmaceuticals, 2005**

In USD PPP



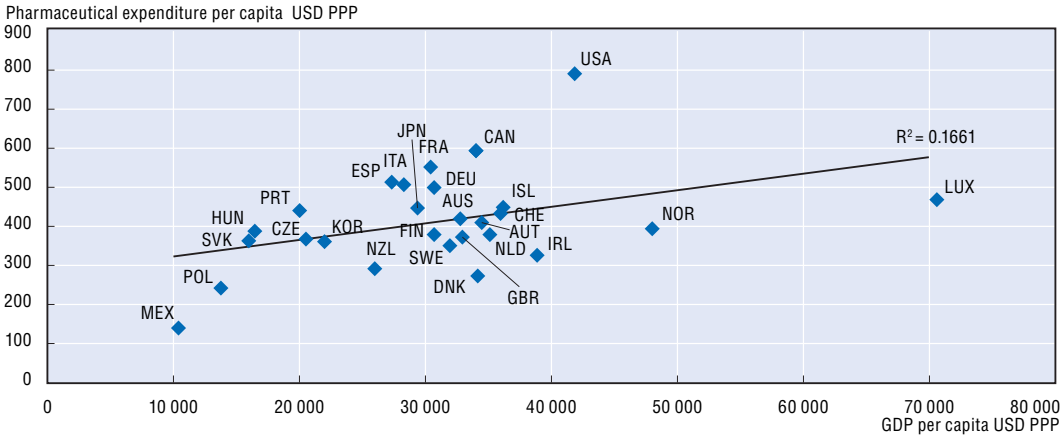
Note: Expenditures were converted from national currency units to US dollars using GDP purchasing power parities. See Box 1.1 for more notes.

1. 2004 (Japan and Hungary) and 2004/05 fiscal year (Australia).
2. Data reported are 2005 pharmaceutical sales at ex-manufacturer prices, which underestimate total pharmaceutical expenditure.

Source: *OECD Health Data 2007* and authors' estimates. See Box 1.1 for more sources.

Figure 1.3. **Pharmaceutical expenditure per capita and GDP per capita, 2005**

In USD PPP



Note: The coefficient on the independent variable "GDP per capita" (0.0043) was statistically significant at the 5% level (t-statistic = 2.18). See Box 1.1 for more notes.

Source: *OECD Health Data 2007* and authors' estimates. See Box 1.1 for more sources.

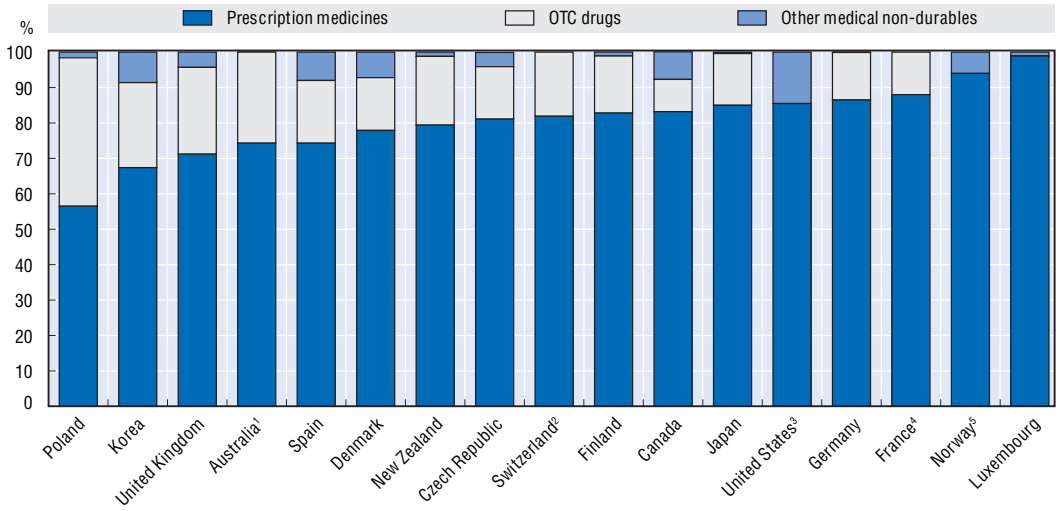
of pharmaceutical demand varies significantly across countries and is relatively inelastic, meaning that expenditure changes with income, but not as fast as income does.

Prescribed medicines consumed outside the hospital setting account for the bulk of pharmaceutical expenditure

Figure 1.4 depicts the share of prescription medicines and over-the-counter (OTC) drugs in total (other than hospital) pharmaceutical expenditures for 17 countries. On average, prescription medicines (including, in some countries, drugs available over-the-

counter that were prescribed for use by a health-care practitioner) account for approximately 80% of total pharmaceutical expenditures, with OTC drugs accounting for 19%. Only 57% of total pharmaceutical expenditures in Poland were for prescription medicines, in contrast to France where prescription medicines accounted for 87% of total spending on pharmaceuticals. Spending on OTC products as a share of pharmaceutical expenditure was by far greatest in Poland, at 42% of total pharmaceutical expenditure. The share of OTCs was lowest in Canada at 9%.

Figure 1.4. **Share of prescription and over-the-counter (OTC) drugs in total pharmaceutical expenditures, 2005**



Note: In some countries, expenditures reported as prescription medicines include prescribed pharmaceuticals normally available in the country without a prescription. See Box 1.1 for more notes.

1. 2004/05 fiscal year; OTC includes medical non-durables and non-reimbursed medicines which account for about 10% of pharmaceutical expenditures.
2. No estimates available for other medical non-durables which probably represent about 5% of total spending on pharmaceuticals.
3. Other medical non-durables includes OTC drugs.
4. No data provided for medical non-durables.
5. Prescription medicines includes OTC.

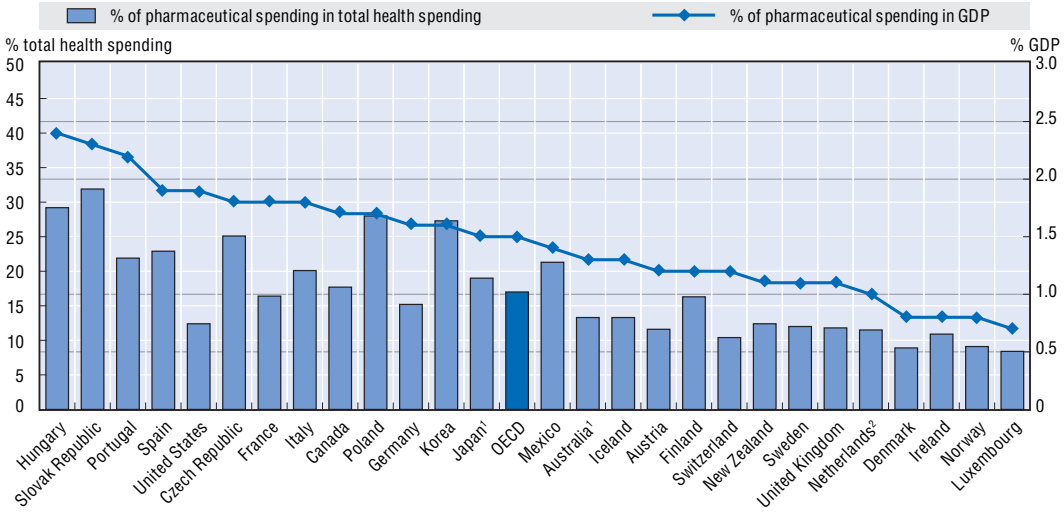
Source: OECD Health Data 2007. See Box 1.1 for more sources.

It is not possible, at present, for most countries to report the share of hospital expenditure that is devoted to pharmaceuticals. Evidence from those countries that can make such calculations suggests that the sum is relatively small in comparison with the amount devoted to drugs used outside the hospital. According to data on spending on pharmaceuticals in hospitals from the 2006 Joint OECD-Eurostat-WHO Health Accounts (SHA) Data Collection (available for only three countries), spending on in-hospital drugs as a share of total pharmaceutical expenditures (in hospital and outside of a hospital setting) was 8% in both Canada (in 2003) and Germany (2004), and 13% in Korea in 2004.

The average OECD country spent 1.5% of its GDP and less than a fifth of its total health expenditures on pharmaceuticals in 2005

The average OECD country spent 1.5% of its GDP on pharmaceuticals in 2005 (Figure 1.5). Of the top five countries, three – Hungary, the Slovak Republic and Portugal – spent 2% or more of GDP on pharmaceuticals. At the other end of the scale, four countries spent less than 1% of GDP on pharmaceuticals.

Figure 1.5. **Share of pharmaceutical expenditure in total health spending and in GDP, 2005**



Note: See Box 1.1 for more notes.

1. 2004 (Japan) and 2004/05 fiscal year (Australia).
2. 2002.

Source: OECD Health Data 2007, except total health expenditure for the United Kingdom (Office for Health Economics Compendium of Health Statistics 2007, estimate for total health expenditure from Table 2.1). See Box 1.1 for more sources.

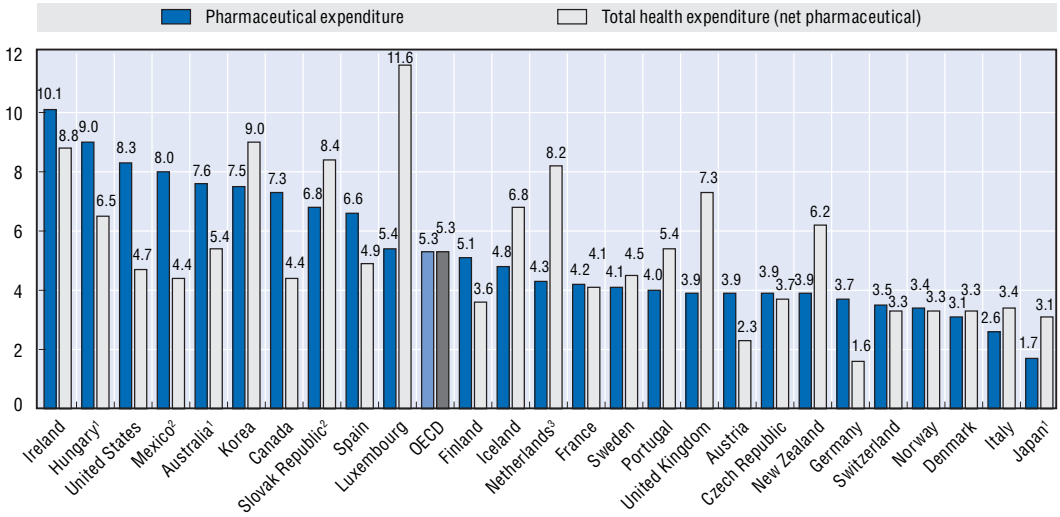
Pharmaceutical expenditure accounts for a relatively small share of OECD countries' health expenditures, less than one-fifth, on average (Figure 1.5). However, it plays a larger role in several countries – about 30% in Hungary, the Slovak Republic, Poland and Korea – and a minimal role in several more – less than 10% in Denmark, Norway and Luxembourg. The countries spending the lowest share of GDP on pharmaceuticals are also the countries for which pharmaceutical spending represents the lowest share of total health expenditure, although the reverse is not consistently true.

Pharmaceutical expenditure has been increasing faster than economic growth

From 1997 to 2005, the average rate of real annual growth in pharmaceutical spending was 5.3%, equivalent to the real annual growth rate in health (net of pharmaceutical expenditure) during the same period (Figure 1.6). The rate of growth of pharmaceutical spending surpassed that of total health expenditures in ten of 25 countries, while being roughly equal in six countries. Both pharmaceutical and total health expenditures grew at a higher rate than the mean annual growth rate of GDP for the countries included in Figure 1.6, which was 3.0% between 1997 and 2005 (OECD, 2007a).

The mean annual growth rate (MAGR) of pharmaceutical expenditure during this period was highest in Ireland (10%) and Hungary (9%) and lowest in Italy and Japan – the only two countries with MAGRs of less than 3%. Low spending growth on pharmaceuticals for Japan is due in part to regular biennial price reviews by the Ministry of Health, Labor, and Welfare. In the 2000 review, prices were lowered by an average of 7%; in the 2002 review prices were cut by an average of 6.3% (ITA, 2004). Increases in the volume of consumption and changes in therapeutic mix were the main reasons pharmaceutical expenditures grew in Canada during this period (Paris and Docteur, 2006), whereas in Mexico, growth in pharmaceutical spending

Figure 1.6. **Real annual growth in pharmaceutical spending and total health expenditure (net of pharmaceutical expenditure), 1997-2005**



Note: Growth rates are calculated using 2000 GDP price levels to deflate pharmaceutical and health expenditure.

1. 1997-2004 (Hungary and Japan) and 1997/98-2004/05 fiscal year (Australia).
2. 1998-2005.
3. 1998-2005. See Box 1.1 for more notes.

Source: *OECD Health Data 2007* and authors' estimates [except total health expenditure for the Netherlands (Centraal Bureau voor de Statistiek, Press Release PB07-041, 16 May 2007) and the United Kingdom (Office for Health Economics Compendium of Health Statistics 2007, estimate for total health expenditure from Table 2.1)]. See Box 1.1 for more sources.

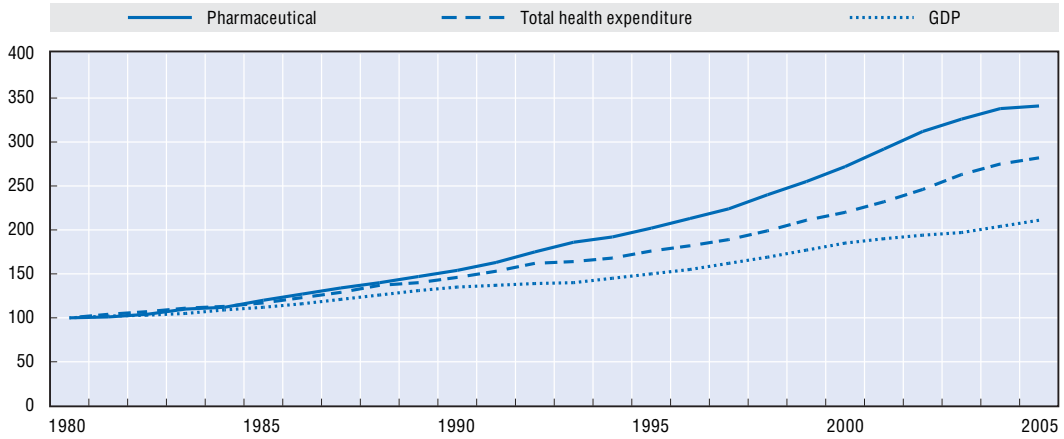
was due mainly to strong growth in retail prices for on-patent medicines due to the relaxation of price controls (Moïse and Docteur, 2007a).

When observed over a longer period of time, pharmaceutical expenditures have increased more than have total health expenditures (net of pharmaceutical expenditure). Figure 1.7 shows the growth in pharmaceutical expenditure, total health expenditure and GDP between 1980 and 2005 (based on 15 countries for which data were available). Total expenditures on pharmaceuticals in 2005 were about 2.5 times greater than in 1980, an increase significantly greater than that for health expenditure, which became 1.8 times greater over the same period. This translates into a mean annual growth rate of pharmaceutical expenditures from 1980 to 2005 of 5.0%, during which time the mean annual growth in total health expenditure was 4.1%. Spending on both pharmaceuticals and health grew significantly more than did GDP during this period.

However, much of the substantial increase in pharmaceutical expenditure relative to total health expenditure during this period can be attributed to a growth spurt in pharmaceutical spending that began in the early 1990s. The mean annual growth rate for pharmaceutical expenditure from 1990 to 1999 was 5.6%, significantly greater than the 4.2% annual growth for total health expenditure; GDP grew at an annual rate of 3.0% during this same period. This is a significant divergence from the trend growth rates experienced from 1980 to 1989, and from 2000 to 2005, during which growth in both pharmaceutical expenditure and total health expenditure were roughly equivalent. The MAGR for pharmaceutical expenditure from 1980 to 1989 was 4.4%, greater than the 3.8% growth rate for total health expenditure. From 2000 to 2005, the MAGRs for both pharmaceutical and

Figure 1.7. **Trend growth in pharmaceutical and total health expenditure for 15 OECD countries, and GDP, 1980-2005**

1980 = 100



Note: Indexes were calculated using national currency units at 2000 GDP prices. Pharmaceutical expenditure is excluded from total health expenditure.

Source: OECD Health Data 2007.

total health expenditures were 5.0%. Pharmaceutical expenditure and total health expenditure growth were both greater than GDP growth for both periods.

Pharmaceutical consumption and relative price levels determine pharmaceutical expenditures

Differences across countries in per capita pharmaceutical expenditure levels reflect differences in the level of retail or end prices paid for pharmaceutical products and in the volume and mix of products consumed.

Retail prices of pharmaceuticals

Prices vary widely across the OECD, with Switzerland, Canada, the United States and Germany highest

It is possible to examine the relative price levels of pharmaceuticals using price indices developed by OECD and Eurostat as input to the development of economy-wide purchasing power parities (Box 1.2). The indices show 2005 price levels relative to the OECD average price. They provide a rough estimate of where a country stands, relative to the OECD average and to other countries. However, the estimates of relative price levels are not sufficiently precise to distinguish between rankings of countries with similar price levels.

The range in price levels across the OECD is wide, with countries ranging from 68% to 185% of the OECD average (Figure 1.8). OECD countries can be categorised in five clusters, according to their relative retail price levels for pharmaceuticals:

1. The highest-priced group includes two countries: Switzerland, with retail price levels of 185% the OECD average, and Iceland, with pharmaceutical prices of 159% the OECD average.
2. Three countries (Canada, the United States and Germany) which had retail pharmaceutical prices between 134% and 127% of the OECD average in 2005.
3. Twelve countries which had price levels between 103% and 120% of the OECD average.
4. Four countries which had price levels between 91% and 94% of the OECD average.

Box 1.2. **Purchasing power parities and comparative price levels for pharmaceuticals**

Purchasing power parities (PPPs) are spatial deflators and currency converters that eliminate the effects of the differences in price levels between countries, thus allowing volume comparisons of GDP components and comparisons of price levels.

As part of their collaborative work on national accounts and PPPs, the OECD and Eurostat have developed pharmaceutical PPPs for input into economy-wide PPPs for OECD countries. Pharmaceutical price data are collected every three years. Improvements in data collection have ensured that the 2005 data are superior to previous years' data. The next round of collection is scheduled for the last quarter of 2008.

Country reporting of retail prices of pharmaceuticals

An original list of 181 drugs was drawn for top-selling drugs in Europe, 75% of which were original drugs and 25% generics. This list was distributed in November 2005 to National Institute of Statistics (NIS) officials in each OECD member country. Respondents were asked to report retail pharmaceutical prices for products considered representative of their respective markets.

For each product (name + form + dosage + package size), reporting countries had to indicate the retail price for a standardised consumption unit (for instance ten tablets for solid oral form, 100 ml for liquids, etc.).

Reported retail prices include distribution margins (wholesalers' and pharmacists' margins/mark-ups), as well as VAT rates. They represent "total costs of pharmaceuticals to the society" (Eurostat, 2007) and not only the share of the cost paid out-of-pocket by final consumers.

Countries reported data for 86 products on average (66 originals and 20 generics).

Purchasing power parities for pharmaceuticals (PPPs)

The PPPs are calculated as quasi-weighted geometric averages of relative prices (parities) between pairs of countries for the basket of products which are representative in both countries. To produce multilateral comparisons, a multi-step procedure is used to adjust for differences in the sets of "representative products" across countries in order to make results obtained for pair countries "transitive".*

Comparative price levels (CPL)

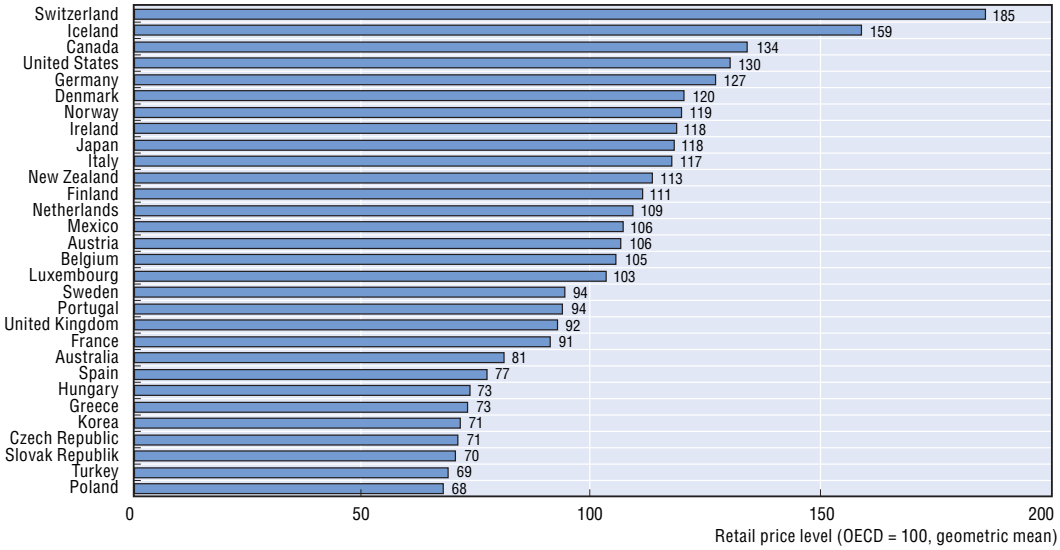
CPLs are calculated as the ratios of PPPs to exchange rates. They provide a measure of the differences in pharmaceutical price levels between countries by indicating the number of units of the common currency (in this case the US dollar) needed to buy the same volume of pharmaceuticals in each country.

Caveats

When retail pharmaceutical sales data at the national level are not available, NIS correspondents may find it difficult to identify which products are representative (sold in sufficient quantities to be considered typical) of their country. Similarly, when prices differ for different market segments, NIS correspondents will not always know the "average" retail price.

*For a more detailed explanation see Chapter 7 and Annex V of OECD (2006), *Eurostat-OECD Methodological Manual on Purchasing Power Parities*, Paris.

Figure 1.8. **Relative retail pharmaceutical price levels in OECD countries, 2005**



Note: Prices were converted to a common currency (USD) using the 2005 average exchange rate.

Source: Eurostat-OECD Purchasing Power Parity Programme, 2007.

5. Nine countries (Poland, Turkey, the Slovak Republic, the Czech Republic, Korea, Greece, Hungary, Spain and Australia) which had price levels between 68% and 81% of the OECD average.

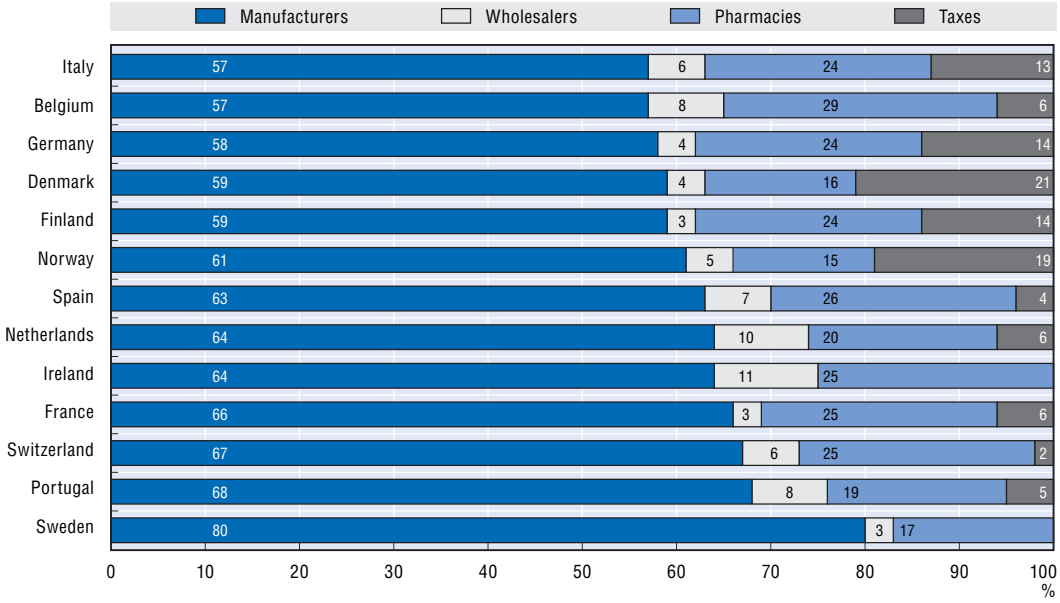
The retail price includes the payment received by the manufacturer plus wholesale and retail mark-ups, plus any VAT or other tax paid by the final purchaser.[3] Accordingly, retail price levels may differ across countries due to differences in the average price for the product received by the manufacturer. However, they can also reflect differences in the distribution margins (wholesale and retail) and in the level of tax included in the price.

Retail price differences are partly explained by differences in tax policies and distribution costs

Figure 1.9 provides an overview of the composition of the average retail pharmaceutical price in selected OECD countries in 2004. It shows, for example, that 80% of the retail price paid for pharmaceuticals accrued to manufacturers in Sweden, compared with only 57% in Belgium. The amount of tax paid by the end purchaser and included in the price of the product ranged from 0 to 21%. Distribution costs accounted for between 20 and 37% of the final price paid. In some countries, fixed fees for pharmacists' services (*e.g.*, prescription fees) are paid by the consumer on top of the price of the product. A table with details of distribution mark-ups and VAT in OECD countries is included in an annex to this chapter.

Box 1.3 illustrates how differences in the components of retail prices contribute to countries' relative positions, drawing on examples of selected countries for which retail prices were analysed. An analysis of the role of pricing and reimbursement policies as determinants of price levels is presented in Chapter 4.

Figure 1.9. **Components of retail pharmaceutical prices, selected OECD countries, 2004**



Source: VFA (2006), The *Pharmaceutical Industry in Germany*, Verband Forschender Arzneimittelhersteller e.V. (German Association of Research-Based Pharmaceutical Companies) Berlin: the original source of these data is the European Federation of Pharmaceutical Industry Associations (EFPIA).

A weak, positive relationship between retail pharmaceutical price levels and national income levels

For any given income level, the range of retail pharmaceutical price levels is very great (Figure 1.10). For example, France, Germany and Japan have a similar income level but pharmaceutical price levels ranging from 91% to 127% of the OECD average. Similarly Australia, Austria and Canada have similar incomes, but pharmaceutical price levels ranging from 81% to 134% of the OECD average. It is likely that other factors, such as pharmaceutical policies pertaining to pricing, reimbursement, distribution and tax, have a greater influence than national per capita income on the relative retail price level of pharmaceuticals. These are explored further in Chapter 4.[4]

Volume of consumption

France, Spain and the United States have the highest pharmaceutical consumption; Mexico has the lowest

The pharmaceutical PPPs developed by the OECD and Eurostat as input into economy-wide PPPs for OECD countries allow pharmaceutical expenditure to be deflated to produce estimates of the volume of pharmaceutical consumption across countries.[5]

Figure 1.11 presents per capita real pharmaceutical expenditures, *i.e.* an approximation of per capita consumption of pharmaceuticals. Fifteen of the twenty-seven countries shown in Figure 1.11 had per capita pharmaceutical consumption levels that were within 20% of the OECD average (USD 532). The three countries with the highest pharmaceutical consumption per capita (France, Spain and the United States) were well above the OECD average, with consumption of about USD 800 per capita or higher. Per capita

Box 1.3. **The role of retail price components in explaining relative pharmaceutical prices**

Some countries with high ex-manufacturer prices also have high mark-ups, resulting in relatively high retail prices. For example, Switzerland has the highest retail pharmaceutical prices in the OECD (185% of the OECD average). Its relative situation is supported by relatively high ex-manufacturer prices for medicines combined with relatively high distribution costs (pharmacy and wholesale mark-ups), despite low VAT (Paris and Docteur, 2007).

While the US retail price level is relatively high (130% of the OECD average), it is roughly comparable to the level in several other OECD countries, *e.g.* Canada and Germany, and is not as high as the highest OECD countries. This finding may be surprising in that several studies have concluded that US pharmaceutical prices (for patented medicines) are highest in the OECD, when assessed at ex-manufacturer price levels (see, for example, ITA, 2004; PMPRB, 2006).[1] However, the US prices reported by US authorities that were used in calculating the price index were collected from Internet pharmacy websites, which include no tax and (presumably) relatively low distribution costs, meaning that the mark-up over ex-manufacturer prices is low, relative to other countries. Beyond this, it is possible that the significant weakening of the US dollar since 2002 has resulted in US prices at ex-manufacturer level that are more comparable to those of other OECD countries.

Canada's retail price levels are comparable to those of the United States. Canada's ex-manufacturer prices for on-patent products are in line with those of the higher-priced European countries of the OECD (Paris and Docteur, 2006). Distribution costs and taxes vary significantly across provinces. Germany's relatively high prices can also be explained by its relatively high ex-manufacturer prices,[2] as well as a relatively high VAT for pharmaceuticals.

As Sweden has relatively high ex-manufacturer prices for pharmaceuticals, its relatively low position with respect to retail prices is explained by its very low-cost distribution chain and exemption of pharmaceutical from VAT (Moïse and Docteur, 2007b).

Mexico's pharmaceutical prices are slightly above the OECD average (106%). The retail price in Mexico includes retail and wholesale margins that are estimated to account for about 42% of the retail price (Moïse and Docteur, 2007a).

The Slovak Republic's low retail prices suggest that ex-manufacturer prices were also relatively low in 2005, given that the Slovak Republic's retail price levels included wholesale and retail margins plus a 19% VAT (relatively high among European countries), which has since been lowered to 10% (Kaló *et al.*, 2007).

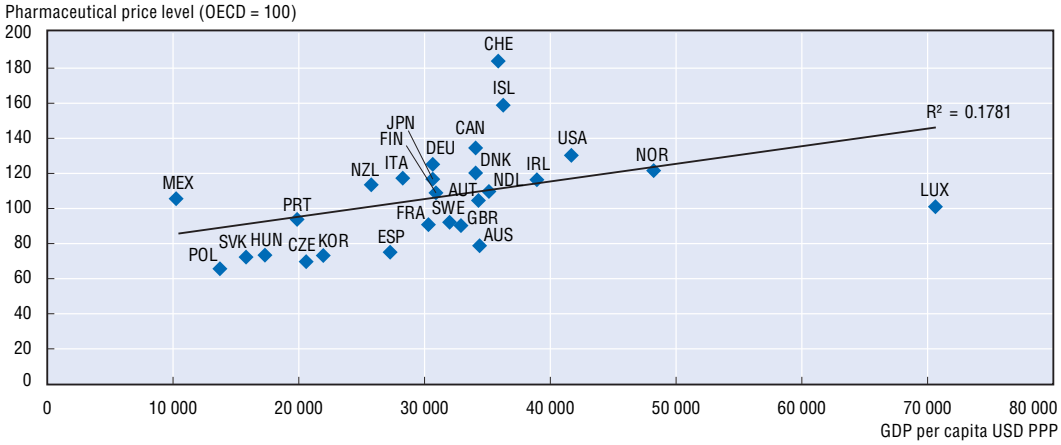
1. A study of price levels by Danzon and Furukawa (2003) found that Japan's prices exceeded US prices at ex-manufacturer level. The difference from the subsequent study by the US ITA may, in part, be due to the fact that the latter study did not take into account off-invoice discounts consented to US health insurance companies, estimated by Danzon and Furukawa at 8-11% of price. All price comparisons are sensitive to differences in methodology and fluctuations in the exchange rate.
2. For example, the UK Department of Health undertook bilateral comparisons of 2005 ex-manufacturer prices for branded medicines with nine European countries (not including Switzerland or Ireland) and found that the German prices were highest (OFT, 2007).

pharmaceutical consumption was exceptionally low in Mexico (USD 120) and Poland (USD 267).

The mix of products consumed varies across countries

The estimates of volume presented in Figure 1.11 do not provide insight into differences in the mix of products consumed across countries. Thus, for example, two countries could appear to have very similar volumes of consumption, while in one, relatively few high-

Figure 1.10. **Retail pharmaceutical price levels and GDP per capita, 2005**

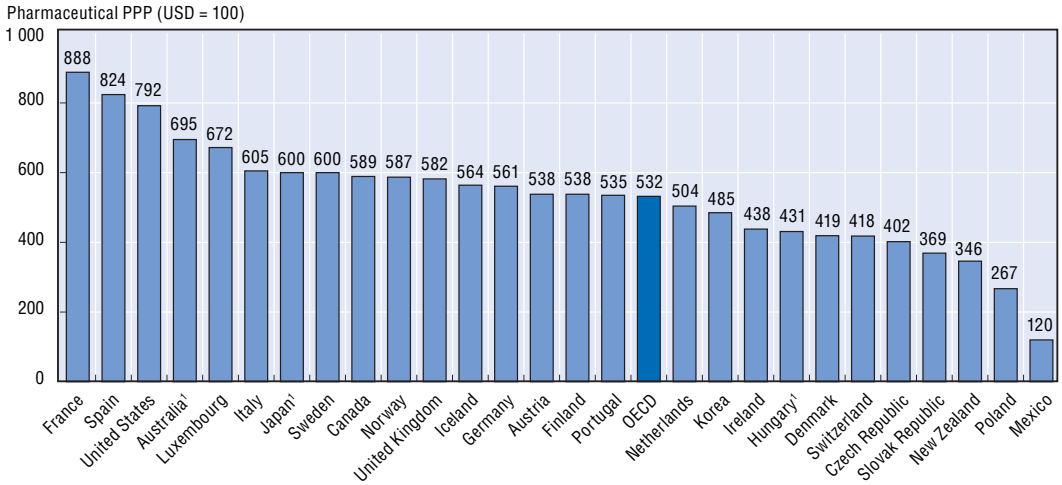


Note: Prices were converted to a common currency (USD) using the 2005 average exchange rate. The coefficient on the independent variable "GDP per capita" (0.001) was statistically significant at the 5% level (t-statistic = 2.33).

Source: OECD Health Data 2007 and Eurostat-OECD Purchasing Power Parity Programme, 2007.

Figure 1.11. **Real per capita spending on pharmaceuticals, 2005**

Volume of consumption, in USD, adjusted for differences in pharmaceutical prices



Note: Per capita pharmaceutical expenditures were converted from national currency units to US dollars using Eurostat-OECD pharmaceutical PPPs (see Box 1.2). The volume of consumption depicted is overestimated in those countries, like Switzerland, where purchasers pay a fixed fee for pharmacy services (*e.g.*, a prescription fee) that is not included in the end price of the product. See Box 1.1 for more notes regarding pharmaceutical expenditures.

1. 2004 pharmaceutical expenditures (2004/05 fiscal year for Australia) were deflated using 2005 retail price levels.

Source: OECD Health Data 2007; Eurostat-OECD Purchasing Power Parity Programme, 2007. See Box 1.1 for more sources on pharmaceutical expenditures.

priced packages were consumed per person where in another, relatively more low-priced packages were consumed.

Studies have revealed differences across countries in the mix of pharmaceutical products consumed. For example, in a study of use and expenditure on pharmaceuticals used in treating cardiovascular disease and stroke, Dickson and Jacobzone (2003) found that cross-country variations in the use of less expensive effective drugs, such as diuretics and beta blockers seemed to be related to "needs", as measured by the Ischaemic Heart Disease burden of disease. However, use of "newer" pharmaceutical agents (calcium

channel blockers, ACE inhibitors, and serum lipid reducers) was higher among those countries that spent a greater percentage of GDP on health.[6]

The volume of pharmaceuticals can also be estimated through the use of defined daily doses (DDDs), a measure of consumption defined as the *assumed average maintenance dose per day for a drug used on its main indication in adults*. Because DDD data are reported by only a subset of countries and relate to only a subset of therapeutic groups,[7] it is not possible to use these data as a check on the overall consumption levels presented above. However, they illustrate different patterns of use, which may well reflect differences in underlying disease prevalence, national prescribing guidelines, or other factors.

Using DDDs per thousand inhabitants per day, the OECD reported information on consumption levels across countries for four different therapeutic groups: the latest anti-diabetics, antidepressants, anti-cholesterols, and antibiotics (OECD, 2007b). Australia has the fourth-largest per capita volume of pharmaceutical consumption according to the deflated expenditure data presented in Figure 1.11. This is consistent with the finding that Australia had the largest per capita consumption of anticholesterols and the second largest of antidepressants in 2005. On the other hand, the country's consumption of antidiabetics was below the OECD average. The Slovak Republic, to take another example, is fourth from the bottom in terms of per capita pharmaceutical consumption in Figure 1.11. In terms of consumption by DDDs per thousand inhabitants per day, the Slovak Republic consumed the third-highest number of antibiotics; however, the country consumed the fewest antidepressants and was the third-lowest consumer of antidiabetics.

Large differences across countries in the availability of medicines on the market suggest that there are significant differences in consumption patterns

Differences across countries in the availability of medicines on the market and the timing of product launch[8] are likely to be indicative of a country's patterns of use, in terms of the mix of older and newer products consumed.

There is evidence of differences across countries in the products available on the market. The percentage of new molecules marketed within ten years of first world launch varies considerably across OECD countries. In 2002, only 25% of all new molecules (representing 462 total drugs) launched worldwide between 1982 and 1992 were available on the market in Australia, compared to 53% in Japan (Lanjouw, 2005). On the other hand, Australia (67%) and Japan (68%) appeared similar in the share of all blockbuster drugs that had been released within ten years of first world launch.[9] Only 38% of all new molecules had been released in the United States within ten years of first global launch; however, 90% of all blockbusters had been.[10]

Further evidence of differences in availability is furnished in Table 1.1. In the table, Lanjouw (2005) presents findings on the length of time it took for new molecules to be launched in OECD countries following their initial global launch between 1986 and 1992. The table's first column shows the number of new molecules, out of 122 launched worldwide between 1986 and 1992, that had reached each country's market by 2002. Only six of these molecules had been marketed in Poland as of 2002, in contrast to Japan, where 77 were on the market.

Table 1.1 also provides evidence of large differences across countries in the speed at which products became available on the market. As indicated in the second column, there were eight countries for which 10% of marketed drugs were launched almost immediately

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Table 1.1. **Launch lags for 122 new molecules that were first marketed in 1986-1992**

In months

	Number of new molecules	Percentile		
		10th	Median	90th
Australia	28	15	46.5	111
Austria	46	12	28.5	73
Belgium	40	6.5	23	90.5
Canada	34	4	32.5	69
Denmark	40	0.5	18	68
Finland	38	11	27.5	85
France	41	0	19	62
Germany	54	0	18.5	45
Greece	44	13	37	120
Ireland	38	0	22.5	88
Italy	57	0	24	74
Japan	77	0	0	85
Korea	53	24	49	110
Mexico	44	8	29	102
Netherlands	47	4	22	49
New Zealand	36	5	26.5	79
Poland	6	34	43.5	98
Portugal	33	20	49	88
Spain	37	18	30	111
Sweden	46	0	17	86
Switzerland	46	2	14	66
Turkey	40	23	55.5	95
United Kingdom	50	0	16	51
United States	46	0	20	69

Note: Launch lags are the number of months between the first global launch of a new molecule and its subsequent launch in the respective country.
Source: Lanjouw (2005).

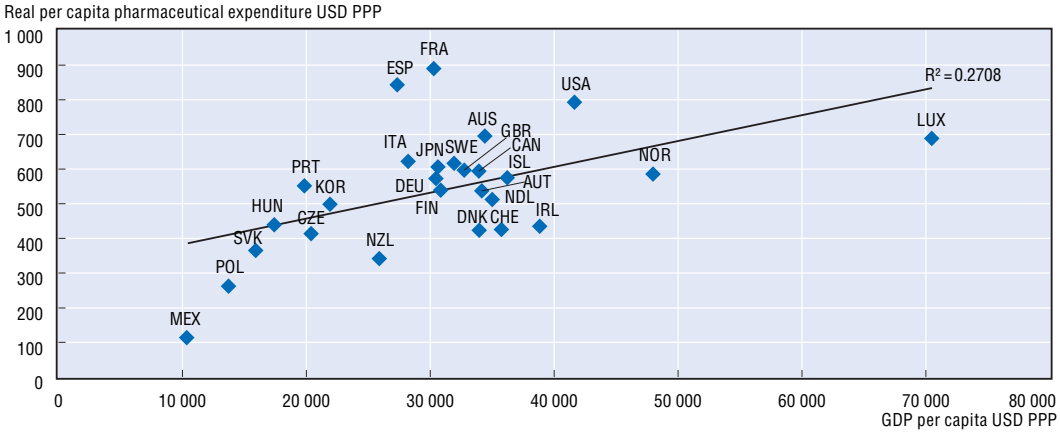
following first world launch.[11] The variation in launch lags across countries is evident from the third column. In Japan, at least half of all new molecules were launched almost immediately following first world launch; in Switzerland, half of all new molecules available there in 2002 had been launched within 14 months. The United Kingdom and Germany also stand out as countries where a relatively high number of new products were introduced rapidly. At the other end of the scale, in Korea, Portugal and Turkey, half of all new molecules that were on the country's market by 2002 still had not been launched four years following first world launch.

Pharmaceutical consumption differences are partly explained by income

Figure 1.12 shows the relationship between per capita GDP and real pharmaceutical expenditure (volume of consumption), with per capita GDP explaining one quarter of the variability in per capita consumption. The main outliers are France and Spain, consuming more than would be expected based on their per capita income, and Mexico, consuming less. Chapter 6 extends this analysis by looking at the relationship between pharmaceutical prices and volume of consumption.

Figure 1.12. **Real per capita pharmaceutical expenditure and GDP per capita, 2005**

In USD PPP



Note: The volume of consumption depicted is overestimated in those countries, like Switzerland, where purchasers pay a fixed fee for pharmacy services (*e.g.*, a prescription fee) that is not included in the end price of the product. See Box 1.1 for more notes regarding pharmaceutical expenditures. The coefficient on the independent variable "GDP per capita" (0.0073) was statistically significant at the 1% level (t-statistic = 3.05).

Source: *OECD Health Data 2007*; Eurostat-OECD Purchasing Power Parity Programme, 2007.

Financing

Most pharmaceutical expenditure is publicly financed, but the public share is lower than for other health spending

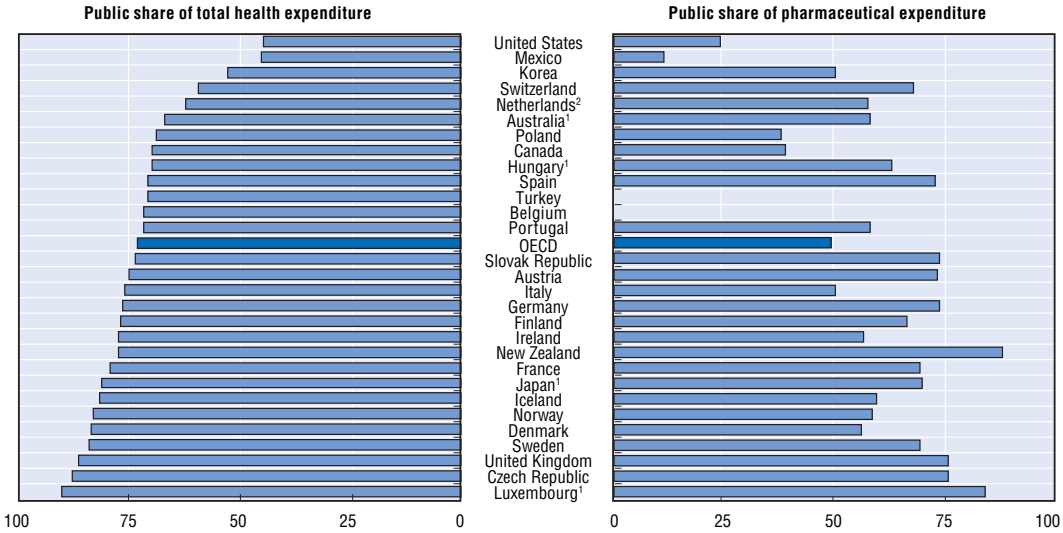
As with other types of health care, the public sector is the primary source of funding for pharmaceutical expenditures. Public funding of pharmaceuticals represented 61% of total pharmaceutical expenditures in the OECD in 2005 (Figure 1.13), much lower than the 72% public sector funding represented in total health expenditure. Public financing of pharmaceuticals was 80% or greater in Luxembourg and Ireland. There were four countries – the United States, Canada, Poland and Mexico – where public sector financing of pharmaceuticals accounted for less than half of total pharmaceutical spending.

While the public sector is the primary funder of pharmaceuticals, the private sector plays a more prominent role in financing pharmaceuticals than it does for most other healthcare services. Table 1.2 shows the contribution of private expenditure to total expenditure for selected categories of health care. In ten of seventeen countries, the private sector plays a bigger role in financing pharmaceuticals than it does for any other type of health care. For example, 61% of pharmaceutical expenditure in Canada in 2005 came from the private sector, whereas private funding was responsible for 37% of out-patient curative and rehabilitative care, 18% of long-term nursing care, and only 9% of in-patient curative and rehabilitative care.

Out-of-pocket expenditure is important for pharmaceutical financing; private health insurance is usually not a significant source

Out-of-pocket spending on pharmaceuticals is greater than all other sources of private financing combined in every country shown in Table 1.2 except France and the United States. Among those countries for which data are available, the share of out-of-pocket expenditure in total pharmaceutical expenditure ranged from 13% in France to 61% in Poland.

Figure 1.13. **Share of public expenditure in pharmaceutical and total health expenditure, 2005**



Note: Data for Greece were not available. Data on pharmaceutical expenditures for Belgium and Turkey were not available. See Box 1.1 for more notes regarding pharmaceutical expenditures.

1. 2004 (Hungary and Japan) and 2004/05 fiscal year (Australia).
2. 2002.

Source: OECD Health Data 2007. See Box 1.1 for more sources regarding pharmaceutical expenditures.

Table 1.2. **Private sector and out-of-pocket (OOP) expenditure as a percentage of total expenditure, by healthcare function, 2005**

Healthcare function	In-patient curative and rehabilitative care		Out-patient curative and rehabilitative care		Services of long-term nursing care		Pharmaceutical and other medical non-durables		Total current expenditure	
Financing agent	OOP	Other private	OOP	Other private	OOP	Other private	OOP	Other private	OOP	Other private
Australia[1]	6%	19%	23%	10%	20%	0%	41%	1%	21%	11%
Canada	2	7	17	20	17	1	32	29	15	15
Czech Republic	2	1	10	0	n.a.	n.a.	24	0	11	1
Denmark	5	0	20	3	11	0	39	5	15	2
France	3	4	13	20	n.a.	n.a.	13	18	7	14
Germany	2	9	16	14	25	3	20	6	12	10
Japan[1]	5	4	19	1	8	5	30	0	16	3
Korea	25	10	46	6	19	8	49	0	40	5
Luxembourg	2	4	10	3	0	0	14	2	7	3
Netherlands[1]	5[2]	29[2]	(2)	(2)	0	7	26[3]	23[3]	8[4]	26[4]
Norway[1]	1	0	36	0	12	0	40	0	17	0
Poland	2	2	36	7	1	8	61	1	28	4
Portugal	n.a.	n.a.	n.a.	n.a.	46	1	39	4	23	5
Slovak Republic	1	0	36	0	n.a.	n.a.	26	0	24	1
Spain	3	6	33	11	22	0	27	0	22	7
Switzerland	5	14	43	8	57	3	30	3	31	10
United States	n.a.	n.a.	n.a.	n.a.	26	11	35	41	13	41

Note: Private financing includes all private sources of financing except out-of-pocket (OOP) payments.
n.a.: not available.

1. 2004 (2004/05 fiscal year for Australia).
2. There is no distinction between in-patient and out-patient curative and rehabilitative care.
3. Medical goods dispensed to out-patients.
4. Total current expenditure (does not include capital formation of health care provider institutions).

Source: 2006 and 2007 Joint OECD-Eurostat-WHO Health Accounts (SHA) Data Collection.

In most OECD countries, private health insurance is not a significant source of financing for pharmaceuticals. There are, however, a few exceptions. In France, for example, private health insurance finances a larger proportion of pharmaceuticals than households paying out-of-pocket (Table 1.2). In both Canada and the Netherlands, private health insurance accounts for about a quarter of total spending on pharmaceuticals. However, it is in the United States where the importance of private health insurers' spending on pharmaceuticals is greatest. Private health insurers spent USD 94 billion on prescription pharmaceuticals in 2005, more than what Japan – the country with the second-highest total expenditures on pharmaceuticals after the United States – spent on all pharmaceuticals.[12]

Cross-country variability in private health insurance financing of pharmaceuticals reflects to a significant extent the role of private health insurance in the health system. In France, 94% of the population is covered through complementary private health insurance which covers the bulk of user cost-sharing from public insurance (PPRI, France Pharma Profile, 2007), and private expenditure on pharmaceuticals other than out-of-pocket spending accounted for 18% of total expenditure. In Canada, private health insurance is the main source of coverage for pharmaceuticals, covering about two-thirds of the population and financing 28% of total pharmaceutical expenditures (Paris and Docteur, 2006). By contrast, in Poland non-profit institutions finance a greater share of pharmaceutical expenditure than private insurance does.[13]

The pharmaceutical industry is important in the economies of several OECD countries

The top pharmaceutical manufacturers' headquarters are concentrated in particular countries within the OECD. Of the top 15 firms, eight are located in the United States and seven in Europe – two each in the United Kingdom,[14] Switzerland and Germany, and one in France. Only one of the top 50 firms is headquartered in a non-OECD country.

Pharmaceutical production is particularly important for Ireland and Switzerland

Pharmaceutical production is concentrated in a few countries, with the United States alone accounting for 39% of global pharmaceutical production in 2004, measured at ex-manufacturer prices (EFPIA, 2006). Europe as a whole produced 36% of all pharmaceuticals, with France accounting for 7% of global production, and the United Kingdom and Germany each producing 5%.

In terms of contribution to the overall economy, pharmaceutical industry production is more important for a number of countries – perhaps none more than Ireland, where pharmaceutical production accounted for 11% of GDP in 2004. The industry is also important to Switzerland, home to two of the top ten global pharmaceutical firms. Pharmaceutical production represented 3.1% of GDP in 2004[15] and contributed significantly to Swiss economic growth during the 1990s (Paris and Docteur, 2007). These countries are, however, each responsible for a relatively smaller share of total global production. By contrast, pharmaceutical production accounted for only 2.0% of GDP in France, 1.9% in the United Kingdom, 1.2% in the United States, and 0.9% in Germany.

On a per capita basis, Ireland's pharmaceutical production was almost EUR 4 000 per person in 2004, five times the per capita production in the United States. Other countries

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that produced more per capita than the United States include Switzerland (EUR 1 883), Denmark (EUR 850) and Sweden (EUR 619).

In relation to the whole economy, industry-financed R&D activities are most important to Switzerland

In 2005, corporate expenditures on pharmaceutical R&D were USD PPP 35 billion in the United States, more than 21 billion in OECD Europe[16] and 7 billion in Japan (OECD, 2007c). About 70% of corporate R&D expenditures in Europe took place in four countries: the United Kingdom (USD PPP 5 billion), Germany (4 billion), France (3 billion in 2003) and Switzerland (USD 2 billion in 2004).

Unlike pharmaceutical production, the countries in which industry-financed R&D is greatest are also those for which expenditures on R&D contribute the most to the respective nations' economies. Research and development financed by the pharmaceutical industry as a percentage of GDP was 0.8% in Switzerland in 2004, 0.6% in Sweden in 2003, 0.5% in Denmark in 2005, 0.3% in the United States (2005), and 0.2% in France (2003), Germany (2005) and Japan (2005).

The R&D activities of the pharmaceutical industry are a significant contributor to the development of a highly skilled, knowledge-intensive workforce. Eurostat estimates show that R&D personnel accounted for 23% of total pharmaceutical industry employment in Sweden in 2002, significantly more than the 16% share in Belgium and the United Kingdom, the two countries with the next highest share (Eurostat, 2005).[17]

Trade in pharmaceuticals is important for several countries

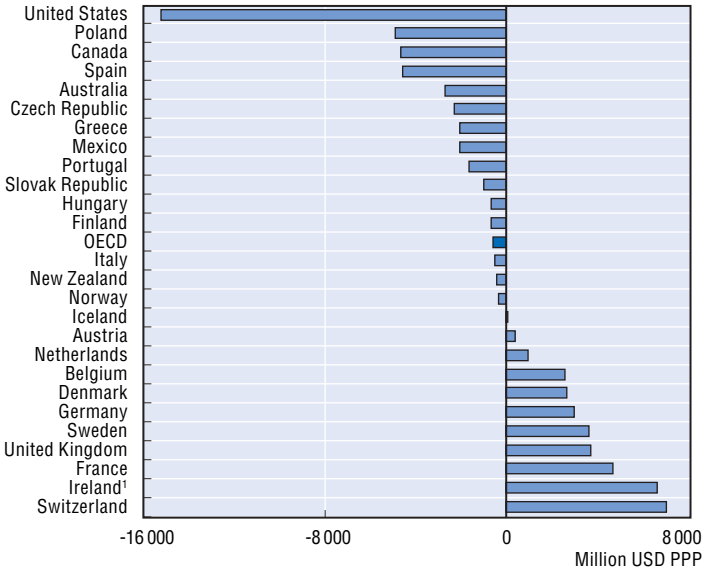
While the United States accounts for a significant portion of the global trade in pharmaceuticals, much of its production is for domestic consumption. With net imports of USD 17.1 billion in 2006, the United States had by far the largest pharmaceutical trade imbalance (Figure 1.14).[18] Net imports of pharmaceuticals in, Japan and Canada – the next highest countries – were approximately USD 5 billion. Switzerland and Ireland were the biggest net exporters of pharmaceuticals, exporting USD 16.4 and USD 15.1 billion, respectively.

Parallel trade and cross-border trade have generated considerable attention from policy makers. Parallel trade activity is greatest within the European Union; it was estimated to account for about 2% of the total pharmaceutical market in 2003, but "growing fast" (Kermani, 2003). The share of parallel trade varies considerably within Europe. Parallel imports were greatest in the United Kingdom, where they made-up 20% of the total pharmaceutical market in 2002, compared to 7% in Germany (Kanavos and Costa-Font, 2005). In Sweden, the generic substitution policy, which mandates that pharmacists substitute the lowest-priced substitutable product for a prescribed medicine, allows parallel imports to be included in the list of substitutable products (Moïse and Docteur, 2007b). These accounted for about 12% of total pharmaceutical sales in Sweden in 2005 (PPRI, Sweden Pharma Profile, 2007). For Greece, it is parallel exports – which accounted for 22% of the total prescription pharmaceutical market – that are important to pharmaceutical industry activity (Kanavos and Costa-Font, 2005). On the other hand, parallel trade is negligible in the Slovak Republic (Kaló *et al.*, 2008).

Although cross-border trade exists throughout the OECD, it is in the United States where it has been a major political issue. Despite the attention that cross-border trade with

Figure 1.14. **Pharmaceutical industry trade balance in OECD countries, 2003**

In million USD PPP



1. 2001.

Source: OECD International Trade by Commodity Statistics, Standard International Trade Classification Revision 3, 2007.

Canada has generated in the United States, the actual dollar value of sales (USD 1.1 billion) represented only 0.5% of total US retail sales in 2003 (Cambridge Consulting, 2004). The volume of cross-border exports to the United States is of greater importance in Canada. Internet pharmacies in Canada seized upon the greater demand for their products in the United States by doubling their pharmaceutical purchases (primarily for cross-border trade) between 2002 and 2003; by 2004, cross-border sales had peaked reaching 8% of total Canadian prescription drug sales. It has since declined, in part because of the effect on relative prices of the weakening US dollar and in part because of manufacturers' successful efforts to cut off supply to pharmacies responsible for cross-border sales (Paris and Docteur, 2006). By contrast, there has been less focus on cross-border trade between Mexico and the United States, although this has been estimated to account for approximately USD 100 million in Mexican sales revenues (Moïse and Docteur, 2007a).

Conclusions

While there are many points in common, OECD countries face different challenges and opportunities with the pharmaceutical sectors of their economies. Pharmaceuticals remain a relatively small, though dynamic, component of total health expenditure in most OECD countries. Even in the United States – with a unique pattern of both prices and consumption that are relatively high, in comparison to other countries – pharmaceutical expenditure accounts for a relatively low share of total health expenditure and a share of GDP that is comparable to that of other countries, including France. In a few OECD countries, particularly Switzerland and Ireland, pharmaceuticals are much more important in terms of the contribution of the industry to national output and economic growth. But in several other OECD countries, particularly those with relatively lower incomes, like Hungary, the Slovak Republic and Portugal, pharmaceutical expenditure is

relatively much more important in health expenditure and as a share of national income. These varying market conditions are likely to influence the relative weight policy makers apply to common policy goals such as access to effective treatments, cost-containment and value, and how they seek to resolve conflicts that may arise among these goals and with industrial policy goals.

In the next chapter, we will provide an overview of the pharmaceutical industry and its activities, and consider how the pharmaceutical industry relates to OECD countries as prospective markets for its products. These two chapters serve as market snapshots, viewed from the perspective of purchasers first, and then sellers. Together, they provide an overview of the global market for pharmaceuticals that is intended to set the stage for the analysis of policies and their impact that is presented in the chapters that follow.

Notes

1. Expenditures were converted to a common currency at 2005 exchange rates and adjusted for cross-country differences in economy-wide price levels using purchasing power parities (GDP PPPs). The resulting expenditure estimates can be interpreted as providing an indication of the value of goods and services that could have been purchased in the country with the funds spent on pharmaceuticals (or the opportunity cost of pharmaceutical expenditure).
2. Estimated elasticities were significant for six of the twelve countries studied using time-series data from 1970 through the mid-1990s. The income elasticity was positive, but less than one, in two countries (United States, Canada), indicating that purchasing behaviour was consistent with what is seen for goods considered necessities. The income elasticity was greater than one in Sweden and Denmark, indicating that pharmaceutical expenditures were a luxury good. The income elasticity was negative but greater than one in absolute value in Finland. In Germany, income elasticity was less than negative one, meaning that pharmaceuticals appeared to be an inferior good (something one buys less of as one's income increases).
3. Because of cross-country differences in distribution costs and taxes, a presentation of the average prices received by manufacturers would result in different relative price levels across countries. However, it is not possible to depict this due to the ways in which taxes and distribution margins are calculated. For example, in some countries, different VAT rates apply to different types of products (*e.g.* prescription-only medicines, reimbursed medicines, etc.).
4. Other studies, including Danzon and Furukawa (2003) have found a relationship between income and pharmaceutical price levels at the ex-manufacturer level, suggesting that the outcome of the interplay between regulation and manufacturer's strategies tends to be consistent with the notion of income-based pricing. The weak relationship with public prices found here suggests that differences in distribution costs and tax policies are important. Even in Danzon and Furukawa's study there were outliers whose prices exceeded what would be predicted on the basis of income per capita, notably Mexico.
5. In order to make comparisons of relative expenditure levels across countries, pharmaceutical expenditures must be converted from national currency units (NCUs) to a reference monetary unit – such as the US dollar (USD) – at the average exchange rate in effect during the expenditure period. A further conversion to adjust for differences in relative price levels across countries results in a measure of "real expenditure" that should reflect only differences in the volumes across countries. So-called purchasing power parities (PPPs), based on relative price levels and currency exchange rates, are the factors used to convert expenditure of different countries into real expenditures.
6. The authors observe that a range of factors could have contributed to these trends, including differences in the incidence or impact of marketing efforts, which concentrate on new products.
7. DDDs are ill-defined for some therapeutic classes, such as oncology drugs.
8. Launch dates do not necessarily coincide with marketing approval dates. For example, a firm may decide to delay launching a product until a decision regarding reimbursement is reached, even if the product has been approved by the marketing authorities.
9. A blockbuster drug is defined as one with annual sales exceeding USD 1 billion.

10. Few products could achieve blockbuster status without having been launched in the United States, given the size of the market.
11. Seven of the eight countries – France, Germany, Italy, Japan, Sweden, the United Kingdom and the United States – were also among the ten leading countries for location of first world launch. The eighth country, Ireland, was the first world launch country for 1.5% of launches, ranking it 14th.
12. As an illustrative example of the weight of American private health insurers in the global pharmaceutical market, one of America's largest private health insurers – Aetna – spent about USD 4 billion on pharmaceuticals in 2002; that is more than was spent on pharmaceuticals in 2005 in 13 OECD countries. (*New York Times*, 24 October 2002, Company News: "AETNA to begin acting as its own drug benefits manager").
13. According to the report from the 2006 Joint OECD-Eurostat-WHO Health Accounts (SHA) Data Collection.
14. One of the firms based in the UK has its R&D headquarters in Sweden.
15. Authors' calculations based on data from EFPIA (2006) using monetary conversion rates and demographic data from *OECD Health Data 2006* (OECD, 2006).
16. Corporate R&D expenditures were reported by 12 countries for 2005; Austria, the Netherlands, Norway, Poland, Spain and Switzerland reported expenditures for 2004; France and Sweden reported expenditures for 2003, and; Luxembourg, Portugal, the Slovak Republic and Turkey did not report any corporate R&D expenditures.
17. Using data compiled by the EFPIA (2006) on the number of employees of member associations' companies and the OECD Directorate for Science, Technology and Industry on total R&D personnel, R&D personnel employed by the pharmaceutical industry as a share of total R&D personnel can be estimated. Data availability limits the comparison to eight countries; the share is greatest in Belgium with 8.4%, followed by Sweden with 6.4%, Austria (3.7%), Germany (2.9%), Italy (2.7%), France (2.3%), Spain (2.0%) and Portugal (less than 1%).
18. This figure is not out of line with respect to the overall trade balance in goods and services; in 2006 the United States' trade deficit was USD 755 billion (OECD, 2007d).

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ANNEX 1.A1

Distribution Mark-ups and Value-added tax for Pharmaceuticals in OECD Countries

Table 1.A1.1. **Distribution mark-ups and VAT in OECD countries, 2007 or last available information**

	Wholesale mark-up	Pharmacy mark-up	Fixed pharmacy fee, dispensing fee or prescription fee	VAT
Australia	7.52% of ex-factory price for the majority of PBS listed items, capped at USD 69.94.	Regressive mark-up scheme, ranging from 10% to 4%, capped at USD 40.00	AUD 5.44	No VAT (or GST) for prescribed medicines. For most OTC, 10%, unless they fall under the GST-exemption (standard rate 10%).
Austria	Two regressive mark-up schemes, depending on the reimbursement category, capped at EUR 23.74.	Two regressive mark-up, ranging from 37% to 3.9%. Pharmacy mark-ups for reimbursed medicine are significantly lower than for non-reimbursed medicines.	15% for private customers. Not under the sickness-fund scheme.	20% (standard rate 20%).
Belgium	Fixed mark-up: 13.1% of ex-factory price, with a maximum of EUR 2.18.	Fixed mark-up: 31% of the wholesale price, with a maximum of EUR 7.44.	–	6% (standard rate 21%).
Canada	Capped, but depends on region and plan. Overall average 5%.	Depending on region and drug plans	Depending on region and drug plans.	0% on reimbursed medicines (standard rate 7%).
Czech Republic	On average 5-7%. Total margin of 29% is shared with the pharmacists.[1]	On average 22-24%. Total margin of 29% is shared with the pharmacists.	–	5% levied at wholesale level (standard rate 19%).
Denmark	Unregulated. On average 4%.	New scheme since 8 April 2007: 8.8% of pharmaceutical purchase price + a constant amount.	DKK 9.25 (EUR 1.24) incl. VAT. On all prescribed medicine.	25% (standard rate 25%).
Finland	Unregulated but indirectly controlled through reimbursement system. Average margin estimated at about 2-4%.	Regressive mark-up scheme based on pharmacy purchase price (a × PPP + b).	Dispensing fee of EUR 0.42 per prescription item.	8% (standard rate 22%).
France	Regulated only for reimbursable medicines. Regressive mark-up, ranging from 10.3% to 2% of ex-factory price.	Regulated only for reimbursable medicines. Regressive mark-up, ranging from 26.1% to 6% of ex-factory price.	Flat fee of EUR 0.53 per box only for reimbursable medicine.	2.1% for reimbursable and 5.5% for non-reimbursable medicines (standard rate 19.6%).

Table 1.A1.1. **Distribution mark-ups and VAT in OECD countries, 2007 or last available information** *(cont.)*

	Wholesale mark-up	Pharmacy mark-up	Fixed pharmacy fee, dispensing fee or prescription fee	VAT
Germany	Maximum mark-up, defined through regressive schemes combining percentages and fixed amounts: • for POM: markup ranging from 15% to 6% of ex-factory price, capped at EUR 72; • for reimbursable OTC: ranging from 21% to 3% of ex-factory price, capped at EUR 61.63.	Fixed mark-up for POM: 3% of wholesale price. Regressive mark-up combining percentages and fixed amounts for reimbursable OTC, ranging from 68% to 8.26% of wholesale price, with a maximum of EUR 118.24.	For POM: EUR 8.10.	16%, increased to 19% per 1 January 2007 (standard rate 16%).
Greece	Fixed mark-up: 8.43% of ex-factory price for all pharmaceuticals.	Fixed mark-up: 35% of wholesale price for all pharmaceuticals.	–	9% (standard rate 18%).
Hungary	All pharmaceuticals: maximum mark-up defined through a regressive scheme combining percentages and fixed amounts, ranging from 12% to 5% of ex-factory price.	All pharmaceuticals: Regressive mark-up combining fixed amounts and percentages, ranging from 26% to 17% of pharmacy purchase price, with a maximum of HUF 850 (EUR 3.43).	–	15% for pharmaceuticals (standard rate 25%).
Iceland	Fixed Margin for POM, no regulation for OTC	Fixed Margin for POM, no regulation for OTC.		14% (standard rate 24.5%)
Ireland	Fixed mark-up: 15% of ex-factory price.	Mark-up on ingredient cost, depending on patient's coverage status: • 0% for GMS patients • 50% for patients covered by Drugs Payment Scheme (DP) and Long Term Illness (LTI) scheme.	Depending on patients' coverage status: • GMS patients: Fixed dispensing fee of EUR 3.26; • Flat dispensing fee of EUR 2.86 for patients covered by DPS and LTI schemes.	0% for oral medicines and 21% for non-oral medicines (standard rate 21%).
Italy	Reimbursable: fixed margin: 6.65% of pharmacy retail price. Non-reimbursable: free margin, around 8%.	Reimbursable: 26.7% of pharmacy retail price, but regressive due to official discount to the NHS up to 5%. Non-reimbursable: free margin.		10% (standard rate 20%).
Japan	Unregulated	Unregulated	Dispensing fee and prescription fee vary with number and class of drug, dispensers, etc.	5% levied at the wholesale level (standard rate 5%)
Korea	Not fixed Average margin of 8.1% for POM (range 3.2-4.0%) Average margin of 9.5% for OTC (range 2.0-3.0%)	Formally no mark-up for POM, although implicit margins exist There is a variable mark-up for OTC	Fixed management and administration fees totaling (KRW 1 252) Dispensing fees paid according to a fee schedule with a fixed and variable component, depending on the length in days of the prescription.	10% (standard rate 10%)

Table 1.A1.1. **Distribution mark-ups and VAT in OECD countries, 2007 or last available information** *(cont.)*

	Wholesale mark-up	Pharmacy mark-up	Fixed pharmacy fee, dispensing fee or prescription fee	VAT
Luxembourg	15.21% for products originating from Belgium or Luxembourg	50.2%; 46.7% if originated in Belgium or Luxembourg.		3% (standard rate 15%).
Mexico	Not fixed.	Not fixed.		No VAT for all medicines (standard rate 15%).
Netherlands	Not fixed.	There is a clawback of 6.82% on pharmacy prices for medicines covered by the Medicines Pricing Act (with a ceiling of EUR 6.80 per prescription).	EUR 6.10.	6% for all medicine (standard rate 19%).
New Zealand	10%.	All pharmaceuticals: 4% if price less than NZD 150. 5% if price more than NZD 150.	NZD 5.16 for most pharmaceuticals (differs for some groups of pharmaceuticals)	12.5% (standard rate 12.5%).
Norway	Unregulated. Average margin of 5-7% for patented medicine. Much higher for other drugs.	Maximum mark-ups for reimbursed and non-reimbursed medicines. 8% of Pharmacy purchase price when PPP ≤ EUR 25, and 5% for PPP > EUR 25.	NOK 21.50 (EUR 2.70).	Standard VAT of 25% (standard rate 5%).
Poland	Maximum mark-up for reimbursed medicines: 9.78% of ex-factory price (incl. VAT). No regulation for non-reimbursed drugs: average mark up: 12-14%.	For reimbursed medicines: maximum mark-up defined through regressive scheme combining fixed amounts and percentages, ranging from 40% to 12% of wholesale price, capped at PLN 12. No regulation non-reimbursed medicine: average 25%.		7% on manufacturer's price (standard rate 22%).
Portugal	Reimbursed medicines: 6.87% of pharmacy retail price without VAT. Non-reimbursed: 8% of pharmacy retail price without VAT.	Reimbursed medicines: 18.27% of pharmacy retail price without VAT. Non-reimbursed: 20% of pharmacy retail price without VAT.	–	5% (standard rate 19%).
Slovak Republic	Maximum mark-up depending on the type of pharmaceuticals: 11% of ex-factory price for reimbursed medicines and for non-reimbursed POM, 4% for very expensive drugs, 5% for OTC drugs and vaccines, 10% for "hospital only" drugs sold by pharmacies.	Maximum mark-up depending on the type of pharmaceuticals: 21% of pharmacy purchase price for reimbursed and for non-reimbursed POM, 10% for very expensive drugs (> 250), 15% for OTC drugs, 7% for vaccines and 10% for "hospital only" drugs sold by pharmacies.	Prescription fee of SKK 5 per prescription of which 25% is for the pharmacy (and 75% for the insurance company).	10% (since 1 January 2007), standard VAT 19% (standard rate 19%).

Table 1.A1.1. **Distribution mark-ups and VAT in OECD countries, 2007 or last available information** *(cont.)*

	Wholesale mark-up	Pharmacy mark-up	Fixed pharmacy fee, dispensing fee or prescription fee	VAT
Spain	All Pharmaceuticals: 7.6% margin for drugs costing < EUR 89.62 and a fixed fee of EUR 7.37 for drugs exceeding EUR 89.62.	27.9% for generic drugs costing < EUR 89.62 and a fixed fee of EUR 37.53 for drugs exceeding EUR 89.62.	–	4% (standard rate 16%).
Sweden	Unregulated. Mark-ups negotiated between Apotek (distribution monopoly) and manufacturers. Average margin estimated 2.7%.	For POM: degressive linear mark-up capped combining proportional and fixed mark-up, capped at SEK 167 (EUR 18). For OTC, mark-ups set by Apoteket.	–	0% for POM, 25% for OTC (standard rate 25%).
Switzerland	Total distribution mark-ups are defined for reimbursed medicines and must be shared between wholesalers and pharmacists. Mark-ups are defined through a regressive linear scheme combining proportional (ranging from 15% to 8% of ex-factory price) and fixed mark-ups, capped at CHF 240. OTC: shared distribution margin.		Pharmacists' services paid according to a fee-schedule.	2.4% (standard rate 7.6%).
Turkey	For all pharmaceuticals, Regressive mark-up, ranging from 9% to 2% of ex-manufacturer's prices.	Regressive mark-ups, ranging from 25 to 10% of pharmacy purchase price.	–	8% for both POM and OTC (standard rate 18%).
United Kingdom	The NHS list price includes wholesalers' distribution margin. Discounts may be negotiated between manufacturers and wholesalers and between wholesalers and pharmacists.	Pharmacies' margins are determined by the difference between NHS reimbursement price and the actual pharmacy purchase price.	Pharmacists receive fees and allowances for their services.	17.5% POM and OTC – but practically 0% as POM is paid for by the government (standard rate 17.5%).
United States	Unregulated. Average of 2-4%.	Unregulated, average of 22-25%.	–	

Note: Includes only fixed pharmacy fees, dispensing fees or prescription fees related to normal dispensing activities, supplemental payments such as fees related to after-hours services are not included.

1. Prices across the Czech Republic differ per pharmacy, as wholesalers can determine the price at which they sell to pharmacists. They thought of establishing a digressive system, as to stabilize prices.

Source: Austria, Belgium, Denmark, Finland, France, Greece, Hungary, Ireland, Norway, Poland, the Slovak Republic, Sweden, Turkey and the United Kingdom: PPRI (2007). Canada: Paris and Docteur (2006), Mexico: Moise and Docteur (2007), Switzerland: Paris and Docteur (2007). Germany, Italy, the Netherlands, Portugal and Spain: ÖBIG (2006). Czech Republic: Praznovcova *et al*. (2003). United States: Danzon (1999). Iceland: Anell (2005). Australia: Australian Tax Office (2007); Medicare Australia (2007). New Zealand: PHARMAC (2007); European Commission, *http://ec.europa.eu/enterprise/phabiocom/docs/tse/newzealand.pdf*; UK Department of Health (2002). Luxembourg and United Kingdom: Paterson *et al*. (2003).

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Chapter 2

The Pharmaceutical Industry and its Activities

This chapter provides an overview of the key characteristics and activities of the global pharmaceutical industry. Its aim in so doing is to provide context for the subsequent analysis of the role of pharmaceutical pricing and reimbursement policy as determinants of key outcomes. It begins with an overview of the pharmaceutical industry and continues with discussions on trends in R&D, output and sales. A final section provides an overview of the product life-cycle management activities used by manufacturers in efforts to maximise profits.

Introduction

The pharmaceutical industry operates globally in terms of sales, production and R&D, with the vast majority of these activities occurring within the markets represented by OECD countries. As such, the profit maximising strategies of pharmaceutical firms reflect global objectives. However, the implementation of these strategies is often country-specific, with some countries more influential than others. This is partly a function of market size – with the dominance of the United States especially important – but it is also a reaction to countries' pharmaceutical pricing and reimbursement policies. Therefore, an overview of the industry and its activities is important to gain a full understanding of the impact of pricing and reimbursement policies.

Concentration of the industry

The global pharmaceutical manufacturing industry consists of thousands of small firms scattered throughout the world, together with several hundred research-based firms that have brought at least one drug to market (Kyle, 2007). However, when viewed by share of total global pharmaceutical sales, the industry appears much more concentrated. In 2006, the top ten firms accounted for 46% of global sales (IMS Health, 2007); the top 50 firms accounted for 71% of global sales (PharmaExec, 2007).

Research and development

The pharmaceutical industry is one of the world's most research-intensive industries. Firms from the pharmaceutical and biotechnology sector accounted for 19.4% of the global top 1 250 firms in terms of spending on research and development (R&D) in 2006,[1] the technology hardware and equipment sector was second with 17.7% of firms (DIUS, 2007a). When considered in terms of R&D as a percentage of sales, no other sector comes close to the pharmaceutical and biotechnology sector; companies in this sector reinvested 15.9% of their sales revenues into R&D, firms in the software and computer services sector were second with R&D comprising 10.1% of total sales (*op. cit.*).

Although complete data on global R&D investment of the pharmaceutical industry is not available, it is clear that investments have increased exponentially since the mid-1980s. R&D spending is also very concentrated; the 15 largest companies in terms of R&D investment accounted for 71% of global pharmaceutical R&D investments in 2006 (DIUS, 2007b).

The output of R&D: trends in pharmaceutical innovation

There is little dispute that pharmaceutical innovation has had a significant and positive impact on the overall health of member countries' populations. Whether or not the increased spending on pharmaceuticals brought about by innovation has offset spending on other types of healthcare is less certain. Furthermore, an apparent decline in pharmaceutical R&D productivity suggests that marginal returns to R&D may be diminishing.

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OECD populations have benefited from pharmaceutical innovation

Several papers have tried to measure the impact of pharmaceuticals on life expectancy using aggregate data on pharmaceutical spending. Lichtenberg (2004) estimated on longitudinal US data that the number of new marketed drugs had a positive impact on longevity. Crémieux *et al.* (2005) estimated that an additional CAD 186 spent on pharmaceuticals in 1998 would have increased life expectancy at birth for Canadian males by one year. Both Frech and Miller (2004) and Shaw *et al.* (2005) found that increasing pharmaceutical expenditure had a positive and statistically significant effect on life expectancy at age 40 for a number of OECD countries. Grootendorst *et al.* (2007) questioned the estimates of pharmaceutical productivity these studies produced as implausibly high, suggesting that the net benefits of pharmaceutical expenditures were overestimated.

Most studies that demonstrate the health benefits of pharmaceuticals are derived from clinical trials that focus on the benefits of a particular active ingredient on a specific group of patients. These studies are often key inputs into cost-effectiveness studies that evaluate the costs and benefits of particular drugs. There exists a smaller group of studies that examine the benefits to society of a particular class of drugs. For example, Cutler *et al.* (2007) estimated that, without antihypertensive drug therapy, there would have been an additional 86 000 premature deaths from cardiovascular disease in the United States in 2001.

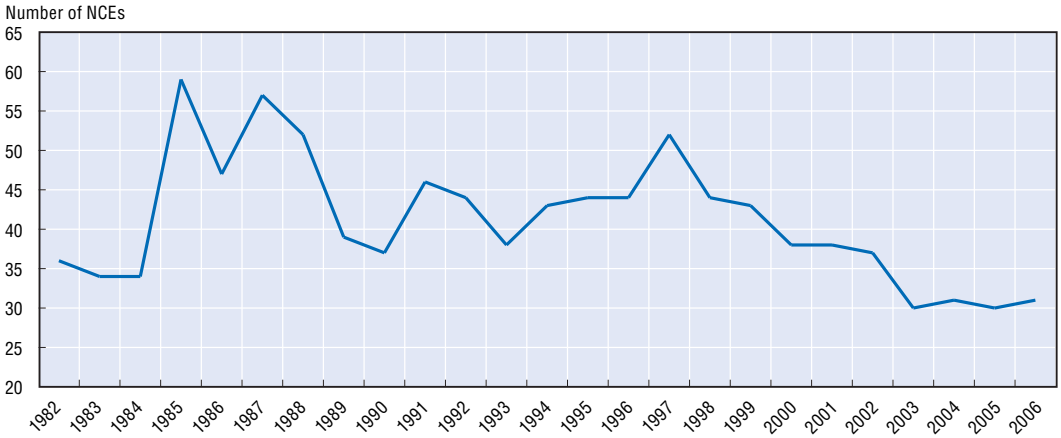
There are few studies that demonstrate the society-wide benefits of pharmaceutical innovation *per se*. In two separate papers, Lichtenberg (2005 and 2007) quantified the impact of new pharmaceuticals on health outcomes and costs. In the first paper, Lichtenberg (2005) estimated that new chemical entities (defined as NCEs not launched anywhere in the world prior to 1982) accounted for between 13-40% of the increase in longevity in 52 countries (including 21 OECD member countries) during the period of 1986-2000. He then estimated that the cost per life-year gained over this period was in the range of USD 2 250 to 6 750. In Lichtenberg (2007), the author estimated the impact of new chemical entities (defined as active ingredients approved by the Food and Drug Administration after 1990) on longevity and medical expenditure in the United States between 1990 and 2003. He found that new pharmaceuticals had a strong beneficial effect on reducing potential years of life lost before ages 65 and 75. Lichtenberg also estimated that expenditures on hospital and nursing home care were about 10% lower than what they would have been otherwise in the absence of new drug utilisation.

In another set of papers, Lichtenberg (2001 and 2002) estimated the differential impact on health care costs of newer *versus* older drugs, the so-called "drug offset" effect.[2] Both papers found a positive drug-offset effect, *i.e.* the use of newer drugs was associated with a decrease in nondrug medical expenditure that was greater than the higher cost of using newer drugs. The drug-offset argument is often pointed to as a major benefit of newer drugs; therefore, it is important that the Lichtenberg (2001 and 2002) results stand-up to scrutiny.[3] In a paper that replicates Lichtenberg's work, Zhang and Soumerai (2007) show that a drug-offset effect does exist, but that it is much smaller than what Lichtenberg had originally estimated. The authors demonstrated that, when some of the assumptions underlying Lichtenberg's papers were relaxed, the drug-offset effect was found to be only 20% of Lichtenberg's original estimate.

The amount of pharmaceutical innovation has varied over the long term

There are several measures by which pharmaceutical innovation can be assessed. The number of patents is an oft-used measure of R&D output, however, the use of patents as an indicator of innovation in the pharmaceutical sector is very limited (Grabowksi and Wang, 2006), perhaps due to strategic patenting which has blurred the link between patents and innovation. The number of new chemical entities (NCEs) entering the global market per year may be a more accurate measure of innovation. As depicted in Figure 2.1, the annual number of NCEs that gained market access globally varied substantially over the period from 1982 to 2006. The mid-1980s saw a dramatic rise in the number of NCEs, followed by a period of volatility in which the number of newly introduced NCEs declined from its peak of 59 in 1985 to 37 in 1990, before rising again to 52 in 1997. Since 1997, the number of new NCEs steadily declined until 2003. The rate has been stable since that date, at about 30 launches annually.

Figure 2.1. **Global trend in market launch of new chemical entities, 1982-2006**



Note: Global new chemical entities (NCE) launches refer to the first international introduction of new chemical entities.

Source: Estimated from Grabowski and Wang (2006) for 1982-1993 and for 1994-2003; IMS Health (2004, 2005 and 2006).

A more precise measure of innovation would make distinctions among NCEs in terms of the levels of innovation each offered. Measuring the level of innovation is not easily done, however. Grabowski and Wang (2006) proposed that innovative pharmaceuticals should include the first NCE in a therapeutic class, as well as NCEs introduced in at least four of the G7 countries. Other studies have tried to measure the level of innovation through the therapeutic advancement or benefit it would have for patients, on the basis of priority status given by the US Food and Drug Administration (CRA, 2004; NIHCM, 2002).

Incremental innovation is the predominant form of pharmaceutical innovation

An important issue when discussing pharmaceutical innovation is distinguishing between incremental innovation and radical innovation.[4] Incremental innovation offers a minor improvement in therapeutic benefit as compared with an existing product, although there is not necessarily agreement as to what constitutes minor *versus* more substantial improvement.

Barral (2004) estimated the level of innovation of NCEs by evaluating 1 460 NCEs launched in one or more of the G7 countries between 1975 and 2002 on the basis of two scales

(Table 2.1): 1) whether the product is a new chemical structure; and 2) whether it provides any therapeutic improvement relative to other products. He found that the percentage of products in the different categories remained stable over time. More than half of new NCEs had a chemical structure already known and offered no improvement over existing therapies, while 10% had both the characteristics of novel chemical structure and therapeutic improvement. According to his research, despite scientific and regulatory changes, the level of innovation has not changed much over these years. The number of NCEs being introduced in several G7 countries, however, has been increasing, suggesting that the industry has become increasingly global in its operations.

Table 2.1. **The level of innovation of new chemical entities (NCEs) launched between 1975 and 2002**

		Chemical structure	
		New	Already known
Clinical interest	Therapeutic improvement	A "very innovative" 143 (10%)	B 295 (18%)
	No therapeutic improvement	C 201 (14%)	D less innovative 821 (56%)

Note: The figures represent the number of NCEs launched on the market in the period 1975-2002 and the percentages between brackets correspond to the average percentage of NCEs assigned to the different categories.
Source: Barral (2004).

Incremental innovation includes follow-on modifications in molecular structure, for example, NCEs with a mode of action comparable to already existing products, the so-called "me-too" drugs,[5] and drugs whose chemical structure is new, but a treatment for the specific disease already exists (Wertheimer *et al.*, 2001). Incremental innovation can also include the re-formulation of existing drugs, in terms of dose or form, which result in a similar but not identical pharmacological action. These incremental innovations comprise a large share of R&D expenditures, as most of them require clinical trials, which are the most expensive part of the development process.

The discovery of new indications for existing products is an important and growing R&D activity, as shown by the number of cases for extensions of indications reported by the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA): the FDA reported about 50 extensions per year over the period of 2003-2006, while the EMEA reported 41 cases of approved extensions of indication in 2006, an increase of 46% compared to 2005.

Several studies have concluded that the bulk of incremental innovation in the pharmaceutical sector has represented little therapeutic improvement to the patient (Hollis, 2005). For instance, a study done by Garattini and Bertele (2002) found that new anticancer drugs that were brought to the European market between 1995 and 2000 had little or no substantial advantages over existing preparations. Similarly, studies showed that the new antihypertensive agents were no more effective than the old ones (Staessen *et al.*, 2001).

The value of incremental innovation depends on the extent to which it is evolutionary rather than duplicative. New products can offer significant advances in terms of improved

efficacy, fewer adverse side-effects, greater patient satisfaction (as tailoring to the individual is possible), better compliance and sometimes even increased cost-effectiveness. Collectively, the accumulated therapeutic benefits of a therapeutic class may be of greater clinical significance than the benefits offered by the pioneer product. A testament to the value of incremental innovation lies in the fact that 81% of the products included on the WHO's Essential Medicine List are replacement compounds, or "me-too" drugs, rather than pioneer medicines (Wertheimer *et al.*, 2005).

Incremental innovation is the rule rather than the exception in technological progress. Innovation in most industries is characterised more by small technological advances rather than by large leaps. Not only is incremental innovation prevalent, it is also important to the innovative process. As the US National Research Council noted: The cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations or technological breakthroughs' (NRC, 1996). This is a point of view echoed by the pharmaceutical industry which notes that incremental innovation is crucial as research consists of step-wise improvement rather than radical, big-bang innovations (IFPMA, 2004).

Productivity of pharmaceutical R&D has declined since the mid-1990s

Since the mid-1990s, the annual numbers of applications for market authorisations received by the EMEA and the US FDA have declined, despite the increase in R&D expenditures by pharmaceutical companies (CRA, 2004; CBO, 2006). Trends in the number NCES approved during the period show a similar decline (see Figure 2.1 above).

This apparent decline in productivity is not necessarily indicative of reduced success in pharmaceutical R&D investment, however. An alternative explanation is that R&D costs have increased. The costs of R&D depend on a multiplicity of factors, such as product development cycles, testing costs and regulatory requirements, which may change over time (OTA, 1993). Moreover, cyclical factors may contribute to current trends. Innovation over time can be seen as a wave-movement or cycle, influenced by scientific opportunities.

Pharmaceutical manufacturing

The production of pharmaceutical products is an integral component of pharmaceutical industry activities. However, for numerous reasons, the manufacturing of pharmaceuticals receives scant attention in health policy discussions. Box 2.1 provides a brief background on the manufacturing and distribution of pharmaceuticals.

An important aspect of pharmaceutical manufacturing is that unit production costs are generally very low in comparison to unit prices. One implication is that this results in a very high reliance of the pharmaceutical industry on intellectual property rights (IPR) protections to deter competitors who could produce copies at low cost without having invested in the R&D that resulted in the innovation in the first place. Another implication of low marginal production costs is a significant reliance on the use of free product samples as a means of promoting new drugs, with an inherent potential to adversely influence physicians prescribing habits. These are two issues that are discussed elsewhere in this report.

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Box 2.1. **Making a drug and getting it to market**

Manufacturing

There are two distinct phases to the manufacturing of medicines: bulk manufacturing and form/filling/finishing.

Active ingredients are manufactured in bulk through a series of chemical or biological reactions. Some manufacturers outsource their bulk manufacturing. This lowers capital investment and human resource costs, but can reduce overall profit margins since tax benefits are usually linked to bulk manufacturing.[1]

Once the active ingredient is manufactured, the last phase of the manufacturing process involves form/fill/finishing (F/F/F). It is during this process that the active ingredient is combined with the incipient ingredients (which can help to process active ingredients more efficiently and enhance absorption), processed into its final form (tablet, capsule, liquid, etc.) and packaged (bottles, blister packs, ampoules, etc.) as the final pharmaceutical product. F/F/F sites are typically not outsourced since manufacturers will usually want to control the final appearance and packaging of the pharmaceutical.

Assessing compliance with good manufacturing practices is an important aspect of national drug regulatory agencies' activities. Pharmaceutical companies are responsible for setting up and maintaining adequate quality control systems in the manufacturing process, including documenting every aspect of the manufacturing and laboratory testing processes.

Distribution (wholesale)

Manufacturers are generally not involved in the distribution of their finished products to the end-user, except in the case of drugs used in hospitals. Pharmaceuticals intended for retail sale will be distributed through wholesalers or distributors before arriving at retail outlets.

There are two basic types of wholesalers in the pharmaceutical distribution chain. Full-line wholesalers must be technically capable of stocking and distributing all pharmaceuticals available on the market. In Europe, it is compulsory that each member state has at least one full-line wholesaler. Short-line wholesalers, on the other hand, do not have the same technical obligations as do full-line wholesalers. They carry small inventories of high-demand products, which they sell as quickly as possible.

Distribution (retail)

Most retail sales of pharmaceuticals occur in community pharmacies. In most OECD countries, pharmacies are required to have a licensed pharmacist on the premises during operating hours.[2] In many European countries restrictions on pharmacy ownership limit the number of pharmacies that can be owned by one individual; there are no large pharmacy chains (such as Walgreen's in the United States or Boots in the United Kingdom and Ireland) in these countries. Sweden is a unique case in that all pharmacies are part of a chain owned by a state monopoly, *Apoteket AB*. Many countries also require the owner of a pharmacy to be a licensed pharmacist; this is not a restriction in North America where many supermarkets have their own pharmacies. In the past few years, a few countries have allowed pharmacies to sell prescription-only medicines over the internet. Only pharmacies are allowed to sell prescription-only medicines. Most European countries presently restrict the sale of over-the-counter medicines to pharmacies, although there is pressure in some countries to liberalise the sale of these products to other retail outlets (ÖBIG, 2006).

1. Tax benefits are linked primarily to the bulk manufacturing phase since tax authorities generally regard this phase – where commodity inputs are translated into the final material – as the one where the greatest value is added to the final product. Multinationals can use transfer pricing to take advantage of these tax benefits by locating bulk manufacturing facilities in low-tax countries.
2. In Mexico, pharmacies are not required to have a licensed pharmacist on the premises; a professional with a health sciences degree must be on the premises if a pharmacy sells psychotropic drugs (Moïse and Docteur, 2007).

Source: Northrup (2005).

Pharmaceutical sales

Nine OECD countries account for 81% of the world-wide value of pharmaceutical sales

Global pharmaceutical sales are concentrated within the OECD. The North America region alone accounts for almost half of total global pharmaceutical sales (Table 2.2),[6] driven by the US market, which accounts for about 45% of the global market. Europe is the second largest region with 30% of global sales. The two largest markets in Europe – France and Germany – each account for more than 5% of global pharmaceutical sales. Representing 9% of global sales in 2006, Japan is the second largest market in the world.

Table 2.2. **Global pharmaceutical sales at ex-manufacturer prices, by region, 2006**

	USD billion	As % of global sales
North America	290	47.7
United States	274	45.1
Canada	16	2.6
Europe	182	29.9
France	34	5.6
Germany	32	5.3
United Kingdom	21	3.5
Italy	21	3.5
Spain	16	2.6
Other	58	9.5
Asia/Africa/Australia	109	17.9
Japan	57	9.3
China	11	1.8
South Korea	9	1.5
Other	32	5.3
Latin America	18	4.5
Brazil	10	1.6
Other	8	2.9
Total	**608**[1]	**100.0**

1. Due to rounding errors, the figures in this column do not add up to the total amount shown.
Source: IMS Health (2007).

Pharmaceutical sales are growing, but at a declining rate

Figures from IMS Health show that the mean annual growth rate of global pharmaceutical sales between 1998 and 2006 was 10% (Figure 2.2). Annual sales growth has not dropped below 7% during this period, although it has been steadily declining from a peak of 14.5% in 1999.

The main contributors to global sales growth have changed between 2001 and 2006. The United States remains the single largest contributor, responsible for half of the growth in global pharmaceutical sales in 2006 over the previous year (Figure 2.3). Emerging market countries (EMC) have supplanted western Europe as the second most important engine for growth. In 2006, EMCs contributed 27% to global sales growth compared with 16% for western Europe. This is in contrast to 2001, when western European countries' contribution to growth was 29% *versus* 13% for EMCs. Declining sales in Japan meant that its contribution to growth was negative in 2006.

Pharmaceutical sales growth in seven key countries – Canada, France, Germany, Italy, Spain, the United Kingdom and the United States – shows how generic drugs are fuelling

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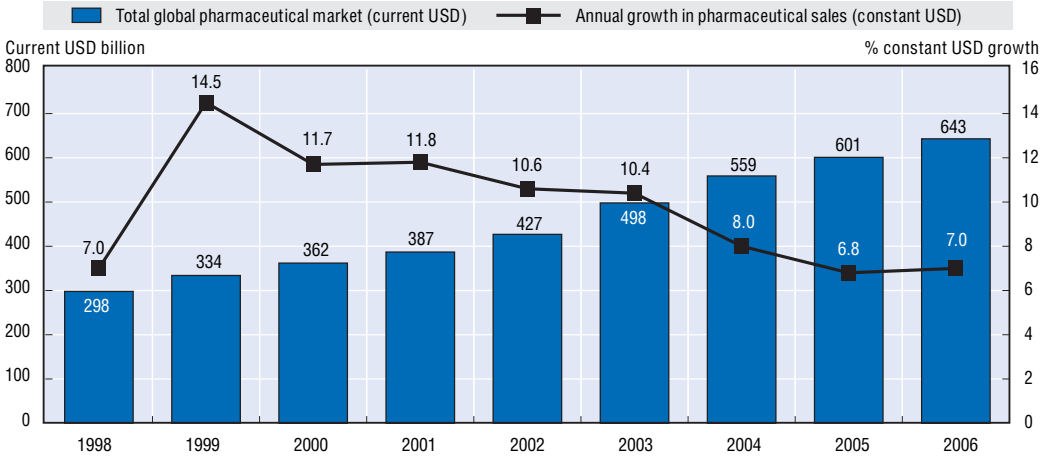
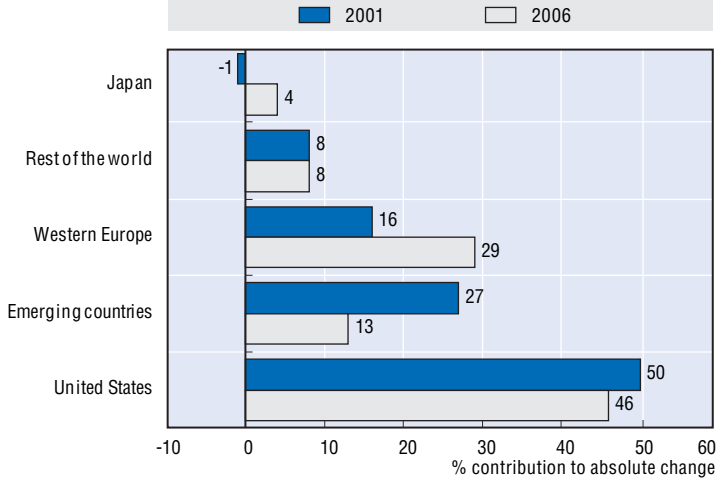
Figure 2.2. **Global pharmaceutical sales growth at ex-manufacturer prices, 1998-2006**



Note: Growth rates are calculated in constant US dollars using the exchange rate as of 31 December 2006, except for the growth rate for 1998 for which the exchange rate of 31 December 2005 was used. Total sales for each year are given in current US dollars.

Source: IMS Health (2006 and 2007).

Figure 2.3. **Contribution to total world sales growth at ex-manufacturer prices, by region, 2001 and 2006**



Note: Based on the growth in sales from the previous year. Sales are converted from local currency to US dollars using the exchange rate of 31 December 2006; this will under(over)estimate the contribution to global sales growth in those countries whose currency depreciated(appreciated) against the US dollar.

Source: IMS Health (2007).

much of this growth. Based on IMS Health data, Worton (2006) shows that between 2001 and 2005, the value of pharmaceutical sales for generic drugs has maintained double-digit annual growth rates in the seven key countries, and has consistently grown at a rate faster than original products since 2002 (*op. cit*). In terms of sales volumes, generic drugs have maintained year-on-year growth rates of at least 5%, in contrast to original drugs, for which sales volumes have been declining since 2002.

One of the more significant trends in the global pharmaceutical market over the past few years has been the growing impact of specialist-driven drugs. In 2004, the increase in

sales over the previous year of specialist-driven drugs was responsible for more than half of the total increase in global pharmaceutical sales from 2003. This was the first time that total pharmaceutical sales growth was driven more by the growth in sales of specialist drugs than primary-care-driven drugs (IMS Health, 2007). In 2006, specialist-driven drugs accounted for more than 60% of global pharmaceutical sales growth, despite the fact primary-care-driven drugs still accounted for the majority of global pharmaceutical sales (62%).

The growth in total sales is explained by changes in price and consumption of existing products, and take up and diffusion of new products. During the past few years, the contributions of these three elements to global sales growth have changed. Based on sales in the top ten global markets over the past seven years, the contribution of volume and mix has steadily declined – from accounting for 60% of total growth in the top ten markets in 2001[7] to 40% in 2006. By contrast, the contribution to growth of the introduction of new products increased from 21% in 2001 to 44% in 2006. Price, on the other hand, decreased in importance as a determinant of pharmaceutical growth in recent years, accounting for 27% in 2003 and just 15% in 2006.

The factors that have been most responsible for pharmaceutical sales growth vary across countries. In North America, the main determinant of growth in 2004 was price. This is in contrast to the growth in pharmaceutical sales in Japan and Europe, where price was a negative determinant but where volume played the largest role in terms of driving growth of pharmaceutical expenditures (IMS Health, 2005).

The value of global pharmaceutical sales is concentrated in a relatively small number of therapeutic classes…

Sales of the top ten therapeutic classes accounted for USD 219 billion or 36% of total global pharmaceutical sales in 2006 (Figure 2.4). In 2006, two therapeutic classes (statins and oncology therapies) achieved sales of at least USD 30 billion each. The loss of patent protection in 2006 for two of the top three-selling statins (Zocor and Pravachol), and the subsequent entry of generics onto the US market, mean that this is likely the last year in which statins will be the top-selling therapeutic class. This is the continuation of a trend in the past few years that has seen the growing influence of very expensive drugs with small target populations, such as the cancer drugs Erbitux and Herceptin, over the less expensive drugs with large target populations, such as proton-pump inhibitors and statins.

… and a relatively small number of products

There are thousands of pharmaceuticals available on the global market, with the number of products varying from country to country; for example, there were approximately 8 650 products on the market in France in 2005, whereas in Italy in 2006 there were 13 070 (PPRI, forthcoming). Despite the extensive variety of pharmaceutical products available, global sales revenues are concentrated in a relatively small number of products; a fraction of these pharmaceuticals generate a significant proportion of global sales revenues. These are the so-called "blockbusters", each of which generates annual sales of more than USD 1 billion.

It is estimated that there were 105 blockbusters on the global pharmaceutical market in 2006, up from just 44 in 2000 (IMS Health, 2007). At a minimum, these drugs would have generated about 16% of total global sales revenues in 2006. However, many blockbusters

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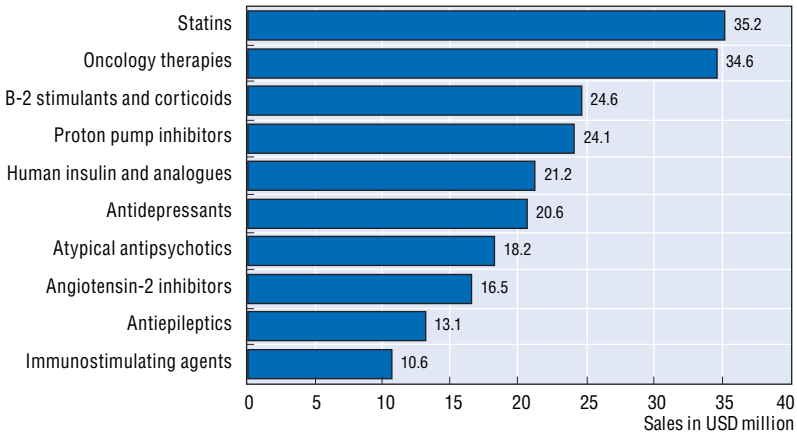
Figure 2.4. **Top ten therapeutic classes by global sales at ex-manufacturer prices, 2006**



Source: IMS Health (2007).

make much more than USD 1 billion annually. For example, in 2006, the top ten selling brands produced sales of USD 60 billion, 10% of the global market (*op. cit.*).

Despite the overwhelming success of blockbusters, there is some doubt as to the sustainability of a business strategy that places enormous importance on developing and marketing them; and hence, doubt about the continued dominance of blockbusters themselves.[8] This has been fuelled, in part, by a shift in the distribution of blockbusters away from primary-care-driven drugs, which accounted for two-thirds of global blockbusters in 2000, towards specialty-driven drugs, each accounting for half of total global blockbusters in 2006 (IMS Health, 2007).[9] The recent, or impending, loss of patent protection for some of the most lucrative blockbusters has also contributed to the perception that the era of blockbusters is coming to an end.

The role of generic products in the market varies considerably across the OECD

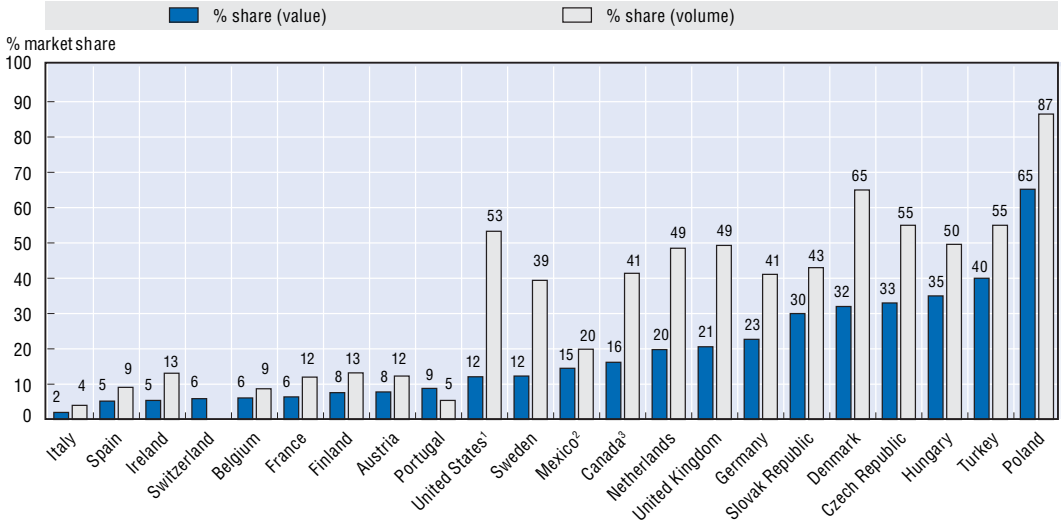
In 2005, global sales of generic drugs were an estimated USD 78 billion, approximately 14% of the total pharmaceutical market by value. North America (38%) and Europe (37%) accounted for the largest shares of sales (Worton, 2006).

Figure 2.5 shows market penetration of generic drugs in 22 OECD countries. In eight countries, generic products represent a small share of all products sold (4-13%), in terms of volume.[10] This strongly contrasts with another group of countries, where generic products are a central part of the market, accounting for between 40% and 70% of all packages sold.

In terms of value, as well, there are two distinct patterns. In several countries, the value of the generics market is small relative to the share of the market in terms of volume.[11] This suggests that the difference between the prices of original products and generics is significant and suggests that the country has been successful in achieving price competition for products once they have lost patent protection. In other countries, including most of those with a low generic share of the market by volume, the gap is much smaller, suggesting a lack of price competition in the unprotected market.

Data from IMS Health for nine OECD countries show that, in countries with low generic penetration in terms of volume share of the overall market (Italy, Spain, Belgium and France), off-patent originals have captured more than half of the volume of sales in the

Figure 2.5. **Market share of generics in terms of value and volume, 2004**



1. *Overview of North American Generic Market*, presentation by R. Milanese, President, RSM Pharmaceutical Services Inc., to the SFBC Anapharm Workshop, Malta, 19 June 2005, *www.anapharm.com/sfbc/upload/sfbc/Generateur/RobertMilanese_Overview.pdf*, accessed 7 September 2005.
2. 2002, ANAFAM (Asociación Nacional de Fabricantes de Medicamentos), *www.anafam.org.mx/quienes/historia.html*, accessed 7 September 2007 (in Spanish).
3. CGPA (2007).

Source: EGA – European Generics Manufacturers Association (2007); except Switzerland EFPIA (2006).

unprotected market (Worton, 2006).[12] Conversely, generics captured a greater volume share of the unprotected market in those countries where generics had at least a 40% volume share of the total pharmaceutical market (United Kingdom, United States, Germany, Netherlands and Canada). Despite low market shares for generic drugs in several key markets (France, Spain and Italy), generic drugs have been showing increasing market penetration since 2000 (*op. cit.*).

Ex-manufacturer prices

A number of studies have assessed prices at the ex-manufacturer level. All such studies are sensitive to the methodology used, notably the basket of products chosen, weights used to convert the prices of multiple products into an average index,[13] as well as the currency exchange rate in effect during the period of study. For this reason, it is important to review findings from several studies using different approaches to obtain an accurate view of the price variation across countries.

The findings from a number of recent studies are reviewed in Annex 2.A1. Both the methodologies used in the studies and their findings vary, suggesting that the product mix used in making the price comparisons is particularly important as a determinant of relative rankings across countries. However, they tend to concur that US ex-manufacturer prices of patented medicines are particularly high, while US generic prices are relatively low. According to several studies, manufacturers sell their on-patent and generic products at relatively high prices in Switzerland and Japan. A number of studies have found that the cross-country price differentials for drugs considered new and innovative was much smaller than for drugs in general.[14]

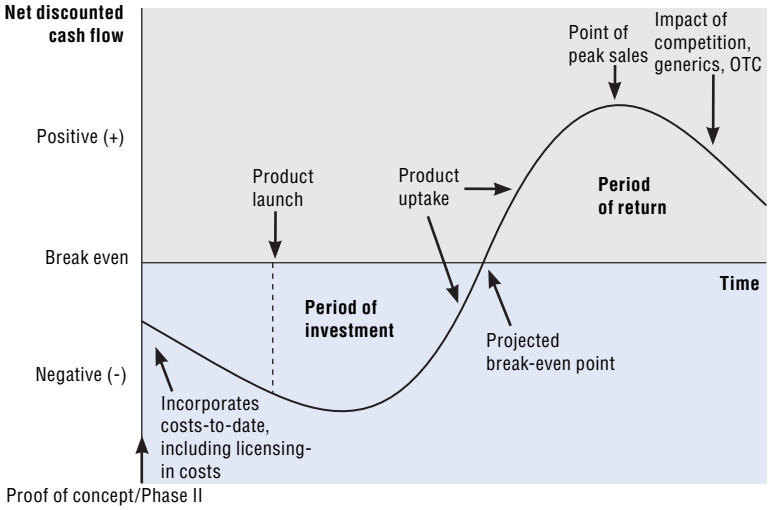
Product life-cycle management

Like firms in other industries, pharmaceutical manufacturers try to maximise profits from their operations. Since unit production costs can be considered independent of the level of production, maximising profits translates into maximising positive cash flows during the life of a product, and particularly during the period in which the product benefits from market exclusivity. In order to meet this objective, a pharmaceutical manufacturer will launch as quickly as possible in the markets with the highest sales potential (in terms of volume and prices), will price its products as high as possible according to market conditions and regulatory constraints, will try to extend the period of market exclusivity, engage in promotional activities to capture as large a piece of the market as possible and aim to expand the potential market for its products. These factors are discussed briefly below; a focused assessment of how manufacturers respond to the increasingly global market for pharmaceuticals – characterised by the potential for parallel trade and external price referencing – is presented in Chapter 5.

Cash-flow profile over the product life cycle

Figure 2.6 illustrates a hypothetical cash-flow profile of a pharmaceutical product over its life cycle (in this case beginning with entry into phase II clinical trials). Prior to marketing approval, R&D expenditure on the pharmaceutical product accumulates as the drug passes through the various preclinical and clinical trial phases, with some dropping

Figure 2.6. **Hypothetical cash-flow profile of a pharmaceutical**



Source: Adopted from Gregson *et al.* (2005).

out at different phases. R&D expenditure per drug for each successive phase is greater than that of the previous phase; DiMasi *et al.* (2003) estimate phase III costs to be more than 3.5 times greater than phase II and 5.7 times greater than phase I costs.[15] Moreover, pre-launch marketing and promotional activities (to promote awareness of the drug before it comes to market) increase pre-launch costs further. By the time the successful product is launched, the firm would have accumulated a significant negative cash flow.

Upon market entry, sales revenues accumulate as the market for the product expands. Eventually, the product should generate sufficient sales revenues (less administrative,[16] production and other relevant costs) to offset the initial R&D investments and start to generate profits. Sales revenues will continue to grow until reaching the point of peak sales, which will depend on the expansion rate of the market, as well as the market entry of therapeutic or generic competitors.

An original product's sales revenues normally decline when it loses patent protection. The reduction in cash flow is primarily due to competition from generic drugs which erode the original product's market share (Grabowski and Vernon, 1992 and 1996; Frank and Salkever, 1997), although the extent of the erosion may be greater for larger markets (Hudson, 2000), for blockbuster drugs (LFN, 2006; Saha *et al.*, 2006), or for original products with the largest price differentials with their generic competitors (Aronsson *et al.,* 2001).

The evidence from studies that have examined the impact of generic competition on the prices of original products is mixed. Some studies have shown that the prices of original products do not change much in response to the entry of generic competitors (Caves *et al.*, 1991; Lexchin, 2004), or that they *increase* (or continue to increase) upon patent expiry (Grabowski and Vernon, 1992 and 1996; Frank and Salkever, 1997). The latter results, which are based on US data, may only be applicable to the United States, since most countries limit the ability of manufacturers to increase their products' prices. There are some studies that show a drop in the prices of off-patent pharmaceuticals in response to generic competitors entering the market, although this will depend on the incentives furnished in the market. For example, in Sweden, the average price drop of five blockbusters that lost their patents between 2002 and 2005 was 73% (LFN, 2006). This may be partly explained by the introduction of mandatory generic substitution by pharmacists. It may also be partly explained by the number of competitors the manufacturers of these five blockbusters faced upon patent expiry of their products; Wiggins and Maness (2004),[17] and Saha *et al.* (2006), both found an inverse relationship between the price of an original product's price and the number of competitors it faces. Most importantly from the payer's perspective, the latter three studies show that generic competition reduces the average price within a product class. Most recently, Frank (2007) showed that in classes with one generic competitor, the average price per dose (relative to the original) is 94%, the average price drops to 52% when there are two generic manufacturers, and is a third of the price or lower when there are five or more generic manufacturers.

Product launch strategies

Differences in availability on the market partly depend on manufacturers' strategic decisions about timing and sequence of product roll-out in various markets. Manufacturers may well choose not to launch products in markets where they are not expected to be profitable, either because the number of prospective patients is too small or the product could not command a price high enough to offset the costs of obtaining market approval and launch.

Danzon *et al.* (2005)[18] found that launches in the major markets are determined by expected price and expected volume, after controlling for income per capita.[19] Both experience of the firm in the launch country (measured by total prior sales in the country) and the fact that the country is the firm's "home country" (*i.e.,* location of headquarters) are positive contributors to early launch. The authors found that launch delay (relative to first global launch) decreases with both relative prices of competitors' products and volume of

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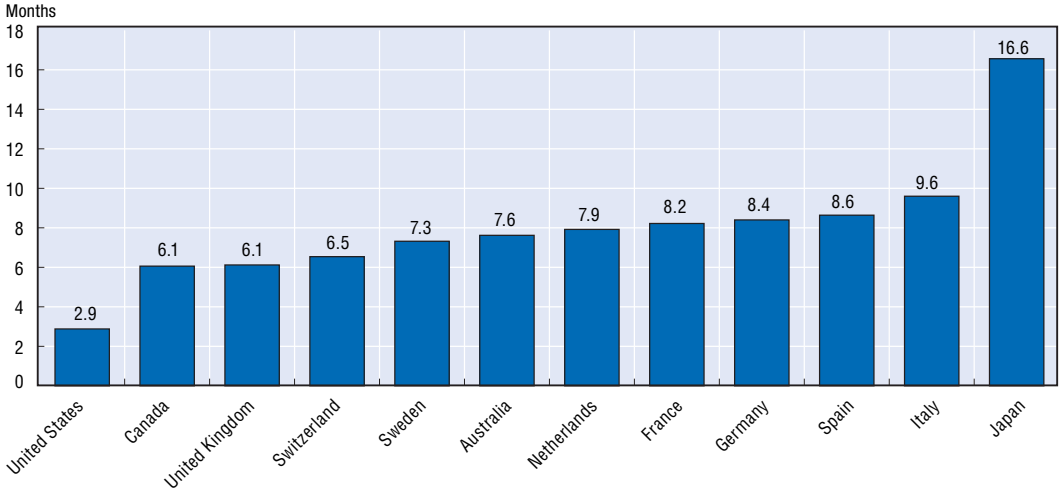
sales in the therapeutic class (used respectively as proxies for expected price and expected volume of sales), after controlling for per capita income, a country's regulatory environment and spill-over potential – in terms of international reference pricing or parallel trade. Kyle (2007)[20] found that a large population and the existence of competitors increased the probability of launch, and launch delays were lower in firms' home markets than in foreign markets.

At the macro-level, the time elapsed between first world application and application in a given country is an indicator of manufacturers' launch strategies (see Figure 2.7). New molecules launched between 1999-2003 were proposed for marketing authorisation in the United States within three months of first global launch, on average, compared with 17 months in Japan. The average lag in Canada and nine large western European countries ranged from 6-9 months.

Figure 2.7. **Average time from first world application for marketing authorisation to application in market, 1999-2003**



Source: Adapted from Pharmaceutical Industry Competitiveness Task Force Competitiveness and Performance Indicators 2005, indicator 25, from Association of the British Pharmaceutical Industry calculations.

Of the 61 new molecules launched in 2005 and 2006, 35 were first launched in the United States, by far the leading country for initial launches. Japan was next with seven first launches, and Germany was third with three initial launches, all of which were simultaneous launches (one launched at the same time as the United States, one with Finland and one launched at the same time as other European Union countries). Mexico, Switzerland, and the Netherlands each had one first world launch. One drug was launched simultaneously in Austria and Denmark, while another was launched simultaneously in Ireland and the United Kingdom (IMS Health, 2007). Nine drugs were launched initially in non-OECD countries.

The countries of first world-launch today have changed from the 1980s and 1990s, when most new launches took place in Europe;[21] today most occur in the United States. This may represent a change in manufacturers' strategies. Another explanatory factor may be the dramatic drop in the time required to obtain marketing authorisation from the US FDA following implementation of a 1992 law increasing funding from user fees in exchange for shorter decision targets.

Parallel to the shift to the United States as the preferred country for first launch, there has also been a shift to a more global market, where new molecules are present in more countries. Of the 300 NCEs available on the global market in 2002 that were launched between 1982 and 1988, almost 40% were launched in three countries or fewer (Lanjouw, 2005). Since the mid-1990s, Lanjouw (2005) noted that there has been a marked increase in the number of countries in which a new molecule was launched shortly after the first world launch, *i.e.* NCEs are being launched in more countries and are reaching market quicker. Data from Danzon *et al.* (2005) appear to confirm this shift; at least half of the 85 global NCEs launched between 1994 and 1999 were on the market in 18 (of 25) countries studied.

Pricing strategies used by sellers to maximise profits

There are two overarching questions a manufacturer must consider when setting a price for its product. First is how well do current therapies treat the targeted disease/condition? Second is how much are payers willing to pay? The answer to the first question will have great influence on the second, although other variables such as income, type of coverage, etc. will also impact on consumers, or third-party payers, willingness to pay.

Under "value-based pricing", the manufacturer takes into account relevant market conditions, such as the degree of innovativeness of its product, the price sensitivity of potential customers, and the number of existing therapies.[22] Gregson *et al.* (2005) put forth a simple equation that encapsulates the value-based price: $V = R \pm D$, where (V) is the perceived value of the product to a specific customer, (R) is the price of the best alternative or reference product (either another pharmaceutical or therapy, such as surgery), and (D) is the perceived differentiation (*e.g.* new dosing regime, degree of innovation, safety profile), both positive and negative, of the manufacturer's product *vis-à-vis* the reference product. Since the value of (R) is exogenously determined, the manufacturer can hope to influence a customer's perceived value of its product through the perceived differentiation (D). A manufacturer therefore seeks to differentiate its products by *demonstrating*, *quantifying*, and *communicating* its value. Demonstrating the product's value means showing its superiority over existing therapeutic alternatives. This is usually done through phase III clinical trials. Quantifying the value of the product means estimating a differential value that can be used for establishing a price-premium against the reference product. This is accomplished through sensitivity analysis of market acceptance of various hypothetical prices, and through the use of normative measures, with pharmaco-economics increasingly being relied upon. Finally, communicating the product's value is done through pharmaceutical promotional activities.

The manufacturers of original pharmaceutical products operate in an increasingly global market, which adds a level of complexity to their pricing strategies since market conditions will vary across countries. Furthermore, given that the elasticity of pharmaceutical demand varies both across countries and across types of products (depending on the clinical benefits of the product with respect to competitors, for example), manufacturers must craft pricing strategies to take into account the particular conditions within a country when defining a pricing strategy. Box 2.2 describes the particular strategies manufacturers may use in a market allowing for strategic price increases.

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Box 2.2. **Pharmaceutical pricing strategies in a competitive market**

In the interest of maximising profits, the manufacturer of a new pharmaceutical product can adopt two alternative strategies in pricing in a competitive market. So-called "skimming pricing" occurs when a manufacturer sets an entry price at the highest possible level (resulting in fewer sales at a higher price) and then gradually reduces the price to capture more of the market. The first strategy is likely to be chosen for innovative drugs for which patients (and their insurers) will have a higher willingness to pay, *i.e.,* those with clear advantage in therapeutic benefit as compared with existing therapies. The second approach, so-called "penetration pricing", occurs when a manufacturer offers a price below that of comparable products in an effort to gain market share, then subsequently raises prices. This approach will be reserved for products that offer little or no advantage in therapeutic benefit as compared with existing therapies.

Pricing strategies differ for pharmaceuticals used in acute *versus* chronic conditions. Treatments for acute conditions tend to obtain relatively high price premia at market entry, with little subsequent change in price. On the contrary, penetration pricing is more used for treatments of chronic conditions with high price increases in the eight years after introduction.

Only two studies taking an empirical look at pricing strategies on the US pharmaceutical market were found, neither of which is recent. The first, a study by Reekie (1978), found evidence consistent with the pricing theories described above. He examined pharmaceutical entry price and price trends for all the NCEs launched in the United States between 1958 and 1975, using US FDA categorization of products according to their level of therapeutic novelty (important therapeutic gain, modest therapeutic gain, and little or no therapeutic gain). Very innovative products were introduced at relatively high prices, by comparison with prices of their competitors, while drugs which were minor variations of existing drugs were priced lower than their competitors. This study found some price convergence after four years of marketing of a product, due both to the decrease of entry price and to the prompt price cuts of competitors in reaction to entry of products with penetration prices.

The emergence of managed care in the US market may well have altered pricing strategies. Nevertheless, the findings are consistent with those of a study undertaken 20 years later, following the advent of managed care. Lu and Comanor (1998) studied 144 NCEs launched between 1978 and 1987 in the US, 130 of which had branded substitutes. When compared to therapeutic competitors, the authors found that more than three-quarters of innovative pharmaceutical products (those that were deemed to have either important or modest therapeutic gains) were introduced with price premiums* while the majority of drugs with little or no therapeutic gain were priced at discount. However, the study revealed great variation in pricing at market entry. Entry prices of NCEs, relative to competitors, ranged from 0.2 to 8.2 for the most innovative drugs, from 0.25 to 13.6 for the intermediate category, and from 0.37 to 6 for the less innovative drugs, with respective averages of 3.11, 2.21 and 1.15. Eight years after market entry, real prices of innovative products had slightly decreased while those of less innovative products had significantly increased.

* In fact, there was considerable variability in the average relative prices rendering the differences among the three innovative classes statistically insignificant. The most innovative products were priced, on average, three times higher than their therapeutic competitors (average computed on 14 NCEs); the average relative price of moderately innovative products was twice the price of therapeutic substitutes (sample of 48 NCEs); and the average relative price of less innovative products was roughly equivalent to the prices of direct competitors.

Strategies to maximise the market exclusivity period and avert generic competition

The management of intellectual property rights has gained considerable importance in many industries as a means to generate profits. Patents play a crucial role in the pharmaceutical sector, in which costs of imitation and production are relatively quite low. Since generic entry very often entails a dramatic fall in revenues for original products, pharmaceutical companies have developed a set of strategies aimed at maximising patent life and/or countering generic entry and competition (Grandfils *et al.*, 2004).

First, pharmaceutical companies usually engage in so-called "strategic patenting", *i.e.* sequential filing of multiple patents for multiple attributes of a single product (basic composition, synthetic production, formulation, etc.).[23] Companies often file applications for new patents just a few months before patent expiry of their existing on-patent products in order to maximize the duration of market exclusivity.

Second, companies introduce line extensions. They create new formulations of existing products (new administration mode, extended release), new dosages, new molecule associations, and chemical derivatives of the original molecule (such as isomers, esters, active metabolites, etc.). Line extensions do not always offer a significant therapeutic advantage over the original product. When these products manage to reach the market before generic entry, they are likely to capture a part of the potential market for generics, particularly in cases where purchasers are not price-sensitive.

Third, in the 1990s many pharmaceutical companies engaged in aggressive strategies to protect their intellectual property rights, engaging in litigation with generic manufacturers for patent infringement. In the United States, pharmaceutical companies were accused of having abused patent litigation in order to benefit from the additional months of exclusivity that were granted in case of litigation by the temporary suspension of generic sales. A few companies were condemned for violation of anti-trust law and required to pay damages to health insurance plans or patients for financial losses due to delayed generic entry (FTC, 2002).

In the Slovak Republic, as in Mexico, pharmaceutical manufacturers have succeeded in making patent linkage[24] a condition for registration of generic drugs (Kaló *et al.*, 2008; Moïse and Docteur, 2007). Legislation passed in 2005 – pushed through with the help of US Embassy and the American Chamber of Commerce Local Area Working Group[25] – requires the Slovak marketing authority to inform the owner of a patent or supplementary protection certificate (SPC) when a manufacturer files an application for marketing authorisation for a generic version of the original product to which the patent or SPC pertains. The agency must contact the Institute for Intellectual Property Rights if there is any doubt regarding the information provided.[26]

Other strategies used by manufacturers to minimise losses from generic competition are the production of a generic by the originator company or by a licensee; a switch to OTC status in cases where the company can count on consumers' brand loyalty; and reduction of the original product's price.

Techniques used by manufacturers to influence the volume of pharmaceuticals sold

Pharmaceutical companies engage in various activities to promote sales of their products. Promotional activities serve two purposes. The first is to try to attract market share away from competitors by increasing awareness of the product and its relative benefits. The second is to expand the total market size of the product, which may include

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promoting alternative applications or increasing awareness of conditions for which the product might be used.

Promotion directed at physicians varies from detailing – office and hospital-based visits of sales representatives – to advertisements in medical journals, as well as gifts and free sample products. Pharmaceutical companies also play a large role in providing medical education and especially continuing medical education, by organising and sponsoring conferences and other events.

The significant role the pharmaceutical industry plays in educating physicians is highly contested. From the physician perspective, sales representatives are a readily available, well-educated and easily accessible source of targeted information about new drug therapies. On the other hand, sales representatives are unobjectively seeking to represent their products to the physicians as being better than any others on the market. The passive promotion[27] of off-label use by manufacturers is another controversial technic used to promote sales (Stafford, 2008). The effect of these promotional activities on physician prescribing behaviour is large, although this influence is not always acknowledged by physicians.[28]

The role of consumer advertisements is increasing, although direct-to-consumer advertising (DTCA) is mainly directed at a few products; half of industry expenditures on DTCA in the United States were for 20 drugs (Donohue *et al.*, 2007). DTCA is allowed only for OTC drugs in most countries, with the exception of the United States and New Zealand. In those two countries, it is allowed for more drugs under specific guidelines. In the United States, television and magazines are the most-used forms of media to promote pharmaceutical products. DTCA, however, cannot stand on its own and for a pharmaceutical promotion to be successful, professionals must also be targeted. Professional detailing thus also plays an important role in preparing physicians for patient requests arising from DTCA (Morgan, 2007), and increasingly the pharmaceutical industry provides physicians with free product samples to be given to consumers.

The influence of the promotional activities is large in most countries. There are codes of practice between the pharmaceutical companies, medical associations and government, to ensure promotional activities to be carried out in a responsible, ethical and professional manner. This is in order to create a balance between the need of promotional activities in terms of information as well as the needs of the patients, industry, and health professionals (ABPI, 2007).

The importance of these promotional activities for sales can be surmised by the large amount of resources directed to promotion by the industry. In the United States, where a total of USD 30 billion was spent on promotion in 2005, such expenditures constituted 18% of the value of pharmaceutical sales (Donohue *et al.*, 2007). Providing free drug samples to physicians constituted by far the largest component of promotional spending (62% of total promotional spending in 2005);[29] the share of total promotional spending devoted to professional promotion was 24%, and DTCA's share was 14%.[30] In the United Kingdom, the OFT (2007) reported that GBP 850 million, or 16% of total drug sales value, was spent on marketing in 2004. As an indication of the importance of promotional activities to pharmaceutical companies, 44% of the people employed by GlaxoSmithKline globally are involved in sales (GSK, 2006).

Based on advertising expenditures only, the pharmaceutical industry spends less on marketing than several other industries. In 2005 in the United States, for example, spending on advertising by the automobile sector (domestic and foreign companies) was

USD 17.5 billion, more than triple what was spent by the pharmaceutical industry.[31] However, if free samples (valued at retail prices) are taken into account, then no other industry spent as much on promotional activities as did the pharmaceutical industry in 2005.[32]

Economic theory suggests an explanation for the importance of promotional activities to the pharmaceutical industry – pharmaceuticals are "experience goods". The quality of experience goods cannot be easily ascertained prior to purchase, unlike so-called "search goods" (DVD players, power drills, etc.) whose qualities are more easily identifiable. Potential consumers of experience goods need to try the good directly in order to make a reliable assessment of its quality. Free samples are an effective means by which prescribing physicians and patients can test new drugs. Low marginal production costs make the distribution of free samples relatively cheap. Furthermore, advertising (be it to consumers directly or to physicians) is important because, with experience goods, consumers need to be constantly reminded of their positive experience lest they defect to a competing product. Advertising-to-sales ratios thus tend to be higher for experience goods than for search goods. Berndt (2001) uses 1998 advertising and sales data to show that average advertising-to-sales ratios for a number of search good firms was significantly lower than for experience goods firms.

Pharmaceutical companies are actively involved in defining disease and disease awareness campaigns as part of their marketing campaigns to expand and create markets. Some forms of this medicalisation have been disparagingly referred to as "disease mongering" – expanding boundaries of treatable illness to develop markets for new products (Moynihan *et al.*, 2002). Disease mongering can take various forms, such as turning ordinary ailments into medical problems, seeing mild symptoms as serious, treating personal problems as medical, portraying risks as diseases and framing prevalence estimates to maximise potential markets (*op. cit.*). While some aspects of this phenomenon are the subject of ongoing debate, little is known about the extent of its impact on public health, medical practice and health spending (*op. cit.*).

Profits of the pharmaceutical industry

The pharmaceutical industry is generally regarded as one of the most profitable. For example, the pharmaceutical industry ranked second to the mining and crude-oil production industry in return on revenues in 2006.[33] Among the world's 15 most R&D intensive industries, the pharmaceutical industry was the most profitable, with profits accounting for 20.3% of total sales in 2006 (DIUS, 2007b).

Crude measures of profitability may not capture the complexities of the pharmaceutical industry. According to the US Congressional Budget Office (CBO), using standard accounting measures – which treat most R&D outlays as expenditures, rather than investments that increase the firm's value – results in overestimates of the profitability of the US-based pharmaceutical industry (CBO, 2006). The CBO reports that, when adjusted for the value of its R&D assets, the industry's actual profitability appears to be somewhat higher than the average for all US industries, but not two to three times higher, as is sometimes reported.

Conclusions

The business of pharmaceuticals is a largely global one where research-based multinational firms dominate. These firms have produced products that have made

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significant contributions to improving the health of OECD populations, yet declining R&D productivity has many questioning whether today's innovative products bring only marginal improvements.

These firms have developed numerous strategies for maximizing cash flow during a product's life cycle. Perhaps the most significant determinants of where and when to launch a product is the expected price and volume of sales a particular product will bring. Pricing policies are an important factor that manufacturers must take into consideration in their pricing strategies, but differentiation in terms of improvements over competitors' products are mainly how manufacturers attract premium prices. Manufacturers influence the volume of pharmaceuticals sold mainly through promotional activities aimed at physicians, with direct-to-consumer advertising prohibited in all countries with the exceptions of the United States and New Zealand. It is during the period of market exclusivity that manufacturers maximise their cash flow and these have developed several strategies to extend that period and delay the entry of generic competitors.

The dominance of the research-based firms is being challenged by an expanding generic industry. As many blockbuster drugs continue to lose patent status in the coming years, and cost conscious governments and third-party payers see lower-priced generics as a means to cut costs, generic manufacturers will continue to consolidate their growing market share in terms of sales volumes across many OECD countries.

The cost differences that make generics attractive will also continue to keep original products within the crosshairs of policy makers. These challenges will vary across OECD countries in line with the variations in ex-manufacturer prices. The United States has garnered significant savings in drug costs with generic drug prices that are four times lower than original prices, yet this is the very reasons the United States spends more per capita on pharmaceuticals than any other country. On the other hand, Switzerland, another country with high ex-manufacturer prices for originals, has not been as successful in capturing the benefits of generic drugs.

Notes

1. Based on the top 160 pharmaceutical firms in terms of worldwide R&D expenditure, as listed by the UK Department of Innovation, Universities and Skills (DIUS) 2007 annual R&D scoreboard of the top 1 250 companies in terms of amount spent on R&D. The Scoreboard was formerly compiled by the Department of Trade and Industry, which was merged with the Department for Education and Skills to form the DIUS.
2. In the first paper (Lichtenberg, 2001), the author analysed data on prescribed medicines from a 1996 panel survey. A drug's age was defined as the number of years since the active ingredient was approved by the FDA. In the second paper, Lichtenberg (2002) extended the analysis of the previous paper to three years of data and used the medical condition as the unit of analysis (rather than the prescription as was done in the previous paper).
3. Zhang and Soumerai (2007) assert that Lichtenberg's two papers on the benefits of newer drugs "are the only published evidence regarding whether, on average, newer drugs result in lower total health care costs".
4. Many studies exist that have tried to separate "run-of-the-mill" (incremental) innovation from those (radical or breakthrough) innovations that "break with traditions in a field" note Dahlin and Behrens (2005), but no consensus on a precise definition has emerged.
5. As often, as not, a "me-too" products is the "loser" in a race between companies that are simultaneously developing a drug for treating the same health problem.
6. All sales figures in this report are calculated at ex-factory prices, unless stated otherwise.

7. The figures for 2001 include Turkey and exclude Brazil among the top ten markets. The figures from 2002 onwards include Brazil and exclude Turkey.
8. For example, see "Beyond the Blockbuster" in the 28 June 2007 issue of *The Economist*.
9. Primary-care-driven drugs are mainly targeted at sufferers of highly prevalent, chronic diseases. Specialty-driven drugs are mainly targeted at rare diseases, or sub-populations of people suffering from chronic diseases. Their potential target populations are small in comparison to primary-care-driven drugs, meaning specialty-driven drugs would have to be priced much higher than primary-care-driven drugs if they are to generate comparable sales revenues.
10. Data on the volume of sales were not available for Switzerland.
11. For example, in the United States, the generic market is more than four times as large when expressed in terms of volume as compared with value.
12. IMS segments the prescription-only medicines market according to whether or not products are patent protected. The protected market includes products protected from generic competition by patents, data exclusivity, supplementary protection certificates, etc. The unprotected market includes generics, off-patent pharmaceuticals and copy products.
13. One of the most critical issues of price comparison studies is that they often present bilateral comparisons between a reference country (A) and other countries (B, C, etc.). As the basket of pharmaceuticals used in the comparison between country A and country B (*i.e.*, those products that are sold in both countries) is not the same basket of goods used to compare prices in A and C, direct comparisons between price indexes for B and C are not appropriate.
14. Calfee *et al.* (2006) estimated the price of innovative (biotech) drugs to be priced lower in the United States than in other countries, although prices of non-biotech drugs were considerably higher (see Annex 2.A1). Roughead *et al.* (2007) found that the price differential between the United States and Australia for the most innovative drugs was less than that for "me-too" products. In an unpublished study comparing prices in France to those in Germany, Italy, Spain and the United Kingdom, Geoffard and Saurí (2008) found the average prices of the most innovative products to be roughly similar (except in Germany where prices were consistently higher), whereas the average price in France for drugs representing minor improvements were generally lower
15. In the United States, for example, nine out of every ten drugs that reach the clinical trial phase do not make it to market (CBO, 2006). These failed drugs are a cost to the manufacturer that must be recouped through the profits of successfully launched products.
16. The administrative costs of pharmaceutical companies – these include advertising expenses, but firms generally do not separate these from other administrative spending in their annual reports – tend to be greater than R&D costs (Innovest, 2006). Another cost of doing business that is potentially very costly, is that of civil liability class-action lawsuits which are particularly important in the United States. For example, Merck paid almost USD 5 billion in 2007 to settle 27 000 lawsuits related to its pain medication Vioxx. This was on top of the almost USD 1.2 billion it paid in Vioxx-related legal fees (see "Merck Agrees to Settle Vioxx Suits for $4.85 Billion", *New York Times*, 9 November 2007).
17. The model estimated by Wiggins and Maness (2004) differs from previous models since they concentrated on drugs in a single therapeutic class, anti-infectives, rather than drugs across several different classes. Not only were the authors able to estimate the effect on original product prices of generic competitors, but also that of therapeutic competitors as well.
18. Danzon *et al.* (2005) analysed launches in 25 large markets of 85 potentially global compounds – defined as launched in either the United Kingdom or the United States – first launched between 1994 and 1998. They modelled the probability of launch and launch delays as a function of expected price and volume of sales, income per capita, a country-fixed effect, and two variables for the "link" between the manufacturing firm and the country (experience of the firm in the country, approximated by total sales of the firm in the country, plus an indicator of whether the country is the firm's home country).
19. Danzon *et al.* (2005) found that countries with the most launches and shortest delays were the United States, Germany, and the United Kingdom – the three countries with unregulated pharmaceutical prices at that time. New Zealand and Portugal – small countries with low prices – had the fewest launches, except for Japan, which, according to the authors, was an outlier with very few launches because of onerous approval requirements, not low prices.
20. Kyle (2007) analysed determinants of launch decisions for a sample of 1 444 products launched between 1980 and 2000 by 278 firms in the 28 largest pharmaceutical markets.

21. According to Lanjouw (2005), 393 new drugs were first launched in one of the EU15 countries between 1982 and 2002, whereas only 163 were first launched in the United States.
22. The market conditions a manufacturer will estimate while undertaking a value-based pricing strategy will change during the product's development due to the long time horizon required to bring a product to market. Therefore, the manufacturer must constantly re-evaluate during the product development stage the market conditions originally estimated.
23. European Generic Association's website *www.egagenerics.com/gen-phrmapatents.htm*, accessed on July 31, 2007.
24. Patent linkage is the practice of linking market approval – or the pricing and reimbursement status – for generic medicines to the patent status of the original pharmaceutical.
25. May 4, 2006 press release of the Embassy of the United States, Bratislava, Slovak Republic (*http://slovakia.usembassy.gov/pr060504.html*, accessed 4 October 2006).
26. Although the provision has not been in place long enough for its legal implications to be tested, this legislation has the potential to shift the legal responsibility to the government agency in cases where a patent is infringed.
27. Most countries prohibit or severely curtail pharmaceutical companies from promoting a product's use for indications not approved by the regulatory authority. Nevertheless, pharmaceutical companies often provide physicians with journal articles about off-label use of a product (Stafford, 2008).
28. The World Health Organisation's Department of Essential Drugs and Medicines Policy has developed a database that summarises the research evidence on pharmaceutical promotional activities in co-operation with several outside experts. Regarding the effect of promotional activities on behaviour, the gathered evidence suggests that doctors rarely acknowledge that promotional activities affect their prescribing behaviour, and that doctors that rely more on industry promotional materials prescribe less appropriately, and more often (*www.drugpromo.info*, accessed 22 October 2007).
29. The cost of free drug samples is calculated at their approximate retail price, thus overestimating the opportunity cost to manufacturers (assuming all free samples could have been sold). At the other extreme, Berndt (2002) states that the opportunity cost to manufacturers of providing free samples should be valued at the marginal cost of production.
30. Data on DTCA spending are representative of major media markets. Professional promotional spending includes professional detailing to hospital and office-based physicians, and advertisements placed in 400 medical journals. Spending on free samples is derived from a panel of 1 200 office staff members in medical practices (sampled from the practices of the office-based physicians used for calculating professional promotional spending) (Donohue *et al.*, 2007).
31. Data on advertising spending by TNS Media Intelligence, a marketing information company, showed that the pharmaceutical industry was 10th in advertising spending in the United States in 2005 (News Release, March 13, 2007, *www.tns-mi.com/news/03132007.htm*). Donohue *et al.* (2007) estimated DTCA expenditures using TNS Media data.
32. This does not include the use of free samples as a selling tactic in other industries. For example, the personal-care products industry – which spent more on advertising than the pharmaceutical industry – also makes extensive use of free samples.
33. Based on the companies included in the *2007 Fortune Global 500* index of the world's largest corporations (*http://money.cnn.com/magazines/fortune/global500/2007/performers/industries/return_revenues/index.html*., accessed 22 October 2007).

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ANNEX 2.A1

Price Comparisons at the Ex-manufacturer Level

Santésuisse (2006) compared the prices of the top 100 reimbursed products in Switzerland with prices in the seven countries used as comparators (the United Kingdom, Germany, Netherlands and Denmark) and subsidiary countries (Austria, France and Italy) in setting Swiss reimbursement prices. The sample represented 56% of Swiss turnover for reimbursable outpatient drugs. The study computed price indexes by weighting foreign-to-Swiss unit price ratios (per tablet or other unit) in 2005, converted using current exchange-rates, by 2004 Swiss sales. In this study, ex-factory prices[1] in direct comparator countries appeared to be 8 to 15% lower than Swiss prices, while prices in "subsidiary" comparator countries appeared to be 28% to 32% lower (Santésuisse, 2006).

IMS Consulting (2003) compared the prices of the top-100 reimbursed drugs in Switzerland, representing 47% of the value of the Swiss market, with prices in a set of OECD countries, in the second quarter of 2003. Price indexes were computed as the unweighted average of elementary indexes taking the Swiss price as the reference, considering only identical form-strengths in all countries, and using current exchange rates for monetary conversion. According to this study, ex-manufacturer prices in Switzerland were higher than prices in any of the seven European countries used as comparators (see above), as well as Sweden. They were also higher than Canadian prices but lower than prices on the US Federal Supply Schedule (used by four major government agencies for purchasing pharmaceuticals).

Annual reports from the Canadian Patented Medicines Prices Review Board present bilateral comparisons of Canadian ex-factory prices of patented drugs with prices in the seven countries considered in the Canadian price regulation (France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States). The average foreign-to-Canadian price ratio for each product was computed, weighted by sales in Canada. Prices were converted by current exchange rates.[2,3] The extent to which the sample of products is representative of the market in the comparator countries is not known. There appears to be a convergence of Canadian prices with European prices over the period 1987 to 2005, as well as an increase in the gap with US prices over this same period (PMPRB, 2006a).[4] In 2005, prices were highest in the United States, where they were 72% higher than in Canada, and lowest in Italy, where they were 16% lower than Canadian prices (*op. cit.*). Another PMPRB report (PMPRB, 2006b), using the same methodology, found that generic prices were highest in Canada, followed by Switzerland where prices were 1% lower than in Canada. They were the lowest in New Zealand (77% lower than in Canada).

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A study published in 2004 by the US Department of Commerce (ITA, 2004) compared the 2003 prices of patented products in the United States with those in ten OECD countries (bilateral comparisons). The sample was composed of the US top 54 patented prescription products containing a single molecule, further extended to all products containing this molecule (on- or off-patent). It represented 26% of drug sales across the comparator countries. Fisher Indexes were calculated based on ex-manufacturer price per standard unit (SU) and per kilogram. Discounts obtained by US purchasers were not factored into the analysis, resulting in overestimates of the price differentials. The study found that ex-manufacturer prices in the comparator countries were about 40-60% below the undiscounted prices of the United States. Prices per standard unit ranged from 41% lower in Switzerland to 67% lower in Japan. By contrast, prices of generics were found to be higher in comparator countries than in the United States, except for Poland (30% lower), Greece (10%) and Australia (same level).

Danzon and Furukawa (2003) compared US prices of 249 molecules[5] in 1999 to prices in eight countries (Canada, Chile, France, Germany, Italy, Japan, Mexico and the United Kingdom). The basket of pharmaceuticals contained both generic and patented drugs, matched by molecule and indication (ATC class), and represents 30-60% of sales in the countries. The authors used IMS data to compare manufacturers' prices at the level of price per dose, with price discounts furnished to big purchasers in the United States estimated at 8%. Price indexes were calculated using US volumes of sales as weights. They found that Japan's ex-manufacturer prices were highest, followed by the United States. Prices in Germany, Italy and the United Kingdom were about 15% lower than US prices. Mexico and Chile had prices about 20% below those of the United States. France's prices were 30% lower than those of the United States, and Canadian prices appeared to be 33% lower than those of the United States. When looking at prices for on-patent originator products only, Japan's prices were still highest, but US prices were higher, relative to the other countries studied. Germany, the United Kingdom and Mexico had prices about 25% below those of the United States. France, Italy and Canada all had prices of originator products that were about 35% lower than those in the United States. The pattern of prices for generic products was quite different. US prices were found to be lower than those in all other countries except Canada, which had generic prices 6% below those of the United States. Italy and Japan had the highest prices for generics.

Danzon and Furukawa (2008) compared ex-factory prices of pharmaceuticals sold in retail pharmacies in 12 countries in 2005. They computed bilateral price indexes for each country, relative to prices in the United Sates, and weighted by US sales volumes. The authors used a number of different adjustment factors to convert prices to US dollars; we report the results for prices converted to US dollars using market exchange rates. US prices were adjusted for estimated discounts and German prices for mandatory rebates. A first index compared ex-factory prices of pharmaceuticals that matched on active ingredient and indication The second index was a refinement of the first, comparing pharmaceutical ex-factory prices by taking into account differences in form and strength which were not accounted for in the first index. The prices compared in the first index covered at least 80% of pharmaceutical sales in all countries except Japan (64%); the second index covered less than 50% of sales in all countries, except Canada, Australia and the United Kingdom.

According to the first index, only Mexican and Japanese prices were higher than US prices (respectively 2% and 11% higher). All other countries had lower prices, ranging from Canada (19% lower) to Spain and Chile (respectively 41% and 44% lower). Results were

similar for the second index. The authors also used the second index to compare prices of on-patent pharmaceuticals and generics separately. They found on-patent pharmaceutical prices to be highest in the United States, regardless of whether or not there were generic competitors. Prices of single-source original products (on-patent medicines with no generic competitors) were lowest in Italy (55% lower than the United States). Prices of multi-source original products (on-patent medicines that faced at least one generic competitor) were lowest in France (37% lower than the United States). By contrast to on-patent medicines, overall generic prices were lowest in the United States. Mexico and Japan had the highest prices for generics, respectively 116% and 111% higher than US generic prices. Generic prices in France and Spain were closest to US prices, where they were about 10% greater.

Calfee *et al*. (2006) found the average ex-manufacturer price of 36 top-selling (non-biotech) drugs in the United States in 2004 was about 50% greater than in Australia, Canada, France, Germany and the United Kingdom.[6] For the 22 top-selling biotech drugs, however, prices in Canada and France were similar to the United States and about 25% lower in Australia, Germany and the United Kingdom. The authors separated the biotech drugs between first-generation and the more innovative, second-generation, biotech drugs. Prices for the second-generation biotech drugs were found to be lowest in the United States, with prices highest in France (24% greater than in the United States). Even in traditionally low-price Australia, the average price of second-generation biotech drugs was lower than in the United States. Roughead *et al*. (2007) found a similar result comparing the prices of innovative between Australia and the United States.

Simoens (2007) compared the Belgian prices of 15 generic medicines, selected by active ingredient and strength, to those in seven European countries (Denmark, Finland, France, Germany, the Netherlands, Norway, Sweden and the United Kingdom) and India. The average price per standard unit (*i.e.* price per tablet or capsule), weighted by the volume of Belgian sales of all available package sizes and generic medicine manufacturers, was calculated for each active ingredient and strength. Prices in France, the Netherlands and Germany were 23 to 31% higher than in Belgium, whereas in the United Kingdom they were only 8% higher. Average prices in Denmark and Sweden were half the price in Belgium. Unsurprisingly, the average price was lowest in India. The author also compared average price levels for "mature" generic markets (those with total sales volumes greater than or equal to 40%) against "developing" European markets (sales volumes less than 40%), to show that the average price level is greater in developing markets.

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Table 2.A1.1. **Bilateral comparisons of ex-manufacturer prices: review of recent studies**

In each study, each comparator country's price index is an average of the foreign-to-reference country price ratio for each product available in the comparator country.

Study	Price comparison	Methodology	Findings	
Santésuisse (2006)	2005 ex-factory prices of the top 100 reimbursed products in Switzerland	Indexes weighted by 2004 Swiss sales. Product prices are per tablet Exchange rate	Switzerland = 100 Denmark = 92 Germany = 86 Netherlands = 85	United Kingdom = 85 France = 72 Italy = 68 Austria = 68
IMS Consulting (2003)	Second quarter of 2003. Ex-factory prices of the top 100 (by value of sales) reimbursed drugs in Switzerland	Indexes are unweighted Comparator country price indexes computed as the un-weighted average of product prices indexed to the Swiss price, considering only identical form-strengths in all countries, and using exchange rates (X-rate) and Purchasing Power Parities (PPPs) for monetary conversion	*X-rate:* United States = 135 Switzerland = 100 Sweden = 90 Canada = 88 United Kingdom = 87 Denmark = 86 Germany = 86 Netherlands = 82 France = 76 Italy = 76 Austria = 75	*PPPs:* United States = 187 Canada = 140 Germany = 120 Italy = 115 United Kingdom = 112 Netherlands = 107 Austria = 106 Sweden = 105 France = 103 Switzerland = 100 Denmark = 94
PMPRB (2006a)	2005 ex-factory prices of patented drugs available in Canada and in each comparator country	Indexes weighted by Canadian sales. The average foreign-to-Canadian price ratio for each product is computed, weighted by sales in Canada. Prices are converted by current exchange rates	United States = 172 Switzerland = 116 Germany = 107 United Kingdom = 106	Canada = 100 Sweden = 97 France = 93 Italy = 84
PMPRB (2006b)	2005 ex-factory prices of generic drugs available in Canada and in each comparator country	Indexes weighted by Canadian sales. The average foreign-to-Canadian price ratio for each product is computed, weighted by sales in Canada. Prices are converted by current exchange rates	Canada = 100 Switzerland = 99 Australia = 85 Germany = 84 Netherlands = 80 United Kingdom = 80	Italy = 76 France = 71 United States = 65 Spain = 58 Finland = 49 New Zealand = 23
Office of Fair Trading (2007).	2005 ex-factory prices, bilateral comparison with the United Kingdom, based on the top 150 branded medicines in the United Kingdom	Indexes weighted by UK sales. Products were chosen by active ingredient and matched on form and strength. Rebates and discounts were not taken into account.	United-Kingdom = 198 Germany = 108 Ireland = 103 Finland = 101 United Kingdom = 100	Austria = 96 France = 96 Belgium = 95 Netherlands = 95 Italy = 84 Spain = 84
US Department of Commerce (2004)	2003 ex-factory prices of US top 54 patented prescription products containing a single molecule, further extended to all products containing this molecule (on- or off-patent)	Fisher Indexes calculated based on ex-manufacturer price per standard unit (SU) or per kg of active ingredient. Figures reported here are for SUs	*(Extended) Patented drugs:* Switzerland = 59 Canada = 54 United States = 100 Germany = 52 Australia = 49 France = 49 Greece = 47 United Kingdom = 47 Poland = 39 Japan = 33	*Generics:* Switzerland = 170 Canada = 140 France = 120 United Kingdom = 110 Germany = 100 United States = 100 Australia = 90 Japan = 90 Greece = 80 Poland = 60

Table 2.A1.1. **Bilateral comparisons of ex-manufacturer prices: review of recent studies** *(cont.)*

In each study, each comparator country's price index is an average of the foreign-to-reference country price ratio for each product available in the comparator country.

Study	Price comparison	Methodology	Findings	
Danzon and Furukawa (2008)	2005 ex-factory prices, all out-patient drugs available in the United States and each comparator country	Indexes weighted by US sales volumes. Prices per dose, converted using exchange rates. Price indexes weighted by US sales. Products matched by molecule-indication-form-strength and formulation US and German prices were adjusted to account for off-invoice discounts and rebates which are not recorded in the data.	*Single-source originator products:* United States = 100 Mexico = 90 Japan = 81 United Kingdom = 76 Canada = 74 Germany = 74 France = 64 Australia = 63 Spain = 62 Italy = 55 *Generics:* Mexico = 216 Japan = 211 Germany = 151 Italy = 150 Australia = 138 Switzerland = 170 Canada = 133 United Kingdom = 131 Spain = 109 France = 108 Germany = 100 United States = 100 Australia = 90 Greece = 80 Poland = 60	*Multiple-source originator products United States = 100* Japan = 99 Mexico = 87 Italy = 68 Germany = 65 Australia = 62 United Kingdom = 61 Canada = 60 France = 37 *OTC products:* United States = 100 OTC products: Italy = 527 Spain = 377 Japan = 362 France = 262 Mexico = 218 United Kingdom = 202 Australia = 195 Germany = 192 Canada = 189 United States = 100
Calfee *et al.* (2006)	2004 ex-factory prices, top 43 selling drugs in the United States (including seven biotech drugs). 2004 ex-factory prices, top 22 selling biotech drugs in the United States (including the seven biotech drugs that were among the top 43 selling drugs).	Indexes weighted by US sales volumes. Price for each drug in each country was a weighted average per standard unit (smallest common dosage). Drugs were separated into biotech and non-biotech drugs. The overall price indexes were calculated on the basis of the 36 top-selling (non-biotech) drugs. Biotech drugs were separated between 1st generation (13 drugs) and 2nd generation drugs (9 drugs). No adjustment was made to US price data to account for off-invoice rebates and discounts which are not recorded in the data. German prices were reduced to reflect mandatory rebates for social health insurance.	*Overall:* United States = 100 United Kingdom = 54 Canada = 50 Germany = 48 Australia = 45 France = 45 *1st-generation biotech:* United States = 100 France = 73 Canada = 66 United Kingdom = 54 Australia = 52 Germany = 49 Australia = 116	*Biotech:* United States = 100 France = 94 Canada = 99 Australia = 78 Germany = 75 United Kingdom = 75 *2st-generation biotech:* France = 124 Germany = 112 Canada = 109 United Kingdom = 105 United States = 100
Simoens (2007)	2005 ex-factory prices of 15 high-selling selected generic molecule-strengths in selected European countries.	Indexes weighted by the respective comparator country's sales volumes. For each molecule-strength, the average price was computed as the average of prices of all existing presentations, weighted by sales in each country. Prices were converted in Euros using exchange rates.	*Average (15 molecules):* Germany = 0.269 Netherlands = 0.260 France = 0.254 United Kingdom = 0.222	Finland = 0.220 Belgium = 0.206 Norway = 0.171 Sweden = 0.123 Denmark = 0.104

Note: With the exception of Simoens (2007), in each study, each comparator country's price index is an average of the foreign-to-reference country price ratio for each product available in the comparator country.

Notes

1. Except in Denmark and the Netherlands where only pharmacy purchasing price was available. The Federal Office of Public Health in Switzerland estimates that ex-factory prices in these countries may be respectively 2-10% and 6-12% lower than the pharmacy purchasing price. Similarly, UK ex-factory prices were estimated by reducing NHS prices by 16%.
2. PMPRB uses a fully-lagged 36-month moving average of spot exchange rates for this purpose. This means that long-term exchange-rate movements will be fully reflected in PMPRB's average price ratios only 36 months after they occur, while a short-term fluctuation will influence the ratios up to 36 months after it has been reversed.
3. These price comparisons are based on "publicly available ex-factory prices" obtained by manufacturers in foreign countries and provided to PMPRB for the review of excessive price (PMPRB, 2002). This means that further confidential discounts or rebates consented by the manufacturers are not taken into account, which could lead to under- or over-estimates of differentials between Canadian and foreign prices.
4. To estimate the US-to-Canadian price ratio, the PMPRB uses an average of publicly available prices supplied by the patentee and of prices from the Federal Supply Schedule (FSS) published by the Veterans Administration. The FSS seldom has more than a 50% weight in the average, and often has a much smaller weight.
5. Molecules were selected from among the US top-350 selling active ingredients as those available in four or more of the studied countries. A key feature of the study is that it focused on molecules, rather than products. Average manufacturer prices in the United States are adjusted to account for manufacturer discounts and rebates.
6. Confidential rebates or discounts were not taken into account. The authors surveyed overseas experts and found the existence of ex-post rebates are between 2 and 7% in Germany, 3.5% in Ireland, 3% in France, and up to 30% off-list prices in the United States (and an estimated 8% off IMS data that were used for the study).

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Chapter 3

Pharmaceutical Pricing and Reimbursement and the Broader Pharmaceutical Policy Environment

The pricing and reimbursement policies used in OECD countries are described and analysed in this chapter. It begins with a description of the coverage schemes that serve to pool risks and defray the pharmaceutical costs borne by individuals. It continues by describing the pharmaceutical pricing schemes employed in OECD countries, including the methods used to limit pharmaceutical prices and define reimbursement price levels. A concluding section provides an overview of aspects of intellectual property rights and marketing authorisation policies that are most important in defining the pharmaceutical policy environment.

Introduction

While each OECD country has a unique mix of pharmaceutical policies, their policy environments share several common features that have important implications for the resulting market dynamics.

First, all OECD countries have established systems of intellectual property rights (IPR) that serve to foster innovation by providing innovators with rights that exclude unauthorised production and sale of an invention for a set period of time. Second, all OECD countries have established regulatory authorities that grant firms the authorisation to market their products on the condition that these meet standards of quality, safety and efficacy. Despite some cross-country variations in IPR and marketing authorisation, the net effect of both these policies is to raise prices by limiting the potential for competition.

Third, in an effort to promote affordable access to pharmaceuticals, all countries have undertaken to subsidise the purchase of pharmaceuticals for some or all of their populations. OECD governments generally treat pharmaceuticals (like health services generally) as a "merit good", whose consumption should not be determined solely by individual preferences and ability to pay (health need is a typical standard by which an individual's pharmaceutical consumption is assessed). Here, there is a great deal of variation among OECD countries, ranging from financing of public clinics providing pharmaceuticals to the uninsured in Mexico, to the tax subsidies for employer-sponsored health insurance benefits in the United States. The net effect is the same: to increase pharmaceutical consumption by reducing or eliminating the direct out-of-pocket cost paid by the consumer.

Coverage schemes

As described in Chapter 1, insurers and public institutions account for most spending on pharmaceuticals, particularly for those medicines dispensed in-hospital and those available by prescription only. Because of their prominence in subsidising pharmaceutical use, coverage schemes play a very important role in influencing pharmaceutical expenditure, price levels and consumption patterns.

The scope of pharmaceutical coverage in OECD countries generally includes medicines dispensed in hospitals as well as medicines prescribed by a physician, although the scope of coverage for in-hospital and out-of-hospital prescription medicines usually differs. In most coverage schemes, medicines furnished during a hospital stay are included in the total charge for the stay.

Some schemes also provide coverage for certain over-the-counter drugs when prescribed by a physician and may also cover self-medication (use of over-the counter drugs without these having been prescribed) under certain circumstances.

Most OECD countries have a common scheme that serves as the primary form of prescription drug coverage for the country's residents. Even where such schemes involve multiple payers, as is the case in Switzerland and the Slovak Republic, they are in essence

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common coverage schemes in that there is little or no permissible variation in the level of drug coverage furnished and the reimbursement prices paid. In some of these countries, a share of the population purchases private health insurance policies that top up existing coverage by subsidising pharmaceuticals not included in the basic coverage scheme (*e.g.,* Switzerland) and covering some or all of the cost-sharing that would otherwise be paid out-of-pocket[1](*e.g.,* Australia, France, Portugal) (OECD, 2004). The extent to which private health insurance finances pharmaceuticals in these countries varies.[2]

Countries that feature multiple forms of basic prescription drug coverage, rather than a single, universal scheme, include the United States[3] and Canada[4], both of which have competing private health insurance plans and publicly financed coverage for eligible population groups. Mexico has several distinct, non-competing social insurance schemes providing coverage for about half the population. Germany has a social insurance scheme that covers about 90% of residents; the remaining 10% opt out and use private health insurance that covers pharmaceuticals and other health care services. There is considerable variation in the extent to which private health insurance finances pharmaceuticals in these countries.[5]

The following sub-sections provide an overview of the key points of differentiation among coverage schemes in OECD countries in terms of:

- the market power of the payers or purchasers,
- the inclusiveness or comprehensiveness of the pharmaceutical coverage,
- the level of subsidy and financial protection furnished,
- the use of benefit management strategies that affect the volume and mix of pharmaceuticals consumed.

Coverage schemes determine the market power of purchasers

A key point of differentiation across OECD countries comes in the policy decision to maximise equity and the prospects for cost control through a common national scheme for pharmaceutical coverage, as has been put in place in most OECD countries, or to maximise consumer choice through a pluralistic system of pharmaceutical coverage. This distinction is important in that the decision largely defines the market power of the payers or purchasers, which is determined by the number of potential customers represented (considered as a share of the total market for a product) and their willingness and ability to pay.

Most types of health care, such as hospital services, are not easily traded across borders. In single-payer coverage systems, purchasers are essentially monopsonists (or in the case of countries characterised by a national health service rather than social insurance, the only provider). As such, they have very significant market power. However, as described in the preceding chapter, the pharmaceutical market is global, with versions of most of the therapeutically important original products sold in most OECD countries. Therefore, no single third-party payer or purchaser of pharmaceuticals can be said to have monopsony power.

Several US purchasers of pharmaceuticals have more market power than do many universal coverage schemes in OECD countries, when measured in terms of population covered and income. The Veterans Health Administration (VHA), for example, one of the largest health care systems in the United States, provides health care to US military veterans. It is financed primarily through general taxation and provides a range of services

including hospital, physician and prescription drug services. In addition to being one of the largest health care systems in the United States, the VHA is also the largest single US purchaser of prescription drugs (IOM, 2000).[6] In 2006, 7.9 million veterans were enrolled with the VA health system (Veterans Affairs, 2006), an enrolment level that exceeds the total population in one third of OECD countries. Beyond this, the largest US pharmaceutical benefits management (PBM) firm,[7] Medco, defines formularies and negotiates pharmaceutical prices on behalf of employers and insurance companies representing 60 million insured people.

Within a country, a system characterised by a single purchaser or payer will have greater power to obtain price concessions from pharmaceutical sellers, as compared to a system in which the national market features multiple schemes operating (and purchasing) independently.[8] However, competing insurers or funds may be able to be more active or discriminating in their purchasing in efforts to meet the demands of those covered, to the extent that those persons are free to choose a competitor – including one that is more or less active in purchasing – if they are dissatisfied.

The comprehensiveness of pharmaceutical coverage varies

A key distinction among coverage schemes is the extent to which they provide coverage for pharmaceuticals available on the market. The most comprehensive schemes, sometimes referred to as "open formulary", cover any drug approved for marketing in the country when it is prescribed by an authorised practitioner. Sometimes, certain categories of products will be explicitly excluded. This type of coverage is also available from some private health insurance schemes that offer primary or supplementary coverage. A variant of this approach – in the sense that all categorically eligible pharmaceuticals are automatically covered upon receipt of marketing authorisation– is the "negative list". Used in very few countries, the negative list indicates which products are not covered (normally this will be an exceptional situation). For example, Germany's social insurance scheme covers all prescription medicines immediately upon market authorisation unless or until they are placed on the negative list. Japan and the United Kingdom also use this approach, as did South Korea prior to 2007.

The most common approach used by third-party payers is to define a list – known as a positive list or formulary – of pharmaceuticals which are subsidised in part or in full. In some cases, virtually all medicines that are proposed for inclusion are included once a decision as to price and/or reimbursement price has been taken.[9] In other cases, purchasers formally select products based on criteria such as effectiveness or cost-effectiveness relative to therapies already covered.[10] In the case of the United States, manufacturers of drugs for which there are therapeutic alternatives often offer payments to PBMs to obtain inclusion on the formularies or to obtain preferred status.[11] In any case, coverage may pertain to all uses of a particular product or be restricted to particular uses (*e.g.,* application as a second-line therapy or limitation to specific target populations). In some coverage schemes, such as the US VHA, selective coverage of medicines and restrictions on coverage are used as a means of managing consumption or controlling costs (see Box 3.1). In other schemes, formularies are comprehensive and coverage of products rarely or never includes restrictions (although other policies may be used to influence consumption of the products).

Some coverage schemes may appear more comprehensive than they are in practice, to the extent that products ostensibly covered (*i.e.,* included on the formulary) are not in fact

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Box 3.1. **Formulary management in the US Veterans Health Administration**

Since 1997, the US Veterans Health Administration has used a National Formulary to help manage its pharmacy benefits. The two main objectives of the National Formulary are to harmonise access to pharmaceuticals across Veterans Administration (VA) regions and to consolidate and maximise purchasing power to negotiate drug prices with manufacturers. The 21 individual Veterans Integrated Service Networks (VISNs) also maintain their own supplementary formularies, and veterans can receive drugs from these formularies as well as the national one.

Following implementation of the National Formulary, the VHA faced criticism that the formulary was overly restrictive, that it adversely affected quality of care, and prevented physicians from meeting the health needs of their patients. The US Congress directed the VA to contract with the Institute of Medicine (IOM) to conduct an in-depth analysis of the effect of the formulary on quality of care, and to compare the restrictiveness, cost and quality of the formulary with other private and government formularies. The IOM concluded that "the VA National Formulary is not overly restrictive. In some respects it is more, but in many respects less, restrictive than other public or private formularies".

National Formulary recommendations are based on drug reviews approved by the US Food and Drug Administration (FDA). Requests for drug or drug class reviews may be made by VISN Formulary Committees and other stakeholders associated with the VA. The VA conducts drug reviews for new FDA-approved drugs focusing on safety and efficacy of the drugs in patient populations similar to the veteran population. VISNs are prohibited from adding new chemical entities (NCEs) to their formularies until the VA has completed a national review. If the VA decides not to list the NCE on the National Formulary, VISNs may still decide to list it on their formularies. If ten or more VISNs add it to their formularies, the VA conducts a new review for consideration of inclusion on the National Formulary.

The National Formulary is partially closed, meaning that not all drugs in particular classes are included and some are subject to restrictions. Listing status generally requires clinical, and increasingly, economic justification. Closed drug classes are major classes that are therapeutically important for the VA population, economically significant, widely utilised and important. Class closures are used as a mechanism to secure lower drug prices (Herdman, 2001), and indeed, substantial price reductions and aggregate savings are typically realised through price-volume contract agreements with manufacturers for drugs included in the closed classes.

Four drug classes were closed in 2000,[1] meaning that the VHA had entered contracts that provide volume-related prices in exchange for committed use, nationwide. Only a few products within a closed class are listed on the National Formulary, and each VISN is required to include these drugs and no others within the class on its regional formulary. A non-formulary exception process exists for patients seeking access to excluded drugs.

The preferred class designation is used to promote the cost-effective use of drugs in a similar, but less restrictive, way. Both steer prescribing and utilisation towards the preferred agents, and both are used to negotiate price-volume agreements with manufacturers. On the National Formulary, two classes are preferred – alpha blockers and calcium channel blockers for treatment of high blood pressure and heart conditions. In these classes, products not designated as preferred products may be used, but prices depend on volume as defined in national contracts.

Box 3.1. **Formulary management in the US Veterans Health Administration** *(cont.)*

In total, the National Formulary generated savings of USD 82.4 million[2] for the five classes that were closed at some point over the IOM study period. Substantial savings were realised through shifts in prescribing behaviour and price reductions from manufacturers. Indeed, the size of the VA population generates considerable bargaining leverage for the VHA when negotiating drug prices with manufacturers, who can expect to secure considerable market share if they are successful in getting their product listed on the national formulary. Conversely, they have much to lose if their product is not listed by the VHA.

The IOM found that larger price reductions were achieved with closed than preferred or open class drugs. With closed class drugs, the price per pill of the most commonly prescribed drugs in the VA system fell by 16 to 41% within three months of a class closure. Overall, most classes remained open as of 2000 (248 out of 254 classes), though it is notable that the four closed classes accounted for approximately 16% of total drug costs in 1998 and 10% of total prescriptions.

1. The four closed classes were: ACE inhibitors, statins, luteinizing hormone-releasing hormone (LHRH) agonists, and proton pump inhibitors.
2. This estimate does not take into account the cost of implementing or managing the formulary – estimated to cost roughly USD 2.9 million over fiscal years 1997-1999.

Source: IOM – Institute of Medicine (2000) and as indicated.

available to patients. For example, availability and accessibility of medicines in Mexico has been hampered by failures of the social insurance schemes and other publicly funded healthcare schemes to keep their pharmacies adequately stocked with products (Moïse and Docteur, 2007a). In the United Kingdom, financial incentives and budget constraints faced by the Primary Care Trusts have been responsible for inequities in access to certain expensive medicines across the country; a phenomenon known as "the post-code lottery" (Walley *et al.*, 2005). Delayed coverage decision-making effectively serves as a form of pharmaceutical benefits management in some coverage schemes. Delays in decision-making may reflect the objectives of cost control, price negotiation or safety considerations. Until recently, US VA policy stipulated that drugs could not be added to the National Formulary until one year after FDA approval.[12] This was designed as a safety-monitoring period in which potential adverse drug reactions could be observed. It was also used to conduct safety, efficacy and cost-effectiveness evaluations of new drugs compared to the most commonly used alternatives (which the FDA new drug approval process does not require) prior to making a formulary listing decision. Following the one-year waiting period, the VA and VISN formulary leaders would work together to make formulary listing and delisting decisions. The VHA faced strong criticism over this policy (Lichtenberg, 2005), and in its comprehensive review of the National Formulary, the IOM found no compelling evidence to support the need for the mandatory wait period. The VA has since abolished it.

Cost-sharing mechanisms

Another key area of differentiation lies in the level at which OECD countries subsidise routine pharmaceutical expenditures and the extent to which they offer financial protection against the risk of incurring high costs associated with the treatment of

catastrophic or chronic illnesses. The key variables are how out-of-pocket spending is determined and whether and how out-of-pocket expenditures are limited.

Most coverage schemes have established cost-sharing for pharmaceuticals, through which patients are required to contribute to the costs of the medicines they use. Cost-sharing requirements are commonly used in coverage schemes to moderate demand for services (by increasing consumer price sensitivity) and shift the burden of financing to patients. In most countries, cost-sharing levels are higher for prescription drugs than for inpatient services or ambulatory care (Docteur and Oxley, 2004). In fact, several OECD countries impose cost-sharing requirements *only* in the pharmaceutical sector. This pattern likely represents policy makers' decisions to vary coverage levels for goods and services to some extent according to the level of patient price sensitivity and consumer discretion associated with consumption of various types of health care.

Coverage schemes vary in the share of the pharmaceutical cost represented by the subsidy. While some schemes (like social insurance in the Slovak Republic) have low or even only nominal pharmaceutical cost-sharing levels, others (like Switzerland and France) subsidise less than three-fourths of the retail price. This results in cross-country differences in the share of expenditures borne by households and contributes to demand for complementary insurance (if permitted). Cohen *et al.* (2006) compared the coverage status of 64 products available in the English National Health Service and in seven major US health plans serving Medicare beneficiaries.[13] About 87% of the drugs were covered, on average, by US drug plans, a share similar to the NHS rate. In the US drug plans, however, pharmaceuticals were subject to deductibles ranging from USD 5 to USD 70 per month, while they were available to patients free of charge in the United Kingdom.

Some forms of coverage include a deductible that must be paid out-of-pocket before the patient is eligible for subsidised pharmaceuticals. Most commonly, the deductible pertains to covered health care generally, rather than to pharmaceuticals specifically.

Cost-sharing may take the form of fixed, or variable, co-insurance rates, or fixed user charges or co-payment amounts. These can vary for different products. For example, in Austria, patients pay a EUR 4 co-payment when purchasing a product that is reimbursed by the social insurance scheme (PPRI, 2007a). In the Slovak Republic, co-insurance rates are variable for different categories of products, ranging from 0% (no co-payment) to 20% (80% of the cost is paid by the social insurance) (Kaló *et al.*, 2008).

The definition of fixed reimbursement amounts for therapeutic clusters

Some coverage schemes define the level of coverage rather than the level of cost-sharing, through the definition of reimbursement limits for classes of bio-equivalent or therapeutically comparable drugs (see Box 3.2). Though such policies are referred to as "reference price policies", they do not directly control the price of the drug, but rather set a fixed reimbursement amount, with patients obligated to pay any difference between the reference level and the retail price of the drug.

The most widely used approach relates to bioequivalent products (same ATC-5 level, *i.e.* same active ingredient or combination of active ingredients), which are placed in reference groups consisting of off-patent products and their generic competitors. In many OECD countries, once a generic competitor enters the market, the reimbursement amount paid by the coverage scheme for the off-patent product is adjusted. For example, the reimbursement level of the off-patent product may be reduced to an amount based on the

Box 3.2. **The use of reference pricing to define reimbursement amounts**

Coverage schemes sometimes use reference prices to set common reimbursement amounts for groups of pharmaceuticals.

Germany was the first country* to employ so-called "reference prices", in which reimbursement of products in a defined group was set at a fixed amount. Since then, several OECD countries have implemented such policies, with specific features in terms of scope (range of products considered for setting reference prices) and reference price setting (the formula used to define the reimbursement level), and the inclusion of patented drugs in the reference price scheme.

Germany introduced fixed reimbursement amounts (*Festbeträge*) for groups of products in 1989. Products are classified according to three levels of "comparability". At the first level, groups are made of products containing the same active ingredient [bioequivalent products, Anatomic Therapeutic Chemical (ATC) classification level 5]. At the second level, groups contain products with pharmacologically/therapeutically comparable active ingredients (ATC 4 level, for example "statins"). At the third level, groups include products with comparable therapeutic effects. *Fesbeträge* are updated on a regular basis, according to a formula taking into account the potential for savings and the number of products available on the market at the proposed price (Le Pape *et al.*, 2000). Initially included in reference price groups, patented drugs were excluded from the scheme in 1995 under industry pressure, but reintroduced in 2004. In 2005, the reference price scheme included products accounting for 60% of the German market (VFA, 2006).

The Netherlands adopted a reference price scheme only a few years after Germany (1991). Products are grouped according to the following criteria: they must have a similar mode or mechanism of action; they must have the same indications for use; there must not be notable differences in properties and adverse effects; they must have the same administration route and target the same population groups (babies, children, adults, older persons). Groups generally correspond to ATC 4 classes or subdivisions thereof. The reference price is determined by successively averaging prices by specialty, by active ingredient, by group and then choosing the price which is just below the computed average unit price per DDD (Le Pape *et al.*, 2000). New drugs are included in a reference group if their producer cannot show evidence that they should not be clustered for clinical reasons.

Following Germany and the Netherlands, many payers and purchasers have adopted a similar approach to defining reimbursement levels. Generally, groups include products with the same active ingredient, but a growing number group drugs that are therapeutic, but not necessary chemical, equivalents.

* The US Medicaid programme, in the state of Maryland, was the first payer to implement reference pricing.

prices of the generic alternatives, leaving patients obliged to pay the difference if they do not switch to the generic product.[14] This is the approach used, for example, in Sweden, where the lowest price-generic alternative is defined as the "reference price", subject to change on a monthly basis (Moïse and Docteur, 2007b).

Several countries – such as Germany, New Zealand and the Slovak Republic – go further, defining certain reference groups (*e.g.*, statins, proton pump inhibitors) on the basis of therapeutic equivalence (products grouped at the ATC-4 level).

Germany has gone even further by classifying certain products that are therapeutically similar, but not equivalent, *e.g.* all anti-depressants have been grouped by the Federal Joint

Commission into a "level 3" cluster. Patented products can be clustered in these so-called "jumbo groups" since 2004 (Paris and Docteur, 2008).

Protection against excessive out-of-pocket expenditure

Patients are sometimes at risk for expenditures associated with a catastrophic illness or accident, in cases where coverage has a defined expenditure limit. For example, a noted feature of the prescription drug coverage in the US Medicare programme is the so-called doughnut hole, which leaves patients liable for 100% of pharmaceutical spending above a certain threshold, with partial subsidies resuming once expenditures reach a higher threshold.[15] Government officials reported that, in 2006 approximately 3 million of 23 million beneficiaries were expected to have reached the point at which the gap in coverage occurred (Lee and Levine, 2006).

On the other hand, Sweden has used a graduated cost-sharing scheme for prescription drugs (excluding inpatient drugs) since 1997. Over the course of a year, patients pay the full cost of reimbursable drugs until they have reached the threshold level in out-of-pocket spending (essentially a deductible). Once the threshold has been reached, patients pay a fraction of the cost of any reimbursable drugs they purchase. The level of the patient co-payment diminishes with the cumulative amount spent until a maximum is reached, above which all pharmaceuticals are provided free of charge to the patient. Families with children under 18 years of age may combine the total cost of all pharmaceuticals prescribed for their children.

Public coverage schemes often employ practices to reduce out-of-pocket expenditures for designated vulnerable groups.[16] Lower cost-sharing or exemptions from cost-sharing requirements are sometimes accorded to vulnerable population groups, particularly for beneficiaries of social assistance, disabled people and those with serious and/or chronic diseases. For example, in Ireland, those certified as having one of several designated long-term illnesses are exempt from cost-sharing requirements for covered medicines (PPRI, 2007e). More exceptionally, cost-sharing levels may differ according to regions, as is the case in Italy (Fattore and Torbika, 2004).

Because the objective of insurance is to defray the costs borne by the patient and protect against burdensome out-of-pocket costs associated with medical need, both public and private payers have an incentive to establish reimbursement prices that include the full contribution from both the payer and the patient (if any), rather than just the subsidy amount. However, there are cases where payers do not seek to constrain sellers to a sales price linked to the reimbursement amount. Such exceptions are normally made to encourage competition on the basis of value among products considered comparable (bioequivalent or therapeutic alternatives), as discussed below. Another approach commonly used to limit out-of-pocket spending is to define or limit the price a seller – manufacturer, wholesaler, pharmacy or all of these components of the supply chain – may charge for medicines that are covered by the payer.

Approaches used to influence the volume and mix of pharmaceuticals consumed

Governments and insurers may seek to influence the volume and mix of pharmaceuticals consumed for a variety of reasons, ranging from cost control to quality improvement. By subsidising expenditure for prescription medicines, health insurance coverage inflates consumption beyond what would be seen in the absence of the subsidy. Coverage schemes in OECD countries differ significantly in the methods employed to

manage the volume and mix of pharmaceutical consumption. Some such policies are geared towards physicians, others pharmacists, and a few directly address patient demand.

Policies geared towards physicians

The ways in which policy makers and insurers try to influence prescribing patterns vary from country to country. In some countries, like Switzerland and Canada, the medical profession itself is considered to be responsible for undertaking any efforts to influence prescribing patterns, and any government initiatives are more geared towards education rather than binding constraints. In these countries, efforts by insurers may be successfully resisted by providers as overly intrusive and inappropriate. In other countries, like Sweden, the health coverage scheme is active – particularly at local levels – in efforts to influence prescribing behaviour.

Sweden is a special case as both local and national governments share responsibility for financing pharmaceuticals and county councils have full responsibility for reimbursing covered medicines. However, the power of these councils is limited as regards the reimbursement list and the price of medicines, thus they try to influence the quantity and type of drugs prescribed. To this end they use Drug and Therapeutic Committees (DTCs), which try to change physician prescribing patterns, and consequently the type and quantity of drugs prescribed. More specifically, DTCs produce lists of recommended first choice treatments and treatment guidelines; and send educators to inform healthcare centres about appropriate use of medicines. The effect of these DTCs is limited, and compliance with recommendations seems to have had an effect only in conjunction with financial incentives (Moïse and Docteur, 2007b).

In an attempt to control rising drug expenditures, Germany introduced collective prescribing budgets in 1993 for all general practitioners in a district. A collective penalty was applied if the budget was overspent. In the years after the introduction of the system, the number of prescriptions, as well as sickness funds' expenditures, decreased. The effect of this measure on quality of care was highly debated. The collective penalties made individual physicians responsible for other physicians' prescribing behaviours, which was seen as unfair. Eventually, the system changed to individual target budgets in 2001, which were, in turn, based upon regional budgets. The effect of this new system, with soft, rather than hard, targets is disputed, based upon evidence from the UK fundholders and indicative prescribing scheme (Walley and Mossialos, 2004). In the Slovak Republic, insurance companies also introduced soft budgets, as physicians resisted hard budgets. Results show little to no effect on prescribing behaviour. Physicians have a different budget target for each insurer they have a contract with, which dilutes the importance of any of the individual budget targets established (Kaló *et al.*, 2008).

Many other types of policies have been implemented in programmes geared at changing the behaviour of providers and pharmaceutical prescribing patterns in order to improve care that would not necessarily be considered strictly as pharmaceutical benefits management (see Box 3.3). In the United Kingdom, where, in 2004, 79% of all prescribed medicines were prescribed using the international non-proprietary name for an active substance, rather than a brand name, a range of policies may have contributed to the outcome, including UK medical school teaching practices and the use of computer software suggesting generic alternatives to branded medicines (Simoens and de Coster, 2006).

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Box 3.3. **Approaches used to influence physician prescribing behaviour**

Clinical practice guidelines are often developed by medical specialists as a guide to physician decision making. Within these guidelines, the overall management of a condition, including best prescribing practice, is proposed. The Canadian Optimal Medication Prescribing and Utilization Service is a programme directed to identifying and promoting best practice in drug prescribing and use, by reviewing and evaluating practice guidelines, rather than developing new guidelines. As the programme has only recently been implemented, it is hard to assess its impact on prescribing behaviour (Paris and Docteur, 2006). In Mexico, the government produced 42 practice guidelines for common diseases, which are not directly aimed at prescribing patterns, but emphasise the use of generics (Moïse and Docteur, 2007a).

Other initiatives used to influence physician prescribing include practice feedback, benchmarking, and continuing medical education (Grol and Grimshaw, 2003; Weiss and Wagner, 2000). Clinical audits and feedback are widely used to assess and stimulate changes in performance regarding guidelines and prescription behaviour. Practice profiling or benchmarking is used in many countries to assess performance of a single provider in comparison with a panel of similar providers. Educational strategies, especially outreach by experts, and mechanisms involving visits and counselling, have proven to be most effective in terms of changing prescribing behaviour (Cantillon and Jones, 1999; Grol and Grimshaw, 2003).

In both Sweden and Switzerland, the pharmaceutical industry and health care professionals adopted a code of good conduct setting forth guidelines and restrictions on education and promotional activities. In Sweden, however, not all county councils have signed the agreement, leading to different levels of co-operation across the country. Some councils have even placed restrictions preventing any direct contact between physicians and the pharmaceutical industry. These county councils should take remedial measures to replace the "educational' role, however biased, of pharmaceutical companies" sales representatives (Moïse and Docteur, 2007b).

In Switzerland, quality circles are the main way in which physician's prescribing is influenced. Quality circles bring together five to eight physicians and one pharmacist on a voluntary basis. These professionals meet regularly to develop collective, evidence-based guidelines, as well as to put these recommendations into practice (Paris and Docteur, 2007). Quality circles have been proven to meet increased quality and efficiency objectives, although the effects on cost savings varied. In addition, participation in these quality circles is validated as part of Continuing Medical Education (CME).

Policies directed towards pharmacists

Many countries have tried to increase the use of generics through generic dispensing policies that allow pharmacists to substitute a generic drug for the prescribed medicine, when the patient agrees and the physician does not object. In most countries that permit generic substitution, physicians can avert substitution by specifying that the prescription should be "dispensed as written". In Hungary, pharmacists are obliged to propose generic substitution, and the proposed substitute must be the cheapest available generic, but the patient has the right to refuse the substitution (PPRI, 2007d). Sweden took generic substitution a step further by mandating substitution by pharmacists of the lowest-cost substitutable product (generic or parallel import) unless a prescription is specified by a physician as "substitution not allowed". The policy seems to have been effective in

generating price competition in the off-patent market and in increasing the market share of generics, and has reduced the average level of co-payments for prescribed medicines (Moïse and Docteur, 2007b). Germany also has mandatory substitution, except where expressly forbidden in writing by the prescribing physician, in cases where the price differential between prescribed product and generic alternative exceeds a certain threshold (ÖBIG, 2007).

The US Veterans Health Administration employs a negative list called the "VA Negative Formulary". It differs from the traditional concept of a negative list, on which listed products are ineligible for reimbursement. Instead, the VA negative formulary lists brand-name drugs for which generic substitution is not permitted, due to concerns with bioequivalence, coding and colour of products or therapeutic equivalence (DVA, 2003). When updated in August 2003, two drugs – Coumadin (warfarin) and Dilantin (phenytoin) – were on the negative list (*ibid.*).

Therapeutic interchange is a commonly applied cost-management tool in the US VHA and is used by about half of US pharmaceutical benefits management firms (Hoadley, 2005). It involves the dispensing of a chemically different drug that is considered to be therapeutically equivalent in that it produces the same therapeutic outcomes and has a similar safety and toxicity profile as the original drug. For example, the therapeutic interchange programme designating lovastatin as the preferred agent within the VHA's statin class came into effect in June 1997. All patients who were taking statins such as pravastatin or simvastatin were switched to lovastatin, the preferred agent. The interchange is reported to have generated equivalent therapeutic outcomes (*e.g.,* cholesterol lowering was the same before and after the therapeutic interchange), equivalent health-related quality of life, and significant cost savings (Patel *et al.*, 1999).

Policies aimed at patient demand

The most commonly used approach to influence patient demand is the cost-sharing requirements used in pharmaceutical coverage schemes. Deductibles and co-payments serve to limit demand by increasing the effective price paid by the consumer. These are sometimes set at one level for all reimbursed products, but are more commonly differentiated, so as to avoid reductions of use of pharmaceutical products considered most important. For example, the Belgian social insurance system defines five categories of medicines, each with a different reimbursement rate (PPRI, 2007b). Those products considered "vital", such as treatments for cancer, are reimbursed at 100% of the price. Products considered "therapeutically important", such as antibiotics are reimbursed at 75% (except for certain vulnerable patients who have an exceptional 85% reimbursement rate). Pharmaceuticals used to treat symptoms are reimbursed at a 50% rate. Similarly, the US private insurer, Humana, also uses a cost-sharing scheme that differentiates products based on type of use, with the lowest co-sharing for drugs that treat acute illnesses and those that are proven to keep patients out of the hospital and the highest for drugs that improve lifestyle with no medical benefit (*e.g.,* drugs for acne, hair loss or sexual dysfunction) (Hoadley, 2005).[17]

Many schemes use differential co-payments to steer use towards products that are less costly for the payer. Most commonly, demand for generics is stimulated by charging differential co-payments for originator drugs (as in Switzerland), or requiring patients who prefer to use an original product for which a generic version is available to pay the difference in price. In the Slovak Republic, the lowest-priced product in a therapeutic group

will be reimbursed at 100% level, whereas other products with higher prices may have co-payments fixed at higher shares (not less than 80%) of the reimbursement price (Kaló *et al.*, 2008). In 2004, 90% of US employees with private health insurance were in plans with a tiered co-payment scheme, of which three-tiered schemes (*e.g.*, generic, preferred and non-preferred drugs) were most common (Hoadley, 2005).

In the US Medicaid programme, dispensing limits, mandated by federal law, are in place to ensure that benefits provided by the different states are "sufficient in amount, duration and scope to reasonably achieve (their) purpose" (Crowley *et al.*, 2005). The three main types of dispensing limits include a restriction on the amount of medication that can be dispensed per prescription, on the number of refills, and on the number of prescriptions per month. The generosity in terms of dispensing limits as well as whether the plan uses hard or soft targets varies widely across the different states. Soft limits are used more often than hard limits, meaning that beneficiaries who have reached their monthly limits are subject to prior authorisation. This gives the beneficiary's provider a chance to provide clinical justification for prescribing above the limit rather than an immediate denial of additional medication.

Prohibition of direct-to-consumer advertising (DTCA) also influences consumer demand for medicines. DTCA is prohibited by law in most OECD countries, although it is allowed in some countries for some OTC medicines. The United States and New Zealand are the exceptions, in that DTCA is permitted for advertisements that meet established regulatory guidelines. Canada has recently revised its policy regarding DTCA, now allowing "reminder ads" as well as "help-seeking ads" (Paris and Docteur, 2006). But the problem of how to properly regulate a mechanism that promotes sales and may inflate prices, but also imparts potentially valuable information to patients, remains.

Pharmaceutical price regulation

Economists know that consumer price sensitivity is low with respect to goods considered necessities, such as pharmaceuticals that are used to combat or prevent a serious illness or debilitating health condition. When the effects of insurance – which reduces the price elasticity of demand for all reimbursed medicines and subsequently increases consumption – are factored in, the demand for pharmaceuticals is "fairly inelastic up to rather high price levels before income effects begin imparting appreciable elasticity" (Scherer, 2000).

Pharmaceutical firms stand to benefit from relatively inelastic demand by pricing at high levels to capture monopoly rents when there is no competition, notably in the case of on-patent medicines for which there is no therapeutic alternative. And even when alternatives exist, competition in pharmaceutical markets is hampered by limits on the information available to those making consumption decisions and by the effects of separating responsibility for the purchasing decision (the physician, in the case of prescription medicines) from responsibility for bearing the cost of the decision (the patient and third-party payer).

Thus price regulation is a policy response to inadequate competition in a market that includes products considered to be necessities and that has been publicly subsidised to avert under-consumption.

Most OECD countries employ either pharmaceutical price regulation or de facto price regulation

The potential for abuse of monopoly power has led two OECD countries with pluralistic coverage schemes – Canada and Mexico – to establish price regulations intended to assure that the prices of patented drugs are not excessive (in Mexico's case this applies to the non-social insurance market only).[18] Their regulations are not linked to any particular coverage scheme or subsidy. Canada's regulation limits the price a manufacturer can charge according to a formula that differs depending on the drug's assignment to one of three categories, based on the extent to which it represents an innovation or improvement over existing products.[19] In its current form, Mexico's price regulation limits the prices paid by consumers that purchase drugs in retail pharmacies to the weighted average of ex-factory prices in the six countries where the product enjoys the highest sales penetration plus estimated (non-regulated) wholesale and retail mark-ups.

Canada's and Mexico's price regulation schemes also serve to offset the market power of monopoly sellers. In Canada's case, numerous private and public plans have not, until recently, sought to engage in active pharmaceutical purchasing strategies or price negotiation (Paris and Docteur, 2006). If price regulation were dropped, payers would likely increase their activity in response to price growth. Conversely, to the extent that purchasers become more active, the rationale for maintaining price control in Canada will diminish. In Mexico's case, half of the population has no coverage for prescription medicines and relies on drugs purchased in retail pharmacies that are financed out-of-pocket (Moïse and Docteur, 2007a). Price regulation thus serves to protect those most vulnerable to the impact of excessively high medicine prices.

In the vast majority of OECD countries, universal coverage schemes act as a combination pharmaceutical subsidy and *de facto* price regulation mechanism that is in effect for subsidised products (whether or not on-patent) nation-wide. This is the case, for example, in Sweden and Switzerland, where pharmaceutical firms submit their proposed ex-manufacturer prices to the pricing and reimbursement authority for consideration with supporting documentation. Once approved, the product is subsidised by the coverage scheme, but the manufacturer may not raise the price without approval; most OECD countries place restrictions on manufacturers' ability to increase prices. Products that are not proposed or approved for reimbursement, including most OTC products, may be sold to consumers in the country at any price.

The US government employs *de facto* price regulation in the case of federal purchasers (*e.g.*, the Veterans Health Administration) and in the Medicaid social assistance programme (Box 3.4) – which provide coverage for about 20% of the US population. These schemes limit the prices manufacturers can charge, using the prices obtained by competing private plans as a benchmark. The US Medicare programme for the elderly and disabled – who are disproportionately heavy pharmaceutical users – does not employ *de facto* price regulation, nor does it use the market power (created by virtue of its coverage of about 14% of the US population) to obtain price discounts. Its market power is decentralised to private plans, whose ability to leverage therapeutic competition has been somewhat curtailed by regulations designed to prevent private plans from risk selection of enrolees that also limit plans' discretion in coverage decisions[20] (Newhouse *et al.*, 2007).

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Box 3.4. **Pharmaceutical pricing in the US Medicaid programme**

Medicaid provides publicly financed health coverage for low-income families with children and low-income aged or disabled individuals. Its enrolment exceeded 55 million, roughly 19% of the US population, in 2003.[1] Approximately 3.6 million were enrolled by virtue of being "medically needy" (those whose disposable income has been reduced by high medical expenses to the extent of meeting Medicaid's financial eligibility test) while the rest qualified as "categorically needy" (low-income persons receiving cash assistance such as supplemental security income) (Crowley *et al.*, 2005).

Financed jointly by the federal and state governments, most responsibility for defining eligibility and service provision criteria, and for administering the programme, is devolved to the states.

While inpatient hospital services, including medications, are part of the mandatory Medicaid benefits package for the categorically needy beneficiaries (but not the medically needy), outpatient pharmacy benefits are not mandatory. All states have opted to provide outpatient pharmacy benefits of some nature, at least for the categorically needy. Most states provide brand name, generic, and some OTC drugs as part of their benefits, but have adopted policies to encourage the use of generic drugs when they are available.

The *Medicaid Drug Rebate Program* requires drug manufacturers who wish to be subsidised by Medicaid[2] to enter into a national rebate agreement with the federal government to provide rebates for outpatient drugs dispensed to Medicaid patients. Manufacturers must agree that the price charged to Medicaid will not exceed the Average Manufacturer Price[3] (AMP) reduced by a rebate percentage. Medicaid law requires states to provide coverage of all FDA-approved medications made by manufacturers who have made rebate agreements.

As of January 2006, the rebate for brand-name drugs is the larger of 15.1% of the AMP per unit, or the difference between the AMP and the best price (BP)[4] per unit and adjusted by the CPI-U based on launch date and current quarter AMP. Reportedly, the rebate given to Medicaid programmes often exceeds 15.1% because of the BP provision (CBO, 2006). The rebate for generic drugs is 11% of the AMP per unit.[5] These rebates are uniform across states and are based on the units purchased.

Supplemental rebate agreements: In addition to the national Medicaid Drug Rebate Program, states may enter into direct price negotiations with manufacturers to secure supplemental rebates. Typically this is done by contracting with a private pharmaceutical benefits manager (PBM), which acts on behalf of the state Medicaid programme to negotiate lower prices from manufacturers. States may negotiate state-specific rebates for their Medicaid population or they may participate in multi-state pooling rebate agreements. With the latter, states pool together their Medicaid beneficiary populations (*i.e.,* total number of beneficiaries) in an effort to increase their purchasing power to negotiate larger rebates and discounts from manufacturers. In 2005, almost half of states received supplemental rebates (Kaiser Family Foundation, 2005).

States are able to negotiate supplemental rebates even though they are required to cover all medicines produced by manufacturers who have made mandatory rebate agreements because they have the authority to restrict coverage. In 2005, preferred drug lists and/or formularies were used in two-thirds of Medicaid plans (Kaiser Family Foundation, 2005). Formulary restrictions vary by state, but exclusions must be justified and excluded drugs must be available through prior authorisation when necessary within 24 hours after request.

Box 3.4. **Pharmaceutical pricing in the US Medicaid programme** *(cont.)*

The state-specific supplemental rebate arrangements implemented in Florida have been recognised as a "best practice" initiative by the US government (HHS, 2004). In 2001, Florida implemented a Preferred Drug List (PDL) in conjunction with state-specific rebates for brand-name drugs. The state's Pharmacy and Therapeutics Committee decides which drug classes to include on the PDL and narrows the list by including only those products that are therapeutically equivalent. Florida's contractor then invites manufacturers to participate in supplemental rebate negotiations of the products within the preferred class. Commencing in July 2004, rebates less than 29.1% of AMP (up from 25.1%) would not be considered by Medicaid for preferred listing status, meaning the drug would likely be subject to prior authorisation criteria. Florida anticipates savings to the tune of USD 24 million from this increase, and does not expect that opposition from manufactures will be substantive enough to threaten the policy change (HHS, 2004).

In 2004, Michigan, Vermont, Alaska, Nevada, New Hampshire, Minnesota and Hawaii received authorisation to enter into a multi-state pooling supplemental rebate agreement. The pooled population consists of approximately 1.1 million Medicaid beneficiaries. Savings ranging from USD 1 million to USD 8 million across states were achieved in the first year, and combined, the supplemental rebate agreement is projected to secure federal savings in the range of USD 19.5 million for fiscal year 2004 (HHS, 2004).

Provisions in the 2005 Deficit Reduction Act (DRA) pertaining to public disclosure of information were intended to improve the evidence base on which states negotiate price agreements with manufacturers, and therefore lead to lower prices. Prior to DRA implementation, manufacturers were required to report their AMP and best price for brand-name drugs to the federal government at the end of each rebate period, with the information protected by confidentiality clauses. The DRA amends this, requiring manufacturers to report their AMP on a monthly basis for both brand-name and generic products. Moreover, as of July 2006, the US Department of Health and Human Services is instructed to report these prices on a publicly accessible website (National Health Law Program, 2006).

Most states differentiate products for coverage and reimbursement by their status as a generic or originator product and implement coverage and reimbursement incentives to encourage the use of generics. Incentives commonly used include charging a lower co-payment for generics, paying a higher dispensing fee to pharmacies that dispense a generic instead of a brand name when possible, paying the generic rate for brand-name drugs, placing generics on preferred drug lists, and taking steps to educate providers about generics (Crowley *et al.*, 2005).

1. By 2005, the Medicaid population had grown to approximately 58.5 million (Crowley *et al.*, 2005).
2. Manufacturers choosing not to participate in the drug rebate programme are not eligible for federal Medicaid coverage of their product(s). Overall, approximately 550 manufacturers and forty-nine states plus the District of Columbia participate in the Medicaid Drug Rebate Program.
3. Average Manufacturer Price (AMP) refers to the average unit price paid to manufacturers for the drug in all states by wholesalers for drugs distributed in retail pharmacies, after deducting discounts. The AMP excludes from its calculation Federal Supply Schedule Prices (Pharmaceutical Pricing Agreement).
4. The best price (BP) is the lowest price paid to a manufacturer for a brand-name drug, taking into account rebates, chargebacks, discounts or other price adjustments. Under the 2005 Deficit Reduction Act, which was implemented in February 2006, generic drugs are now included in the calculation of BP. Prices charged to certain government purchasers are statutorily excluded from best price, including prices charged to the Veterans Affairs and the Federal Supply Schedule (described in chapter text). BP data are not publicly available.
5. Centers for Medicare and Medicaid Services, Medicaid Drug Rebate Program, *www.cms.hhs.gov/MedicaidDrugRebateProgram*, accessed 13 March 2008.

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Market-based pharmaceutical pricing in OECD countries

Throughout the OECD, free or market-based pricing is commonly used in markets for products sold over-the-counter (OTC), with exceptions in cases where OTC products are reimbursed by the coverage scheme. Very few countries regulate the price of patented, non-reimbursed OTC drugs.

On the other hand, there are only three OECD countries (the United States, Germany and the United Kingdom) where pharmaceutical manufacturers are not constrained in establishing their sales prices at market entry.

Although manufacturers in the United States can set list prices for new products freely at market entry, their freedom is checked, on the one hand, by *de facto* price regulation used in certain public programmes, as discussed above, and by competition among insurers in the private sector. In the private sector, the PBMs employed by self-insured employers and health insurance plans use formulary management techniques such as tiered co-payments to influence the mix and volume of consumption, thus giving them leverage to negotiate discounts in cases where products have therapeutic comparators.

In Germany, manufacturers are also free to set their price at market entry. The reference price system is designed to foster price competition among products with therapeutic alternatives. Until 2007, manufacturers faced no regulatory constraint when setting entry prices for new and truly innovative products which could not be clustered with therapeutic alternatives, and health insurance funds were passive payers.[21] However, German authorities have regularly used price freezes, price cuts and mandatory rebates to contain pharmaceutical costs. And the latest reforms seek to promote price competition by strengthening funds' capacity to steer volume towards particular products in exchange for price discounts (Paris and Docteur, 2008).

In the United Kingdom, manufacturers can freely set entry prices of all pharmaceuticals, including those covered by the National Health Service. However, after market entry, pricing is subject to a specific set of constraints due to the Pharmaceutical Pricing Regulation Scheme (see the section on profit control later in this chapter). Beyond profit control at the individual company level, the scheme includes price control mechanisms imposing restrictions on price increases after market entry and regularly entailing across-the-board price cuts. However, by contrast to what happens in other countries, manufacturers are expected to consent to an average price cut (7% in 2007) while retaining some flexibility in the choice of products whose price will be cut (OFT, 2007).

In most of the other countries where free or market-based pricing is possible for prescription medicines, it is allowed only for those drugs which are not reimbursed by the universal coverage scheme. In most OECD countries, this constitutes a relatively small or very small minority of the drugs authorised for sale in the market by prescription, given the importance of coverage to product sales.

Regulators, payers and purchasers use a mix of techniques for defining price levels

Although the motives and rationale for regulating pharmaceutical prices and defining reimbursement prices are different, similar techniques are used in both cases. This section describes the different techniques used to set price limits or reimbursement amounts in OECD countries.

External price benchmarking

External benchmarking of pharmaceutical prices in other jurisdictions is the most widely used technique to limit prices or reimbursement prices in OECD countries. It is perceived by public authorities as a means to assess the fairness or appropriateness of the proposed (or actual) price in relation to what is paid elsewhere.

The use of external benchmarking requires an explicit or implicit notion about how pharmaceutical prices ought to differ across countries, and how they should be similar. The reference pricing policies employed by OECD countries reflect different perspectives on these questions. For example, for its regulation of the prices of patented medicines, Canada selected comparator countries deemed to share its goals of encouraging innovation in the pharmaceutical sector and the domestic presence of a vibrant research-oriented pharmaceutical sector. Mexico uses different comparators for each product, based on the countries with the highest level of sales. The Slovak Republic's comparators also vary by product, as they include the manufacturer's country of origin in addition to countries in close geographic proximity.

Table 3.1 shows that European countries generally refer to each other, *i.e.* they tend to choose countries with similar economic comparability and/or geographic proximity. Austria, on the one hand, benchmarks its prices against the average for the entire European Union – except Bulgaria and Romania (PPRI, 2007a). The Czech Republic, on the other hand, only references Greece, Hungary and Poland (economic and geographic proximity), and Portugal (economic proximity). Despite its economic and geographic proximity, it does not reference the Slovak Republic, even though both countries were once part of the same country.

Germany and the United Kingdom – both of which allow free pricing for innovative drugs at market entry and are often first- or early-launch countries – together with France, are the three countries most commonly referenced. To some extent, this may be opportunistic in that these countries are likely to have prices available for reference soon after first global launch. There are five OECD countries – Australia, Japan, Korea, Mexico and Turkey –not referenced by any OECD member countries.

The way in which the benchmark prices are used also varies across countries. For example, the Slovak Republic sets its price cap at 10% above the average price in the three lowest-priced countries among those referenced. Switzerland is flexible in how the comparator prices are taken into account, disregarding outliers and bringing in alternative countries for consideration when few prices are available.

According to Inazumi (2008), external benchmarking in Japan is used to adjust the price of a new drug if it differs significantly from the average of the drug's price in France, Germany, the United Kingdom and the United States. If the price of a new drug with no therapeutic comparators or a new drug with a significant therapeutic added-value over therapeutic comparators is three-quarters that of the average overseas price, then the price will be increased. If, on the other hand, the price of a new drug, with or without therapeutic comparators, is found to be 1.5 times greater than the average overseas price, then the price will be lowered (Inazumi, 2008).

External price benchmarking is also used by payers within countries, in those countries with pluralistic systems. In Canada, one of the largest provinces, Quebec, requires that manufacturers who wish to sell their products in the province offer the product at the lowest price at which the product is sold elsewhere in Canada (Paris and

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Table 3.1. **The use of external price benchmarking in OECD countries, as of 2007**

Country of regulation	Australia	Austria	Belgium	Canada	Czech Republic	Denmark	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Italy	Japan	Korea	Luxembourg	Mexico	Netherlands	New Zealand	Norway	Poland	Portugal	Slovak Republic	Spain	Sweden	Switzerland	Turkey	United Kingdom	United States	Scope
Australia	–																														Reimbursed drugs
Austria[1]		–																													Reimbursed drugs
Belgium			–																												
Canada				–																											Patented drugs
Czech Republic					–																										Reimbursed drugs
Denmark						–																									All
Finland							–																								All
France								–																							Covered, very innovative
Germany									–																						
Greece										–																					All new drugs
Hungary											–																				All new drugs
Iceland												–																			Prescription drugs
Ireland													–																		GMS-covered prescription only.
Italy														–																	All
Japan															–																Reimbursed drugs
Korea																–															
Luxembourg																	–														Reimbursed drugs
Mexico[2]	Six countries with the highest sales																														Patented drugs sold in the private market
Netherlands																			–												Reimbursed drugs
New Zealand[3]																				–											
Norway																					–										Prescription drugs, covered or not
Poland																						–									
Portugal																							–								Covered drugs
Slovak Republic[4]																								–							Imported drugs
Spain																									–						Covered and non-OTC drugs
Sweden																										–					
Switzerland																											–				Covered drugs
Turkey[5]																												–			Reimbursed drugs
United Kingdom																													–		
United States																														–	

1. Austria benchmarks prices to the EU member states with the exception of Romania and Bulgaria.
2. In Mexico, benchmarking is based upon a voluntary agreement by manufacturers.
3. Comparisons for benchmarking appear to be informal in New Zealand.
4. In the Slovak Republic, the price in the country of manufacture is also taken into account if it is not one of the reference countries.
5. In Turkey, the "country basket" of five comparator countries is chosen every year. The table presents the 2005 situation.

Source: Australia: Sweeny (2004); Austria: PPRI (2007a); Belgium: Eggermont and Kanavos (2005), Mrazek and Mossialos (2004); Canada: Paris and Docteur (2006); Czech Republic: Praznovcova et al. (2003); Denmark: PPRI (2007g); Finland: PPRI (2007h); France: PPRI (2007i); Germany: Paris and Docteur (2008); Greece: Yfantopoulos (2007); Hungary: PPRI (2007d); Iceland: Icelandic Medicines Control Agency (2004); Ireland: PPRI (2007e); Italy: Laux and Gruger (2007); Japan: Inazumi (2008); Korea: Laux and Gruger (2007); Mexico: Moïse and Docteur (2007); New Zealand: PHARMAC (2002); Norway: PPRI (2007j); Poland: PPRI (2007k); Portugal: Laux and Gruger (2007); Slovak Republic: Kaló et al. (2008); Spain: Antonanzas *et al.* (2007); Sweden: Moïse and Docteur (2007); Switzerland: Paris and Docteur (2007); Turkey: PPRI (2007l); United Kingdom: PPRI (2007m)..

Docteur, 2006). In the United States, manufacturers are required by law to furnish their lowest US price to the Medicaid social assistance programme, or to forego sales to a plan serving 55 million people. In addition, the US Federal Supply Schedule (FSS) is a regulated price schedule that requires manufacturers to offer qualified government purchasers their most favoured commercial customer prices, effectively limiting by law the price of brand-name drugs to 76% of the non-federal average manufacture price (Sales *et al.*, 2005).[22] For

about a third of brand-name drugs included on the FSS, a lower price, known as the "Big Four Price" is set for the four largest government purchasers (the Department of Veteran's Affairs, the Department of Defense, the Public Health Service and the Coast Guard) (Roughead *et al.*, 2007).

Internal reference pricing

Internal reference pricing, *i.e.* pricing drugs by reference to therapeutic comparators, is commonly used by payers and regulators to define the price or reimbursement price of certain drugs – most often generic drugs and, less commonly, therapeutic alternatives – at market entry.

While external price referencing, as discussed above, necessarily involves questions about how prices should differ across jurisdictions, internal price referencing also requires difficult decisions – usually implicit – as to how to value differences across products, particularly incremental improvements. In some countries, products representing incremental improvements are not permitted to obtain a premium price over existing therapeutic alternatives. In others, such improvements may be permitted a premium over the price of existing products; however, a key distinction comes in whether the payer pays part of the premium in the form of higher reimbursement price, or whether any premium is to be paid by the patient through additional cost sharing.

The use of internal reference pricing to benchmark the price of original products at market entry

At least four OECD countries (Canada, France, Japan and Switzerland) consider the prices of similar products already on the market – internal price referencing – as a guide to pricing new products that have therapeutic comparators.

In Canada, the PMPRB is in charge of classifying new patented entrants in one of three categories, according to the level of novelty of the new product (see Table 3.2). Only the most innovative products – those classified in Category 2 – will be granted a premium for innovation, *i.e.* a price higher than those of therapeutic comparators. Less innovative products (Categories 1 and 3) must have prices limited to that of pre-existing comparators.

In Japan, the Ministry of Health, Labour, and Welfare is responsible for determining the reimbursement price of drug applications. Drugs deemed to be truly innovative are eligible to receive an Innovativeness Premium which can price it 70 120% greater than the price of a comparator product. Lesser innovative products can be priced 35 60% greater than a comparator product (Usefulness Premium I). Drugs that are considered to have minor therapeutic improvements can still receive a premium price of 5 30% a comparator's price (Usefulness Premium II). Orphan drugs (10-20%) and paediatric drugs (5-20%) are also eligible to receive premium prices

France and Switzerland also consider the degree of new entrants' innovativeness for the purpose of negotiating the prices of new drugs being considered for addition to the positive list. In France, the Transparency Commission (Amélioration du service médical rendu) assesses the therapeutic value of each new drug being considered for reimbursement, as well as its comparative therapeutic advantage over existing alternatives, and rates the degree of a therapy's innovation according to a five-level scale (see Table 3.2).[23] Although products classified in Categories I to IV, *i.e.* presenting some degree of innovativeness in terms of effectiveness, reduction of side effects or patients'

Table 3.2. **Categories used by pricing authorities to differentiate drugs according to therapeutic value**

Pricing authority	Products considered to have high therapeutic value	Products considered to have little or no added therapeutic value, compared with existing therapy
PMPRB (Canada)	Category 2: the first drug to treat effectively a particular illness or one which provides a substantial improvement over existing products (including significant potential cost savings), often referred to as breakthrough.	Category 1: a new Drug Identification Number (DIN) of an existing or comparable dosage form of an existing medicine usually a new strength or existing drug (line extension) Category 3: a new drug or new dosage form of an existing medicine that provides moderate, little or no improvement over existing medicines
ASMR (French transparency commission)	Category I: Major therapeutic progress Category II: Important improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects	Category III : Moderate Improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects Category IV: Minor Improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects Category V: Absence of improvement
Ministry of Health, Labour and Welfare (Japan)	Innovativeness Premium: new drugs that meet the following criteria *a)* clinically useful novel action mechanism; *b)* objectively demonstrated higher efficacy or safety compared with the comparable drug; and *c)* objectively demonstrated improvement in treatment for the disease or injury for which the new drug is indicated. Usefulness Premium (I): a drug that satisfies two of the three requirements for the Innovativeness Premium	Usefulness Premium (II): a drug that satisfies any one of the three requirements for the Innovativeness Premium or is produced using an innovative manufacturing technique that resulted in objectively demonstrated higher clinical usefulness compared with the comparable drug
Swiss Drug Commission	Category (a) Therapeutic breakthrough Category (b) Therapeutic progress	Category (c) Savings compared to other drugs Category (d) No therapeutic progress and no savings Category (e) Inappropriate for social health insurance

Source: Canada: PMPRB (2006); France: Haute Autorité en santé, Commission de la Transparence, *www.has-sante.fr*, accessed 6 July 2007; Japan: Tsumani (2008); Switzerland: Paris and Docteur (2007).

comfort, may claim a higher price than their competitors, products classified in Category V (with no improvement) will be required to offer a lower price than existing comparators to access the positive list.

The Swiss law also refers to a classification of new entrant drugs according to their level of therapeutic novelty and their potential for savings over existing treatment to be used at the time of consideration for inclusion in the positive list (see Table 3.2). The principle for pricing listed drugs is very similar to the French one: Swiss law calls for a premium to be awarded to products defined as innovative, as appropriate. This means that, theoretically, only Categories (a) and (b) are eligible for such a premium. However, in practice, Switzerland's Drug Commission does not undertake formal decisions regarding classification of new entrants and price premiums are reportedly granted to new products which are the first or the second entrant in a therapeutic class.[24] On the other hand, new drugs which are not more effective than existing ones – Category (c) – are supposed to be priced at a lower level if they are to be included in the list.

Both countries make exceptions to this practice, generally allowing the second entrant in a therapeutic class – which does not necessarily offer therapeutic improvement over the first entrant – the same price as the first entrant. In France, any drug following the first entrant in a therapeutic class by less than three years will share the category of innovation assigned to the originator on the grounds that head-to-head clinical trials were not possible due to parallel development of the two products[25]. This provides the Economic Committee for Health Products (CEPS) justification for allowing the subsequent drug(s) to have the same price as the first entrant. In Switzerland, the decision criteria are applied less formally, but the practice is similar. In both countries, subsequent "me-too" drugs with no therapeutic improvements will normally be priced at lower levels.

Generic price linkage

Several OECD countries use internal reference pricing to regulate the price of generic entrants at the time of inclusion in the positive list. Through this practice, known as generic price linkage, the generic is priced at market entry at a discount by reference to the price of the original product.

This practice may be considered as a specific case of the internal price referencing schemes in France and Switzerland, since generics are, by definition, drugs which are not innovative and that should be priced with a discount to be listed for reimbursement. However, in the case of generic price linkage, the amount of the discount is explicitly defined by the regulator.[26] In France, since 2006, generic drugs must be priced at least 50% below the price of the off-patent original. At market entry in Switzerland, generics included in the positive list must be priced at least 30% below this reference price (Paris and Docteur, 2007). In addition, if the price of the originator is lowered at the time of the systematic re-assessment occurring two years later, the price of generic alternatives is supposed to remain at least 15% lower.[27] In any case, if the price of the originator is lowered by its manufacturer, generic manufacturers are not obliged by the law to further reduce their price.

Increasingly, regulators also revise the prices of originals at generic entry; this is the case for instance in Austria, and in France since 2006 (Grandfils, 2007). In France, the CEPS is now supposed to propose a price reduction not only for the off-patent original preparation, but also for other on-patent drugs of the same therapeutic class at the time of generic listing.

Pricing based on pharmaco-economic assessment

Cost-effectiveness analysis[28] and other methods of pharmaco-economic assessment are used to put in perspective the (incremental) cost of a medicine with its (incremental) potential in terms of relevant health outcomes *(e.g.,* improvements in patient health or reductions in disability).

Formal cost-effectiveness studies can be used in two ways to determine whether a product will be reimbursed/subsidised and/or at which price:

- When therapeutic alternatives are available, incremental cost-effectiveness is usually used to make decisions as to whether the new product can be considered "worth" the additional cost.
- When no therapeutic alternative is available, an implicit or explicit definition of a cost-effectiveness threshold is required (Eichler *et al.*, 2004).

Since the introduction in Australia in 1993 of the systematic use of pharmaco-economic assessment in the reimbursement process, most OECD countries use pharmaco-economic assessment in their pricing and reimbursement decisions to varying degrees (Drummond *et al.*, 1999; Dickson *et al.*, 2003; Sorenson *et al*, 2007).[29]

Pharmaco-economic assessment is a technically challenging exercise. Its practice requires a multidisciplinary approach rooted in economics, encompassing a range of disciplines including pharmacology, epidemiology, biostatistics and medicine. This poses problems for smaller or lower-income countries who may not have enough skilled scientists to enable them to carry out systematic pharmaco-economic assessments; for example, in both Mexico and the Slovak Republic, pharmaco-economic evaluations are one

of several criteria assessed for reimbursement purposes by the respective authorities, yet the resources for properly evaluating these are clearly lacking (Moïse and Docteur, 2007; Kaló *et al*., 2008).

It is very difficult to assess the degree to which countries make effective use of cost-effectiveness analysis. Surveys give some indications (Dickson *et al*., 2003; Drummond *et al*., 2003). In those countries with prominent programmes making use of cost-effectiveness analysis (see Box 3.5), a few key distinctions are evident. First, some programmes take budget considerations in mind as a mitigating factor, influencing the outcome, whereas in other systems, budget considerations are taken into account at other levels *(e.g.,* in developing clinical protocols). Second, most programmes take the perspective of the payer, considering only those costs associated with product use that are borne by the payer, although the Swedish system adopts a broader social perspective. All such systems face a number of important common challenges, including the question of the value assigned to incremental improvements, to what extent to use surrogate endpoints *(e.g.,* tumour shrinkage) in place of outcomes such as improvements in health and disability status, and how to proceed in the face of uncertainty about efficacy.

Payers begin to conclude risk-sharing agreements when evidence of cost-effectiveness is low

Health insurers and public plans seek to obtain maximum value, in terms of health benefits, from their drug purchases. Yet very often, reliable information on the outcomes of a product in general use is unavailable at the time of decision-making. For this reason, an "outcome guarantee", or risk-sharing scheme, provides an attractive approach, particularly where outcomes are in question or the product has a prospectively large cost

Box 3.5. **Approaches used in pharmaco-economic assessment**

Several OECD countries now undertake pharmaco-economic assessment, or closely review the assessments provided by pharmaceutical firms, in the course of pharmaceutical coverage and pricing decisions.

England and Wales implemented pharmaco-economic assessment with the creation of the National Institute of Clinical Excellence (NICE). In England and Wales, new medicines are subsidised by the National Health Service (NHS) as soon as they are marketed, unless they are on a negative list. The mission of NICE is to provide pharmaco-economic assessments and make recommendations on whether the drug should be used or not in the NHS. Studies have inferred from official decisions implicit thresholds at which products are considered cost-effective and found, for instance, that NICE had an implicit threshold ranging from GBP 20 000 to 50 000 per quality-adjusted life year. NICE decisions are binding for primary care trusts and physicians, although the latter retain the responsibility of prescribing appropriate treatments to patients. Positive decisions are sometimes accompanied by additional funding to the NHS to make sure that the new drug is affordable. However, the use of cost-effectiveness is far from comprehensive in the United Kingdom, as NICE does not evaluate all drugs entering the market.

Australia's Pharmaceutical Benefits Advisory Committee serves a function similar to that of NICE, making recommendations as to whether new products should be listed on the positive list used in Australia. In a commentary reviewing studies of NICE and PBAC, Henry *et al.* (2005) noted that the PBAC and NICE appeared to use a similar threshold in terms of cost per quality-adjusted life-year (QALY); however, the PBAC rejects a higher proportion of drug applications with lower cost per QALY values. Possible explanations put forward by the

Box 3.5. **Approaches used in pharmaco-economic assessment** *(cont.)*

authors include a difference in the willingness to accept data known to be error-prone, given that PBAC has direct responsibility for estimating budgetary impacts and recommending prices, which NICE does not.

Canada's Common Drug Review (CDR) is an intergovernmental body which evaluates new chemical entities and new combinations to form an official recommendation as to whether a drug should be included in the formularies of participating publicly-financed drug plans. As of late August 2006, 51 drug reviews have been completed since the CDR's implementation, resulting in recommendations that the federal government, provinces and territories not list in their public drug plan formularies half of the new drugs reviewed (Paris and Docteur, 2006). Some negative recommendations are based on a decision that the product is not cost-effective at the price listed, although the actual cut-off point in terms of QALYs per Canadian dollar (or other metric) is not made explicit. Another important factor is whether surrogate outcomes (such as reduced cholesterol level) are accepted in place of desired health outcomes, such as reductions in morbidity or mortality.

Sweden's Pharmaceutical Benefits Board (LFN) was created in 2002 to decide on inclusion of products in the national positive list at the price proposed by the manufacturer. The question of whether the product is cost-effective at the proposed price is a primary consideration (Moïse and Docteur, 2007b). Incremental cost-effectiveness against prevailing therapy is assessed. Sweden's use of cost-effectiveness analysis is unusual in two respects: First, costs and benefits associated with a product's use are considered from a social perspective, rather than from the perspective of the payer. Second, Sweden employs multiple thresholds at which a product may be considered cost-effective, in order to take into account factors such as the importance of the condition treated by the product for population health and the relative need for a new therapy.

Pharmaco-economic assessment is used by both public and private payers in the United States. About two-thirds of all private health plans used pharmaco-economic assessment in their formulary management decisions in 2004.[1] Among public purchasers of drugs, the Department of Defense's Pharmacoeconomic Center uses pharmaco-economic assessments as part of its formulary management.[2] For the administration of Medicare, in 2007 the Centres for Medicare and Medicaid Services stipulated that pharmaco-economic assessment may be used in formulary management.[3]

Several other countries use pharmaco-economic assessment systematically for informing pricing and reimbursement decisions. In Finland, the Netherlands and Norway, pharmaco-economic assessments are mandatory for reimbursement applications for new drugs. In Belgium, pharmaco-economic assessment is used by the social insurer (INAMI) to evaluate reimbursement applications for new drugs with a therapeutic added-value compared to existing therapeutic alternatives.

Many countries ask manufacturers to submit pharmaco-economic assessments as part of their reimbursement applications, although it is not always clear to what extent this information is used in the decision-making process. Austria, Hungary, Ireland and New Zealand include pharmaco-economic assessments as one of several criteria when deciding on reimbursement applications, whereas in Denmark it is not mandatory, but the manufacturer may submit pharmaco-economic evaluations when applying for reimbursement. Finally, Germany has just recently incorporated pharmaco-economic assessment into its pricing and reimbursement process; an independent body (Institute for Quality and Efficiency in Health Care, or IQWiG) has a legislative mandate to perform pharmaco-economic assessments to inform decisions regarding which health technologies, including pharmaceuticals, should be funded within the statutory health insurance system.

1. According to Cohen (2004), 65% of private health plans in 2004 followed the guidelines for pharmaco-economic assessment as set out by the Academy of Managed Care Pharmacy.
2. See Department of Defense Pharmacoeconomic Center, , *www.pec.ha.osd.mil/mission.htm*, accessed on 29 May 2008.
3. Centres for Medicare and Medicaid Services (2007), *Medicare Modernization Act: Final Guidelines – Formularies*, available at *www.cms.hhs.gov/PrescriptionDrugCovContra/DOWNLOADS/CY07formularyguidance.pdf*, accessed on 29 May 2008.

impact. Under a risk-sharing arrangement, a pharmaceutical company and coverage decision-makers agree on the expected outcomes from a drug in a given indication. If the drug fails to fulfil these expectations, when used under appropriate conditions, the pharmaceutical companies will (partly) refund the health service for the costs (Chapman *et al.*, 2004). Reducing the risk associated with decision-making should make it easier for patients and their doctors to try expensive medicines and make it easier for manufacturers to sell their products (see Box 3.6).

Box 3.6. **Risk-sharing arrangements for pharmaceuticals**

One of the most well-known examples of risk-sharing agreements is the scheme for multiple sclerosis drugs in the United Kingdom. Since May 2002, the NHS has paid for four multiple sclerosis products (Avonex, Betaferon, Copaxone and Rebif) under a risk-sharing scheme. The scheme was agreed after the drug treatments were not recommended for use on the basis of cost-effectiveness grounds by NICE. Under the scheme, the price of the drugs will vary according to evidence regarding its effectiveness derived from patients participating in the scheme. If actual outcomes do not meet expectations, within a margin of tolerance, the company will have to lower the price of the product – which is about USD 20 000 a year per patient.

Another such scheme was introduced on a trial basis in 2000 in the United Kingdom, between the North Staffordshire Health Authority, Keele University and Parke-Davis (now Pfizer), to provide an outcomes guarantee for statins in lowering blood cholesterol concentrations. The scheme was set up after the Health Authority was looking for ways to disseminating best practice for cardiovascular diseases without using excessive resources, or protecting the health service from paying when the drug did not work. At the end of the project all treatment targets were met or exceeded and no refunds made (Chapman *et al.*, 2004).

In the United States, risk-sharing schemes are said to be in development but few specific examples have surfaced publicly. One example is that of Pfizer and Florida Medicaid. They created a risk arrangement in which Pfizer guaranteed Medicaid savings. Pfizer has promised to achieve USD 33 million of savings in a disease management program, in return for inclusion of all of its products on a new restrictive formula (Posey, 2001). Pfizer focused on disease management, including hiring nurses, for high users, who have chronic conditions, such as diabetes, asthma, or heart disease. Pfizer thus takes complete financial risk that the disease management programmes will contribute to reduced health care expenditures.

Other pricing methods used by regulators and payers

Less commonly, regulators and payers in OECD countries use other techniques to limit the prices or set the reimbursement prices of pharmaceuticals.

Passive price taking

Germany is unusual in that the reimbursement level of on-patent pharmaceutical products for which there are no therapeutic comparators is defined according to the list price proposed by the manufacturer without negotiation (*i.e.,* the social insurance scheme acts as a passive price-taker). Coverage is automatic and does not depend on any assessment of value or budget impact.

Profit control as an indirect price control

The United Kingdom uses what amounts to indirect price control by limiting pharmaceutical companies' profits accruing from their operations on UK territory through its 50-year old Pharmaceutical Price Regulation Scheme (PPRS) (see Box 3.7). The dual objectives of preventing any abuse of monopoly position and containing costs in the National Health Service led UK authorities to sign an agreement capping the pharmaceutical industry profits in exchange for a flexible framework for price setting. Manufacturers are free to set the price at market entry. Further increases are limited by the PPRS. If a company's rate of profit exceeds the authorised level, it must reduce the general price level of its products in a manner designed to pay back excessive returns to the NHS, but it remains free to decide on which products will see price reductions as well as to increase prices of other products.

Box 3.7. **The British Pharmaceutical Price Regulation Scheme**

The Pharmaceutical Price Regulation Scheme (PPRS) was implemented in 1957 in the United Kingdom, with the objective of ensuring value for money for the NHS, while at the same time providing the industry with incentives to invest in new and improved medicines.

The scheme has been changing quite considerably over the years (OFT, 2007). Currently the allowable profit is set at 21% return on capital employed and 6% return on sales to the NHS. Maximum margins are allowed before excess profits triggers a rebate to the Treasury or underperformance (minimum margin) may trigger permission to increase prices. The Department of Health (DoH) assesses the company's profit yearly, but only companies with branded sales in excess of GBP 25 million annually are required to regularly submit financial returns (OFT, 2007). The PPRS provides positive incentives for pharmaceutical firms by allowing R&D costs to comprise 20% of UK National Health Services (NHS) turnover, which is higher than worldwide average (Mossialos *et al.*, 2004). Consequently, the PPRS encourages innovation and R&D pharmaceutical investment within the United Kingdom.

The system is positively regarded by many pharmaceutical companies, especially in comparison to alternatives in place in other countries. This is mainly due to the stable and favourable business climate created through a relationship between the DoH and the industry which allows for negotiations of profit margins and other regulatory measures (Mossialos *et al.*, 2004). Furthermore, drugs can be freely launched and priced, after market approval, without any lengthy price negotiations. For the DoH the system is favourable due to the low administrative costs of the PPRS as a team of ten people members operates the scheme with use of minimum resources.

These favourable conditions, however, have been lessened due to frequent price cuts agreed upon during the PPRS negotiations. The companies, however, have some flexibility in deciding which products prices will be cut, known as price modulation. Nonetheless, these cuts have not led to a decline of the rising pharmaceutical expenditure rates, as the increase in pharmaceutical expenditure is attributed to an increased number of prescriptions per head of the population rather than increases in the price of prescriptions (OFT, 2007). This system of price cuts is argued to become part of a strategic game, between the DoH and the pharmaceutical industry (*ibid.*).

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Cost-plus pricing

In some OECD countries, the reimbursement pricing scheme takes production costs into account to set or negotiate prices for certain pharmaceuticals – usually generic versions of original products. This is, for example, the approach used in the Slovak Republic to limit the ex-manufacturer price charged by producers based domestically (exclusively generic manufacturers), and also the approach adopted by Poland. Spain uses a cost-plus approach in which the ex-factory price of a listed drug is determined according to production costs, plus a standard rate of return set at 10 to 12%.

Price-volume agreements

Given the low marginal cost of production, pharmaceutical firms may be willing to negotiate based on the total value of sales, rather than on a per-unit price basis. This prospectively offers lower-income countries a way to provide some access to medicines without potentially compromising the value of manufacturers' sales elsewhere, but there is a need to make sure that products are not diverted to other markets.

Purchasers, public or private, may conclude price-volume agreements at a product level in order to obtain price reductions when volume increases. The French CEPS (see Box 3.8) sometimes enters into so-called volume-price agreements for products with high sales potential, but the "price reduction" takes the form of rebates, paid at the end of the year by the manufacturer with no consequences for the listed price.

Procurement and tendering

Procurement and tendering approaches to pharmaceutical purchasing are used in many countries for purchasing hospital products and by some coverage schemes. However, the case studies undertaken in the course of work on the OECD pharmaceutical pricing policy project revealed that there is little systematic information, even within countries among stakeholders and experts, on the procurement of pharmaceuticals by hospitals for inpatient and outpatient use. This stands to be an important future issue, given growing developments in the area of oncology and other high-cost areas.

In many countries (*e.g.,* Switzerland, Mexico, the Slovak Republic, Canada), hospitals have a certain degree of freedom to devise their own formularies. They may undertake purchasing on an individual basis or collectively, as a way of pooling purchasing power. They may negotiate with manufacturers or wholesalers, or undertake calls for tender for multiple-source products. Manufacturers often provide very heavy discounts, resulting in nearly cost-free medicines, in some cases, as a device intended to induce sales in the retail market (to the extent physicians will decline to switch a patient to another product upon discharge).

Coverage schemes which act as pharmaceutical purchasers, rather than agents that reimburse patients or pharmacies for the products purchased by patients, also use so-called procurement policies, defining the way in which they purchase pharmaceuticals. For example, the US Veterans Administration engages in bulk pharmaceutical contracting with manufacturers in order to standardise benefits across VA regions and to secure price reductions from bulk purchasing. Competitive bidding among brand-name drugs within drug classes is said to be the most contentious, but most important, aspect of VA contracting (Sales *et al*. 2005). Mexico's social security schemes also achieve significant discounts from the retail prices charged in Mexico by using tendering processes to stock the pharmacies and hospitals serving those covered by the schemes (Moïse and Docteur, 2007a).

Box 3.8. **The French State – Industry agreements**

In France, the Economic Committee for Health Products (hereafter CEPS) signs every five years a national "framework agreement" with the pharmaceutical industry association (known as LEEM). This agreement includes commitments from both parties on different shared objectives, such as the exchange of information, a national target for pharmaceutical expenditures (see below), the promotion of a rational use of drugs, and increased use of generic and OTC products. The agreement also states that very innovative products will be priced by the manufacturer, the CEPS retaining the right to oppose the price set if it is not consistent with the price in four EU countries (the United Kingdom, Germany, Italy and Spain) or for public health motives. The CEPS may ask pharmaceutical companies to conduct post-marketing studies to observe how new medicines are used in practice. In case of high risk of misuse and overuse, companies must commit themselves to promote the appropriate use of their products and to be accountable for their promotional activities to the CEPS (CEPS and LEEM, 2003).

The CEPS further signs individual annual agreements with almost all of the companies operating in France. These agreements include information on products' prices and may include provisions linking the price of a specific product to volumes sold, to the "real conditions of use" (for instance, if the average dose prescribed is not compliant with approved conditions for use, the manufacturer will have to pay rebates) or to the average daily cost of treatment (when a drug exists in different dosages and/or formulation, an expected average daily cost should not be exceeded).Individual agreements also include a targeted turnover for current year, beyond which the company will have to pay rebates (CEPS, 2006).

The Parliament annually sets a growth target for manufacturers' revenues drawn from the sales of out-patient reimbursed drugs, beyond which companies will be asked to pay rebates. Then, the Economic Committee for Health Products – the French pricing authority – further defines, in consultation with the industry, how this global target can be differentiated by therapeutic class. A therapeutic class affected by growing clinical needs or by the entry of new products will be allowed a greater targeted growth rate than a therapeutic class in which a leading product will lose its patent or a class whose consumption is deemed too high by health authorities.

For instance, in 2005, the growth target for pharmaceutical industry's revenues in France was +1%. Growth targets for sales of vasodilatators and expectorants were respectively of –15% and –12%, while classes of HIV and hepatitis antivirals and the class containing new drugs to treat rheumatoid polyarthritis and psoriasis were allowed respectively +20% and +121% growth. Since the global target was exceeded in 2005 (sales grew by almost 6%), companies paid 40% of the excess amount, according to a complex formula taking into account their sales in each therapeutic class and the kind of products they sell (innovative and orphan drugs are not "taxable" in the first months after market entry, and generics are never taxable). Overall, the 2005 rebate accounted for 2.3% of the French turnover on reimbursed outpatient pharmaceuticals (CEPS, 2006).

In cases where there is only a single source for a product, procurement policies will not fundamentally differ from policies consisting of negotiating reimbursement prices. There may be two differences: if procurement takes the form of call-for-tender, it will exclude part or all of potential competitors (manufacturers or wholesalers) from the subsidised market; if prices set for reimbursement purposes are often maximum prices – on which

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manufacturers may consent rebates to wholesalers – direct procurement will lead to a fixed price for direct sale by the manufacturer.

All components of the retail price of pharmaceuticals are subject to regulation

Pharmaceutical price regulation schemes generally focus on ex-manufacturer prices

Price regulation schemes (direct or *de facto*) generally focus on defining maximum ex-factory prices of medicines. However, there are some exceptions, such as the Mexican scheme, which addresses the maximum retail price paid by end consumers, and the Slovak scheme, which pertains to the final reimbursement price. In the case of Mexico, with strong competition at the retail level, this means that the impact of any limiting effect of the regulation on prices may fall proportionally more on retailers, than on manufacturers or distributors. In the case of the Slovak Republic, regulating the reimbursement price should be functionally equivalent to regulating the ex-manufacturer price, given that maximum wholesale and retail margins are set in law, and rebates and discounts are prohibited.

From a technical point of view, countries differ in the approach taken for pricing, ranging from linear (in which a product with double the amount of the active ingredient will cost twice as much) to flat (when the price is based on the active ingredient, irrespective of the strength used in the particular product) to regressive (in which products with stronger formulations have higher prices, but the price does not increase in proportion to the increase in strength). All these pricing methods have different implications for outcomes in terms of price levels and in the size of package, formula and strength of dosage that manufacturers will propose to offer on the market.

Regulation of distribution costs is common

Most OECD countries regulate distribution margins by different methods. Regulation of wholesale margins generally takes the form of fixed or capped mark-ups on ex-factory price. Regulation of pharmacists' payments adopts various schemes: fixed or capped mark-up on wholesale price, and/or fixed fees to remunerate pharmacists' services.

The distribution chain faces important regulatory constraints in most countries, ranging from requirements relating to product supply and out-of-hour services to limits in settlements and ownership of establishments. Arrangements for pharmaceutical distribution used within OECD countries will not be discussed here, but regulation of distribution margins is often linked to specific features of the system.

Many OECD countries regulate price increases and try to contain pharmaceutical expenditure growth

Many OECD countries regulate price increases after market entry. In countries with national insurance schemes and positive lists, opportunities for manufacturers to increase prices are very limited. In Switzerland for instance, pharmaceutical companies are required to file an application for any price increase explaining why the price should increase. The United Kingdom, which allows manufacturers to price freely at market entry, does not allow price increases in the following year. In Canada, price increases are limited to inflation. Some countries do not control price increases; this is the case in the United States and Germany.

However, Germany, like other countries has sometimes imposed freezes on price increases in order to contain pharmaceutical costs. Germany is also one of those countries in which policy makers regularly mandate across-the-board rebates to tackle deficits of the health insurance funds. In 2005, manufacturers had to consent to fixed rebates on listed price for a given period (16% in 2005). The rebates applied to products subsidised by the health insurance funds, not private insurers.

Several OECD countries have implemented policies in which manufacturers and/or distributors are required to pay rebates or claw-backs. For instance, in the Netherlands, pharmacists are required to offer discounted prices to their clients, as a policy intended to pass on a share of savings realised in purchasing medicines (PPRI, 2007f). This claw-back takes the form of a fixed percentage discount on retail prices, set by agreement between the ministry of health and welfare and the pharmacists' association.

In France, manufacturers have to pay rebates when the turnover they realise in the French market for reimbursed medicines exceeds the targeted growth rate set by the Parliament. This policy has reached a certain level of sophistication and differentiates rebates to be paid by manufacturers according to therapeutic classes and products' innovativeness, in order to meet public health objectives and to establish what is viewed as an appropriate reward for innovation (see Box 3.8).

Several EU countries have implemented policies to encourage parallel imports as a cost-saving mechanism. For instance, in Denmark, Germany and Sweden, pharmacists are required to inform patients when a less-expensive imported version of a product is available. In Germany, pharmacists are required to replace branded pharmaceuticals with parallel imports when the latter are available at a discount of 15% or more (ÖBIG, 2007). In some countries, pharmacists receive incentives to dispense parallel imports or cheaper drugs; included parallel imported ones (the Netherlands, Norway, Sweden and the United Kingdom). Finally, policies result in lower cost-sharing for patients for the purchase of drugs that were parallel imports in Denmark, the Netherlands and Sweden (Kanavos *et al.*, 2004).

The stability, consistency and predictability of regulation

The pharmaceutical industry puts a great emphasis on the need for stability and predictability of regulation scheme. In this respect, the 50-year old British Pharmaceutical Price Regulation Scheme may be considered as the most stable environment for industry since the rate of profit derived from operations in the British market is not only capped but also guaranteed to a certain extent. The profit cap is negotiated every five years between NHS authorities and the British association of pharmaceutical manufacturers.

Other OECD countries have tried to confer some stability to the pharmaceutical environment through periodic agreements setting the scene for several years. In France for instance, the committee in charge of pharmaceuticals pricing signs five-year agreements with the French association of manufacturers to define shared objectives and to establish principles for price settings and annual rebates calculation (see Box 3.8).

Ultimately, the perceived importance of consistency in application of pricing regulations may strongly depend on the degree to which outcomes of such regulation are perceived as favourable by the industry. In assessments of the reimbursement and pricing procedure made by the two associations representing pharmaceutical industry in Switzerland, representatives of Interpharma, which represents the interests of Swiss companies, described the procedure as "flexible", without indicating that this flexibility

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proved unduly problematic from an industry perspective, whereas VIPS, representing foreign companies operating in Switzerland, indicated that the unpredictability of the system was problematic in some respects (Paris and Docteur, 2007).

Other aspects of the pharmaceutical policy environment that affect the achievement of policy goals

A number of pharmaceutical policies are important in their prospective impact on the timely availability of products in the market, the diffusion of those products and the level of consumption the product will see over its life cycle. Chief among these policies are those that affect market authorisation and those that set standards for enforcement of intellectual property rights.

Intellectual property rights and enforcement

Intellectual property rights have a critical role in the pharmaceutical sector. They guarantee both a period of market exclusivity and a monopoly price through patent rights. They also determine the potential for parallel trade.

Standards and enforcement of intellectual property rights determine the length of time during which a product retains market exclusivity, thus serving as an important determinant of national pharmaceutical expenditures. They play a very influential role in manufacturers' strategic decisions.

While there is some variation in IPR rights and enforcement across the OECD, there has been some harmonisation within the European Union (see Annex 3.A1).

IPR also plays an important role in pharmaceuticals in that it defines, via patent and trademark exhaustion[30] provisions, the opportunities for parallel trade, affecting the ability of pharmaceutical firms to segment the global market through price differentiation (see Box 3.9). As far as OECD countries are concerned, parallel trade is authorised within the European economic area (EAA), *i.e.* European Union plus Iceland and Norway. A derogation on parallel imports from some EU countries was established at the time of their accession to the European Union: Portugal and Spain in 1995 and the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, the Slovak Republic and Slovenia in 2004.

Marketing authorisation policies

Marketing authorisation policies are important in the sense of the timeliness of considering applications and issuing decisions, as well as in their stringency, relative to the other marketing authorities. These two aspects of the policies are important determinants both of manufacturers' strategic decisions with respect to the national market, and of national pharmaceutical expenditures. In both cases, the relevant variable is the total length of time on the market and the period in which an original product has "market exclusivity" before being subject to competition from generic competitors.

Timeliness of market authorisation decisions varies

Figure 3.1 illustrates the average time from application for market authorisation to approval in the 1999-2003 period. It shows that Australia, Canada and Japan had longer delays than their American and European counterparts.

Box 3.9. **Intellectual property rights (IPR) exhaustion regime**

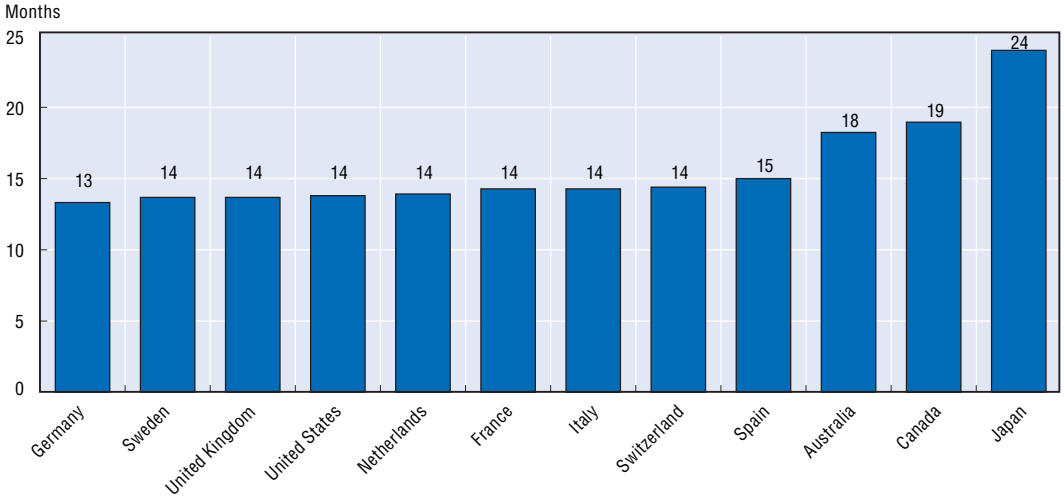
Parallel trade is regulated by general provisions pertaining to intellectual property rights (IPR), exhaustion regimes of the General Agreement on Tariff and Trade and to some limitations of the Trade-Related Aspects of Property Rights (TRIPS) agreement. An intellectual property right (*e.g.* patent or trademark) is said to "exhaust" or end when the patent's or trademark's holder has no more control on its products after the first sale. In such a case, the buyer is free to re-sale the products to anybody at any price. GATT and TRIPS agreement allow countries to define their own exhaustion regimes, unless they have signed bilateral or multilateral agreements with binding provisions on exhaustion regime.

In a regime of national exhaustion, the first sale of the patented or trademarked product by the patent or trademark holder in the country generally exhausts his patent and trademark rights in this country. Subsequently, the buyer may re-sell the product to whoever he wants. Conversely, if the first sale occurs in a foreign country, the patent or trademark holder's rights in the home country might not be exhausted and unauthorised importation of the drugs into the country may infringe upon its patent or trademark. The United States and Switzerland, for instance, have national exhaustion regimes of IPR's rights.

A regime of regional exhaustion means that patent and trademark rights end upon original/first sale within the region (for instance EU), making parallel trade possible, but are not exhausted by first sale outside this region (prohibiting parallel import from countries outside the region).

Under an international exhaustion regime, if a product patented in the country is sold anywhere in the world under either the country's patent or a foreign patent, this exhausts the patent holder's rights under the country's patent. The patent holder cannot restrict importation into the country unless he structures the initial sale in a manner to ensure that exhaustion does not happen, *e.g.* by imposing geographical restrictions on sale. For instance, Canada has a regime of international IPR's exhaustion.

Figure 3.1. **Average time from application for market authorisation to approval, 1999-2003**



Source: Adapted from Pharmaceutical Industry Competitiveness Task Force, Competitiveness and Performance Indicators 2005, indicator 26, from Association of the British Pharmaceutical Industry calculations.

Policies can be used to affect timeliness

Policy makers can take steps to ensure that new products have the potential to be launched on the market quickly by investing adequately in market authorisation reviews to ensure reviews that are both thorough and timely. A well-designed fast-track procedure can aid in moving priority medicines through quickly. In the case of European Union countries, enhanced collective activity (see Annex 3.A2) has meant that market access for some original drugs is no longer as heavily dependent on the capacity of the national authority. However, generic products, many of which are produced for national markets, continue to rely on prompt decisions regarding bioequivalence and substitutability from national market authorities.

Policy changes can increase timeliness of market authorisation decision-making. For example, in 2003, Health Canada launched the Therapeutics Access Strategy, the major focus of which was improving the performance, efficiency and timeliness of the drug review process. As of August 2006, Health Canada eliminated the backlog in pharmaceutical market authorisation decisions and has made progress in meeting internationally comparable drug review targets for pharmaceuticals. Consequently, average and median review times in Canada have declined significantly since 2003 (Health Canada, 2006).

An increased risk of compromised drug safety is a potential consequence of quicker approval times, however. Several studies using US data have examined the relationship between approval times and safety, with mixed results. Friedman *et al.* (1999) and Berndt *et al.* (2005) did not find any association between reduced approval times for Food and Drug Administration (FDA) approved drugs and subsequent withdrawals from market due to safety concerns. Contrary to these findings, a comparison of approval times and drug withdrawals between the United States and Canada found that shorter approval times in the United States were offset by more drugs being withdrawn from market for safety reasons (Rawson and Kaitin, 2003). Furthermore, Olson (2002), using the number of reported adverse events for drugs on the market as an indicator of drug safety problems,[31] showed that shorter FDA approval times were associated with increases in adverse drug reactions leading to death or hospitalisation.

Rudholm (2004) employed the same methods as Olson (2002) for Swedish data to show that shorter approval times for the Swedish Medical Products Agency were associated with more adverse drug reactions, although the effects were considered to be small; a one-year decrease in approval time was associated with an average of between 2.56 and 3.86 additional adverse events.

Responsibility for defining whether generic products can be substituted for originals

In some (but not all) countries, marketing authorisation agencies are responsible for indicating whether generic products can be considered not only bioequivalent, but also substitutable for an original product, taking into account aspects of a product that may affect the relative efficacy of the product. This is the case, for example, in Sweden (Moïse and Docteur, 2007b). Once a generic drug has received approval for marketing in Sweden it is eligible for inclusion in the List of Substitutable Products – the list of generic drugs and parallel imports that can be substituted for the original product under Sweden's generic substitution law.[32] Sweden's Medical Products Agency (MPA) decides whether or not a generic drug will be included in the list. However, the MPA can only initiate the process of

determining if the generic is substitutable after the Pharmaceutical Benefits Board – the agency responsible for determining whether or not a drug will be reimbursed under Sweden's pharmaceutical reimbursement system – has made a reimbursement decision; a process which can take between two and six months. In addition, the manufacturer of the original product can appeal a substitution decision, which automatically removes the generic from the List of Substitutable Products until the courts have resolved the issue. These processes effectively add to the period of the original product's market exclusivity.

Conclusions

This chapter has illustrated that pharmaceutical pricing and reimbursement policies are an important component of the pharmaceutical policy environment, but they are not the only tools by which policy makers affect the price, volume and mix of products used in a country. Subsequent chapters will investigate the role of pharmaceutical pricing and reimbursement policies in contributing to national performance in meeting domestic policy goals as well as external effects.

Notes

1. In Switzerland, such coverage is forbidden by law (Paris and Docteur, 2007).
2. For example, private health insurance finances 18% of pharmaceutical expenditure in France, compared to 3% in both Portugal and Switzerland, even though private policies in the latter are purchased by 80% of the Swiss population (Paris and Docteur, 2007). In Australia, private insurance finances 1% of pharmaceutical expenditure.
3. In the United States, most people have private health insurance coverage that includes coverage for prescription medicines, including medicines furnished in hospital. About 15% (elderly and disabled persons) have coverage through the Medicare social insurance programme, which provides coverage through competing private insurance plans. About 20% (poor) have coverage through the Medicaid social assistance program, which differs by state.
4. In Canada, hospital drugs are covered through the universal Medicare program. Most Canadians have private health insurance, subsidised or organised by their employers, that provides coverage for prescription medicines used outside the hospital. Provinces and territories provide such coverage to seniors, social assistance recipients, and persons with special needs. Federal programmes exist for indigenous peoples and federal government employees.
5. Private health insurance finances about 41% of pharmaceutical expenditures in the United States and about 29% in Canada. In Germany on the other hand, 6% of pharmaceutical expenditures are financed through private health insurance. Mexico is notable in that private health insurance finances only 1% of pharmaceuticals, despite the fact private sources account for almost 90% of pharmaceutical expenditure (Moïse and Docteur, 2007a).
6. The VHA is owned, operated and managed by the US Veterans Administration. This contrasts with the Medicare social insurance and Medicaid social assistance schemes, which reimburse private providers for providing publicly financed medical services.
7. PBMs work with third-party payers (private and some public insurers) to manage drug benefit plans and develop drug management tools. In addition to offering basic services such as claims processing, PBMs also help define which drugs will be paid for, negotiate prices and rebates agreements with manufacturers on behalf of third party payers, and help determine the amounts that pharmacies receive and co-payments consumers pay when prescriptions are filled. Core PBM services include management of formularies, rebate agreements, pharmacy networks, mail-order pharmacy service, claims adjudication, generic substitution, and disease management programmes. PBMs manage pharmacy benefits for over 50% of the total US population with prescription drug coverage, and process prescription drug claims for more than two-thirds of all prescriptions written in the United States (The Health Strategies Consultancy LLC, 2005).
8. Until 1997, the US VHA operated on a decentralised basis, with weaker negotiating powers and "vast" price differences for certain pharmaceutical products purchased by different VA facilities (IOM, 2000).

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9. For example, Switzerland and the Slovak Republic do not exclude any effective medicines that are eligible for coverage (Paris and Docteur, 2007; Kaló *et al*., 2008).
10. This is the case for many of Canada's provincial coverage plans, for example, which exclude products not found cost-effective at the price proposed by the manufacturer.
11. These payments generally take the form of flat allowances, (formulary or access payment) with high variations across drugs and according to restrictiveness of the formulary (higher allowances for being on more restrictive formularies): they vary from 0 up to 27% of total sales (FTC, 2005). Manufacturers' payments may be progressive and linked to the market share, *i.e.* the market share of the drug in its therapeutic class (PBM's prescriptions compared with the national market).
12. The notable exceptions were drugs categorised by the FDA as priority review drugs, meaning that they were believed to offer significant improvement over existing drugs in terms of treatment, diagnosis or prevention of a disease. These were considered on a case by case basis (IOM, 2000). In practice, only new drugs for the treatment of HIV/AIDS were listed before the end of the one-year wait time.
13. The sample included all drugs appraised by the UK National Institute for Clinical Excellence between 1999 and 2005 that were authorised for marketing in the United States. Within each health plan, the authors examined the lowest-premium option offered that used a three-tier formulary, considering that this best represented the coverage furnished to beneficiaries of the Medicare drug coverage scheme. Drugs not included in formularies but whose costs were included in Medicare physicians' payment scheme were considered as covered by the benefit.
14. Most often, there are exceptions in cases where a physician decides that a switch would be problematic for clinical reasons.
15. Medicare pays 75% of initial drug costs up to USD 2 250 after a USD 250 deductible, but then pays nothing until drug expenses reach USD 5 100, after which Medicare pays 95% of all costs.
16. In a review of the literature, Lexchin and Grootendoorst (2004) show that increases in out-of-pocket payments decrease prescription drug use, with potential negative health effects for the poor and chronically ill.
17. Between these extremes are drugs needed to maintain health (such as treatments for chronic conditions) with lower cost-sharing than drugs that boost workplace productivity (*e.g.*, allergy medicines).
18. Switzerland exercises "price surveillance", on the same grounds. All goods and services produced by cartels or firms in monopolistic position (private or public), as well as goods and services subject to government regulation, are monitored by the Price Council. The Council is charged with taking action to hinder excessive prices or excessive price increases and making policy recommendations on regulated sectors. It issues annual reports geared at informing consumers about price levels (Paris and Docteur, 2007).
19. Breakthrough products cannot exceed the median price in seven comparator countries (France, Germany, Italy, Sweden, Switzerland, the United States and the United Kingdom). New formulations of existing products must have a price that bears a reasonable relationship to what is already on the market in Canada. Products that offer moderate, little or no therapeutic advantage over existing products are limited to the price of the comparable products on the market. Price increases are limited by growth in the consumer price index.
20. For example, the requirement that plans must list "all or substantially all" of the drugs in the antidepressant, antipsychotic, anticonvulsant, anticancer, immunosuppressant and HIV/AIDS categories has generated controversy (McAdams and Schwarz, 2006). Participating plans argue that offering a limited formulary provides them with bargaining leverage to negotiate price reductions with manufacturers. When many drugs within the same class are listed, their bargaining leverage declines.
21. Things may change with the introduction of cost-effectiveness assessment and maximum reimbursement prices in the 2007 reform (Paris and Docteur, 2008).
22. US purchasers eligible to use the Federal Supply Schedule can and do negotiate prices that are lower than what appear on the Federal Supply Schedule, however, using techniques such as blanket purchase agreements (BPAs), under which the purchaser agrees to purchase only from a particular supplier.
23. The Transparency Commission is composed of clinical experts and is part of the High Authority on Health.

24. The premium generally amounts to 10 to 20% of the price of therapeutic comparators, when there are any, but premiums granted to breakthrough drugs are not limited in this respect. Higher premia may be awarded for drugs with limited market potential, such as orphan drugs (Hunkeler, 2006).
25. See Réglement intérieur de la Commission de Transparence du 22 June 2005.
26. By contrast, no minimum discount is set for non-generic drugs with no therapeutic improvement over existing comparators.
27. Swiss policy makers intend to reform this system so that, in the future, regulation of generic prices will occur only at market entry.
28. Cost-effectiveness analysis is the most commonly used form of pharmaco-economic assessment. Other techniques, such as cost-benefit analysis or cost-utility analysis, might be used under certain circumstances (Dickson *et al.*, 2003).
29. Information on the use of pharmaco-economics for most OECD countries is also available from the International Society for Pharmacoeconomics and Outcomes Research (*www.ispor.org/peguidelines/index.asp*).
30. The term "exhaustion of patent or trademark rights" refers to a provision of intellectual property law that defines the conditions under which patent or trademark owners' rights expire. For example, a regime of regional trademark exhaustion means that the trademark owner forfeits control over the re-sale of its products within a given region once he has sold them. This provision allows parallel trade in Europe.
31. Using adverse drug reactions (ADRs), as opposed to drug withdrawals, lowers significantly the statistical variation because there are significantly more reported adverse events – 16 148 ADRs requiring hospitalisation and 5 243 leading to death in the Olson study – than there are drug withdrawals – 22 in the Berndt *et al.* study.
32. Sweden's generic substitution law stipulates that a pharmacy is obliged to substitute the cheapest generic drug available for the prescribed product.

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ANNEX 3.A1

Pharmaceuticals and Intellectual Property Rights in the European Union

Patents

There is no single, centrally enforceable EU-wide patent. A European patent refers to patents granted by the European Patent Office (EPO). Under the European Patent Convention (EPC) treaty, the EPO provides a single, harmonised procedure for granting patents in the European Union. Applications can be made in one of the official languages of an EPC contracting state to the EPO's offices in Munich, but processing of the patent is done in one of the three official languages of the EPO (English, French and German).The applicant designates which EPC countries it wishes to file for patent protection. A favourable decision by the EPO grants a patent in each of the designated states. However, the determination of ownership, validity and infringement are subject to respective national laws. Furthermore, while a national court may invalidate a patent in one country, the European patent remains valid in the other designated countries. A European patent is, in effect, non-unitary across all EU countries and independent in each.

The EPC does impose some limits on its signatories. The basis for determination of validity of a patent by national law is limited to a few reasons, but the standard on which the determination is made is that of national law. The convention also requires all jurisdictions to give a European patent a term of 20 years from the filing date, either the date of filing with the EPO for a European patent or for an international application under the Patent Cooperation Treaty.[1]

Supplementary Protection Certificate

A holder of a pharmaceutical patent still in force in the European Economic Area can apply for a supplementary protection certificate (SPC), an extension of rights for said patent. An SPC is a unique, patent-like IPR that comes into force after the patent expires, for a maximum period of five years. There is no single European SPC; applications are made on a country-by-country basis. The term of the SPC depends on the time between patent application and granting of marketing authorisation.[2] An SPC is a tool governments use to compensate manufacturers for the lengthy period of time it sometimes takes for granting marketing authorisation, however it does delay the entry of generic drugs onto the market.

Bolar provision

The so-called Bolar provision[3] of the Hatch-Waxman Act, enacted by the US Congress in 1984, granted drug manufacturers the right to "make, use, offer to sell, or sell … a patented invention" for uses related to submission of information under Federal law regulating drugs.[4] The use by generic manufacturers of pharmaceuticals still under patent protection for the purpose of submitting information to regulatory agencies for obtaining marketing authorisation has, until recently, been governed in Europe by each member state's national law.

The European Commission (EC) concluded that a provision for generic manufacturers similar to the Hatch-Waxman Act should be permitted for all member states. In 2004, the EC revised Directive 2001/83/EC on the Community code relating to medicinal products for human use, to include the following amendment:

> "Conducting the necessary studies and trials … and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."[5]

Member states had 18 months from April 2004 to implement the Directive into their national laws.

The amendment clearly allows the use of on-patent medicines by users other than the holder of the patent for "conducting the necessary studies and trials" for "consequential practical requirements", but left uncertain the legality of other actions, such as supplying or exporting on-patent medicines to generic manufacturers. By using the ambiguous wording "consequential practical requirements", the EC has apparently left the interpretation to national courts (Ashurst, 2005).

Data exclusivity

Complementary to Bolar provisions are legislation that protect the clinical trial data that original product manufacturers are required to submit in their applications to regulatory agencies for marketing authorisation. The original product manufacturers argue that such protection is necessary; otherwise they are at an unfair disadvantage since generic producers can use these rather expensive data at no cost. The generic producers reply that not having access to these data act as a restriction on producing generic products, thereby limiting the availability of cheaper alternative pharmaceuticals.

One of the European Commission's amendments to Directive 2001/83/EC revised EU aspects of data protection. It provided that test data supplied by the manufacturer of an original product, as required by marketing authorisation legislations, are protected for a period of eight years following the first marketing approval in a member state. This period of protection is followed by a two-year period during which generic versions of the original product may not be launched on the market of any member state, although marketing authorisation can be granted during this period. Finally, the original producer can obtain an additional one-year period of market exclusivity beyond the two-year period if, during the eight-year data exclusivity period, the producer obtains marketing authorisation for additional indications which bring a substantial clinical benefit compared with existing therapies. In effect, this new regulation creates the so-called "8 + 2 + 1" formula which guarantees the original producer a period of market exclusivity equivalent to ten years, with the possibility of extending that exclusivity to 11 years (Sanjuan, 2006).

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Member states had until 30 October 2005 to implement the new Directive. In the face of opposition to the new law from prospective member states who were not able to vote on it, these states can request derogation. The law came into full effect in November 2005, meaning that the first generic drugs to be affected by this law will not come on to the market in the European Union until 2015.

Notes

1. The Patent Cooperation Treaty provides a unified procedure for filing patent applications.
2. For the purpose of granting an SPC, marketing authorisations granted in Switzerland are also considered since Liechtenstein automatically accepts authorisations granted in Switzerland.
3. In 1984, Roche Products Inc. sued Bolar Pharmaceuticals Corp. Inc. for violating its patent for flurazepam-HCI. Bolar had obtained some of the active ingredient from a foreign manufacturer and had started the bio-equivalency studies necessary for obtaining marketing approval for a generic version of Roche's patented product, prior to the patent's expiration. A court of appeal overturned a lower court's decision, saying that Bolar had violated Roche's patent. This judgment meant that generic manufacturers could not conduct bio-equivalency studies for obtaining marketing authorisation until the patent of the original product expired.
4. Drug Price Competition and Patent Term Restoration Act [Public Law 89-417, 35 USC. paragraph 271(e)(1)].
5. Directive 2004/27/EC, Article 10(6), 31 March 2004.

ANNEX 3.A2

Marketing Authorisation in the European Economic Area

Authorisation for marketing a medicine within the European Economic Area (EEA)* is granted through the competent authority of any EEA country – valid within the particular country – or through one of the recognised procedures for obtaining authorisation in more than one EEA country. The holder of a marketing authorisation valid within the EEA must have an established presence within the EEA.

The London based **European Medicines Agency (EMEA)** was established in 1995 to coordinate the evaluation and European market authorisation for both human and animal medicinal products. The EMEA operates under the aegis of the European Commission's DG Enterprise, to which it forwards its opinions for approval for final marketing authorisation in all member states.

There exist three procedures for obtaining marketing authorisation in more than one EEA country: the centralised procedure, the mutual recognition procedure, and the decentralised procedure.

The **Centralised Procedure (CP)** is used to obtain a marketing authorisation valid in all EEA countries. The procedure is mandatory for, but not limited to, biotechnology, AIDS, cancer, diabetes, neurodegenerative disorder medicines as well as orphan drugs. Applications submitted to the EMEA by manufacturers are evaluated by the Committee for Proprietary Medical Products (CPMP) – comprised of two experts nominated by each member state. The CPMP subcontracts the assessment to two rapporteurs selected from a pool of 3 500 drug evaluation specialists in national regulatory agencies. The CPMP has 210 days from receipt of the dossier to provide a recommendation to the European Commission for final approval; however the clock can be stopped when rapporteurs request additional information from the applicant. Total accumulated time during which the clock is stopped generally should not exceed six months.

The Decentralised and Mutual Recognition procedures are based on the principle of recognition by other member states of a first approval granted by the authorities of one member state.

Through the **Mutual Recognition Procedure (MRP)**, manufacturers can apply for marketing authorisations in designated "Concerned Member States" (CMS) by validating the marketing authorisation *previously granted in another member state* – the "Reference Member State" (RMS). The competent authority in each CMS has 90 days in which to decide

* The EEA is composed of the 27 European Union member countries plus Norway, Iceland and Liechtenstein.

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whether it agrees with the RMS' marketing approval decision. In case of disagreement, the RMS sends the concerns to the CPMP; if a consensus is not reached after a further 60 days, the procedure moves into arbitration by the CPMP.

The **Decentralised Procedure (DP)**, introduced in 2005, increases the EMEA's co-ordinating role to facilitate the harmonisation of marketing approvals. Manufacturers of new products *not yet marketed in one of the EEA member states* (and not obliged to use the CP), as well as generic versions of original products authorised through the CP, designate a Reference Member State to undertake the assessment. Identical dossiers are submitted to Concerned Member States where approval is also sought. The RMS steers the approval process, seeking agreement on elements that must be harmonised in CMSs and provides a decision. A maximum of 210 days is granted (including a maximum of three months for clock stops to allow for applicants to respond to objections raised during evaluation) to the RMS and the CMSs to come to an agreement on the full dossier. If agreement is not forthcoming then an additional 90 days are granted for arbitration, with a final decision by the CPMP. The recommendation is then forwarded to the European Commission for final decision on granting or refusing a marketing authorisation valid in all Concerned Member States.

The main difference between the MRP and the DP is that the latter is sought in cases where no marketing authorisation has been granted in an EEA country. Under the MRP and DP, manufacturers have greater control over the choice of RMS than with the centralised procedure.

A manufacturer can apply for a **national marketing authorisation** for products not obliged to go through the centralised procedure, if it intends to market a pharmaceutical in only one EEA country, or as a first step in the Mutual Recognition Procedure. Recent legislation to increase transparency requires that national regulatory bodies make marketing authorisations available "without delay" and publicly release clinical documentation, assessment reports and reports on the reasons that underlie the decision. Generic manufacturers often seek approval through national procedures for two reasons: 1) expiry dates of patents and supplementary protection certificates differ from one country to another, and 2) original products may have different forms, strengths, and labelling across countries, necessitating different studies to prove bio-equivalence. Since 2005, however, generic manufacturers have the option of going through the centralised procedure in cases where the original product was approved through the centralised procedure.

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Chapter 4

The Impact of Pharmaceutical Pricing Policies on Performance in Meeting Health Policy Goals

This chapter reviews OECD countries' efforts to achieve prompt access to, and appropriate use of, effective medicines, to control pharmaceutical expenditure and to increase value for money in public pharmaceutical expenditures. It begins with an assessment of the role of pharmaceutical pricing and reimbursement policies in promoting public health. Analysis of the impact of pricing and reimbursement policies on pharmaceutical price levels follows. In the subsequent section, the means by which these policies are used to contain costs is examined. The final section looks at how successful pharmaceutical pricing and reimbursement policies are in getting good value for money in pharmaceutical spending

Introduction

As is true in other areas of health policy, pharmaceutical policy decisions may well require trade-offs across competing policy objectives. The primary reason why policy makers intervene in pharmaceutical markets is, of course, to promote public health by fostering prompt access to effective medical treatments. And as elsewhere, payers are increasingly concerned with being able to demonstrate that they attain good value for money in their expenditures in pharmaceuticals.

Subsidisation of individuals' pharmaceutical consumption limits the likelihood of access being threatened on affordability grounds. But public subsidisation of individuals' pharmaceutical consumption often creates pressure to contain costs. Policy makers respond in a number of different ways that attempt to control both price and volume, but these force trade-offs with other policy goals.

Promoting public health

Pharmaceuticals play an important role in the prevention and treatment of disease. Innovative medicines are one of the key factors in medical advances that have helped populations worldwide to live longer and healthier lives. Pharmaceutical breakthroughs in the past decade have been responsible for undisputed advances in preventing and treating diseases, such as AIDS, cervical cancer and influenza. Innovations with broader, but less dramatic public health impact, such as new forms of asthma medicines, have also made it possible for patients to be treated with greater convenience and comfort.

Recognising the central role of pharmaceuticals in the practice of medicine today, policymakers in all OECD countries have intervened significantly in pharmaceutical markets in their efforts to foster prompt access to effective medical treatments. Good access to medicines depends on a number of conditions, primarily availability and affordability. At least in the short term, policies to ensure availability and promote affordable access may most readily appear to be at odds with cost-containment objectives. However, as discussed below, certain pharmaceutical pricing and reimbursement policies aid in meeting both objectives.

Ensuring prompt access to effective medical treatments

Below we identify and assess various pharmaceutical pricing and reimbursement policies that impact on access to effective medical treatments.

Pricing and reimbursement policies explain only a small part of differentials in drug availability in OECD countries

Availability of medicines on the market depends on several factors discussed earlier in this report, including manufacturers' launch decisions and factors pertaining to marketing approval. The most obvious way pricing and reimbursement policies affect availability is in

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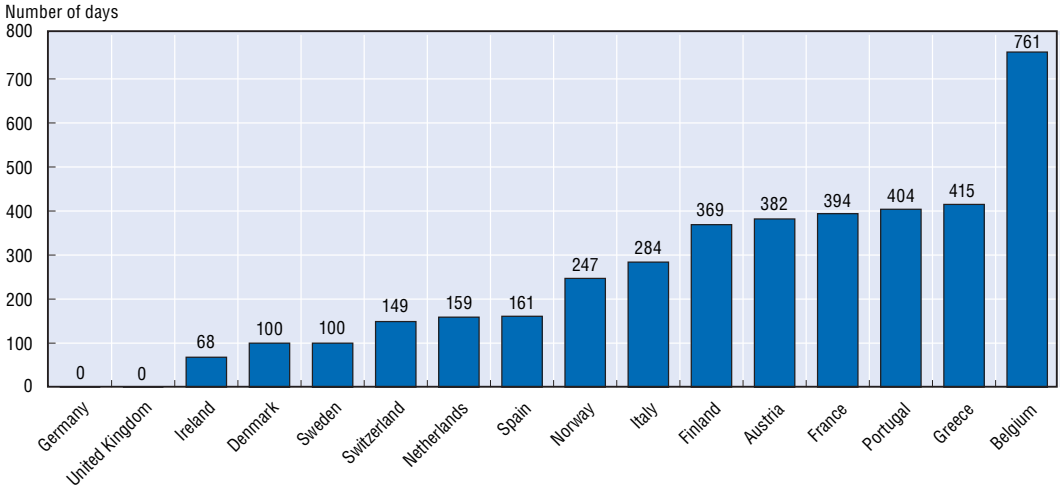
the delays in issuing pricing and reimbursement decisions; another way is via the potential influence on manufacturers' launch strategies.

Figure 4.1 illustrates the variation across several European countries in the average time from a manufacturer's pricing and/or reimbursement application to decision for drugs approved for marketing between 1997 and 2001. These data show considerable variation, with the average delay in Belgium being particularly long – almost twice as long as the country with the second longest delays, Greece. At the other extreme, reimbursement and pricing delays do not exist in Germany and the United Kingdom in which drugs are reimbursed as soon as they are approved, unless or until added to the negative list. More recent data suggest that some countries (notably Austria, Belgium and Finland) have made substantial progress in reducing these delays – perhaps in response to the EU Transparency Directive[1] – although delays were noted to have increased in most countries (PICTF, 2006).

Figure 4.1. **Average number of days from pricing and reimbursement application to decision, 1997-2001**



Note: The data pertain to 78 pharmaceutical products granted marketing approval – between 1 January 1997 and 30 June 2001 – through the European Commission's centralised or mutual recognition procedures. The data were derived from a questionnaire sent to the holders of marketing authorisations for each of these products in each of 14 EU member states (excluding Luxembourg) plus Norway and Switzerland. The total delay calculated for each drug includes three types (where relevant): 1. Pricing delay – the elapsed time from the date the pricing application was made to the date price approval was granted; 2. Reimbursement delay – the elapsed time from the date the reimbursement application was made to the date the company "was first informed about the reimbursement decision"; 3. Publication delay – (only in countries for which publication of a decision in an official journal is a prerequisite for reimbursement) the elapsed time from the date the company was notified of the reimbursement decision to the date the authorities published the decision.

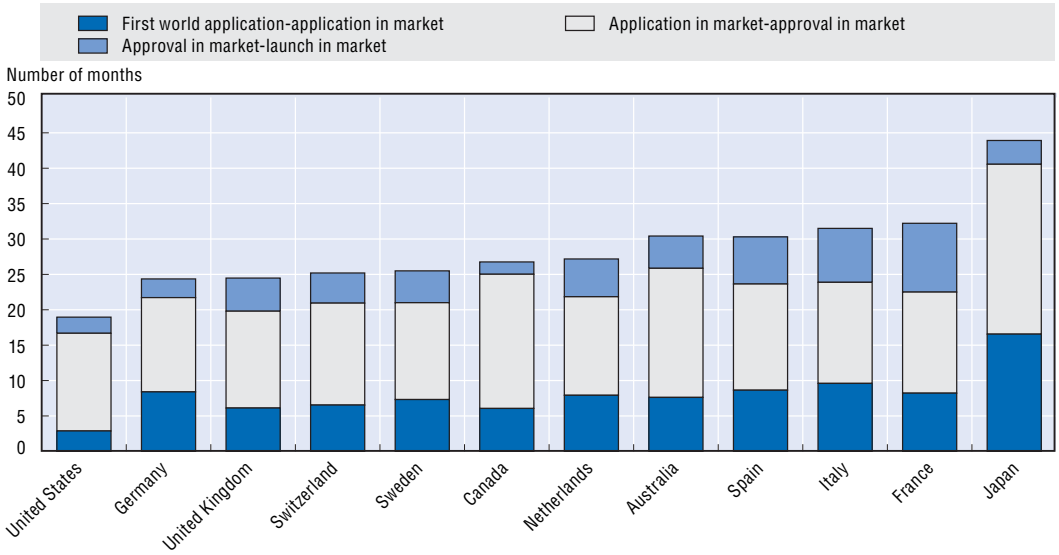
Source: Cambridge Pharma Consulting (2002).

Though firms may launch new products immediately after obtaining approval from the relevant marketing authority, they generally wait for reimbursement and pricing decisions in countries with national coverage schemes using positive lists (*i.e.*, most European countries). In the United Kingdom[2] and Germany, for which the default status of new prescription medicines is coverage, any delay between market authorisation and the launch of new products is not due to pricing or reimbursement decisions. The situation in the United States and Canada is different in that manufacturers may launch their products just after market approval but without any guarantee that they will be subsidised by health

insurance plans. In Canada, private insurers generally cover all marketed drugs (except in Quebec), while public purchasers establish positive lists, with variable and significant delays associated with reimbursement decisions (ranging from 300 to 600 days). In the United States, private and public plans use more or less restrictive formularies, but no listing time is reported.

A 2006 study (PICTF, 2006) looked at delays between first worldwide launch and availability in twelve OECD countries, for the set of new products launched between 1999 and 2003 (Figure 4.2). New products were available most quickly in the United States, with an average 19-month lag. The European countries had lags ranging from 24 to 32 months, with Germany and the United Kingdom having the shortest delays, but only marginally shorter than Switzerland and Sweden. Japan came in with the longest lag, an average of 44 months.

Figure 4.2. **Average number of months between first world application for marketing authorisation and launch in country, 1999-2003**



Source: Pharmaceutical Industry and Competitiveness Task Force, Competitiveness and Performance Indicators 2005, from Association of the British Pharmaceutical Industry calculations

The elapsed time between the first application for marketing authorisation in the world and the launch of the product in a particular market can be divided into three distinct periods: 1) time from first world application to application in market, 2) time from application in market to approval in market, and 3) time from approval in market to launch in market. The third period roughly corresponds with pricing and reimbursement delays in many countries, although there are further launch delays even in those countries (*i.e.,* Germany and the United Kingdom) where pricing and reimbursement considerations should not be a factor. Figure 4.2 shows that delays associated with marketing authorisation explain most of the total delay, accounting for an average of half the total time elapsed between first world application and launch. Canada and the United States had the shortest average delays in launch following market approval. Pricing and reimbursement policies can be designed to minimise delays so as to reduce the potential for inducing delays in product launch. Sweden, for example, took steps to minimise the

impact of its stricter reimbursement assessment process, which took effect in 2002 (Moïse and Docteur, 2007b). Recognising that formal cost-effectiveness requirements can delay market access, the agency responsible for pharmaceutical pricing in Sweden allows a manufacturer to make an application for reimbursement as much as 180 days in advance of expected receipt of market authorisation. It is thus feasible for a product to be placed on the positive list at the same time as the granting of marketing authorisation in Sweden. Similarly, France allows those who have applied to the EMEA for centralised marketing authorisation to file an application to French reimbursement and pricing authorities before market approval has been granted. Moreover, the French Economic Committee on Health Products has committed itself to examine first and with shorter delays, those drugs that have been classified as innovative by the Transparency Commission.[3]

Beyond delays imposed by listing procedures, pricing and reimbursement policies have been found to influence the availability of drugs by affecting manufacturers' launch strategies. Several studies have investigated this issue, examining whether the presence of price regulations in a given country has an effect on launch probability and delay. They used multivariate models to control for the impact of other variables on launch strategies. Danzon *et al.* (2005) found that countries with strict price regulation (as assessed by the authors) had a lower probability of launch, even when market conditions (expected price and volume) are controlled for. Lanjouw (2005)[4] found that extensive price regulation had a negative impact on the probability of launch within two years. The negative impact of moderate regulation was found to depend on the country's income level, however, with no reduction in the probability of entry when GDP per capita is over USD 12 088. On the other hand, Kyle (2007) found price regulation to have a substantial impact, reducing the probability of launch by 25% in countries with price regulation.

The studies concur that the existence of price regulation and scope or stringency can delay market launches, even when controlling for other factors, although the researchers found differences in the extent of the impact. Pricing and reimbursement delays were found to have a significant impact, but were not the most important determinant. As discussed in Chapter 1 of this report, many factors other than price regulation serve as key determinants of launch timing.

If price regulations limit pharmaceutical prices to an amount below the manufacturer's reservation price (the price beneath which it will not agree to sell the product), it may choose not to launch the product in the market. In addition, decisions not to reimburse medicines – to not add them to a positive list or to place them on a negative list – are very likely to affect availability in the country; manufacturers may choose not to launch the product in the market because low expected sales may be insufficient to offset market entry costs. Negative reimbursement decisions can also reduce sales by reducing effective demand; physicians are less likely to prescribe medicines – not listed on a formulary – in coverage schemes where they face incentives to prescribe medicines on a formulary or preferred list and patients may be less willing to consume a medicine for which the effective price as increased in comparison with covered medicines that are comparable.

Policies can improve access to medicines not available on the market

Even if best practices to ensure availability of medicines are followed, variability in the timing and availability of medicines across markets will persist. However, this does not in and of itself necessarily indicate that access to those medicines is compromised. OECD

countries often have policies to foster access to medicines not available on the market, which help to ensure that patients can get exceptional access when needed. For example, in Switzerland, doctors and pharmacists may obtain authorisation to treat a specific patient by importing pharmaceuticals which are not yet, or no longer, approved in the country (Paris and Docteur, 2007). Canada has a similar programme, although eligibility is limited to those with a serious or life-threatening condition (Paris and Docteur, 2006). These types of policies minimise the impact of delays in terms of their impact on access.

Pharmaceutical coverage affects the affordability of expensive new medicines

As was described in the previous chapter, comprehensive pharmaceutical coverage is the norm in almost all OECD countries. Cost-sharing levels vary, but patients are generally responsible for paying at least a portion of their medicines' costs, even if general safeguards are in place so that these costs are not unduly burdensome. Nevertheless, in some cases access may be hindered for patients with costly or chronic conditions in countries where some patients face relatively high out-of-pocket costs for medicines. For example, cost-sharing levels in some Canadian provinces are in some cases high enough to have impaired use of needed medicines (Paris and Docteur, 2006). Knaul *et al.* (2006) showed that pharmaceutical expenditure is most onerous for the poorest households in Mexico; among households that had spent at least 30% of their disposable income on health in 2000, spending on pharmaceuticals accounted for half of their expenditure on health.

Despite some limitations, policies can be used to limit the risk of affordability problems. As described in Chapter 3, many OECD countries make special coverage provisions for those in need, including exemptions and caps on out-of-pocket spending, and, accordingly, relatively few patients in OECD countries are unable to obtain needed medicines simply because they cannot afford them. For example, Sweden uses a graduated cost-sharing mechanism whereby the co-payment diminishes as out-of-pocket payments increase over the course of a year. Total yearly outlays for patients are capped at SEK 1 800 (Moïse and Docteur, 2007b).

Of course, patients can face significant affordability problems, particularly in the case of payers that decide not to subsidise or reimburse certain very high-priced products that are found not to be affordable, from a budgetary perspective, or cost-effective at the offered price. These exceptional situations provide the most clear-cut examples of the trade-off between the policy goals of cost containment and access.

Very expensive drugs sold mainly in hospitals are a case in point. Under some circumstances, a drug may be available and listed for reimbursement but not purchased by hospitals, either because the budget is not sufficient or because the payment scheme does not provide the right incentives. Typically, payment per case does not provide incentives to furnish exceptionally expensive treatments to patients in a given diagnostic-related group (DRG – a unit for payment in the remuneration system for hospitals based on diagnosis and services rendered), unless specific funding is made available, through earmarked annual budgets or through drug reimbursement on top of DRG payments.

The problems of uptake of expensive drugs is vividly illustrated in a study by the Karolinska Institute on the uptake of new cancer drugs (Jönsson and Wilking, 2007). Though the authors show that uptake is highly variable across products, some general trends are observable. The United States has, in most cases, the most rapid uptake and

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higher levels of per-capita sales than other countries have, even several years after introduction. Within Europe, Austria, France and Switzerland show the fastest uptake; the United Kingdom generally has lower uptake than other countries. Canada, Australia, Japan and New Zealand all had lower uptake of new cancer drugs than the European average, although Canada and Australia had higher uptake than the United Kingdom. New EU members (Poland, Hungary and the Czech Republic) had the slowest uptake, likely reflecting relative affordability.

Another analysis shows high discrepancies in formulary listing for ten orphan drugs in European countries, ranging from one in Hungary to ten in France (de Varax *et al*., 2004). The study notes that real accessibility is further defined by hospital payment schemes and available budgets, with possible discrepancies at the regional level in some EU countries.

Similarly, the availability of very expensive drugs may differ within countries, as was the case in England and Wales prior to the creation of the NICE. In Canada, the Cancer Advocacy Coalition (2005) showed that the effective access to 20 cancer drugs was highly variable, treatments being available in some provinces but not others at any point in time.

The role of pricing and reimbursement policies in averting under-use of effective medicines

Ensuring appropriate use of effective medicines is a goal that policy makers share. And here, there is evidence that OECD countries have some progress to make in ensuring a better match between need and use. The extent to which pricing and reimbursement policies may help to tackle these shortcomings in the quality of care is analysed in this section.

Even in OECD countries, many people do not get the medicines they need

There is evidence to suggest significant variability across countries in the use of medicines, although this is based on limited data (see Chapter 1). While international differences in disease incidence and treatment guidelines contribute to some of the differences seen (National Heart Foundation of Australia *et al*., 2005; Hockley and Gemmill, 2007), the degree of variation in use supports the hypothesis that there is under-use of some medicines in some countries, as compared with the level of use that could benefit patients.

Even within countries, the research literature provides evidence that not all patients get the medicines they need. A recent study of medication use among US adults found evidence that medications appropriate for a patient's condition were not prescribed for 63% of patients studied (Shrank *et al*., 2006).[5] Somewhat surprisingly, given the differences in coverage across the US population, insurance status was not found to be a factor contributing to the quality differences found, suggesting that this quality shortfall was not likely to be attributable to differences in the level of coverage and cost-sharing for particular medicines. The underuse of effective medicines is not confined to the United States. For example, a study of the use of antihypertensive medicines in seven OECD countries found that two-thirds to three-quarters of hypertensives in the European countries studied were untreated, compared with slightly less than half in the United States (Wolf-Maier *et al*., 2004).

There is ample evidence that patients fail to comply with prescribed treatment regimes, both for long-term chronic conditions and shorter acute episodes (such as antibiotic use). The World Health Organization estimated that adherence to long-term therapies for chronic illnesses in developed countries averages just 50% (WHO, 2003).

Beyond the affordability of very expensive medicines, patients' demand for pharmaceuticals has been found to be price sensitive for certain populations and types of products, although the degree of sensitivity varies for different effective price levels and populations (see Box 4.1). As cost-sharing requirements in most OECD countries are low, the impact of small changes in the effective price patients face is also minimal. However, significantly higher prices or higher cost-sharing requirements will inevitably create some barriers to access for low-income populations or those with chronic needs, with possible consequences for the consumption of health care services and patients' health status.

Averting clinically inappropriate use of medicines

There is some evidence of drug misuse and overuse. For example, some European countries and the United States have had to face high antibiotic resistance due to the over-consumption of antibiotics (Schrag *et al.*, 2001; and Goossens *et al.*, 2005).

Box 4.1. **The price sensitivity of consumer demand for pharmaceuticals and potential consequences of increases in cost-sharing**

Affordability is a difficult concept to measure, in part because it is sometimes hard to disentangle problems relating to people's ability to pay from their willingness to do so. However, research has found that some consumers are sensitive to the prices they pay out-of-pocket for pharmaceuticals, reducing and foregoing consumption when prices are perceived as excessive and changing consumption patterns in response to price changes.

Many studies investigated the link between patients' out-of-pocket costs and the demand of pharmaceuticals. Some of them estimated the price-elasticity of the demand for pharmaceuticals, at aggregate as well as at individual levels (see Gemmil *et al.*, 2007 for a recent review). Though related to different contexts (different countries, different population sub-groups, different therapeutic classes and different types of cost-sharing), these studies show that higher out-of-pocket payments are linked to lower volumes of consumption. However, when data from the studies were combined for the purpose of meta-analysis, the authors found that the demand for prescription drugs is relatively inelastic (–0.2), implying that across the developed world, consumers are not particularly responsive to changes in out-of-pocket prices for prescription drugs. The authors speculate that this may be due to a perceived necessity of prescription medications and a lack of suitable substitutes. It could also be explained by the fact that cost-sharing tends to be low in most developed countries, given that price elasticity of demand varies at different price points.

Poor and vulnerable parts of the population are more likely to be sensitive to changes in cost-sharing. Lexchin and Grootendorst (2004) reviewed studies measuring the impact of increases in cost-sharing on vulnerable populations (poor, beneficiaries of social assistance, people with chronic diseases and/or with poor health status) in OECD countries. Though the review included all studies published in English and French ,the 24 studies found were all based in the United States or Canada, with the exception of two studies which were based in Belgium and New Zealand. Virtually all studies demonstrated that an increase in cost-sharing resulted in decreases in drug use by low-income people and the chronically ill. The authors estimated the price elasticity of demand for these vulnerable populations to range between –0.34 and –0.50, *i.e.* demand was more elastic than it was for the entire population.

Box 4.1. **The price sensitivity of consumer demand for pharmaceuticals and potential consequences of increases in cost-sharing** *(cont.)*

The Cochrane collaboration undertook in 2006 an exhaustive review of the impact of pricing policies on a range of outcomes (Aaserud *et al.*, 2006). Of 246 studies reviewed, only 20 met the high standard of evidence quality set by the authors and only 15 of them were effectively assessed for technical reasons. All but one analysed the impact of reference price policies, *i.e* policies which result in one or several drugs (the reference drug) being available at no out-of-pocket expense, while other drugs of the same therapeutic class will generally be available to patients willing to pay the price differential out-of-pocket. Four studies reported an increase in the use of the reference drug after the implementation of reference prices, ranging from 60% to 196%, and persisting after 6 months. Four studies similarly reported a decrease in use of drugs with cost-sharing ranging from -19% to -42%. Changes in total drug consumption in the affected therapeutic class were inconsistent or not significant.

A few studies analysed the impact of changes in cost-sharing for different types of drugs, classified according to their clinical value. At least two studies show that consumers forego both "essential" and less essential medicines in response to changes in cost-sharing (Tamblyn *et al.*, 2001; and Leibowitz *et al.*, 1985). Results from the Rand Health Insurance Experiment (Leibowitz *et al.*, 1985) showed that consumers reduced both essential and less-essential services in response to increased cost-sharing requirements. In Tamblyn's study of Quebec seniors, the decrease in consumption was higher for non-essential medicines than for essential ones.

Sometimes patients get medicines they do not need. A Rand study of quality of pharmacology care for US adults found that inappropriate medicines were prescribed in 16% of cases (Shrank *et al.*, 2006). In France, therapeutic protocols in the treatment of hypercholesterolemia published by the agency in charge of health technology assessment are not always followed by doctors. Though the protocols recommend prescribing medications for patients who are above a certain threshold of low-density lipoprotein (LDL)-cholesterol, a study found that one third of French doctors prescribed medicines for patients who had a LDL-level inferior to the recommended threshold (CNAMTS, 2003).

Payers can employ a range of techniques to improve quality of care and contain costs by limiting the inappropriate use of medicines. As seen in Chapter 3, some of these techniques directly rely on formulary management, such as limitations in drug prescriptions (prior authorisation, second line treatment). Across-the-board cost-sharing increases have been used periodically in OECD countries, with the double aim of increasing the private share of funding and offsetting consumption increases induced by moral hazard. However, these blunt instruments run the risk of impairing access to needed medicines in addition to those that are less effective or unnecessary.

While coverage, pricing and reimbursement policies are important to ensure access to medicines, these are necessary but not sufficient to ensure appropriate use. Pharmaceutical policy may encourage appropriate use of medicines by many other means, such as providing doctors with evidence-based and balanced information about pharmaceutical products or ensuring that professional bodies have engaged in these activities. These policies were described in Chapter 3, with some examples taken from the

case studies conducted as part of the present study, although no in-depth assessment of their impact was made.

The impact of pricing and reimbursement policies on pharmaceutical price levels

The outcome of pricing policies, in terms of aggregate impact on price levels, largely depends on the market power of the purchaser or regulator (population represented in terms of number and income), as discussed in Chapter 3. But also important are the purchaser's motives and ability to act in ways that influence the volume of a product consumed.

Purchasers and regulators do not necessarily aim to get the lowest possible price

Pharmaceutical purchasers seek to maximise an array of objectives, not limited to cost containment. Private health insurance firms operating on a for-profit basis have strong incentives to contain their pharmaceutical expenditures. Consequently, they will seek the lowest possible price for any given pharmaceutical and try to minimise the volume of subsidised pharmaceuticals used by insured populations, with the exception of those products for which use may be considered to save the insurance company costs, by avoiding hospitalisation, for example. Balancing these incentives to limit expenditures, depending on market or regulatory pressures, is the need to provide pharmaceutical benefits that are adequately comprehensive and accessible.

Responsibility for public cost containment and pressure to achieve good value for money provides public purchasers with the incentive to achieve low prices, but this is very often tempered in practice by other goals. Notably, payers are under pressure from citizens and stakeholders to promote public health and to ensure prompt access to effective medical treatments. In several OECD countries (*e.g.*, Canada), there is pressure to use pharmaceutical policy to serve the objectives of industry policy, by offering relatively high ex-manufacturer prices or other concessions intended to incent or reward domestic pharmaceutical industry activity[6] (see Box 4.2).

Purchasers in some OECD countries (*e.g*, Sweden, Switzerland) seek to use their purchasing arrangements to reward and/or foster firms' investments in pharmaceutical R&D. Sweden, for example, reimburses products at any price proposed by the manufacturer that allows for use of the product to be cost-effective in Sweden from a social perspective. The reimbursement authority does not seek to obtain the lowest possible price (Moïse and Docteur, 2007b). Another example is the "innovation premium" awarded in Switzerland to products that are first or second entrants in a class, accounting for a premium of 10-20% over the price of therapeutic comparators already on the market (Paris and Docteur, 2007).

For all these reasons, price regulation may not necessarily result in lower prices than what could be obtained in a market where insurers compete on the basis of their performance in furnishing best value for money. Indeed, proponents of the idea that competition among private insurers would result in the lowest possible prices available in a market made these arguments in the recent US debates on expansion of the Medicare programme to offer prescription drug coverage.[7]

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Box 4.2. **Pharmaceutical cost containment and industry policy: conflicts between policy goals**

Examples of pharmaceutical policies that benefit the pharmaceutical industry without obvious benefits for governments, citizens or patients can be found in a number of OECD countries and jurisdictions within countries with a significant domestic presence of the pharmaceutical industry. For example, the Canadian province of Quebec uses a reference-pricing scheme to set common reimbursement levels for off-patent original products and generic alternatives, but reimburses off-patent originals at the list price for 15 years after listing, irrespective of patent status (Paris and Docteur, 2006). In Sweden, manufacturers' applications for reimbursement and negative reimbursement decisions are kept confidential by the pricing and reimbursement authority, benefiting manufacturers who may not want information on their pricing strategies to be public knowledge (Moïse and Docteur, 2007b).

The desire of governments to attract pharmaceutical industry activities (*i.e.,* R&D, production) may well influence pharmaceutical policy, although there is little reason to believe that providing favourable market conditions (*e.g.,* high prices) will be a significant determinant of firms' decisions as to where to establish headquarters and undertake R&D, in particular. For example, pharmaceutical R&D activities in Canada have not appreciated significantly, despite a pricing policy linking Canadian prices of patented medicines to the prices in countries with significant pharmaceutical sectors, and agreement with the industry to increase R&D activities in Canada (Paris and Docteur, 2006).

The increasing globalisation of R&D has forced governments to rethink the basic premises behind policies intended to attract domestic activity (Karlsson, 2006). Government policies must now take into account the nature of the globalisation of private R&D: characterised in large part by companies seeking "centres of excellence" to maximise knowledge spillovers (Karlsson, 2006; Nilsson, 2006). Industrial policies such as low corporate taxes* may influence manufacturers' decisions regarding location of production facilities, but pharmaceutical pricing policies are unlikely to be a factor, given that firms benefit from industry-friendly market characteristics whether or not they are based in the country.

* For example, Ireland's 10% corporate tax rate on manufacturing has played a key role in attracting direct foreign investment from pharmaceutical multinationals (OECD, 1997), leading to an almost twelve-fold increase in pharmaceutical production between 1985 and 2002, with R&D increasing only five times during the same period (OECD, 2007).

The ability of purchasers to obtain price concessions varies across purchasers and products

Private and public payers alike may be motivated to obtain a low price and be able to influence volume by formulary and benefits management. Therefore, the difference between price negotiation between two interested parties (*i.e.,* a pharmaceutical benefits manager covering 60 million people with multiple plans and formularies) and reimbursement price regulation is not necessarily obvious, in terms of outcome.

Payers and purchasers who are constrained by forces of competition or regulation from taking actions that affect the quantity of a pharmaceutical product purchased will have no ability to negotiate or limit its price. So, for example, indemnity insurers in Canada and the United States are purely price-takers, in that they reimburse insured persons for the cost of any prescribed pharmaceutical product authorised for marketing, less the cost-sharing amount defined by the rate of co-insurance established in the insurance policy.

Similarly, public coverage schemes in some OECD countries are obliged to cover every drug authorised for marketing and are effectively price-takers, able to obtain price concessions only if they have discretion to put restrictions or limits on coverage, or to steer consumption to one drug over another. Typically, countries with national formularies do not select drugs within a therapeutic class: during price negotiation – where this occurs – manufacturers are virtually assured that their drug will be listed, the question being more "at what price"? Under such circumstances, they may be less inclined to consent to discounts or rebates.

In the United States, pharmaceutical benefit management (PBM) companies are not required to list all drugs in a therapeutic class, thus having power to direct volume when there are competing drugs in a therapeutic class.[8] A report by the US Federal Trade Commission (FTC, 2005) showed that PBMs generally do not list all statins available on the US market, for instance. Where competing products are available, PBMs contract with manufacturers to obtain payments (usually considered to be rebates) in exchange for an advantageous formulary status for their drug, *i.e.* "preferred drug" status, listing without restrictions, etc.

If a new pharmaceutical product is effective and without therapeutic competition, both public payers and private insurers will be under pressure to provide coverage and will have limited bargaining power to obtain concessions from the manufacturer. On the other hand, to the extent there is competition from generic or therapeutic alternatives, the outcome will depend on market power and objectives of the purchaser, public or private. Of course, manufacturers also have negotiating power, even when therapeutic competition exists; they may choose not to launch a product, or not to seek a listing on a formulary or positive list, if they believe that profits can be maximised by focusing their sales efforts in selected markets. Variation across markets in the availability of products suggests that these decisions are common.

Strategies used in pricing have different predictable impacts on outcomes

The multiple policy instruments used in pricing and reimbursement have a predictable impact on price levels, as reviewed below.

Methods widely used to cap prices are arguably arbitrary and gameable

A fundamental problem in pharmaceutical price regulations is defining the appropriate price level or cap. A range of approaches, described in Chapter 3, are used.

In practice, external price benchmarking is often used, but the rationale for selecting particular benchmarks is not always explicit. As a result, the impacts can be unpredictable. Despite very different contexts, price regulation in both Canada and Switzerland has reduced the gap in prices with the richest European countries, but increased the gap with US prices (Paris and Docteur, 2006 and 2007). In Mexico, on the other hand, there may be no impact on prices obtained by manufacturers because the system is loosely regulated and readily gameable (Moïse and Docteur, 2007a).

The widespread use of this pricing scheme across OECD countries presents a number of drawbacks. First, it provides a strong motive for strategic launch and pricing, raising questions as to the appropriate level of price in the early launch countries. Manufacturers have incentives to launch first in countries that do not regulate entry prices and that can afford high prices in order to have the list prices in these countries referenced by others. As

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demonstrated in previous chapters, Germany and the United Kingdom – early-launch countries that allow free pricing for innovative drugs at market entry – are two of the three countries most commonly used as references, suggesting that many countries using external benchmarking to limit prices are, in fact, referencing the price selected by the manufacturer rather than a regulated price.

Second, in some countries the list price is disconnected from the price actually paid by purchasers. If regulators of referencing countries rely on listed prices to make their decisions, they may pay higher prices than they intend to pay.

Finally, the way in which caps are defined and the way in which negotiations are led have a predictable impact on the outcomes of regulation. Fixed and well-defined rules, such as capping the allowable price at the average of prices in comparator countries, makes the system highly predictable for manufacturers. Choosing the median has the advantage of not being sensitive to outlier prices in comparator countries. When definition of the maximum price is more vague, such as "should be consistent with prices of comparators" (like in France) or when the negotiation is described as "flexible", there is more room for case-by-case negotiation between authorities and manufacturers, which renders the process less transparent and its impact less predictable.

Internal price referencing – pricing drugs by reference to therapeutic comparators – seems reasonable on the surface; however, the referenced products must themselves have price levels that are consistent with consumer willingness to pay for the product. Beyond this, internal referencing still requires decisions as to which variations warrant premia and at what level those premia should be established.

Price caps are sometimes linked to production costs, an approach used mainly for generic products. The ability of firms to manipulate cost data makes such systems of dubious ability as a control. All of these methods face challenges on the grounds that they are arbitrary and readily gameable by manufacturers with strategic launch and pricing strategies.

Product-specific agreements linking volumes and prices

The discounts and rebates on list prices consented to by manufacturers as part of product-specific price-volume agreements with purchasers and/or regulators are generally not known, since these agreements are most often confidential. In France, these rebates amounted to 0.94% of French companies' turnover in recent years and are highly concentrated on a few products and firms (Cour des Comptes, 2004; Comité économique des produits de santé, 2007).

Similarly, US public and private purchasers do not publish information about the discounts they get from manufacturers. However, the US Federal Trade Commission (FTC, 2005) obtained confidential information on contracts between a sample of PBMs (among which were the largest ones) and 11 big pharmaceutical companies, using these data to estimate the discounts granted by PBMs to plan sponsors on the average wholesale prices (AWP) in 2003. For brand-name drugs, those discounts ranged from 16% to 27.9% of sales in contracts with less restrictive or open formularies, with larger discounts in contracts with more restrictive formularies (FTC, 2005, p. 37). In addition, the study provides estimates of payments furnished by manufacturers to have their drug included in the PBM's formulary. In total, the FTC study revealed that manufacturers consented to rebates of USD 6.34 per brand prescription,[9] on average, for inclusion of their drugs in PBMs formularies, 71% of

which were concentrated on the top 25 brand name drugs. PBMs sometimes share these rebates with plan sponsors, with retention rates ranging from 37% to 91%.

Tendering, mainly used by public plans for generic listing, can be considered as a specific type of volume-price agreement since it offers the manufacturer the opportunity to set a price conditional on a specified volume of sales.

The definition of fixed reimbursement amount for drug clusters fosters price competition

Reference prices schemes commonly foster price competition and result in harmonisation of prices within clusters. Where they have been applied, pharmaceutical firms have generally dropped their list prices for products upon inclusion in reference groups because of concern about the prospective loss of market share. In Germany, in April 2006, only 7.5% of all products included in reference-price groups were priced above the reference price (Paris and Docteur, 2008). However, there have been a few recent exceptions in which manufacturers have chosen not to drop their prices, indicating either that manufacturers believe that consumers will be willing to pay extra for these products, or that the potential cost in terms of impact on prices in other markets is too significant.

The prospective impact of reference price schemes depends heavily on both the design of the scheme (nature and number of clusters, the way reimbursement amount are set, whether patented drugs are included or not) as well as other characteristics of the health systems likely to foster competition within clusters (such as the substitution option or obligation for the pharmacists, obligation of the physician to inform patients about potential cost-sharing, etc.). The schemes with the greatest scope of prospective impact, in terms of the downward pressure exerted on price, undertake clustering at the therapeutic level (rather than the bioequivalent level), set a reference price at a level allowing generic competitors to enter the market and allow clustering of patented products with similar and efficacy and safety profiles. However, this type of clustering is technically and politically difficult to implement.

Some analysts have argued that prices of non-clustered drugs may be inflated by reference price policies because manufacturers will seek to recuperate losses in revenues in this market segment. In fact – except in specific contexts such as the British one – manufacturers have incentives to maximise the price of each individual product at each period rather than to accept unnecessary price concessions in the non-clustered market. What is likely to happen, however, is that manufacturers will focus their promotional efforts on non-clustered products, with the aim of increasing consumption of those products which are more profitable.

What are the comparative price levels of pharmaceuticals in OECD countries?

Academics, public institutions and private stakeholders have tried to provide estimates of the impact of pricing policies on price levels, using approaches that rely on normative assumptions. In the following section, we assess the effectiveness of countries' approaches to pharmaceutical pricing by comparing retail price levels of pharmaceuticals to general consumer price levels in OECD countries.

Pharmaceutical price levels roughly correspond with economy-wide consumer price levels in most countries

A comparison of retail pharmaceutical price levels with economy-wide price levels can offer some insights into the impact of pharmaceutical pricing policies on retail prices for

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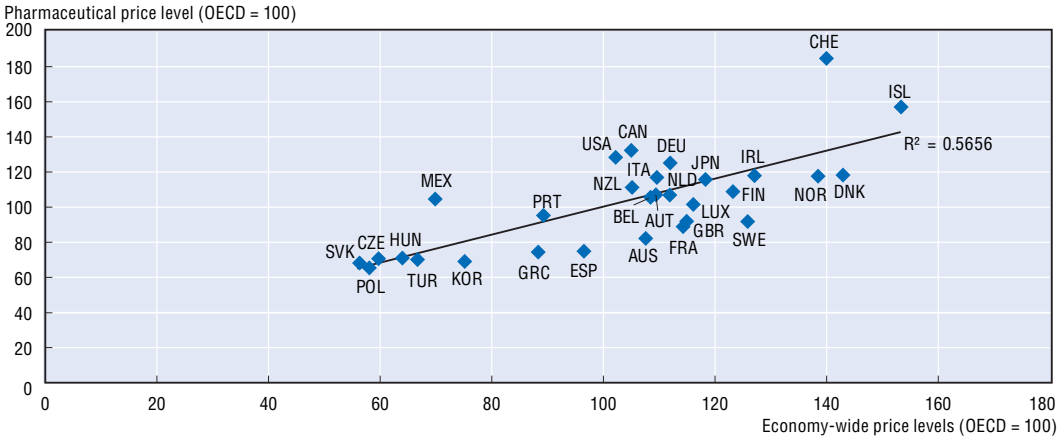
pharmaceuticals. It is important to keep in mind that pharmaceutical prices that are out of line with economy-wide prices may reflect factors other than pharmaceutical pricing policies. Notably, value-added taxes on pharmaceuticals are often lower than VAT on other goods; in many cases (*e.g.*, Australia, Belgium, Greece, Finland, France, Hungary, Italy, the Netherlands, Poland, Sweden, the Slovak Republic, and the United Kingdom) pharmaceuticals are exempt from this tax. On the other hand, Austria, Denmark, Ireland, and Norway apply the standard VAT to all pharmaceuticals (PPRI, forthcoming).

Annex 4.A1 provides details of an analysis demonstrating that two-thirds of OECD countries had retail pharmaceutical price levels in 2005 that were consistent with their economy-wide price levels.[10] The results are summarised in Figure 4.3. Retail pharmaceutical to economy-wide price differentials in Switzerland, Mexico, Canada and the United States exceeded the OECD average by a considerable margin. Sweden, France,[11] the United Kingdom, Denmark, Spain and Australia had pharmaceutical price levels that were notably lower than their economy-wide price levels. Exemption from VAT or lower rates for pharmaceuticals explains much of the observed deviation in the case of France, the United Kingdom and Sweden.

Figure 4.3. **Retail pharmaceutical price levels and economy-wide price levels, 2005**



Note: Prices were converted to a common currency using the 2005 average exchange rate. The OECD average is the geometric mean. The coefficient on the independent variable "Economy-wide price levels" (0.7917) was statistically significant at the 1% level (t-statistic = 6.04).

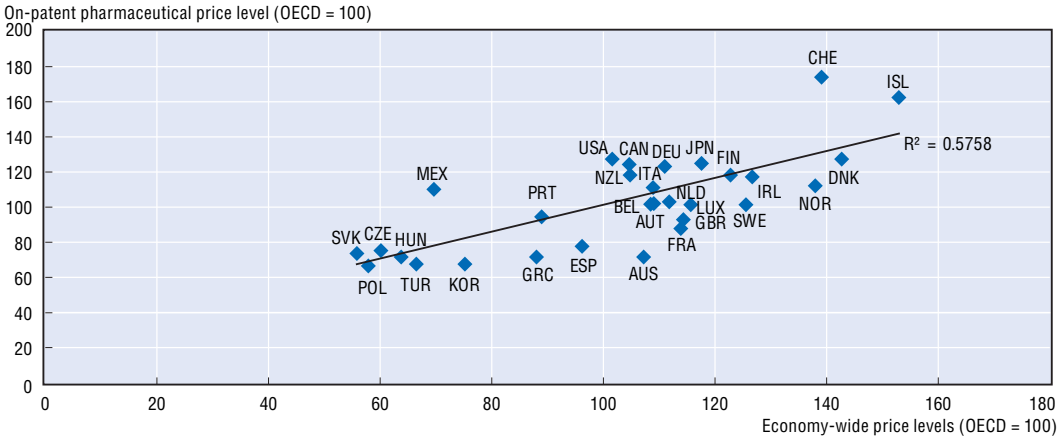
Source: Eurostat-OECD Purchasing Power Parity Programme, 2007.

In addition to differences in VAT rates, inconsistency between price levels for pharmaceuticals and those seen economy-wide may be partly attributable to the effects of pharmaceutical pricing schemes. For instance, Switzerland subsidises pharmaceuticals at the level proposed by the manufacturer, as long as the price is generally consistent with that offered in European comparator countries (Denmark, Germany, the Netherlands and the United Kingdom). However, as Switzerland is not uncommonly the first launch country in Europe and uses international benchmarking in a very flexible manner, manufacturers tend to obtain relatively high prices for their products (Paris and Docteur, 2007). In the United States, significant subsidies for pharmaceuticals provided by insurance (approximately 75% of the total expenditure on prescribed medicines is financed by private insurance or public coverage) may be a contributing factor to higher pharmaceutical prices

relative to economy-wide prices. Relatively high US prices may have a spill-over effect for Canada and Mexico, in that manufacturers will be less inclined to price to market in those countries that have cross-border trade with the United States, as discussed in Chapter 5.

Because price regulation is often justified by the perceived need to counterbalance the market power of manufacturers, it is interesting to look at relative price levels for original products (Figure 4.4).[12] Five countries – Switzerland, Mexico, the Slovak Republic, Canada and the United States – had retail price levels for original medicines that exceeded their relative position in the OECD in terms of economy-wide prices in 2005, *i.e.* the differences between original price levels and economy-wide price levels were greater than one standard deviation from the OECD average.[13] Australia, France, Sweden and the United Kingdom appear to have had relatively low retail prices for original products in 2005, as does Norway.

Figure 4.4. **Original pharmaceutical price levels and economy-wide price levels, 2005**



Note: Retail prices were converted to a common currency using the 2005 average exchange rate. The OECD average is the geometric mean. The coefficient on the independent variable "Economy-wide price levels" (0.7604) was statistically significant at the 1% level (t-statistic = 6.16).

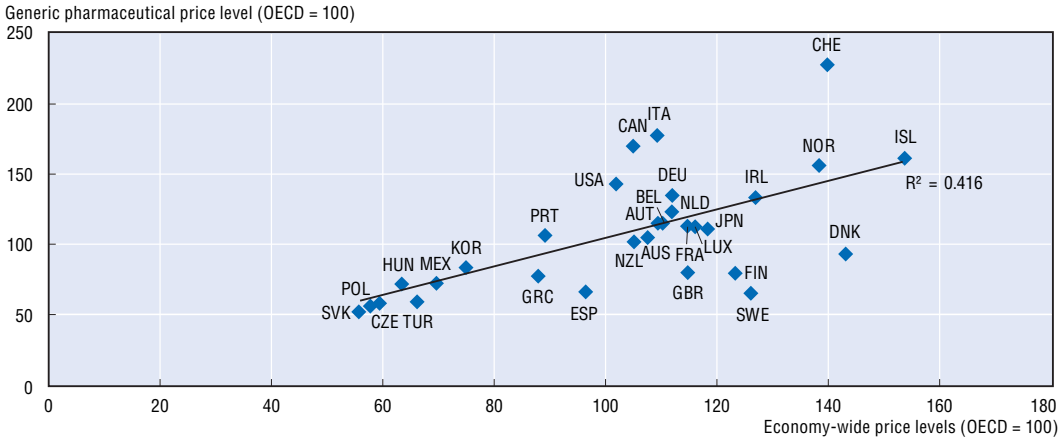
Source: Eurostat-OECD Purchasing Power Parity Programme, 2007.

In Canada's case, the gap between original product and economy-wide price levels may partly reflect the impact of its pharmaceutical price regulation, at least to the extent that retail price levels for original products are consistent with ex-manufacturer prices of on-patent medicines. As noted in Paris and Docteur (2006), the aim of Canada's regulation was not to bring on-patent ex-manufacturer price levels in line with its prices economy-wide, but rather to bring them in line with the average of its European comparators, to which it has succeeded. However, these comparators (France, Germany, Italy, Sweden, Switzerland, and the United Kingdom) all have economy-wide price levels that exceed Canada's.[14]

Finally, a look at price levels for generic products provides a sense of the extent to which countries have achieved price competition upon patent expiry (Figure 4.5), Most countries do not rely on market forces to foster generic competition, rather setting maximum reimbursement prices for generic drugs (see Chapter 3).

The vast majority of OECD countries had retail pharmaceutical price levels in 2005 that were consistent with their economy-wide price levels, *i.e.* difference in price levels was

Figure 4.5. **Generic pharmaceutical price levels and economy-wide price levels, 2005**



Note: Retail prices were converted to a common currency using the 2005 average exchange rate. The OECD average is the geometric mean. The coefficient on the independent variable "Economy-wide price levels" (0.9942) was statistically significant at the 1% level (t-statistic = 4.47).

Source: Eurostat-OECD Purchasing Power Parity Programme, 2007.

less than one standard deviation from the OECD average. Notable exceptions are Switzerland, Italy and Canada, with generic pharmaceutical prices in 2005 greatly exceeding prices economy-wide, and Sweden and Denmark, with generic drug prices that were far below economy-wide prices.

This finding is consistent with the conclusions of the OECD case studies of Canada and Switzerland, which in both cases pointed to regulatory failures and lack of competition in the countries' off-patent markets. However, these countries have very different generic market profiles: while generics account for 41% of the total market value in Canada, they only account for 6% of the market in Switzerland (see Chapter 2).

These results also lend support to the findings from the case study of Sweden, a country which has established very strong incentives for generic price erosion through its policy mandating substitution of the lowest-priced bioequivalent and substitutable product, and permitting monthly price changes (Moïse and Docteur, 2007b). Furthermore, the financial incentives faced by physicians, pharmacies and patients are aligned to favour lower-cost generics (and parallel imports, where available), which has allowed Sweden to achieve high generic penetration of the market with a relatively low share of the value.

Pricing and reimbursement policies certainly influence the prices of generics and off-patent original drugs. Differential cost-sharing (with higher co-payments for brand-name drugs) have been shown to have a significant impact on generic penetration. Such policies are widely used by PBMs in the United States in formulary design. However, other incentives directed at physicians, pharmacists and patients for generic prescribing, dispensing and use play a crucial role are in shaping competitive markets. These policies and their impact have not been systematically investigated in the course of this project, but analysed in case study reports.

Policies succeed in containing price growth

Pharmaceutical price growth is readily controlled in most countries, as is consistent with the evidence on the factors responsible for recent growth in the value of

pharmaceutical sales presented in Chapter 1. Many countries (*e.g.*, Sweden, the Slovak Republic) do not permit increases in pharmaceutical prices, except under exceptional circumstances, or limit pharmaceutical price growth to growth in prices in the economy (*e.g.*, Canada, Mexico). The United States is notable among OECD countries for its annual growth in pharmaceutical prices, which have in recent years exceeded growth the economy and in other parts of the health sector. This finding provides support for the idea that manufacturers use so-called penetration pricing (launching a product at a price below competitors followed by price increases) for me-too products to gain foothold in a competitive market, as discussed in Chapter 2.

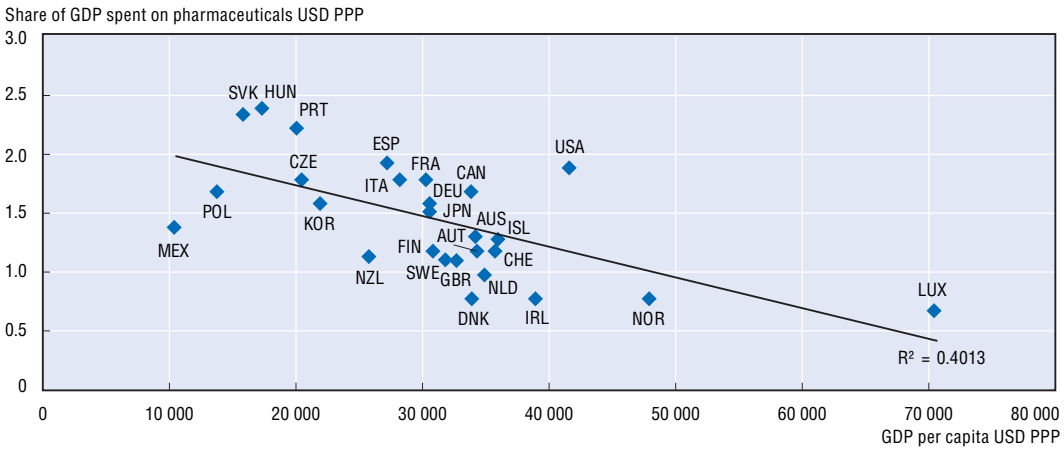
Pharmaceutical cost containment

The variation across OECD countries in the share of national income devoted to pharmaceuticals is significant – varied between 0.7% and 2.4% – and greater than the variation seen in the share of income devoted to health expenditure (net of pharmaceutical expenditure), which varied between 4.3% and 13.4% in OECD countries in 2005.

This wide variation raises questions about whether and which countries may be over or under-spending, although the most appropriate benchmarks for spending are debatable. It is interesting to observe the spending levels in the countries that can be said to have markets for pharmaceuticals that are closest to operating freely. For example, Germany spends 1.6% of its income on pharmaceuticals and the United States spends 1.9%. However, in both countries, about three-quarters of pharmaceutical spending is financed by insurance, which will tend to inflate spending.

This overly simplistic observation fails to take into account the relationship between income and pharmaceutical expenditure, however. Countries with higher per capita incomes tend to spend a lower share of total income on pharmaceuticals (Figure 4.6), contrary to the share they spend on health expenditure as a whole (Figure 4.7). This is consistent with the idea that pharmaceuticals are considered a necessity, for which

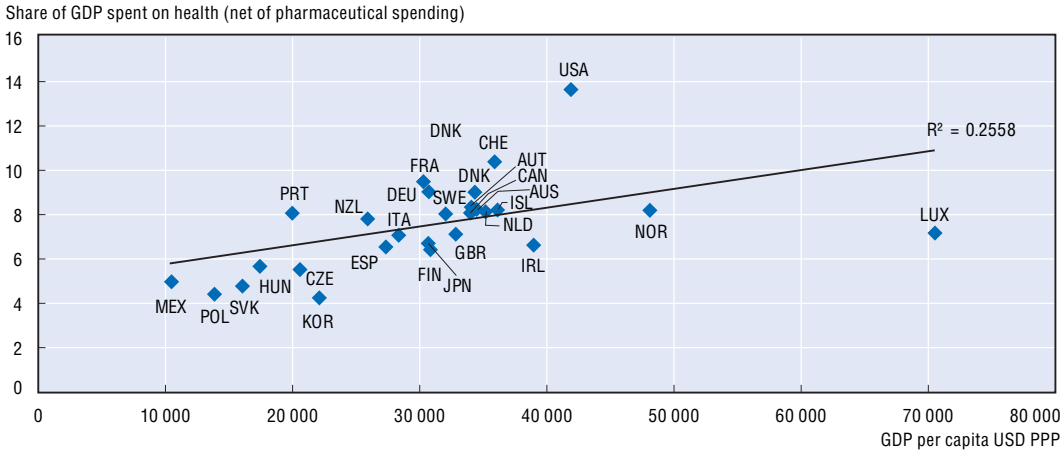
Figure 4.6. **Share of GDP spent on pharmaceuticals and income per capita, 2005**



Note: The coefficient on the independent variable "GDP per capita" (–0.00003) was statistically significant at the 1% level (t-statistic = –4.09).

Source: *OECD Health Data 2007.*

Figure 4.7. **Share of GDP spent on health (net of pharmaceutical spending) and income per capita, 2005**



Note: The coefficient on the independent variable "GDP per capita" (–0.00008) was statistically significant at the 1% level (t-statistic = 2.93).

Source: OECD Health Data 2007.

spending will rise with income, but not as fast as income does. The difference in what is seen between pharmaceutical and health expenditure may be partly due to the role of health-care related labour costs, which rise with national income, as well as the tendency of poorer countries to under-report a portion of health expenditure consisting of informal or under-the-table payments to health care providers.

Another consideration is the level of spending relative to other valued goods and services. In 2005, for example, Canada devoted 1.7% of its income to pharmaceutical expenditure. In the same year, 2.2% of GDP went to clothing, 3.4% to motor vehicles, 1.1% to alcohol and 1.0% to tobacco. It is difficult to use such macro-level information to inform decision-making at a micro level, however.

Setting aside the difficulty in assessing the appropriateness of pharmaceutical spending levels, a policy objective in some countries has been to constrain the rate of growth in pharmaceutical expenditure. Pharmaceutical spending that rises faster than the rest of health spending and economic growth raises concerns about affordability and sustainable financing. Nevertheless, rapidly growing pharmaceutical spending is not necessarily undesirable, from the perspective of social welfare, as long as there is no more valuable use of available resources. It is also possible that some added spending on pharmaceuticals, particularly ones that prevent hospitalisations or conditions requiring further treatment, could offset spending in the health sector(see Chapter 2) or in other areas where costs are borne socially.

Means to contain drug expenditures through financial incentives have only marginal impact

Chapter 3 provided an overview of a full arsenal of approaches used by payers in efforts to control their expenditures on pharmaceuticals, including profit controls, clawbacks, negotiated rebates, price-volume agreements, risk-sharing arrangements, tendering, cost-sharing (or cost-shifting), and using parallel trade. In the sections below, we assess the relative utility of these approaches to assist in pharmaceutical cost containment.

Macro-level cost-containment tools allow countries to obtain marginal discounts on pharmaceuticals

Macro-level cost-containment measures generally lead to small repayments from the industry and have arguable effectiveness on containing costs. Several countries use macro-economic rebates and clawbacks to contain pharmaceutical expenditures. Though these tools respond to different approaches – profit caps, turnover caps, clawbacks – and are geared towards different actors – industry, pharmacists – they generally allow national health insurers or governments to recuperate a small share of total expenditures.

The British profit control scheme (Pharmaceutical Price Regulation Scheme, PPRS) led to profit repayments representing only 0.01% of companies PPRS revenues over the period 1999-2004 (OFT, 2007).[15] Pharmaceutical companies generally managed to price products in a manner to not exceed the cap set by negotiation, though the scheme incidentally provided incentives to innovate in accounting methods to shift part of companies' profits to other countries. Moreover, the rationale for setting the profit cap is arguable and the scheme does not guarantee that it leads to the best possible use of available resources (*op. cit.*).

Rebates paid annually by the pharmaceutical industry to the French health insurance funds are higher. It is generally not possible to distinguish between annual repayments related to the macro-level cap regulation from those related to product-specific confidential agreements. Nevertheless, between 2000 and 2003, total repayments ranged from a low of 0.86% of total turnover in 2002 to a high of 2.03% in 2000 (Cour des Comptes, 2004). In 2006, an exceptional year during which the turnover cap set for out-patient reimbursable drugs was not exceeded, companies did not pay any rebate relating to the macro-level cap (Comité économique des produits de santé, 2007).

In Germany, the government periodically takes measures to reduce the deficits of the health insurance funds. In 2004, it required rebates from both pharmaceutical manufacturers (16% of the price of non- clustered drugs in 2004) and pharmacists (EUR 2 per prescription pack in 2004). In addition, a moratorium on price increases in the non-clustered market and the lowering of reference prices have contributed to cost-containment in 2004. German measures are generally proportionate to financing needs and thus can be considered as effective cost-containment measures. However, rebates are set in relation to the funding needs of health insurance funds and may seem arbitrary and unpredictable (compared to regulations based on annual caps for pharmaceutical expenditures).

Tendering can be used to achieve significant savings

Tendering can often lead to significant savings in cases where the purchasing power is great and there are multiple potential sources for the product. Manufacturers and wholesalers will have very strong incentives to provide the best possible price, given that providers who are not successful will not sell any products to the purchaser. Where generic alternatives are available, bidding can be successful in reducing payments to the level of marginal production costs. The VA estimates that it has achieved over USD 1.5 billion in total cost avoidance through national contracting efforts between 1996 and 2003 (Sales *et al.*, 2005). Mexico's social insurance programmes use tendering for interchangeable generics to achieve very significant savings over the retail cost of medicines (Moïse and Docteur, 2007a).

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Cost-sharing is possibly the most effective instrument to contain costs, but raises other problems

Pharmaceutical cost-sharing (*e.g.,* co-payments, deductibles) that is not differentiated by type of medicine can be considered to have two purposes: tempering demand for medicines (by reducing moral hazard) and obtaining co-financing for subsidised pharmaceuticals.

Cost-sharing has been shown to be effective in reducing demand although the effects may fall disproportionately on lower-income and chronically ill patients (see Box 4.1).

Reference price policies are an often used means to co-finance subsidised pharmaceuticals. Their net impact in terms of cost-containment is difficult to assess. First, not only does such an assessment require evidence on costs trends for clustered products, but also for those which are not clustered in order to capture all potential effects on pharmaceutical expenditure trends. Second, it requires a sound empirical methodology that allowing for the disentangling of the effect of the reference price policy from the effects of other concurrent policies and contextual market features (Puig-Junoy, 2005).

According to the Cochrane collaboration review (Aaserud *et al.*, 2006), only two studies provide reliable estimates of the impact of reference prices on health plans' drug expenditures. They both analysed the introduction of reference prices in the British Colombia health benefit for seniors. They showed contrasting results across therapeutic classes: a 5% increase in expenditures after six months in the ACE inhibitors class, contrasted with an 18% decrease in the class of Calcium Channel Blockers (both anti-hypertensives), a 47% decrease in the nitrates class (cardiac drugs), and a 38% decrease in the H2RAs class (antacids).

The prospective impact of reference price schemes depends on several factors: how products are clustered, how reimbursement amounts are set, and what are the other incentives established in the system. Beyond this, reference pricing systems may result in increases in cost-sharing which may, in turn, hamper access to treatments and have negative health outcomes, especially in vulnerable parts of the population (see Box 4.1).

Encouraging parallel trade may have a short-term impact on public insurers expenditures, though cost-savings may be captured by distributors

Parallel trade has resulted in moderate savings for health insurers and the national health systems of importing countries of the European Economic Area, thanks both to increased use of cheaper imported drugs and to decreases in prices due to competition, though the main beneficiaries of parallel trade have been intermediaries (see Enemark *et al.*, 2006 for a review). The most recent study estimated both direct (consumption at a lower price) and indirect (downward pressure on prices) savings achieved in Denmark and Sweden thanks to parallel trade. In 2004, these savings represented, respectively, 1.4% and 1.9% of Danish and Swedish total pharmaceutical expenditures (Enemark *et al.*, 2006; and OECD, 2007). Only direct savings were estimated for Germany and the United Kingdom; they represented 0.4%[16] and 1.7%, respectively, of total pharmaceutical expenditures.

However, savings from parallel trade have been declining (Enemark *et al.*, 2006) and the potential for further savings may be limited by price harmonisation within Europe and by strategies employed by manufacturers to limit parallel trade (see Chapter 5).

Pursuing good value for money in spending on pharmaceuticals

There is no single measure by which to assess the value for money that OECD countries attain in their pharmaceutical expenditure. Ideal indicators would assess the amount of health improvements attributable to pharmaceutical expenditure. Lacking these, it is useful to look at a range of partial indicators that provide information that is actionable from a policy perspective. For example, countries differ in the extent to which they achieve price competition of different sorts: for products (whether or not on-patent) with therapeutic alternatives and for products that have gone off-patent and are subject to competition from generic alternatives. In addition, countries vary in the degree to which they have established cost-effective pharmaceutical distribution systems. We review differences in cross-country performance by these indicators, together with information on the role of pricing and reimbursement policies in contributing to performance, below.

Pricing and reimbursement practices that affect value for money

In the pharmaceutical sector, securing value-for-money means concentrating public spending on pharmaceuticals which are necessary, effective, and used appropriately, and obtaining the best possible price. Interventions at both micro- and macro-levels are likely to improve value-for-money of pharmaceutical spending.

Subsidy design is a means to achieve value-for-money

The first objective for OECD countries should be to concentrate public subsidies on drugs which are effective and considered necessary to prevent or treat illnesses. However, the frontier between health problems and well-being issues is not always easy to draw. Recent debates about the inclusion/exclusion of life-style drugs in public and private drug benefits illustrate the dilemma that purchasers may face (Walley, 2004). For instance, the English NHS decided to cover smoking cessation drugs and obesity treatments on public health grounds while Germany decided to not cover these drugs. In France, obesity drugs are not covered because they are not considered to be effective enough and smoking cessation drugs have been subsidised only since 2007 up to EUR 50 per year.

Many countries do not subsidise, or have stopped subsidising, OTC and low-cost medicines. However, it should be kept in mind that OTC status is determined on safety grounds by the authorities that grant marketing authorisations, which is not necessarily linked to therapeutic utility and effectiveness. This means that de-listing OTC drugs may render some important and effective drugs (for instance, pain-killers or antihistamines) unaffordable for some groups of patients. Countries can help ensure access to OTC drugs by vulnerable populations by organising the distribution chain in a way that promotes price competition, *i.e.* authorities should not restrict the distribution of OTC medicines to pharmacies. Countries could also erect safety nets for the most vulnerable parts of the population, although the design of such a scheme may be difficult for drugs that are not subsidised.

The problem is different for private purchasers since they can offer different levels of guarantees and premiums, among which plan sponsors or consumers are able to choose their preferred option.

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Obtaining the best possible price for a given therapeutic value

A range of policies aim at obtaining the best possible price for a given therapeutic value, including promoting price competition in off-patent market segments, setting common reimbursement amounts for groups of drugs clustered according to bioequivalence, class or therapeutic similarity, and encouraging parallel importation of the cheapest products. As the impact of the two last options has been assessed in earlier sections of this chapter, we examine below the prospective impact of policies promoting competition on the off-patent market.

Patent expiry opens the road for generic competitors and may put pressure on prices of off-patent products. Although price competition does not always result in lower prices for off-patent originator products, the use of cheaper generics is expected to lower substantially the average cost of treatment. However, a number of conditions are important to maximise the impact: patients (though cost-sharing) must be price sensitive, doctors and/or pharmacists must have incentives to prescribe or dispense cheaper drugs, and several generics – qualified as substitutable for the originator – must be available in the market.

We have already shown that countries perform very differently in terms of generic market share by value and by volume. However, success in generic competition is not necessarily linked to market share. Some countries have obtained low generic prices but still have low penetration of the market by volume (indicating that the incentives of physicians, pharmacists or patients may not be aligned in favour of the lowest-price alternative). Others have obtained high penetration of the market by volume, but have not obtained significant price erosion.

The impact of efforts to link a medicine's price with the value and benefits it offers

As discussed in Chapter 3, some pricing and reimbursement schemes consider a product's value either explicitly or implicitly. Pharmaceutical purchasers are increasingly making efforts to link the price or reimbursement level with the incremental benefits offered by new drugs with therapeutic comparators. Often, new products are compared in terms of relative cost-effectiveness with comparable products, as variously defined. Less commonly, regulators or purchasers define explicit thresholds at which products may be considered cost-effective at a given price, given assumptions regarding use and effectiveness.

The characteristics of the scheme will largely determine the prospective impact of the use of pharmaco-economics in decision-making on efficiency of health and/or drug expenditure.

First, an important issue emerges in the question of which costs and benefits to value in a cost-effectiveness assessment, depending on whether the payer's perspective[17] or a social perspective[18] is adopted (see Chapter 3). These different approaches will result in different assessments of absolute and relative value of a product. Moreover, their potential impact on health systems varies.

In a free and unsubsidised market, the willingness and ability to pay of individual consumers would define price elasticity, suggesting that the payer perspective results in a better approximation of market outcomes. However, to the extent that there are externalities associated with pharmaceutical consumption *(e.g.,* health improvements resulting in increased worker productivity), markets would underestimate the value of the

products. This suggests that adopting the social perspective would result in an outcome that comes closer to maximising social welfare.

The social perspective can be at odds with responsibilities and objectives of decision-makers in charge of ensuring efficient use of resources allocated to the health system, however (Brouwer *et al.*, 2006). Interventions deemed cost-effective at the societal level may well be costly and not cost-effective at the health-payer level.

Another important feature is the definition of cost-effectiveness thresholds for decision making. As seen in Chapter 3, countries have been reluctant to define thresholds and sometimes seem to employ several implicit thresholds, as well as ignoring them, as sometimes is the case for orphan drugs or for drugs treating life-threatening diseases for which no treatment is yet available (Eichler *et al.*, 2004). Beyond these considerations, how should the cost-effectiveness threshold be set to reflect citizens' willingness-to-pay for drugs?

The World Health Organisation (2002) has suggested that a cost-effectiveness threshold equal to three times the GDP per capita per DALY (Disability Adjusted Life Year) could be a cut-off point for financing health interventions, endorsing the implicit assumption that revenue is the main determinant of citizens' willingness to pay. According to such a principle, the cost-effectiveness threshold in 2004 would be 108 000 USD/DALY in the United States and 53 000 USD in New Zealand (figures presented in Eichler *et al.*, 2004). Several studies have inferred implicit cost-per-QALY thresholds from past decisions of assessment bodies, but give somewhat contradictory results (Eichler *et al.*, 2004; Henry *et al.*, 2005). Henry *et al.* (2005) found that NICE and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) had very comparable upper thresholds (49 000 AUD/QALY for NICE and 52 400 AUD/QALY for PBAC), beyond which the probability of listing or positive recommendation for use is virtually nil.

Finally, pharmaco-economic assessments do not always operate from the same perspective. NICE assessments generally consider a class of products or different interventions, while other assessment bodies consider isolated products (Sweden[19]) or even a product's indications separately (Canada, Australia). Most often, regulators and payers respond to evidence that products are less cost-effective for certain indications by restricting listing of the product to cost-effective uses, rather than to establish distinct prices – though such a solution could be envisaged (for instance by asking the manufacturer to produce different packages for different indications). However, this might be difficult to enforce in practice, particularly as various actors in the distribution chain would face incentives to substitute a lower-priced equivalent product.

Only a few studies considered the extent to which recommendations or decisions from pharmaco-economic processes had an impact on the uptake of products with positive recommendations or listings. Sheldon *et al.* (2004) showed that positive recommendations for the use of taxanes in treating breast cancer and for the use of anti-obesity drugs had a significant impact on NHS doctors' prescribing. McMahon *et al.* (2006) showed high variation in provincial and federal drug plans formulary listings in Canada after the Common Drug Review's decisions, likely to influence drug consumption.

In a context of fixed budget constraints, adoption of new and costly technologies (either high priced or with large population targets) are likely to divert health funds from other health interventions that could potentially be more cost-effective. In order to avoid such distortions in fund allocations, the governments in England and Wales decided

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in 2002 that any positive recommendations of NICE should be allocated the corresponding funds to allow local providers to purchase the new technology. Any new technology approved is thus supposed to lead to supplemental funding – though NHS authorities may incorporate future expected decisions in their annual budgetary exercise.

In the case of recommendations or listings for restricted use, incentives or regulatory controls have a role to play. Wherever health providers are constrained by budgets, they will tend not to use drugs beyond listed or recommended indications. In other circumstances, controls may be necessary to ensure that drugs are prescribed appropriately.

The reliability of information submitted by those with financial interest in drug coverage, as well as the uncertainty of clinical claims raise problems for decision-makers. A study on PBAC decisions showed that the probability of acceptance of a technology was higher – cost-effectiveness being constant – when the level of confidence in clinical claims was higher (Harris *et al.*, 2006).

Risk-sharing arrangements may provide a means of linking price to value and reducing the cost of mistaken or inadequately informed decisions regarding subsidies. However, until now, these schemes have only rarely been used and overall results are not available. In any case, periodic reviews of assessment are highly desirable since effectiveness in "real use" has sometimes proved to be different than claimed efficacy.

Efficient distribution of medicines

The share of retail prices accruing to wholesalers and pharmacists is highly variable across countries (see Table 1.A1.1 in Chapter 1). Though these differences are partly explained by differentials in labour costs across OECD countries, they undoubtedly reflect differences in the efficiency of drug distribution, representing a significant frontier for value improvements in many OECD countries.

Some countries or purchasers recently introduced fixed fees to pay pharmacists' services. Fixed fees present the advantage of not being linked to the prices of medicines. Indeed, there is no obvious reason to link the remuneration of distribution chains to the price of medicines. If some products require particular storage features, their management could be paid accordingly. On the other hand, the definition of caps may foster competition between distributors and finally reduce retail prices, at least if the final purchaser benefits from a part of the savings.

Conclusions

While access to medicines in the OECD countries studied appears to be at a very high level, there is room for improvement. This is possible without sacrificing cost control. Efforts to improve value for money in public spending on pharmaceuticals could do a lot to free up resources that could be better spent enhancing the availability, accessibility and appropriate use of effective medicines. Many, if not all countries have some room for improvement in this respect. They could good get better value for their money by maximising use of generic alternatives to off-patent original products, fostering generic price erosion through competition, ensuring efficient distribution systems for prescription and OTC products, and becoming more sophisticated in their reimbursement pricing strategies.

Notes

1. The Transparency Directive (Directive 89/105/EEC) adopted by the Council of the European Union in 1989, sets maximum delay periods for pricing and reimbursement decisions to EU member countries (90 days after manufacturers' application for reimbursement and 90 days for reimbursement, which makes a total of 180 days) and calls for the use of more transparent criteria in decision-making.
2. Some NHS primary care trusts have delayed reimbursement for some drugs that were being assessed by NICE by as much as 32 months. This so-called "NICE blight" applies to a relatively small number of drugs (Cohen *et al.*, 2007).
3. Agreement signed between the French pharmaceutical industry association and the Economic Committee on health products (*www.leem-media.com/leem-image/leem/document/412.pdf*, accessed 1 August 2007).
4. Lanjouw (2005) analysed a sample of 836 new pharmaceuticals, launched in 68 countries over 20 years (1986-2002). She measured the probability of entry in each country (within two years and within ten years) against a set of variables representing the level of IPR protection, the existence and scope of price control (depending on whether some or all of the market was regulated), market opportunities (population size and structure), economic variables (GDP/capita, and other variables), demand-side regulation (adoption of an essential drug list, use of national formulary, of national guidelines), and potential for imitative competition (share of total R&D expenditure in GDP).
5. The study utilised 133 pharmacologic quality-of-care indicators developed by experts for use with data collected through survey interviews and medical record reviews.
6. For example, the comparator countries for international benchmarking of pharmaceuticals prices in Canada were selected as ones that had or aspired to have a strong national presence of the pharmaceutical industry (Paris and Docteur, 2006).
7. See, for example, the 2004 testimony of US Centers for Medicare and Medicaid Services Administrator Mark McClellan before the US Finance Committee, in which he argued that "using competition to drive price negotiation will maximize savings on drug prices, as well as, or better than when government does direct price negotiation".
8. The bargaining power of Medicare prescription drug plans (PDPs) was weakened by a provision of the Medicare Modernization Act requiring PDPs to offer drugs within each therapeutic category and class (Atlas, 2004). This provision was interpreted as requiring PDPs to list "more than one drug" in each therapeutic class. The US Pharmacopeia (USP) is in charge of defining the relevant therapeutic classes, in consultation with stakeholders, to help PDPs to structure formularies and curtail them from "skewing formularies away from the drugs needed by beneficiaries with the costliest conditions". The definition of therapeutic classes is important as the bargaining power of PBMs decreases as the number of classes increases. The USP defined 146 classes in 2004, while PBMs were asking for no more than 90 and manufacturers for more than 200 classes (Atlas, 2004).
9. The rebate is computed for a "normalised brand prescription", *i.e.* adjusted for differences in length/size of prescriptions among studies PBMs. We were not able to compute how much this represents in PBMs total expenditures.
10. Consistency was defined as having the difference between the country's pharmaceutical price level and its economy-wide price level less than one standard deviation from the OECD average.
11. France's pharmaceutical price level may overstate the prices paid, to the extent that they do not take into account confidential rebates negotiated with manufacturers. Manufacturers may be willing to grant such concessions to France because of its high volume of drug consumption and because lack of transparency ensures that the low prices in France will not influence the prices manufacturers are able to obtain in other markets.
12. It is likely that the original products include both on-patent and off-patent originals. Furthermore, some countries may have reported prices for original products that were still patent protected, whereas the price for the same product in another country may have been reported for an off-patent original. The extent to which this is a problem is not known.
13. This similarity may be partly explained by the fact that 75% of products in the master list for which prices were sought are original products. However, data correspondents were instructed to report prices for a mix of products representative of the mix of products sold in the country.
14. Canada also uses the United States – whose economy-wide price levels are close to Canada's – as a reference country in its patented medicine price regulation.

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15. Companies with branded prescription drugs with NHS sales exceeding 1 million GBP in 2004 were required to reduce prices by 7% from 1 January 2005.
16. The authors note that savings from parallel trade in Germany were exceptionally low in 2004 due to other cost-containment measures adopted the same year, which made parallel trade less attractive.
17. NICE in the United Kingdom adopts the payer perspective, considering the net cost to the National Health Service associated with a net benefit obtained by the patient.
18. The LFN in Sweden, on the other hand, adopts a broader social perspective, taking into account net costs and benefits that accrue to society and not only the health service (Moïse and Docteur, 2007b).
19. Sweden's pharmaceutical pricing agency (LFN) has undertaken retrospective class reviews for products approved for reimbursement prior to the LFN's inception in October 2002.

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ANNEX 4.A1

The Relationship between Retail Pharmaceutical Price Levels and Economy-wide Price Levels in OECD Countries

It is possible to examine the relative price levels of pharmaceuticals using price indices prepared by OECD and Eurostat as input to the development of economy-wide purchasing power parities (PPPs), which are used to convert nominal expenditure levels to real expenditures by adjusting for differences in the price levels and currency exchange rates (see Box 1.2 for more details).

This annex provides a detailed comparison of economy-wide price levels with the level of retail pharmaceutical prices. The comparison begins with an overall assessment, then considers price levels for original and generic products.

Retail pharmaceutical price levels compared with economy-wide price levels

A comparison of retail pharmaceutical price levels and economy-wide price levels reveals some interesting findings (Table 4.A1.1).

Pharmaceutical price levels roughly correspond with economy-wide price levels in most countries

Two-thirds of OECD countries' pharmaceutical price levels[1] are consistent with their relative economy-wide price levels – consistency being defined as the difference between pharmaceutical price levels in a country and its economy-wide price levels being at least one standard deviation away from the OECD average. For instance, Belgium's economy-wide price level in 2005 – when converted to USD PPP – was about 5% above the OECD average and its pharmaceutical price level was about 9% above the average.[2] Similarly, Portugal had an economy-wide price level and a pharmaceutical price level that were both slightly below the OECD average.

Switzerland's pharmaceutical prices are even higher than prices overall

Switzerland has the third highest economy-wide price level in the OECD (140% of the OECD average) and the highest pharmaceutical price level (185% of OECD average), but it is notable that the margin on the pharmaceutical side is significantly greater than that for prices overall.[3] Even when taking into account high prices across the board, Swiss pharmaceutical prices are still notably high. Differential tax treatment may contributes somewhat to the difference – reimbursed medicines are subject to a 2.4% tax rather than

Table 4.A1.1. **Economy-wide price levels and retail price levels for pharmaceuticals, 2005**

	GDP-PPP comparative price level (OECD = 100)	Pharmaceutical comparative price level (OECD = 100)	Difference between pharmaceutical and economy-wide price level
Iceland	153	159	6
Denmark	143	120	–23
Switzerland	140	185	46
Norway	138	119	–19
Ireland	127	118	–9
Sweden	126	94	–32
Finland	123	111	–12
Japan	118	118	–1
Luxembourg	116	103	–13
United Kingdom	115	92	–23
France	114	91	–23
Germany	112	127	15
Netherlands	112	109	–3
Austria	110	106	–4
Belgium	109	105	–4
Italy	109	117	8
Australia	107	81	–27
New Zealand	105	113	8
Canada	105	134	29
United States	102	130	28
Spain	97	77	–20
Portugal	89	94	4
Greece	88	73	–15
Korea	75	71	–4
Mexico	70	106	36
Turkey	67	69	2
Hungary	64	73	9
Czech Republic	60	71	11
Poland	58	68	9
Slovak Republic	56	70	14
Standard deviation			19.2

Note: Price levels are expressed as a percentage of the OECD average price level, which is computed as a geometric mean. Countries that were more than one standard deviation away from the OECD average: pharmaceutical price level less than economy-wide price level – Denmark, Sweden, the United Kingdom, France, Australia and Spain; pharmaceutical price level greater than economy-wide price level – Switzerland, Canada, the United States and Mexico.
Source: Eurostat–OECD Purchasing Power Parity Programme, 2007.

the 7.6% tax applied to most other goods. However, the tax differential is small compared to the price gap and compared to other European countries with a minimum VAT of 15%.

Denmark's pharmaceutical prices are relatively high, but not as high as general prices in its economy

Denmark has relatively high overall prices, standing at 143% of the OECD average, and relatively high pharmaceutical prices, at 120% of the OECD average. Differential taxes are not a factor as Denmark's 25% VAT applies to pharmaceuticals as well as other goods and services.

In some countries, relative pharmaceutical prices deviate from economy-wide prices

Mexico has very low economy-wide prices and average pharmaceutical prices

Mexico's economy-wide prices are just 70% of the OECD average. Its pharmaceutical price level stands at 106%, however, suggesting that drugs in Mexico are much more expensive, relative to other goods and services sold in Mexico, than they are elsewhere. Danzon and Furukawa (2003 and 2008) found the same result in two separate, but similar studies comparing pharmaceutical ex-manufacturer prices.

Canada and the United States have average economy-wide prices and high pharmaceutical prices

The United States had an economy-wide price level that was 102% of the OECD average, while its public pharmaceutical price level was relatively high at 130% of the OECD average.[4] The situation is similar in Canada, with an economy-wide price level that was 5% above the OECD average and a pharmaceutical price level 34% greater than the OECD average.

Australia and Spain had average economy-wide prices and low pharmaceutical prices

Australia stands out in the other direction, with economy-wide prices that exceeded those of the OECD average by 7%, but with pharmaceutical prices at just 81% of the OECD average. Differential taxes may account for some of the difference, but the tax rate is too low to account for all of the difference; prescription medicines as well as OTC medicines are exempted under certain circumstances from the standard Goods and Services Tax (VAT) of 10%. At 97%, the economy-wide price level in Spain was not significantly different from the OECD average, but the pharmaceutical price level was 77%, much lower than the OECD average.

Sweden, France and the United Kingdom have high economy-wide prices and low pharmaceutical prices

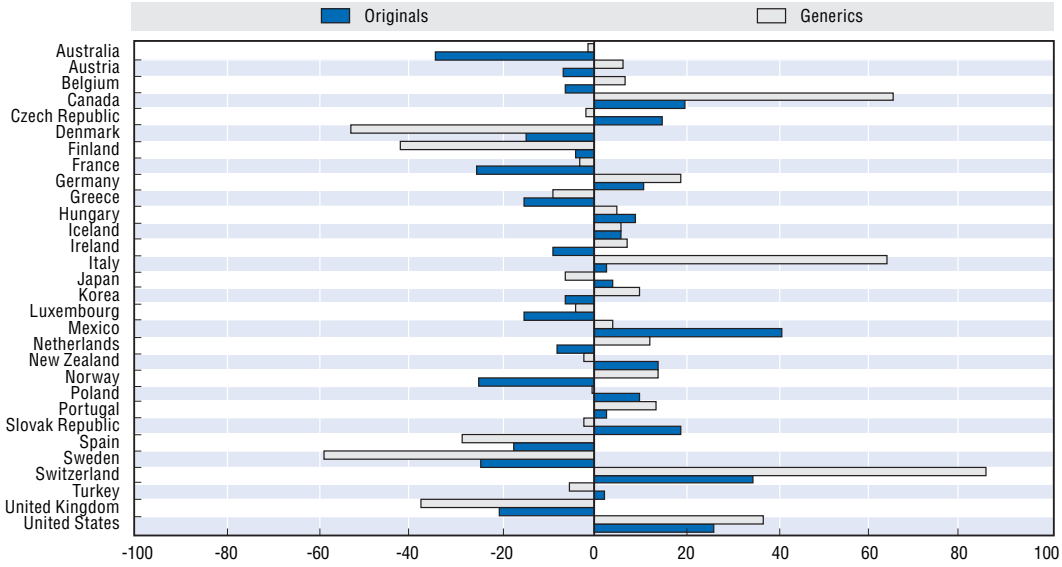
Sweden stands out in having economy-wide prices that were 126% of the OECD average, but pharmaceutical prices that were only 94% of the OECD average. France and the United Kingdom were similar, but the difference between economy-wide prices and pharmaceutical prices was less pronounced.

In all three cases, a differential treatment of pharmaceuticals in application of VAT may explain much of the variation between the pharmaceutical and economy-wide price levels. France applies a 2.1% VAT for reimbursed pharmaceuticals and a 5.5% VAT for non-reimbursed pharmaceuticals, compared to a 19.6% standard VAT. The United Kingdom has no VAT for pharmaceuticals furnished at National Health Service pharmacies; its 17.5% standard VAT applies to OTC and hospital medicines. Sweden exempts prescription-only medicines from its 25% VAT, but this is charged for OTC drugs. All of these tax rates reflect the situation in 2006 (PPRI, forthcoming).

Pharmaceutical price levels for original and generic products

Figure 4.A1.1 reveals a mix of patterns in relative price levels for original and generic products in OECD countries.

Figure 4.A1.1. **Retail price – economy-wide price level differentials for original and generic pharmaceuticals, 2005**



Note: Price levels are expressed as a percentage of the OECD average price level, which is computed as a geometric mean. The light (dark) shaded area represents original(generic) – economy wide price level differentials that fall within one standard deviation of the OECD average.

Source: Eurostat–OECD Purchasing Power Parity (PPP) Programme, 2007.

Pharmaceutical price levels roughly correspond with economy-wide price levels in most countries

Overall, most OECD countries' original and generic price levels do not differ substantially from their economy-wide price levels. Twenty-one countries had original price levels consistent – defined similarly to overall retail price levels – with their economy-wide price levels. Slightly more countries (22) had generic price levels consistent with their economy-wide price levels, although this is likely a statistical artefact due to the higher variability in generic price levels.

In some countries, relative original and pharmaceutical prices deviate from economy-wide prices

Sweden's and the United Kingdom's original and generic price levels are much lower than their economy-wide price levels

Sweden had the fifth lowest generic price level of any country, 67% lower than the OECD average price level for generics. This result is in large part due to Sweden's generic substitution policy. Although its original price level was the same as the OECD average, this was still substantially lower than its economy-wide price level. In both cases, the exemption from VAT for prescribed medicines contributes significantly to the price differentials with economy-wide prices.

Both original and generic retail prices in the United Kingdom were lower than the OECD average, especially generics (77% of the OECD average). The government pays the standard VAT (17.5%) for prescription medicines dispensed in retail pharmacies, essentially an exemption from VAT for prescription medicines. It is likely, therefore, that differences in

VAT applicability explain a significant portion of the difference between original and generic price levels with economy-wide prices.

Three countries have original and generic price levels that are much greater than their economy-wide price levels

Price levels for both original products and generics were considerably higher than economy-wide price levels in Canada, Switzerland and the United States. Switzerland in particular, had price levels that were substantially greater than the OECD average; the price level for originals was 74% greater than the OECD average, whereas that for generics was 125% greater. Despite the fact these high prices reflect Switzerland's standing *vis-à-vis* other OECD countries regarding economy-wide prices, the difference with its economy-wide prices are notable. In part the differential with economy-wide price levels reflects the exemption from VAT afforded to prescription medicines, but it also reflects Switzerland's pricing policies (Paris and Docteur, 2007).

In Canada's case generic pharmaceutical price levels are a more of an outlier than are original price levels; generic prices are 70% greater than the OECD average compared to 25% for originals (Canada's economy-wide price level is virtually equal to the OECD average). These results confirm the findings from the case study for Canada, especially with regards to generics (Paris and Docteur, 2006).

On one level the finding for the United States is not surprising considering it is generally acknowledged as having one of the highest pharmaceutical price levels among OECD countries (at least for ex-manufacturer prices) and economy-wide price levels that are almost identical to the OECD average. However, it is somewhat surprising to find that US generic prices are 39% greater than the OECD average. Several studies have shown that, although original prices in the United States are among the highest in the world, price levels for generics tend to be much lower (ITA, 2004; PMPRB, 2006; Danzon and Furukawa, 2008).

Original price levels in Australia, France and Norway are lower than their economy-wide price levels

Original price levels in Australia are fourth lowest among OECD countries even though its economy-wide price level is slightly above the OECD average. There is no VAT for prescription medicines in Australia, which may explain some of the difference with economy-wide price levels. However, differential VAT rates may be less of a factor in explaining why the original – economy-wide price level difference is greater than for most other OECD countries, since the standard rate of VAT (10%) is lower than most OECD countries.

France is similar to Australia, although its original and economy-wide price levels are slightly greater. In France, the VAT for prescription-only medicines is lower than it is for other goods, which at 19.6% is almost double the rate in Australia.

The reason why original prices in Norway are significantly lower than economy-wide prices is probably due to the relatively high overall prices in Norway. The price level for original products in Norway is slightly above the OECD average, but economy-wide price are the fourth highest in the OECD. Furthermore, the standard VAT rate is applicable to prescription medicines ruling differential VAT rates as a possible explanation.

Original prices in Mexico are larger than economy-wide prices

Mexico has an economy-wide price level that is significantly lower than the OECD average, but a price level for original drugs that is greater than the OECD average. With generic prices that are in-line with its economy-wide price level, the relatively high price of originals in Mexico can explain much of the the difference between original prices and economy-wide prices observed earlier in this Annex.

Generic price levels in Denmark and Finland are lower than economy-wide price levels

The difference between generic prices and economy-wide prices in Finland is lower than all countries except Sweden and Denmark. A significantly lower VAT rate for prescription medicines than for all other goods offers a partial explanation. This is not the case in Denmark, where the standard VAT rate applies to prescription medicines.

Italy has a much higher generic price level than its economy-wide level

Italy's generic price level was second highest among OECD countries. With only an above average economy-wide price level, the difference with the generic price level was third largest, being roughly the same as for Canada. The VAT rate in Italy for all goods is double the rate for prescription medicines.

Notes

1. It is important to note that the price levels being considered are retail prices, which include the price received by the manufacturer plus wholesale and retail mark-up, plus any VAT or other tax paid by the final purchaser. A presentation of the average prices received by manufacturers would result in different relative rankings across countries.
2. Note that price levels should be used to provide a rough estimate of where a country stands relative to its peers. They are not sufficiently precise to be reliable in distinguishing ranking of countries with similar price levels.
3. The very low level of penetration of generic products in the Swiss market, compared to other countries offering high ex-manufacturer prices for patented medicines (*e.g.*, the United States, Canada and Germany), likely contributes to Switzerland's relatively very high retail price level.
4. The 2005 prices reported by US officials from the Bureau of Labor Statistics (BLS) were below those in the 2007 US Federal Supply Schedule, widely considered to be among the lowest US prices. According to BLS officials, the data were obtained from a check of several Internet pharmacies.

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Chapter 5

The Impact of National Pricing and Reimbursement Practices on Prices and Availability of Medicines in Other Countries

This chapter examines the transnational impact of national pricing and reimbursement policies. Pharmaceutical pricing policies, and their impacts on prices and availability of medicines, are becoming more exportable in a globalised market. This chapter documents these and assesses the extent of their transnational effects. The various strategies that manufacturers in a globalised pharmaceutical market use in response to national pricing policies are also examined. Finally, the extent to which pricing policies and manufacturers' strategies have led to convergence among countries in pharmaceutical prices is assessed.

Introduction

In a global pharmaceutical market, the impacts of national pricing and reimbursement policies, designed with national objectives in mind, transcend borders with transnational implications. The pharmaceutical policy environment is changing, with national markets becoming ever more integrated, and this in large part is a direct result of globalisation. Trade is easier, mobility is easier, and communication is easier than ever. These trends show no sign of reversing – rather the contrary..

National pricing policies are likely to impact the availability and prices of drugs in foreign countries

Pricing policies can affect the availability and prices of drugs beyond countries' borders through several channels. The most obvious and direct impact of a country's policy is when it is taken up by other countries. Recent history shows that several pricing policy tools have been widely adopted by OECD countries, among which are external benchmarking and reference pricing. Globalisation is a second route by which national pricing policies may have a cross-border impact as growing international trade in pharmaceuticals – including parallel trade – is likely to lead to some convergence in prices across borders.

The expected effects of cross-pollination of pharmaceutical pricing practices

To assess the degree to which national pricing and reimbursement policies stand to influence policies in other countries, we tracked the origins and the diffusion across OECD countries of the use of three techniques with direct or indirect impact on pharmaceutical prices: *i)* pharmaco-economic assessment; *ii)* international benchmarking; and *iii)* therapeutic referencing.

Pharmaco-economic assessment

Since the introduction in Australia in 1993 of the systematic use of pharmaco-economic assessment in the reimbursement process, many OECD countries have begun to use pharmaco-economic assessment at different stages of pharmaceutical policies, including for reimbursement and pricing procedures (Drummond *et al.*, 1999; Dickson *et al.*, 2003).

One country's use of pharmaco-economic assessment should not be expected to have any direct implications for the price or availability of medicines outside the country. Moreover, pharmaco-economic studies are generally not considered to be transferable across countries because of differentials in countries' costs and epidemiological contexts. There is no reason to believe, therefore, that the proliferation of pharmaco-economic studies will result in more price convergence between countries. Nevertheless, some countries – notably some of the newest EU member states that lack the sophisticated infrastructure to undertake systematic pharmaco-economic studies on their own – use the

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results of pharmaco-economic studies in other countries – mainly the EU15 states – in their pricing and reimbursement decisions (Gulásci, 2007).[1] This has been facilitated by the creation of a European network of health economic evaluation databases (EURONHEED). To the extent that pharmaco-economic studies are *generisable* and *transferable*,[2] the possibility of some influence on price convergence cannot be ruled out.

International benchmarking

Following the adoption of external price benchmarking in Canada in 1987 as part of its price regulation process, more than half of OECD countries have begun using international benchmarking for drug pricing and/or reimbursement policies, mainly to regulate the price of medicines at market entry (see Chapter 3).

When external benchmarking is used for *new* drugs without therapeutic alternatives, manufacturers will often launch innovative drugs in countries where they are free to set market entry prices (*e.g.,* the United States, Germany and the United Kingdom) or in countries where they are likely to obtain relatively high prices (*e.g.,* Switzerland). Such a predictable sequence, confirmed by further analysis, calls into question the effectiveness of external benchmarking as a means of limiting the price charged by a manufacturer, as discussed in Chapter 4. Furthermore, one of the predictable impacts of such a policy is some international harmonisation in pricing, in the direction of higher prices.

Evidence that this in fact occurs comes from experience in cross-jurisdictional price referencing within countries. For example, the requirement that the US Medicaid programme obtain the best possible price in the US market resulted in price increases for some private purchasers (CBO, 1996). The largest discounts that pharmaceutical manufacturers consented from the wholesale price fell from an average of more than 36% in 1991 to 19% in 1994, which CBO attributed to the Medicaid best-price provision.

Germany's prices are used as a benchmark in most countries that employ external price benchmarking. Stargardt and Schreyögg (2006) assessed the impact of a price change in Germany on EU15 countries that use external price benchmarking for setting reimbursement prices (Austria, Greece, Ireland, Italy, Luxembourg, the Netherlands and Portugal) The authors estimated[3] the hypothetical impact a one euro price reduction in Germany[4] would have on the prices of new and old[5] drugs in countries that use external benchmarking; for example, the direct effect of the reduction for a new drug in Germany on the price in Austria (which benchmarks Germany) would be a price reduction of EUR 0.09. Furthermore, there would be an additional reduction of EUR 0.15-0.19 due to an indirect effect (Austria benchmarks several countries which benchmark Germany).

Reference pricing in Germany may have cross-border impacts through the medium of external price benchmarking. For example, Switzerland explicitly introduced a policy of reviewing Swiss prices against those in comparator countries (the list of which includes Germany) two years after patent expiry in order to benefit from the price decreases occurring in Germany thanks to reference pricing (Paris and Docteur, 2007). Such actions may lead manufacturers to modify their strategies in terms of launch sequences. It also could contribute to reduced price differentiation across therapeutic groups in countries that rely on external price benchmarking, even if the countries themselves do not use reference pricing.

There is also evidence that international benchmarking could have a negative impact on the availability of drugs. Danzon *et al.* (2005) showed that countries with lower prices

have fewer drug launches and longer delays for launched products, even after controlling for GDP and expected volumes of sales, which the authors interpret as an impact of the potential for low prices to spill over into other markets or incite parallel trade (in Europe).

In conclusion, the net impact of reimbursement and pricing policies in one country on other countries' drug prices is not simple to assess. External benchmarking provides the greatest opportunity for price convergence and is the most direct way in which national drug prices policies stand to impact other countries' prices.

Globalisation, parallel and cross-border trade should lead to price convergence

Globalisation undoubtedly increases the cross-national impact of national policies. First, market harmonisation and the diffusion of information – notably on prices paid in other countries – make regulators, payers and purchasers more aware of what others are paying for particular products and more likely to urge pharmaceutical companies to consent to lower prices. Second, the threats parallel trade and cross-border trade pose for manufacturers are likely to play a role in shaping manufacturers' pricing and product launch strategies.

Market harmonisation and transparency in pricing prevent manufacturers from using price discrimination

In recent decades, the pharmaceutical sector has become increasingly concentrated as multinational firms have increased their dominance of the global market (see Chapter 1). For example, the share of global pharmaceutical sales accruing to the top ten manufacturers increased from 28% in 1987 (WHO, 2004) to 46% in 2006 (IMS Health, 2007). More than ever, the same products are distributed worldwide, facilitating both cross-country price comparisons and international trade.

The diffusion of information about prices paid by consumers in other countries clearly creates a hurdle to market segmentation and third-degree price discrimination by the pharmaceutical industry. NGOs and governments in less developed countries pressure pharmaceutical companies to obtain lower prices, sometimes using the threat of compulsory licensing to achieve their goals.[6] On the other hand, there is no international consensus that pharmaceutical prices should vary according to differences in the ability to pay. For example, the implementation of the Medicare Modernization Act in the United States in 2003 caused animated debates about the prices paid by Americans compared to those paid in other industrialised countries.

Though regulatory authorities in developed countries extensively use international benchmarking in pricing and reimbursement decisions, reliable price information is not always readily available. In some cases, regulators or purchasers agree with the pharmaceutical industry to disconnect the prices actually paid from listed prices by implementing confidential rebates on listed prices. However, recent initiatives tend to favour more information sharing, at least at the European level. For instance, the European Commission funded project on pricing and reimbursement policies (PPRI) provided officials responsible for pricing and reimbursement decisions with opportunities to share information informally, not only on pricing and reimbursement policies but also on price levels. Information available for developing countries is also an area of focus, as the World Health Organization and Health Action International have developed a tool allowing price comparisons for certain products between developing countries to encourage better-informed decision-making in those countries.[7]

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Some analysts have argued that too much transparency in international pricing is likely to encourage legally permissible parallel trade as well as illegal cross-border trade and thus impair the availability and affordability of drugs in poor countries, as a consequence of the strategies used by originator manufacturers (Ridley, 2005).

Parallel and cross-border trade, if fully developed, would promote price convergence

Kanavos *et al.* (2004) extensively reviewed the literature on the expected costs and benefits of parallel trade in the pharmaceutical sector. To summarise, parallel trade is expected to increase competition and global welfare by limiting market segmentation and abusive price discrimination. In pharmaceutical markets, it is expected to lower prices in destination countries and to mitigate price differentials. In terms of welfare, losses in revenue for the price-discriminating monopolist are expected to be over-compensated by consumers' welfare gains in the destination country. However, the total welfare effect is not known since the balance between losses and gains is difficult to measure.

Parallel and cross-border trade do not represent large shares of the pharmaceutical market in OECD countries (see Chapter 1), although they can be substantial for some products, *e.g.* it has been reported that, in Sweden, AstraZeneca lost almost all domestic sales for some of its products to parallel imports (Arfwedson, 2004). The threat of parallel trade is likely to impact both policy making and manufacturers' strategies, as demonstrated in the following section.

Manufacturers use various strategies in order to maximise net revenues in the global market and counter spill-over effects of national policies

In the globalised pharmaceutical market, companies launching drugs on an international basis develop pricing strategies to maximise net revenues across all potential markets. When markets are not separable, the firm will need to develop a pricing strategy that takes into account not only local market conditions, but also how the price it attains in one market will affect prices and demand for parallel trade in other countries (see Box 5.1). The end result is that firms may establish higher prices in particular markets (*i.e.,* those with relatively high price elasticity of demand) than would be profit-maximising if markets were separable. Evidence that manufacturers use both strategic launch and discriminatory pricing to maximise worldwide revenues, as well as other strategies to prevent the specific risks of parallel trade and cross-border trade, is considered below.

Product launch strategies in a global market

Danzon and Epstein (2008) assessed the impact of prices in foreign countries on the probability of launch in a given country and found that the probability of launch in a given market is not affected by prior launch in Spain, Portugal or Greece (low-price countries).[8] The authors did find that prior launch in high-price countries (Germany, non-EU countries) did have a positive effect on the probability of launch, although this effect was also seen for two low-price countries (France and Italy). As reported earlier, Danzon *et al.* (2005) found that manufacturers delay launches, or do not launch at all, in low-price countries to minimise spill-over effects.

However, the main drawback of these studies is that they generally consider the time elapsed between first launch in the world and launch in each country, without being able to distinguish the result of company's launch strategies from results of regulatory processes.

Box 5.1. **Manufacturers strategies in a world of separable markets**[1]

If markets are separable, firms maximise net revenues by launching as promptly as possible in *all* markets and by charging higher prices in countries with relatively higher per capita incomes. When markets are not separable, firms' actions must take into account potential spill-over effects when setting or negotiating prices with major purchasers (public or private) or officials who decide on reimbursement (including price in some countries).

The maximum price (P^{max}) for a new product in a given country will be a function of three variables: 1) the prices of existing therapeutic competitors; 2) the difference in cost-offsets between the new product and existing therapeutic competitors; and 3) the cost-effectiveness of the new pharmaceutical (itself a function of the new drug's efficacy relative to competitors). All three of these variables are positively influenced by the level of the country's per capita income.

If a firm is able to set the price of its new product at the maximum price then it will extract all social surplus. Therefore, one would expect that this price will not hold as manufacturers interact with the government (acting as the decider on reimbursement and/or price setter) or purchaser(s) who will have a reservation (offer) price above which they will not pay for a new pharmaceutical.[2] Other things being equal, the offer price will be lower in those countries where there are budget concerns associated with high expected volume of sales or otherwise. This may result, in some cases, in government's preferring a delayed launch in the expectation of obtaining a lower price; or even no launch if there is no real possibility that the manufacturer will agree to the offer price.

The firm will have a reservation (ask) price below which it will not sell the new product. The ask price will be a function of the potential market size of the country, *i.e.* the country's per capita income and potential volume of sales. Furthermore, since markets are not separable, the ask price will be conditional upon the country's potential for spill-over effects. Under such circumstances, it may be preferable for the firm to delay launch in the country in the hope of negotiating a higher price if the lost revenue from launching later is less than the revenue loss that would occur in other countries due to spill-over effects. The firm may not launch at all if the revenue loss from spill-over effects exceeds the expected revenues accrued from launch.

1. The theoretical framework discussed in this text box is adopted from Danzon *et al.* (2005).
2. Danzon's framework does not specify reservation prices in the case where there are multiple purchasers within a single country (such as is the case in the United States where private purchasers operate alongside public purchasers), although the basic principle of a price above which the purchaser would reject should apply. In this case, the unique offer price for the country can be thought of as the aggregation of the offer prices of the various purchasers.

In some cases, strategic launches may result in the non-launch of certain drugs in some countries. For example, there is at least one recent example of a cancer drug that was not launched in Canada, where it would have been limited by regulation to a European price level (Paris and Docteur, 2006).[9] The manufacturer may have been concerned about either cross-border trade or political pressure to lower the price in the United States, where the price was approximately double the European level.

Pricing strategies in a global market

Manufacturers also resort to pricing strategies to avoid parallel and cross-border trade or to avert downward pressure on prices that could occur as a consequence of external

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benchmarking. The most obvious strategy is to avoid significant price differentials between countries by establishing relatively uniform list prices and negotiating confidential rebates in countries with greater price sensitivity. For instance, pharmaceutical prices in Mexico are higher than one would expect, given relatively low income and low prices in Mexico generally; one possible explanation for this is that it may be partly due to the threat of cross-border trade with the United States (Moïse and Docteur, 2007). Manufacturers would rather forego some retail sales they could have had in Mexico than risk increasing the volume of US cross-border trade with Mexico (or increase pressure to allow parallel imports). In Canada, one pharmaceutical firm refused to lower the listed price of a drug which had been judged "excessive" by the Prescription Medicine Prices Review Board (PMPRB, 2006) by almost 60%. Instead, it signed an agreement with the PMPRB guaranteeing that no Canadian purchaser would pay more than the maximum price allowed by the PMPRB. Such a disconnection between listed and effective price clearly aims to render the price less attractive for potential US purchasers (Paris and Docteur, 2006).

One obvious method to avoid parallel trade would be for manufacturers to increase product prices in low-price countries, thus reducing the arbitrage possibilities of parallel traders. However, most countries strictly curtail the ability of manufacturers to increase pharmaceutical prices, effectively limiting manufacturers' room to manoeuvre in this regard.

Danzon and Epstein (2008) explored the impact of cross-national spillovers on launch prices and showed that the impact of prices set in other countries on launch prices in a given country varies according to the category of drugs. They provide evidence to show that launch prices of superior[10] products are positively related to the lowest price received in high-price countries,[11] but the launch prices of inferior products are positively related to the lowest price received in high-price EU countries only.

Other techniques used to avert parallel or cross-border trade

Launch and pricing strategies are not the only means used by pharmaceutical companies to protect their interests from the risk of parallel and cross-border trade. They have also tried to ration the supply of their products in potential source countries; develop superficially different products (involving minor variations such as package sizes, a technique known as product proliferation) for marketing across countries; and use litigation and lobbying to increase barriers to parallel trade.

Several pharmaceutical companies have used supply-chain management strategies in order to ration the supply of products in countries which could potentially be a source of parallel or cross-border trade. In low-priced EU countries, for example, companies furnish wholesalers supplying national markets with quantities necessary to cover national needs and refuse to furnish products to exporters. In Spain, some companies choose to differentiate prices according to their purchaser and to sell drugs at higher prices to exporters than to wholesalers serving the national market. Although these "dual-pricing" practices have been challenged by parallel traders in courts or by appeals to the national anti-trust authority, the final decision regarding their legality has yet to be decided.[12] In Canada, manufacturers also rationed the supply to wholesalers supplying pharmacies believed to be responsible for cross-border trade with the United States (Paris and Docteur, 2006).

Two other strategies aiming to bar parallel trade rely on so-called "product proliferation" strategies. Parallel traders have to obtain – and purchase – a licence from the

destination country's licensing authority to be authorised to import a product; the imported product must have the same composition, form and strength as an existing product in the destination country. Manufacturers can thus use product proliferation to either reduce parallel trade opportunities – by applying for marketing authorisation for different dosages and strengths in different countries – or to increase parallel traders' costs of repacking – by giving different brand names to identical products in different countries. Kyle (2007) provides some evidence of the actual use of these strategies in the European Union. She also demonstrates that products which were likely to be the source or target of parallel trade were more likely to be discontinued by the originator than other products.

A variation of product proliferation strategies has occurred in Canada, as the result of an effort to avoid the impact of external price benchmarking across payers within the country. When Quebec instituted a policy requiring that the province obtain the best price offered to other purchasers in Canada, some manufacturers developed subsidiaries to serve the market in British Colombia, where a tendering process had resulted in low prices for certain products (Paris and Docteur, 2006).

Manufacturers also undertook litigation arguing that repackaging was interfering with consumers' ability to identify the manufacturer. The European Court of Justice has detailed the conditions in which repackaging is possible without infringing on trademark law (Kyle, 2005).

Last but not least, the pharmaceutical industry lobbies vigorously against legislation authorising parallel trade. Debates on the opportunity to authorise parallel trade in the United States and in Switzerland have been ongoing since the end of the 1990s.

There is some evidence of market entry price convergence among OECD countries

In an efficient market, the "law of one price" (LOOP) holds that prices of identical goods converge to a single price for all; buyers seek lower prices while sellers seek higher prices with both sides arriving at a unique market price. In reality, inefficiencies prevent markets from achieving a single price.[13] Instead of converging to a single price (absolute version of the LOOP), prices in the global (or regional, in the case of Europe) pharmaceutical market may converge to fall within a band with an upper and lower limit, stabilising over time (relative version of the LOOP). This would be consistent with the concept of price dispersion where such a band would be considered a measure of trading frictions in the market for pharmaceuticals.

The question of price convergence most often relates to the convergence of market entry prices received by manufacturers. However, few studies specifically address this issue and most studies compare prices at a given date in different countries, independently from the date of launch. It is necessary to consider both types of studies, since prices can vary along the drug's life-cycle. For instance, in very competitive markets, high entry prices may be reduced after a few years by the entry of competitors while lower entry prices set by regulation may remain unchanged for a longer period of time (Lu and Comanor, 1998).

What is the evidence of price convergence?

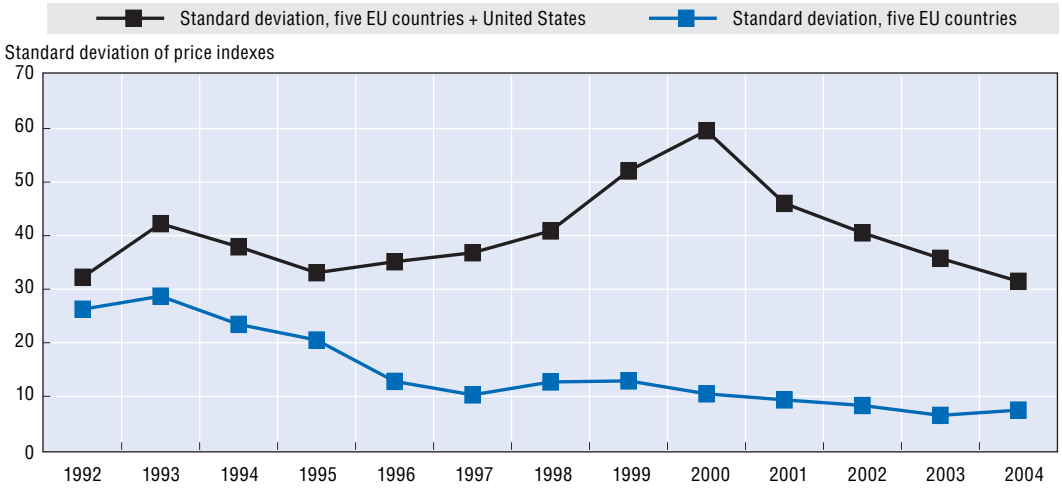
It would be inappropriate to use different studies containing price comparisons at different dates to draw definite conclusions about the trend in cross-country price dispersion, as price comparisons are very sensitive to methodology (Danzon and Chao,

2000). The only way to draw conclusions about such a trend is to either consider studies derived from longitudinal data or those that use the same methodology over time.

The UK Department of Health (DoH) presents such data in the reports on the Pharmaceutical Price Regulation Scheme (PPRS) it submits to Parliament on an almost yearly basis.[14] The DoH has computed price comparisons for several EU countries and the United States from 1992 to 2004, using the same methodology. The DoH selects the active ingredients of the top-selling brand name drugs in the United Kingdom and computes the average ex-manufacturer price per dose for each of these molecules in each country, using all available forms/strengths. Bilateral comparisons are undertaken by matching UK products to products in each of the comparator countries; in 2004 these products covered 27 to 48% of expenditures on brand name drugs in England. Multilateral comparisons are made for products available in all countries and therefore encompass a much smaller part of the market and a smaller set of countries. They are converted using current exchange rates and results are consequently influenced by changes in currency parities.

These comparisons indicate some price convergence for European countries but less so when the United States is included (Figure 5.1). However, these results must be

Figure 5.1. **Multilateral comparisons of UK pharmaceutical prices to comparator countries' prices, 1992-2004**



Note: Ex-manufacturer prices converted using current exchange-rates. The United Kingdom is the reference country. The other countries are France, Germany, Italy, the Netherlands, Spain and the United States.

Source: Department of Health, Pricing Regulation Scheme, *Reports to Parliament* (1997-2005)

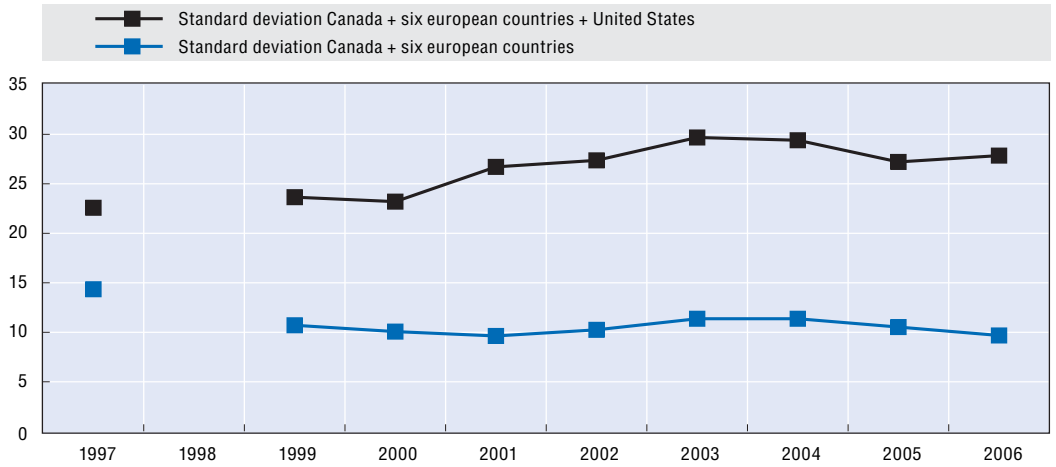
interpreted with caution, because of exchange rate fluctuations. For instance, the Spanish currency depreciated by 36% compared to the UK pound between 1992 and 2000 and then appreciated by 10% between 2001 and 2003. Nevertheless, prices in European countries have been converging since the early 1990s. US prices do not appear to converge with UK prices and the apparent convergence of the last period is partly due to changes in parity between the British pound and the US dollar (during the period the GBP/USD exchange rate rose from 0.57 in 1992 to 0.69 in 2001, before falling to 0.55 in 2004).

Annual reports from the Patented Medicines Prices Review Board (PMPRB) present bilateral comparisons of Canadian ex-factory prices of patented drugs with prices in the

seven countries referred to in the regulation defining excessive prices (France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States). Bilateral comparisons are based on patented products available in Canada and in the comparator country. The average foreign-to-Canadian price ratio for each product is computed, weighted by sales in Canada. Prices are converted to Canadian dollars using current exchange rates.[15, 16]

In the 2005 report, foreign-to-Canadian price ratios are published for the years 1987, 1997 and 2004. The trend shows evidence of a convergence in patented drugs' prices. When US prices are excluded from the analysis, the standard deviation of price indexes decreased from 19.0 to 9.7 over the period (Figure 5.2). The gap between US prices and prices in other countries appears to have grown over the period, although results may be blurred by large changes in exchange rates during this period.

Figure 5.2. **Bilateral comparisons with Canada of ex-manufacturer prices for patented pharmaceuticals, 1997 and 1999-2004**



Note: Ex-manufacturer prices converted using current exchange–rates. Canada is the reference country. The other countries are France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States. In 1987 the standard deviation was 27.9 for the seven countries and the United States and 19.0 when the United States was excluded.

Source: PMPRB (2006).

Though they do not apply to the same set of products – top-selling drugs independent of patent status for the UK study and all patented drugs for the PMPRB, although there may be some overlap – the two studies lead to similar conclusions: there is evidence of convergence between drug prices in the United Kingdom and those of comparator countries (similarly between Canada and comparator countries) when the United States is excluded from the sample of comparator countries.

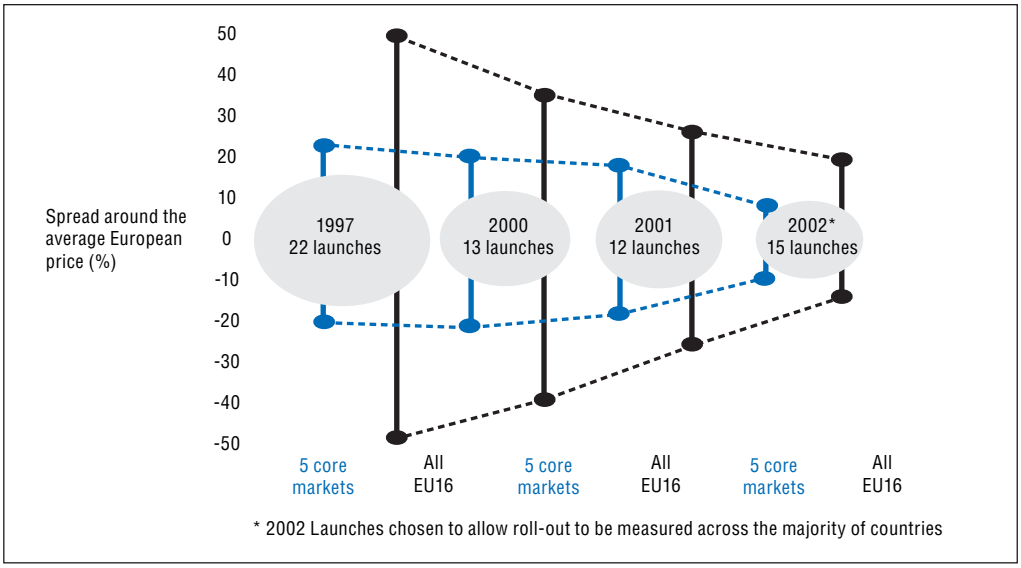
What about price convergence in the European market?

Within European Union countries, manufacturers have been encouraged to adopt a strategy to set or negotiate prices (see for instance, Kucher, 2000). This strategy, known as the "price corridor" strategy, consists in setting a reference price for several countries and a "margin" within which the prices of each country will be allowed to float. Companies are encouraged to set both a "soft upper limit" (price beyond which there is a risk of parallel trade) and a "hard lower limit" (the price that no subsidiary in any country is allowed to

undercut, because of expected adverse effects on both parallel trade and external referencing). This strategy is seen as intermediate between one of "decentralised pricing", *i.e.* setting a price for each country which maximizes the manufacturer's profit given the country's ability to pay, and one of "centralised pricing", *i.e.* setting a unique price for an entire zone to take into account the potential threat of parallel trade or international price referencing by national authorities.

To the extent that manufacturers have increasingly employed such strategies, convergence in ex-manufacturer prices in Europe would be expected. Indeed, there is some evidence of price convergence within Europe for newly launched products (Figure 5.3). According to IMS, average price differentials across the top five markets in Europe was less than 15%, which is generally considered as the threshold at which incentives for parallel trade are created (Cambridge Pharma Consulting, 2006).

Figure 5.3. **Price convergence of market entry prices in the EU countries**



Source: Cambridge Pharma Consultancy (2006).

In a recent study, Kyle *et al.* (2008) tested the hypothesis of drug price convergence in the European Union. The authors used a sample of products that included all prescription drugs of 36 therapeutic classes sold in retail outlets or in hospitals for which sales data in 30 countries from 1990 to 2004 were available. The sample contained 1 023 chemicals or chemical-combinations, 20% of which are still on-patent. The quantity-weighted average price across all presentations was computed for each chemical combination. The main outcome measures were mean price differentials and other means of dispersion within EU countries compared with within non-EU countries. The results suggest no substantial reduction in price dispersion within EU countries. There are several possible reasons why their results differ from the other results presented earlier, *e.g.* the other studies included fewer countries and compared prices for on-patent medicines only.

Not surprisingly, comparisons of wholesale and retail prices give a different picture. Considering a sample of eight innovative and reimbursed products, approved through the European Commission's Centralised Procedure, and used in outpatient care, Martikainen *et al.*

(2005) found high differentials in wholesale and retail prices across selected European countries (Belgium, Denmark, Finland, France, Ireland, the Netherlands, Spain, Sweden and the United Kingdom). The maximum difference between the highest and the lowest price was EUR 66 (81%) for the wholesale price, EUR 138 (124%) for the retail price without VAT, and EUR 214 (123%) for the retail price including VAT.

What do we know about price convergence for other types of goods?

To understand the extent to which price convergence in pharmaceutical markets is linked to price regulation rather than usual market characteristics and increased globalisation, we looked for studies analyzing worldwide price trends in other products in the same or similar markets. Four of the five studies examined were limited to the European Union. All give some evidence of price convergence, albeit with an increase in dispersion for some sub-periods. The first one analyses price dispersion across Europe for different categories of products for the 1990-2003 period (Engel and Rogers, 2004). The study shows a decline in price dispersion within the whole period, marked by a sharp decline in the early 1990s, followed by a slight increase between 1998 and 2003.[17] Price dispersion of non-tradable goods (services) has declined over the period but is still larger than the dispersion in prices of tradable goods, as would be expected given that trade competition can only directly impact on tradable goods. However, further results show that price dispersion within countries (between cities) has declined over the same period, which cannot be directly attributed to international trade. The second study examined price convergence for 115 tradable-tradable products groups[18] (as defined by Eurostat) for the EU15 countries over the period 1995-2002 (Allington *et al.*, 2005). They tested the hypothesis that the drive towards monetary union among countries in the Economic and Monetary Union (EMU) would lead to greater price convergence then among non-EMU countries. The results of their analyses confirm the hypothesis. In addition, the authors found evidence of convergence among all EU15 countries over this period.

The third study focuses on car markets in five European countries for the period 1970-2000. It highlighted some degree of price convergence but also the persistence of important price differentials between the cheapest and the most expensive country (Goldberg and Verboven, 2005). The authors explained the persistence of "market segmentation" by trade barriers enforced by national regulatory authorities or by the European Commission (type approval,[19] national registration,[20] and selective and exclusive distribution[21]). Moreover, the study period end date of 2000 coincides roughly with the introduction of the euro as a common currency for four of the five countries in their study (Belgium, France, Germany and Italy), the United Kingdom being the exception; a period during which greater convergence would be expected. A more recent study on the European car market focused on the period of 1995 to 2005 (Gil-Pareja and Sosvilla-Rivero, 2008). The authors found evidence of price convergence among the EU15 countries from 1999 onwards. Furthermore, prices converged even earlier for the 11 countries that adopted the euro.

The final study assessed the trend of price dispersion for 101 tradable goods in 108 cities from 70 countries of all the world's regions between 1990 and 2005 (Bergin and Glick, 2007). Price dispersion decreased by 19% over the whole period, but two different trends are observable. Price dispersion first decreased between 1990 and 1997, by 30% and has increased since then (by 11%). Looking for explanations for this reversal in trend, the authors concluded that the upwards trend in price dispersion is largely explained by the rise in oil prices (a proxy for transportation costs) during this period, as far as cities from

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developing countries are involved in the estimate of price dispersion (between developing countries or between industrialised and developing countries), but that fluctuations in oil prices do not fully explain the increase in price dispersion for the set of industrialised countries.

In conclusion, public prices of tradable goods have been converging in the 1990's and slightly diverging since then. The price convergence is observable within the European Union but price differentials remain in markets with trade barriers (such as the car market). By contrast, studies analysing trends in ex-factory listed prices of pharmaceuticals suggest a uniform trend in price convergence over the period within a small sample of countries including several EU countries, Canada and Switzerland.

Conclusions

The pharmaceutical market was formerly characterised by pharmaceutical sellers with global operations and perspective facing national purchasers with policies that were quite insular and inward-looking. This has changed and we are moving toward a new market dynamic. Pricing to market is not possible in an era of free trade and external price referencing. This may well result in problems in the availability and affordability of some medicines in some countries, both within and particularly outside the OECD, unless policy makers change pricing and reimbursement policies to adapt to the new market dynamic.

Notes

1. To varying degrees, many of the new EU member states introduced requirements for demonstrated cost-effectiveness for pharmaceuticals. For example, the Slovak Republic's pricing policies require cost-effectiveness studies to be submitted for reimbursement application, although the ability of the state to properly evaluate these is lacking (Kálo *et al.*, 2008).
2. Boulenger *et al.* (2005) define generalisability as "the degree to which the results of an observation hold true in other settings" and transferability as "the data, methods and results of a given study are transferable if *a)* potential users can assess their applicability to their setting and *b)* they are applicable to that setting".
3. The model they used included a formula for each country that uses international benchmarking.
4. According to the authors, the price reduction could be the result of a deliberate strategy by a manufacturer or through mandatory price reductions for which there are precedents in Germany.
5. An old drug was defined as any drug that received marketing authorisation in Italy prior to 1997. This distinction was made because Italy has not used international benchmarking to determine reimbursement prices since 1997.
6. For example, in 2007 Thailand announced it was going to use compulsory licensing to obtain generic versions of on-patent drugs to treat HIV and heart disease (it had already done so in late 2006 for the antiretroviral drug Efavirenz produced by Merck). Merck and Abbott (maker of the HIV drug Kaletra) subsequently offered price reductions – 55% less in the case of Kaletra ("Thailand takes on drug industry, and may be winning", *International Herald Tribune*, 11 April 2007).
7. This tool allows users to compare prices paid for essential medicines in low-income countries: *www.haiweb.org/medicineprices/*.
8. They categorised the countries as follows: low-price EU countries (France, Italy, Spain, Portugal and Greece); high-price EU countries (Germany, the Netherlands, Sweden and the United Kingdom); large high-priced non-EU countries (Canada, Japan, Switzerland and the United States); middle income countries (Brazil and Mexico).
9. At least one Canadian province exceptionally decided to cover the costs of patients receiving the drug in US hospitals.
10. In this chapter, the four therapeutic classes are further divided in sub-classes where some drugs have a superior risk-benefit profile compared to other competitors in the class (*e.g.* in the anti-

ulcerants class, H2 antagonists and proton-pump inhibitors are considered to be, respectively, inferior and superior drugs).

11. See note 10.

12. In 2001, the European Commission (EC) ruled in a complaint by a group of parallel traders against the dual-pricing practices of Glaxo Wellcome (now GlaxoSmithKline, GSK), that GSK's practices infringed Article 81 which prohibits agreements which distort or restrict competition. On 27 September 2006 the European Court of First Instance overturned the EC's main finding – that the intent of GSK's scheme was to restrict competition – although it agreed with the EC that it had that effect. The case is on appeal to the European Court of Justice (De Souza, 2007).

13. When products are denominated in different currencies, the unique price that the "law of one price" would predict would take into account exchange rates (see for example Bruce and Purvis, 1985; Froot and Rogoff, 1985; Levich, 1985).

14. Reports have been submitted for the following years: 1997, 1999, 2000, 2001, 2002, 2003, 2004 and 2005.

15. The PMPRB uses a fully-lagged 36-month moving average of spot exchange rates for this purpose. This means that long-term exchange-rate movements will be fully reflected in the PMPRB's average price ratios only 36 months after they occur, while a short-term fluctuation will influence the ratios up to 36 months after it has been reversed.

16. These price comparisons are based on "publicly available ex-factory prices" obtained by manufacturers in foreign countries and provided to the PMPRB for the review of excessive price (PMPRB, 2002). This means that further confidential discounts or rebates consented by the manufacturers are not taken into account, which could lead to under- or over-estimates of differentials between Canadian and foreign prices.

17. The period when dispersion increased coincides with the period during which 11 European countries adopted the Euro as their official currency on 1 January 1999. This is contrary to what international trade theory would predict: the creation of a common currency reduces potential arbitrage opportunities and thus should lead to price convergence.

18. They also examined 46 non-tradable products groups, for which they found no evidence of convergence among EMU countries as compared to non-EMU countries.

19. Type approval: each country had a set of vehicle requirements, requiring costly modifications to imported vehicles. Though the EC produced a common list of "essential requirements" in the 1970's, most countries had kept co-existing national standards until this system became mandatory in 1993.

20. Quotas on imports from third countries (mainly Japanese cars) had existed at national levels and were replaced by a common import quota in 1993, accompanied by a system of "national registration" allowing some control at the national level. The common quota was banned in 2000.

21. During the 1970s and 1980s, suppliers instructed their dealers not to sell to unauthorised resellers and did not carry out after-sales services on imported cars. In 1985, an EC regulation institutionalised several of these practices as a block exemption to European competition rules. The system of selective and exclusive distribution was introduced, in which manufacturers can choose their dealers and prohibit them from selling to independent resellers (selectivity) and have the right to appoint only one authorised dealer in a geographically limited territory and prohibit dealers from active selling policies outside their assigned territory (exclusivity). These rules were somewhat relaxed in 1995 and more drastically liberalised in 2002.

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Chapter 6

The Impact of Pharmaceutical Pricing Policies on Pharmaceutical Innovation

This chapter describes the determinants of R&D in the pharmaceutical sector and the key factors that contribute to R&D decisions. It next considers the role played by pharmaceutical pricing and reimbursement policies in influencing the level and type of innovation. It evaluates the incentives and disincentives for investment in R&D that may be created by pricing and reimbursement policies, and considers the extent to which these policies also influence the level of financing available for investment.

Introduction

Private R&D investment in the pharmaceutical industry is motivated primarily by expected returns on investments, given scientific opportunities (the state of the art in a therapeutic area or in a mode of production) and the comparative advantages of firms. Pharmaceutical pricing policies are among several policy variables that influence the returns on investment in R&D that in turn serve to foster and finance new investment. Methods used to establish price levels, particularly techniques by which products are differentiated for price premia, provide market signals that steer investment towards particular types of innovation.

Pharmaceutical R&D investment

As in other industries, private R&D investments in the pharmaceutical industry are motivated primarily by expected returns on the investments, along with other determinants such as scientific opportunities (the state of the art in a therapeutic area or in a mode of production).

How does a firm decide to invest in pharmaceutical R&D?

Viewed from the perspective of economic theory, a pharmaceutical firm will undertake an R&D investment if the net present value of total costs[1] is exceeded by the net present value of total future expected returns to that investment. In addition, pharmaceutical firms are competing with each other and with firms operating in other areas of business, to attract investment from shareholders; thus, the future returns must be attractive, relative to alternative investments. Finally, a firm will select between competing alternative R&D projects those which have the highest expected returns.

Thus decisions rely on estimates of both expected costs and expected returns on investment, as discussed in more detail below. Of course, both expected costs and benefits may in turn be influenced by myriad factors, including but not limited to the impact of expected future policies. Thus, estimates must be based on core assumptions about expected scenarios and take into account sensitivity to various factors.

The costs of R&D investments

The decision to undertake R&D (and to continue with a development initiative in process) is based on assumptions and expectations regarding the future.[2] Estimating R&D costs is challenging because pharmaceutical R&D is risky (meaning that there is a significant likelihood that any given investment will be unsuccessful and thus have no direct payoff) and the time horizon of the R&D process is long. Box 6.1 summarises the various steps a pharmaceutical takes on the way from conception to market.

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High risk of failure imposes a significant cost

The low probability of success in any one venture makes the R&D process risky.[2] The pharmaceutical industry reports that only five of every 5 000-10 000 chemical compounds initially tested ultimately receives approval from the US Food and Drug Administration (PhRMA, 2006). Researchers looking at this question have estimated that 91% of drugs that reach the clinical trial stage do not make it to market (CBO, 2006).

Failed drugs are a cost to the manufacturer. Therefore, the full R&D costs for a firm include both those drugs that make it to market and those that fail along the way. The success of a pharmaceutical firm's R&D investment portfolio accordingly depends on the discounted future returns of those drugs that successfully reach the market exceeding the R&D costs of those drugs, plus the costs of those that failed to reach market.

Box 6.1. **Getting a drug to market**

There are several distinct phases in the research and development of a pharmaceutical product. Decisions on whether or not to proceed with a development project are taken at various junctures.

Drug discovery. Numerous researchers in private industry, government and academia search for promising compounds that show potential for treating diseases. A promising compound can then be tested in the preclinical testing phase.

Preclinical testing. A new compound is tested *in vitro* and in vivo in laboratory animals. If the manufacturer believes the compound is promising, it will apply to the national marketing authorisation agency for permission to begin Phase I clinical trials in humans. For drugs in development in the United States, the application will describe the compound's pharmacological profile, as well as results of short-term toxicity testing in at least two animal species.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), as reported in GAO (2006), only five in every 10 000 compounds tested successfully passes these first two stages. PhRMA estimates that this process typically takes 6½ years. Dickson and Gagnon (2004) estimate it can take anywhere between one to three years in the United States, with an average of 18 months, for completion of preclinical testing.

Phase I. The first of the clinical trial phases in humans are conducted in a small number of normal, healthy volunteers to determine the safe dosing range and toxicity of the compound. If the compound is still promising, the manufacturer will proceed to Phase II clinical trials.

Phase II. In Phase II clinical trials, the compound is tested in a larger sample of volunteers who have the medical condition the product is intended to treat. If at this point the compound is still promising, the manufacturer will proceed with Phase III clinical trials.

Phase III. Clinical trials in this phase use larger samples of subjects with the disease of interest. Different dosing quantities or schedules can be tested during this phase than those used in Phase II trials. The primary purpose of a Phase III trial is to demonstrate efficacy. Phase III trials are also more likely to detect safety issues since they have more subjects than Phase II trials, but post-marketing surveillance and pharmacovigilance systems are needed to detect rare side-effects since Phase III sample sizes are too small to reliably detect rare adverse events.

Box 6.1. **Getting a drug to market** *(cont.)*

PhRMA estimates that one of every five compounds that enters the clinical trial phase successfully completes Phase III trials (GAO, 2006). It can take anywhere between two to ten years for a potential drug to go through the three clinical trial phases, with an average of five years (Dickson and Gagnon, 2004).

Marketing authorisation application. If, after Phase III testing, a manufacturer believes the compound is promising as a viable pharmaceutical product, it will apply for authorisation to market the drug with the relevant marketing authorisation agency. In the United States, this process can take anywhere from two months to seven years, depending on the Food and Drug Administration's assessment of the degree of innovation of the product. Between 1999 and 2003, the average time from application to approval varied between 13 months in Germany to 24 months in Japan (PICTF, 2006).

Source: Dickson and Gagnon (2004).

Time adds to cost and uncertainty

The time it takes to get a drug through the R&D process and onto the market is considerable. Dickson and Gagnon (2004) estimate that time elapsed from preclinical trials to approval can be anywhere from 3.2 to 20 years, and that it takes, on average, 8.5 years, from preclinical testing to approval, for a drug to reach the market in the United States. Other researchers have found an 11.8 year average process (Di Masi *et al.,* 2003).

The long time horizon adds to the uncertainty of R&D. Technological advances can occur rapidly, underlying the challenge of estimating future R&D outlays based on experience and current information, although the risk of erroneous decisions is mitigated by opportunities to consider, in light of outcomes and new information, further R&D investment before each new phase in the R&D process. Because costs associated with bringing a new drug to market are concentrated in the final phase, in which clinical trials are conducted (Di Masi *et al.*, 2003), this is a particularly important juncture for decision-making.

R&D costs estimated in hundreds of millions of US Dollars per success

Estimating R&D costs, and thus the minimal expected returns for approved medicines required to induce investment, is a difficult exercise. Perhaps the most oft quoted figure for the estimate of drug development costs is that produced by DiMasi *et al.* (2003), who estimate that it costs USD 802 million in drug development costs to bring a product to market. This figure includes the costs of investigational drugs that fail to make it to market; a real cost to pharmaceutical companies since failed drugs cannot generate sales revenues to pay for their costs. Most importantly, the estimate of drug development costs also includes the opportunity cost of developing a drug, which, due to the length of time required to develop a drug, accounts for *roughly half of the total development cost*.

The DiMasi estimate has been criticised by other researchers (*e.g.,* Light and Warburton, 2005a and 2005b; see reply in Di Masi *et al.*, 2005a and 2005b) because of issues pertaining to the methodology (*e.g.,* reliance on a non-random sample of firms, recourse to confidential data). Nevertheless, there is consensus that introducing a new drug entails costs of hundreds of millions (USD).

Obviously the costs of any single R&D initiative will vary. Adams and Brantner (2006) found that drugs designed to treat respiratory disorders such as asthma had an expected

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capitalised cost per approved drug of USD 1 134 million, while drugs to treat dermatological conditions cost an average of USD 677 million. Beyond this, deliberate investments in incremental innovations, such as changes in formula strength, will normally be less costly than initiatives aimed at producing a new chemical entity. These must be separated from me-too drugs which are similar to the original, innovative product already on the market. The R&D costs of me-too drugs would be lower if they were the result of deliberate decisions by manufacturers to avoid many of the R&D costs of the original product. However, if me-too drugs are the result of a manufacturer losing out to a competitor in getting a similar drug to market, then the me-too drug would have roughly the same R&D costs as the original product.

Although, as presented in Chapter 2, investment in pharmaceutical R&D accounts for only about 16% of global sales revenue, the economic cost of financing this investment is greater in that proceeds from the investment are accrued years after the investment. Estimates of the economic costs of R&D investment range from about 30 to 40% of sales (OFT, 2007).

Public investments defray private costs

Public investments in R&D (see Box 6.2) and other public policies intended to foster innovation constitute important support for private R&D investments. They effectively reduce the cost of R&D, although researchers have not succeeded in parsing out the relative contributions of each.

Box 6.2. **Private investment in pharmaceutical R&D benefits from public support**

The pharmaceutical industry is a significant user of publicly funded research. The common understanding of the collaboration between public and private sector is that public institutions invest in basic research that would be under-funded without government intervention due to the inability to exclude others from benefiting from the gains from such research. However, public institutions have limited ability to develop products and bring them to market. On the other hand, pharmaceutical companies have a comparative advantage in development activities, drawing on the results of research results to create new products. In practice, public institutions generally undertake basic research, make the results publicly available and then concede licences on their patent rights to private companies against royalties on sales.

In the pharmaceutical sector, public involvement in the R&D process is not limited to basic research. Indeed, public institutions are often involved at the end of the process through publicly financed hospitals participating in the final phase of a product's clinical trials. Although direct costs associated with conduct of these trials may be funded by the product manufacturer, it is reasonable to think that infrastructure costs linked to these trials are not met by the industry.

Apart from direct investments in the R&D process, public institutions may wish to allocate funds for R&D activities undertaken by the industry. It could be the case if a government wants to encourage the development of a product, for which market incentives are not sufficient to generate private investments.

Though public investments in research are generally considered as an incentive and a driver for private investments, public R&D might also serve to some extent as substitutes, crowding out prospective private R&D, an issue that has been raised in some papers (CBO, 2006). Public R&D and private investment do not always work separately.

Box 6.2. **Private investment in pharmaceutical R&D benefits from public support** *(cont.)*

Increasingly, partnerships between public institutions and private companies are being developed to pool together their respective strengths. Many governments and publicly funded universities now have an "Office of Technology Transfer" to help them identify research of potential commercial significance.

Apart from direct participation and funding of research, many governments try to influence private R&D through policies that promote innovation and industrial support, and those that provide protection for intellectual property. Some analytical papers (see, for example, Jaumotte and Pain, 2005) have tried to assess the impact of public policies on innovation and found some evidence of a positive impact on R&D. However, these studies looked at whether R&D conducted within *a country* was increased; none of these studies presented results at the global level. Whether public innovation policies have contributed to a net increase in global R&D or if national policies influence only or primarily the localisation of R&D in a sort of "zero-sum game" attracting R&D investments from one jurisdiction to another, has yet to be determined.

Expected return on R&D investments

In addition to an estimate of the fully capitalised R&D costs, R&D investment decisions depend on the estimated expected future returns on investment. Initial investment will take place only if the expected return on investment exceeds the estimated costs of investment by a margin sufficient to satisfy investors,[4] and the R&D process will cease at any point where the expected future costs exceed foreseen returns. The estimates of potential returns on investment take into account demography, epidemiology and socioeconomic factors.

These factors are often used to calculate expected growth in a therapeutic class. Demographic, social and cultural factors all play a part in forecasting the total population eligible for treatment in a given a therapeutic area. For example, business analysts have predicted that in 2010, 11 of the top 20 diseases in terms of potential market value will be diseases more common in older adult populations, and that the top disease area in 2010 will be obesity (Northrup, 2005).

Market size is a crucial factor

At the most basic level, the potential market size of a new drug is the estimated population at some future point in time that will be affected by 1) the number of persons affected or likely to be affected with the health condition or disease the product is designed to treat or to prevent, 2) the ability of that population to pay for the medicine, and 3) the degree of willingness to pay for treatment. These factors are amenable to influence by industry, policy makers and other interested parties.

Potential market size is important because it is essential to estimate the potential future sales revenues upon which expected profits depend. The sales revenues used to estimate expected profits (expected sales revenue less expected costs of production, promotion and distribution) are those generated over the lifecycles of those pharmaceutical products that are approved for marketing.[5]

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Earlier returns on investment are more valuable than later ones

Pharmaceutical R&D investment decision makers must contemplate how readily prospective products are likely to be adopted and diffused in the markets where they are to be launched. All things equal, a product that will yield early returns will be preferred to one in which returns are likely to be delayed in some or all markets. Comparisons of expected future returns are based on the net present value of each investment.[6]

Expected returns on investment will be low for some types of innovation, affecting investment decisions

The use of market signals to determine investment in R&D means that the development of treatments for particular conditions or population groups will not be profitable. Because the number of prospective treatment candidates affects market size and expected future sales revenue, market signals do a poor job of inciting investment in treatment for rare conditions. Likewise, because of the importance of ability to pay as a factor influencing market size, market signals are not effective in inducing investment in pharmaceuticals needed to treat conditions that afflict predominantly poor populations. Reliance on market signals results in pharmaceutical R&D choices that may not necessarily coincide with global public health concerns, with companies systematically favouring the development of treatments targeted to chronic diseases affecting citizens of rich countries, whereas important needs have been identified for treatment of acute conditions as well as treatments of vaccines to fight pandemics in developed countries (Kaplan and Laing, 2004). Because of this disconnect, the public and charity sectors were called to participate in R&D investments for neglected diseases and for AIDS in developed countries.

Directing R&D investment to particular types of innovation

It is argued that incremental innovation receives more R&D attention compared to radical innovation because this entails less risky and less costly investments. They may involve lower R&D costs, and more of the parameters of the prospective market and demand may be better understood. Firms have an incentive to invest in drugs that have the highest expected returns, reducing the incentive to invest in pioneering research (Domínguez *et al.*, 2007; and Hollis, 2005).

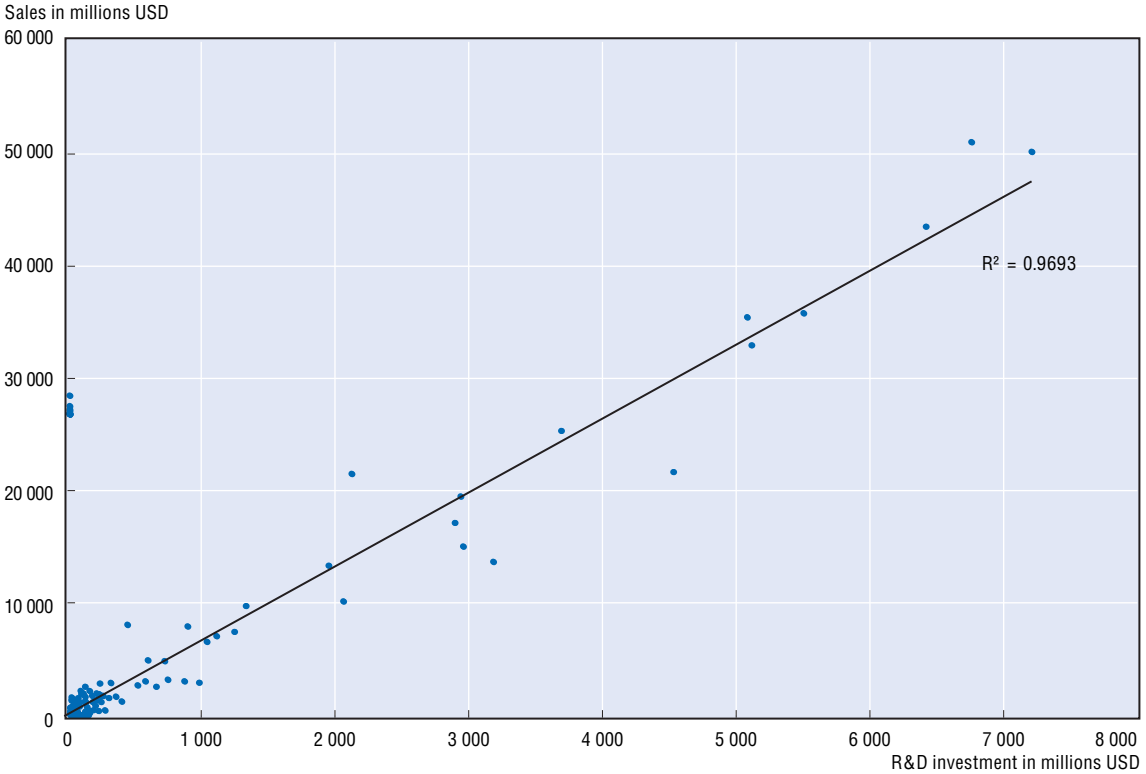
The link between sales revenues and R&D

It is likely that sales revenues act as a proxy for expected returns on investment. Grabowski and Vernon (2000) provide evidence to show that the period of rapid rises in sales revenues in the 1980s coincided with a sudden burst of the pharmaceutical industry's overall profit margin. Rising sales may have signalled potential investors of the rising profitability of pharmaceutical firms, thus inducing greater investment in R&D – the same study also showed that R&D productivity was also rising during this period, following a short period of decline.

Further anecdotal evidence in a report by the US General Accounting Office suggests that firms take account of sales revenues in their R&D investment decisions (GAO, 2006). As stated by an industry consultant in the report, shareholders expect large pharmaceutical companies to develop drugs that will provide sales revenues of USD 200 million to USD 500 million per year. Indeed, the emphasis on developing blockbuster drugs, described as drugs that have the potential to reach USD 1 billion in annual sales, has been the dominant trend in the pharmaceutical industry over the past ten years (*op. cit.*).

There is a high degree of correlation between sales revenues and R&D expenditures. The latest data from the UK Department of Innovation, Universities and Skills R&D Scoreboard (DIUS, 2007) show a very strong relationship between R&D expenditures and sales for the largest 151 pharmaceutical firms worldwide in terms of expenditures on R&D (Figure 6.1).

Figure 6.1. **R&D expenditures and sales in the pharmaceutical industry, 2006**



Note: The data were prepared on the basis of annual reports and consolidated accounts received up to and including 31 July 2006. Annual reports with a year-end older than 30 months from the cut-off date or a publication date older than 24 months from cut-off date are excluded.

Source: DIUS (2007).

Some researchers (*e.g.*, Henderson and Cockburn, 1996) have pointed to a scale effect for R&D in the pharmaceutical industry. In this view, R&D expenditure is directly proportional to the amount of sales revenues available to undertake R&D investment, although the evidence is mixed (Symeonidis, 1996); the firms with the greatest sales are the ones with the largest R&D investments, which may explain why most global R&D investments are undertaken by the large multi-national firms. Symeonidis (1996) argued that large firms are better able to spread the risks of R&D uncertainty since they can undertake several projects at one time.

The impact of reduced R&D productivity on future investment

As discussed in Chapter 2, there is evidence of declining productivity in pharmaceutical R&D, although some analysts believe that this is a cyclical downturn rather than a persistent change. From the perspective of future innovation, reduced productivity is a concern because increased costs per success mean that proportionally greater sales are required to generate the type of returns needed to incent future investment.

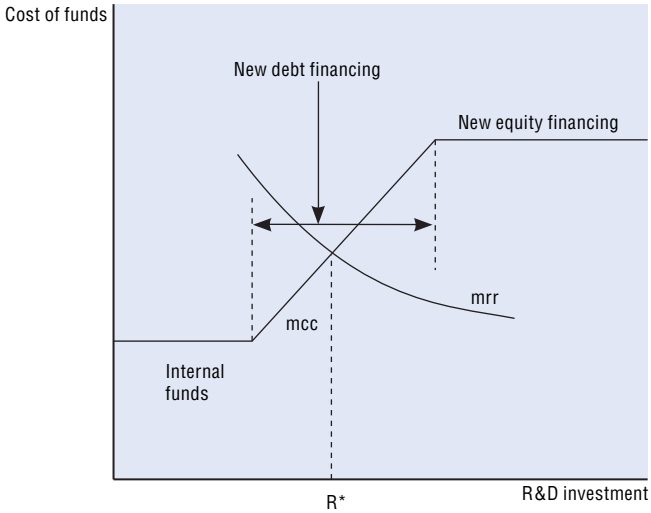
Sources of financing for R&D investment

Global sales revenues of pharmaceutical firms are the primary source of funding for private R&D, at least for established companies.[7] However, there are alternative modes of funding R&D, notably venture capital.[8] These alternatives have gained particular importance in the biotechnology sector, where most firms have yet to bring a product to the market and thus must rely on external funding, usually equity financing (Golec and Vernon, 2007).

One reason why sales revenues serve as a primary source of R&D financing is that such financing is available at relatively lower cost compared to outside sources of funding such as new debt or equity financing (Grabowski and Vernon, 2000; Golec and Vernon, 2007). In a world of perfect capital markets, the opportunity cost to the firms of using external funding to finance R&D investments is equal to the cost of using internal funds. However, managers in pharmaceutical companies have more knowledge of the potential of new molecules, at each stage of development, than do outside investors. This asymmetry of information means that external investors and/or lenders will require a risk premium to compensate them for the risk of unknown information, raising the cost of financing R&D investments relative to internal funds.[9] Thus the amount of sales revenues available will help determine how much R&D investment *can be* undertaken.[10]

Economic theory suggests that a firm will undertake an R&D investment at the point where the marginal rate of return (mrr) on investment is equal to the marginal cost of capital (mcc) – the opportunity cost of alternative investments. The optimal amount of investment will be at the point where the mrr schedule – alternative R&D projects arranged in descending order of their rates of return –intersects the mcc schedule. In Figure 6.2, R* depicts the optimal amount of R&D investment for a particular firm.

Figure 6.2. **The R&D investment decision**



Source: Adopted from Grabowski and Vernon (2000).

According to Grabowski and Vernon (2000), the shape of the mcc schedule is divided into three segments: a lower segment that represents the cost of internal funds, a rising segment representing the cost of new debt financing, and a higher segment that represents the cost of equity financing.[11] This reflects the fact that using internal funds is a less costly

way to finance R&D. Accordingly, R&D that is self-financed will proceed at lower thresholds in terms of total expected returns on investment.

Ways in which pricing and reimbursement practices contribute to trends in innovation

Pricing and reimbursement policies can create incentives or disincentives to invest in R&D, in ways that affect both the level and the orientation of private R&D investments.

Pharmaceutical pricing schemes can influence the level of investment in R&D

Pharmaceutical pricing and reimbursement policies stand to affect innovation through multiple channels, influencing both the *incentives* to invest in private R&D and the *costs of investment*. The main channel of prospective influence is the impact of pricing and reimbursement policies on the *expected return on investment* in R&D. Such policies also serve as one of several types of determinants of the funds available for investment in R&D, most directly via their role in influencing manufacturers' sales revenues from national markets. They can also have an indirect impact, to the extent that they influence the prices and consumption of medicines in other countries, thereby further influencing the global sales revenue that serves as an important source of funding for private R&D.

Pharmaceutical pricing schemes are one of several variables influencing profitability of investing in pharmaceutical R&D

Given the predominant role played by OECD countries in contributing to global pharmaceutical sales of the research-based pharmaceutical industry, the mix of pharmaceutical pricing schemes employed in OECD countries stands to affect R&D investment incentives by affecting its profits.

Of course, pricing schemes and the price levels that result from them are only one factor among many that influence the value of sales and the profits achieved by the research-based pharmaceutical industry, in a particular market and globally. And furthermore, pricing schemes are only one variable among many that are amenable to policy interventions, including policies that influence volume of consumption and policies that influence the period of market exclusivity, such as IPR standards and enforcement, and policies pertaining to the prescribing and dispensing of generic alternatives to original products. For instance, a producer of an innovative product could theoretically achieve more profits through the life-cycle of a given product in a market that has a lower price, but low competition in the protected market (meaning that an off-patent product will hold market share and higher prices longer), than in a market with a higher price but high competition in the unprotected market.

Pharmaceutical pricing schemes affect prices, thereby distorting investment incentives

The most direct route by which pharmaceutical pricing schemes can affect profits and incentives to invest in future innovation is by constraining prices, relative to what manufacturers would otherwise charge given their assumptions of consumers' sensitivity to prices.[12] It is far from clear that all price regulation schemes are effective in affecting prices, however. For example, the OECD found little evidence to suggest that the pharmaceutical price regulation scheme used in Mexico presently has any significant impact on the prices at which pharmaceuticals are sold by manufacturers (Moïse and

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Docteur, 2007a), even though there may be an impact in terms of capping the range of retail prices charged in pharmacies.

Conversely, to the extent that policies result in higher profits than would occur in the same market in the absence of intervention – as is likely to be the case in a subsidised market with weak controls on price and volume – incentives to invest in future innovation are increased. However, as market-based pricing will not necessarily result in prices that are socially optimal (as discussed in Chapter 3), given heavy subsidies for pharmaceutical purchases throughout the OECD, it stands to reason that profits accruing in those markets where pricing is largely market-based may result in signals to over-invest in pharmaceutical R&D beyond what is socially optimal.

Pricing schemes can affect profits by influencing the uptake and diffusion of new products

As discussed in Chapter 4, pricing schemes (among other factors) may also contribute to differences in the patterns of adoption and diffusion of new medicines. These patterns are important, from the perspective of the incentives they create for innovation, in that early returns on investment will be discounted less than later returns. Thus markets with relatively quick uptake are more profitable than countries in which uptake is delayed, all else being equal (price, volume of consumption and speed of diffusion).

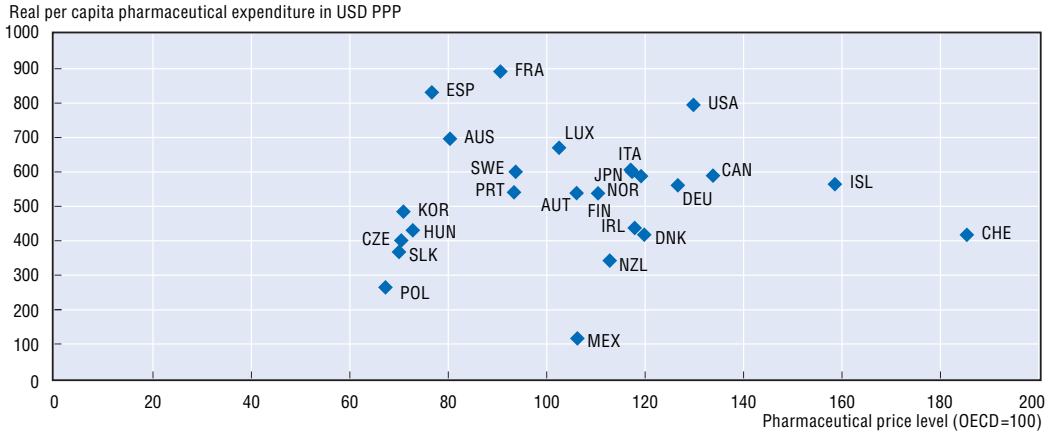
Profits are affected by both price and volume

Of course, all other things equal, higher prices will result in more profits. But it is unreasonable to assume that volume of consumption is unaffected by price levels, as some studies have done to facilitate estimation of the financial impact of pharmaceutical price regulation on manufacturers' returns (ITA, 2004). In fact, it is likely that there is a close relationship between price and volume in some countries, particularly in those where pharmaceutical purchases are subject to budget constraints. In such cases, obtaining lower prices through regulation or negotiation may allow for increased volume of consumption. Because the marginal costs of production represent only a small fraction of the sales price in the case of most original products, firms can make volume-price trade-offs that result in equivalent sales revenue and profits for the industry, provided any spillover to other markets can be prevented.

Figure 6.3 shows no relationship between retail price levels and per capita volume of pharmaceutical consumption for the OECD as a whole, but a price-volume trade-off is consistent with the pattern seen for certain countries. France has the highest per capita consumption, but retail prices that are below the OECD average level. Australia and Spain also have relatively high per capita consumption and low retail prices. Switzerland has the highest retail prices for pharmaceuticals, but a volume of consumption that is significantly below the average. Mexico has by far the lowest level of consumption and retail pharmaceutical prices that exceed the OECD average. The United States stands out in having both retail prices and volumes of consumption that are relatively high, an unsurprising outcome for a subsidised market with low consumer price sensitivity in the absence of price regulation. Of course, the relationship is further affected by affordability, to the extent that per-capita income affects prices or consumption preferences.

Agreements between manufacturers and purchasers that take a broader view of returns and expenditures, rather than focusing on the price aspect of the equation in isolation, are attractive in providing a way of taking a comprehensive view. Negotiations that take into account both price and volume, and prospectively outcomes as well – in the

Figure 6.3. **Retail pharmaceutical price levels and real per capita pharmaceutical expenditure, 2005**



Note: Real per capita pharmaceutical expenditures (per capita volume of consumption) were converted from per capita pharmaceutical expenditures (measured in national currency units) using Eurostat-OECD pharmaceutical PPPs (see Box 1.2). The volume of consumption depicted is overestimated in those countries, like Switzerland, where purchasers pay a fixed fee for pharmacy services (*e.g.*, a prescription fee) that is not included in the end price of the product. See Box 1.1 for more notes regarding pharmaceutical expenditures. Pharmaceutical expenditures for Hungary and Japan are for 2004 and 2004/05 fiscal year for Australia; these were deflated using 2005 retail price levels.

Source: Eurostat-OECD Purchasing Power Parity Programme, 2007 and *OECD Health Data*, 2007.

case of products that are high-cost, low-volume, and high-risk – can be used to provide a means of negotiating over the main points of concern to both buyer and seller, and to avoid the problems associated with externalities of price decision making (see Chapter 5). As described in Chapter 3, such negotiations are already in place in a few countries, and are beginning to be used by purchasers in other OECD countries, on an experimental basis.

Pharmaceutical pricing schemes also affect the resources available for investment in pharmaceutical R&D

To the extent pricing schemes reduce the level of sales revenue accruing from global sales of pharmaceuticals sold by research-based firms, they effectively reduce the low-cost capital available for investment in R&D, thereby increasing investment costs. Firms will continue to invest when expected returns on investment exceed expected costs, but R&D investment levels will be lower due to the higher financing costs associated with an increased reliance on outside funding sources when present sales revenues are reduced.

Practices used to set relative prices for different types of products affect relative profits/ROI and give firms incentives to invest in different types of innovation

By sending signals as to what extent pharmaceutical innovation is valued by purchasers and the relative value attributed to different types of innovation, pricing and reimbursement policies can create incentives or disincentives to invest in R&D, in ways that affect the orientation of private R&D investments.

For instance, the extent to which prices or the volume of purchases are used to reward the level of innovation may create incentives as to how to direct investment (in other words, whether to aim to build on existing products or seek to develop new molecular entities). As discussed earlier in this report, incremental innovation is acknowledged to provide benefits to patients by reducing side-effects, increasing convenience, or enhancing

comfort, sometimes in ways that enhance compliance with treatment regimes (*e.g.,* by changes in formula that affect the frequency of the medication schedule). The question which is generally raised is the appropriate reward for incremental innovation.

Similarly, a willingness to pay relatively higher prices for treatments in certain therapeutic areas (*e.g.,* life-threatening conditions), relative to others, provides incentives to invest in these areas. To the extent these conditions are rare, prices may need to be very much higher to compensate for low sales volumes. Finally, the prospect of reimbursement may encourage investments in therapeutic areas believed likely to qualify for reimbursement in drug coverage schemes.

External price benchmarking incents development efforts geared towards very marginal product differentiation

The very widespread prevalence of external price referencing has implications for the type of R&D undertaken by pharmaceutical firms. To create barriers to external price referencing (and to avert the threat of parallel trade) firms are likely to invest in development to produce marginal modifications (*e.g.,* formulations, dosage) of existing products – with no benefit to patients in terms of therapeutic effect, convenience or otherwise. Differentiation of products marketed in different countries renders price comparison and benchmarking more complex (and potential parallel trade more difficult and more costly).

The impact of therapeutic referencing on R&D investments geared towards incremental innovation

As described in Chapter 3, purchasers often use therapeutic referencing to define the price of a new drug by comparison with available alternatives, granting a premium to innovative products and seeking discounts for less innovative ones. This theoretically replicates what would happen at market entry in a perfect market in which well-informed consumers would accept higher prices for new goods only if these were utility enhancing relative to alternatives. This practice is thus not *per se* likely to provide incentives for R&D that are in any way different than those produced by a free market – at least at the beginning of the R&D process: no firm would engage in early stage of R&D process without the ambition to produce an outcome that is innovative, unless market perspectives are particularly high and even expandable (which can be the case for some chronic diseases). However, the practice of therapeutic referencing may influence late stages of the R&D process, in which firms try to discover new applications for their products in order to differentiate them from potential competitors and obtain price premiums. This does not necessarily lead to more new products but to more applications, formulations or other line extensions.

Some purchasers consider the incremental cost-effectiveness of new products in order to make yes/no decisions about inclusion in positive lists. The net effect of such policies is to increase the risk of investing in R&D – and thus its prospective costs – by setting purchasing dynamics of "all or nothing" rather than a question of "how much" subsidy. (The same situation holds in the case of purchasers who choose not to purchase any of certain original products, despite their effectiveness.) This will effectively discourage the development of less innovative products (*i.e.,* ones that are variations of existing products). If firms knew that all effective pharmaceuticals that meet basic standards for effectiveness and safety would be eligible for a subsidy determined by the product's assessed value to the

purchaser, the risk of investment is lower than one faced if a prospective investor knows that there is some likelihood that his product may be rejected.

Reference price systems disincent investment in product differentiation that has little value to purchasers

Reference price schemes – in which common reimbursement levels are set for a group of products, with consumers required to pay any price charged above the common level – are very likely to affect the types of R&D investments. Whenever reference price systems include patented drugs in clusters based on therapeutic equivalence (rather than generic bio-equivalence), or similarity as is the case in Germany, their impact on the relative price level is potentially high (see Chapter 4). To date, most payers have refrained from grouping pharmaceuticals in large groups based on therapeutic equivalence or similarity. As long as Germany is the only large market to use this so-called "jumbo-grouping" of pharmaceuticals for setting reimbursement amounts, it may not significantly reduce the incentive to invest in follow-on drugs for sale in lucrative markets. Firms can greatly benefit from engaging in significant product differentiation in order to avoid having their drugs clustered in reference groups that include generics. Firms are thus likely to invest in R&D in order to demonstrate effectiveness for additional applications or for specific target populations, to the extent that this helps them avoid being clustered with potential competitors.[13]

Of course, German-style reference pricing only has an impact on the absolute and relative prices obtained by pharmaceutical producers to the extent that consumers are unwilling to pay a premium for incremental improvements. In theory, a system in which a reimbursement price is based on a judgment of the product's value (allowing incremental increase in reimbursement price for product of added benefit), then allowing consumers to pay the remainder, is attractive in that it allows consumers to send signals regarding the value they place on convenience, comfort and other factors that are generally not taken into account when grouping pharmaceuticals according to therapeutic effect. Such a system provides a disincentive to produce incremental innovations whose advantages would not be apparent to consumers. However, such competition is difficult to establish in the prescription drug market – where direct-to-consumer advertising is almost universally prohibited – but not impossible; information on a product's non-therapeutic advantages over its competitors can be conveyed through promotional activities pharmaceutical companies direct at prescribers – acting as consumers' agents.

Differentiating prices or payments based on product value should incent investment in more valuable innovations

To the extent that pharmaceutical producers profit more from innovations that have the greatest value to patients and society, they will face incentives to invest more in R&D to produce such therapies. Subject to the constraints of scientific progress, pharmaceutical innovations should be expected to focus on the types of conditions for which new therapies are rewarded by highest profits. To the extent that recent innovations have focused more on life-style drugs and relatively minor conditions rather than life-threatening or disabling ones, it is likely that the former have been found to be more profitable, given the level of R&D investment required in comparison with the returns on investment. This suggests either that pricing and purchasing methods are failing to take therapeutic value adequately into account, or that societies have a higher willingness to

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pay for treatments for minor conditions (in other words, a pharmaceutical that improves 1 million complexions may have higher collective value than one that extends 1 000 lives).

Defining cost-effectiveness thresholds could help to steer innovation towards value

Purchasers have to date been reluctant to adopt, in a public manner, definitive cost-effectiveness thresholds (a proxy measure of a payer's willingness-to-pay for a particular product or therapeutic intervention, expressed as a ratio of cost to health-outcome). Although such thresholds raise a lot of ethical issues, they may be used in firms' R&D investment decision-making processes to estimate a range of expected returns on investments, according to different levels of effectiveness, price and volume (Vernon *et al.*, 2005).

The impact of firms' use of cost-effectiveness thresholds is uncertain. On the one hand, cost-effectiveness thresholds could discourage R&D investments with low expected ROI at the threshold. On the other, they may encourage R&D investments in other prospective products by reducing investment risk; cost-effectiveness thresholds reduce the variability in firms' estimations of payers' maximum willingness-to-pay (Vernon, *et al.*, 2005) – and by extension reduce variability in expected ROI. Furthermore, the authors argue that such thresholds may encourage firms to propose prices higher than they would do absent regulation as long as the threshold is not exceeded. This is a potential problem from a static efficiency perspective, but not necessarily so from the perspective of dynamic efficiency since such price premia may be desirable as a reward for valuable innovation.

Use of a single cost-effectiveness threshold is limited because it fails to distinguish among different types of conditions for which therapies may be more highly valued. The approach taken by Sweden is interesting in that multiple implicit thresholds are employed, allowing products to treat conditions for which need for new therapies is greatest to have higher thresholds (Moïse and Docteur, 2007b). Thus these products can be considered cost-effective at a higher price.

Although purchasers generally do not publish their cost-effectiveness thresholds, explicit thresholds may hold some promise as a means of providing incentives for investment in R&D to address orphan diseases. Hollis (2005) states that countries may gain from publishing their willingness-to-pay for orphan drugs as a way to incent development (by defraying the risk of investment).

Constraints on price increases may encourage incremental innovation

Regulation of price increases may also send signals to firms that encourage incremental innovation. Bartoli (2002) showed that innovations from the French pharmaceutical industry were oriented towards slight modifications of existing products and related this behavior to the fact that manufacturers were not normally allowed to increase the price of products while they could expect a price premium for new products, even for those that were not particularly innovative. French regulation has changed since then and a price premium may be more difficult to obtain at market entry, but rigidity in price increases may continue to influence the incentives to invest in slight modifications of existing drugs.

Conclusions

The pharmaceutical industry is now global and R&D investment decisions are made at the global level. Thus the marginal impact of any one country's policies will be proportional to market size and thus minor,[14] unless countries choose to coordinate their policies to send stronger and consistent signals to the market about what they value. Of course, this will be impeded to the extent countries have legitimate differences in the type of innovation they value (prevalence of disease, cultural values, etc.).

Nevertheless, even absent coordinated effort, features of national markets and national policy practices may encourage firms to invest in R&D in order to differentiate products and segment markets, especially when national policy impacts may have spillovers on other countries' price levels. The practice of external price benchmarking means that early-launch countries in particular are likely to have an impact on incentives for investment that is disproportionate to the size of the market. This suggests that it is particularly important that prices established in those countries present an accurate reflection of willingness to pay.

Stability and consistency of pricing policies is important, in that this affects manufacturers' risk associated with responding to current incentives. The impact of policies on investment decisions will partly depend on the extent to which firms can have reasonable expectations that policies will be generally consistent over the medium to long-term time horizon.

In a perfectly competitive market, consumer choice would be expected to result in a level of manufacturer profits that would yield the socially optimal level of investment in R&D. However, pharmaceutical markets are imperfect in a number of important respects, most notably in the degree to which individual consumption is subsidised through insurance. Thus, in the existing market, policy makers must strive to establish policies that approximate the socially optimal outcome as closely as possible.

Efforts to link the level of expenditure for a given pharmaceutical to the value of the benefits offered by the new product are promising in this respect, to the extent they can be used to estimate willingness to pay, and aid in negotiating payments based on considerations of the volume of consumption and unit price. As discussed in Chapter 3, pharmaco-economic assessment is a challenging and value-laden exercise. Nevertheless, it offers the most promise for arriving at socially optimal outcomes in terms of promoting the right level and type of R&D investment.

Pharmaco-economic assessment has an income-dependent outcome. Because the economic value of the therapeutic benefits and savings will vary by income, new pharmaceutical products will have different values in different countries. Thus adoption of pharmaco-economic evaluation on a widespread basis would be expected to result in an outcome in which national expenditures for innovative products (though not necessarily unit prices) would be correlated with income, and countries would make differential contributions to the financing and incentivising of future R&D.

While pharmaceutical policy approaches that replicate market signals can be successful for products used to meet the demands of the developed world, they will not be adequate to incent investment in medicines to treat conditions that occur largely in poor countries. Alternative mechanisms to incent or finance R&D for such products may well be required. While these are beyond the scope of the current OECD study, they are the subject of ongoing work by WHO and others.

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Notes

1. Costs include the capital invested in undertaking the necessary research and for developing the product for the market, production costs and spending related to promoting the product.
2. Kaló (2004) provides a typical example of this decision process. The clinical research team establishes a product profile and estimates the probability of success at major decision points. The marketing team uses this information to estimate the potential market size and define the scope of market penetration for each different outcome scenario. The health economist or strategic pricing expert develops an economic model, which quantifies the economic value based upon the target product profile in all scenarios. This information is used to predict the potential revenue at each different development scenario. Each scenario includes reasonable estimates about development costs, and ultimately production and marketing costs. These input parameters are used to calculate the expected net present value of the return on investment.
3. Potential investors can minimise their risk by diversifying their investments into a number of different R&D projects. In such a way, investors can obtain an average expected cash flow that is more predictable than the expected cash flow from a single project (OTA, 1993).
4. In the case of a privately held firm, the firm managers make decisions based upon the demands of shareholders.
5. Chapter 2 provides an overview of the approaches manufacturers use to influence the returns on a product through life-cycle management within a country, and Chapter 5 describes ways in which manufacturers implement a global strategy aimed at achieving the greatest possible total profits.
6. The standard discount rate used in the pharmaceutical industry is generally in the 10-12% range, with a higher rate used if the product is deemed to be particularly risky (Gregson *et al.*, 2005).
7. Of course, global sales revenues also finance firms' operating costs, marketing and other overhead costs.
8. Pharmaceutical companies also use mergers and acquisitions to invest in the development of compounds discovered by other companies.
9. Grabowski and Vernon (2000) cite a number of theoretical reasons for the difference in the cost of internal *versus* external funds, including: transaction costs, tax advantage, agency problems, costs of financial distress, and asymmetric information (see Hubbard, 1998, for a review of the literature on capital-market imperfections and investment).
10. However, they do not determine how much R&D investment should be undertaken by the firm, nor whether or not investment should take place.
11. The authors cite work on firm investment behaviour to support the construction of the marginal cost of capital schedule. For more information on the theoretical underpinnings of this work see Hubbard (1998).
12. The degree to which price changes will affect consumption – and therefore profits – will depend on consumers' sensitivity to prices. As stated earlier in Chapter 3, the demand for drugs at a macro-level has been found to be relatively inelastic for developed countries (although certain sub-groups of consumers may be more sensitive to price changes). Therefore, the change in consumption in response to a change in price will be proportionally smaller, thereby imparting a larger change in sales revenues – and profits – then if consumption would have changed in proportion to the change in price.
13. In Europe, pharmaceutical firms can obtain an additional year of data protection for new applications of existing products (see Annex 3.A1). Bioequivalent generic producers will be unable to market their drugs during this period. It is not clear, however, that this has a serious impact on pricing or sales, given that physicians are free to prescribe off-label uses and reference price groups are based on products, rather than applications.
14. Exceptions being the United States – due to its importance in the global pharmaceutical market – and those countries referenced by others using international benchmarking.

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Conclusions

The OECD project on pharmaceutical pricing policy has taken a close look at the evolving market for pharmaceutical products and the ways in which pricing policies serve to shape that market, yielding a number of conclusions.

As tools for meeting a range of pharmaceutical policy objectives, the approaches most widely used in OECD countries to arrive at prices for pharmaceuticals – external and internal price referencing – are problematic in a number of respects. International price benchmarking (or external referencing) is readily gameable by the pharmaceutical industry and – by reducing firms' willingness to price to market – contributes to access and affordability problems in the lower-income OECD countries, some of which spend close to a third of their health-care resources on pharmaceuticals. Perhaps just as importantly, the prices derived through external benchmarking practices are unlikely to serve as an accurate reflection of the product's value – in terms of the health improvements, consumer convenience and other benefits offered by the product – to consumers in the country undertaking the referencing, given the practice of referencing to early-launch or high-sales countries over ones that are similar in terms of characteristics like income, price level, health costs and health status. The practice of agreeing to confidential rebates that create a gap between the public list price and the actual price paid heightens this problem.

Therapeutic price referencing (or internal referencing) is better in this respect, in that there is explicit consideration of whether the added benefits from a new product are worth the added expenditure. Policies that limit reimbursement of similar products to a common level provide pharmaceutical firms with incentives to invest in differentiation of products to avoid inclusion in an existing group, but risk failing to reward incremental innovations when consumers lack information needed to assess value. In terms of the impact for innovation, the most problematic scenario is therapeutic referencing that does not allow manufacturers to price above therapeutic competitors, even when the product offers some improvement. Avoiding such potential distortions provides a rationale for policy makers to limit their interventions in the market to the definition of reimbursement levels or public purchase prices, while allowing pharmaceutical firms the freedom to define their sales prices. Under this approach, other policies may be needed to ensure equitable and affordable access to high-cost medicines.

Efforts to link the level of expenditure for a given pharmaceutical to the value of the benefits offered by the new product – using tools such as pharmaco-economic assessment – are promising in several important respects. From the perspective of obtaining good value for pharmaceutical expenditure, this approach is attractive in that it can aid in negotiating payments based on considerations of a product's ability to deliver desired outcomes. Ideally, pharmaco-economic assessment would be employed in a broader scheme of health-technology assessment to make value considerations explicit in health expenditure

decision-making across the board, rather than limited to a single type of care. Such an approach would help to ensure that increased efficiency of pharmaceutical expenditure does not come at the expense of efficiency of expenditure in the health sector more broadly.

Pharmaco-economic assessment is also a promising approach for promoting the right level and type of R&D investment, by giving better signals to industry as to which innovations are most highly valued. It can also be used as a tool to establish market-based incentives for investment in treatments for rare conditions.

Because the economic value of the therapeutic benefits (net of costs or savings associated with the use of a product) will vary across countries according to their income, health care costs, epidemiology, and other factors, new pharmaceutical products will have different values in different countries. Thus, adoption of pharmaco-economic evaluation on a widespread basis would be expected to result in an outcome in which national expenditures for innovative products would differ on the basis of income. At the same time, a move to value-based payment may well result in increased expenditures for certain types of pharmaceutical products in certain countries.

Pharmaco-economic assessment, as with health-technology assessment more generally, is a technically challenging and value-laden exercise. Nevertheless, the perceived value of making an explicit consideration of costs and benefits in price and reimbursement decision-making has led about a third of OECD countries to move forward in this area, and several have developed programmes that can provide models for further advances.

Beyond pharmaco-economic assessment, price-volume agreements and risk-sharing agreements represent another interesting development in pricing policy. These practices are attractive in that they take the emphasis off the question of unit price, with a focus on benefits obtained for a given level of expenditure. This is consistent with the perspective of policy makers, who are concerned about the level of total expenditures and the value for money attained, and with reducing the risk associated with decision-making when there is uncertainty as to either the size of the prospective market or the outcomes to be expected. It is also consistent with the interests of pharmaceutical firms, who care about the return on investment achieved through sales revenues, a function of both price and volume. Thus, an environment in which all those who could potentially benefit from use of a drug had affordable access could be a win-win outcome for both parties to the transaction.

Nevertheless, it should be noted that not all OECD countries are in a position to take full advantage of price-volume agreements at present. Reimbursement policy in a number of countries stipulates that *all* products in a therapeutic class that are approved for market must be reimbursed. This is justified as a means of providing equal access to the market for pharmaceutical firms, but may in some cases limit the scope for use of coverage restrictions that prefer one drug to another.

At present, the lack of a firm foundation for pharmaceutical pricing policy is reflected in an eclectic mix of policies being employed in ways that are often internally inconsistent. For example, establishing reimbursement mechanisms for pharmacies that link fees to product prices is inconsistent with measures to encourage substitution of lower-priced generic products when these are available. In another example, the practice of encouraging parallel imports of on-patent products to obtain the lowest possible price diminishes the innovation incentive embedded in the price differential, which is hard to reconcile with practices seeking to establish value-based prices within the country.

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The pharmaceutical market was formerly characterised by pharmaceutical sellers with global operations and perspective facing national purchasers with policies that were quite insular and inward-looking. This has changed and a new market dynamic is emerging. Pricing to market is increasingly not possible in an era of freer trade and external price referencing. This may well result in problems in the availability and affordability of some medicines in some countries, both within and particularly outside the OECD, unless policy makers change pricing and reimbursement policies to adapt to the new market dynamic.

At least two future scenarios can be foreseen. First is the status quo, with a continued convergence of list prices – particularly for the most innovative products – and pressure for policy makers and third-party payers to avoid transparency in their pricing actions. To have affordable access to medicines, policy makers in lower-income countries may need to increasingly rely on confidential agreements to obtain lower effective prices through rebates or discounts, and thus discourage any external spill-over impact of their list prices. A second possibility could be envisaged if policy makers were to agree that variation in pharmaceutical prices and expenditures is appropriate and desirable, foregoing external benchmarking and seeking to define prices or expenditures for a given product that reflect the product's assessed value within the country. This would set the stage for a situation in which greater transparency would be feasible. The viability of this second scenario would, however, depend on the continued success of manufacturers in limiting the extent of parallel and cross-border trade.

Under either scenario, improvements in the incentives for R&D depend on whether there is an improvement in the match between countries' pharmaceutical expenditures (overall and for particular products) and the value their citizens place on medicines. In this respect, there may be circumstances under which it would be both desirable and feasible to disconnect the financing of pharmaceutical R&D from the profits of the industry – notably in the case of so-called "orphan drugs", where market signals result in under-investment. Investigating the technical feasibility of various approaches to alternative financing and the policy implications of doing so is, however, beyond the scope of the present report.

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Glossary

Active ingredient: the chemical substance contained in a *pharmaceutical* which is responsible for its therapeutic effect. Some pharmaceuticals contain more than one active ingredient (combination product).

Active substance: see *active ingredient*.

Anatomic Therapeutic Chemical (ATC) classification system: in this WHO classification system *pharmaceuticals* are divided into different groups according to the organ or system on which they act and/or their chemical, pharmacological and therapeutic properties. The ATC Classification system is divided into five levels. ATC 4 level defines a *therapeutic group*, whereas ATC 5 level defines a single *active ingredient* or a fixed combination of active ingredients. A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses.

Bioequivalent pharmaceuticals: are considered to be bioequivalent if they contain the same molecule (in the same form, dosage type and strength) and are released into, and absorbed by, the body at the same rate. See *generic*.

Brand: the trade or marketing name**.** Brand names used to designate a particular *pharmaceutical* product may differ across countries.

Brand name: see *brand*.

Claw back: a scheme under which *third-party payers* recoup (part of the) *discounts/rebates* granted between various parties to *pharmaceutical* sales transactions, *e.g.* wholesalers and *pharmacists*.

Co-insurance: *cost sharing* in the form of a set proportion of the cost of a service or product.

Compound: see *active ingredient*.

Compulsory license: a license to use a patent, copyright, or other exclusive right that a government forces the holder to grant to others. Compulsory licensing allows generic *manufacturers* to make and sell *generic* versions of *on-patent pharmaceuticals* before patent expiry, in exchange for royalty payments to patent holders.

Co-payment: insured patients' contribution towards the cost of a medical service covered by the insurer. Can be expressed as a percentage of the total cost of the service (also known as co-insurance) or as a fixed amount.

Cost-effectiveness analysis: compares the cost per unit of outcome of alternative therapies with the aim of identifying the most efficient therapy.

Cost sharing: terms of coverage by a *third-party payer* specifying how the patient's share of the costs of health care will be calculated. Cost-sharing mechanisms include

co-payments (known as user fees in tax-financed coverage systems), *deductibles* and co-insurance.

Cross-border trade: the act of importing *pharmaceuticals* into one country (the "import" country) from another (the "export" country) for the purpose of personal consumption in the import country.

Cross-country referencing: see *external price referencing*.

Data exclusivity: protection of an originator pharmaceutical company's data preventing other parties from using these data for a commercial purpose. Concretely, this protection prevents *generic* product *manufacturers* from proceeding to clinical trials and health authorities from evaluating generic product *market authorisation* applications during this period. In the European Union, this period was harmonised to eight years in 2004.

Deductible: patient's share in the form of a fixed amount which must be paid for a service or of total cost incurred over a defined period by a covered person before a *third-party payer* covers all or a percentage of the rest of the cost.

Defined Daily Dose (DDD): the assumed average maintenance dose per day for a *pharmaceutical* used for its main indication in adults.

De-listing: dropping a *pharmaceutical* from a pharmaceutical list (*e.g. positive list*), often resulting in exclusion from *reimbursement*.

Direct-to-consumer advertising (DTCA): the advertising of aimed directly at the public.

Discount: a price reduction granted to specified purchasers of a *pharmaceutical*.

Dispensing fee: payment of the *pharmacist* for the service of dispensing a *pharmaceutical*.

Distributor: a *pharmaceutical* company that sells products it does not produce itself under a licence obtained from the *manufacturer*. Also refers to all actors in the pharmaceutical distribution chain, such as wholesalers or retailers.

Drug: see *pharmaceutical*.

Effectiveness: the extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.

Efficacy: the extent to which an intervention produces a beneficial result under ideal conditions.

Efficiency: a measure of the extent to which health care resources are being used so as to maximisevalue for money.

Evergreening: strategies employed by an originator pharmaceutical company (see *original product*) to extend the patent life of an original product by applying for patents for various attributes of the product on a sequential, rather than simultaneous basis.

Ex-factory price: the *manufacturer's* posted price, in some countries also referred to as list price. Discounts or other incentives offered by *manufacturers* result in an effective price that is lower than the ex-factory price.

External price referencing: the practice of comparing *pharmaceutical* prices across countries. There are various methods applied and different country baskets used.

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Formulary: list of products reimbursed or paid for by a *third-party payer*. See also *open formulary*.

Framework agreement: agreement between social health insurers, national health services or ministries with pharmaceutical *manufacturers* establishing guidelines for policies relating to *pharmaceuticals*. Framework agreements may include provisions relating to *pricing*, promotion, etc. They are used in countries such as France and Spain.

Free pricing: a policy under which *manufacturers* are free to set prices at the level or levels which the market will bear, free from government intervention.

Generic: bioequivalent version of an *original product*. There are branded and *unbranded generics* on the market. Branded generics also have a specific trade name, whereas unbranded generics use the *international non-proprietary name*.

Generic name: see International Non-proprietary Name.

Generic substitution: practice of *pharmacists* substituting a *generic* pharmaceutical, either a branded or *unbranded generic*, for a branded *pharmaceutical*.

Health technology assessment (HTA): the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

Internal reference pricing: a method to compare prices of products in a country with the price of identical (*ATC*-5 level) or similar products (*ATC*-4 level). Often performed in the course of a *reference pricesystem*.

Internal price referencing: see *internal reference pricing*.

International Non-proprietary Name (INN): Identifies *pharmaceutical* substances and *active ingredients*. Each INN is a unique name that is globally recognised and is public property.

International price benchmarking: see *external price referencing*.

List price: see *ex-factory price*.

Manufacturer: a pharmaceutical company that produces *pharmaceuticals* and very often also searches for and develops new drugs. See also *distributor*.

Manufacturer price: see *ex-factory price*.

Market(ing) authorisation: a licence issued by a regulatory agency approving a pharmaceutical for market use based on a determination by authorities that the *pharmaceutical* meets the requirements of quality, safety and efficacy for human use in therapeutic treatment. Also known as a sanitary license.

Me-too: an *original product* that is approved subsequent to another product that is comparable or similar in composition and in therapeutic effect to the me-too product.

Medicinal product: see *pharmaceutical*.

Medicine: see *pharmaceutical*.

Negative list: list of *pharmaceuticals* not covered by a *third-party payer* (see also *positive list*).

New chemical entity (NCE): a drug approved for *marketing authorisation* with an *active ingredient* not present in any drug previously approved by a regulatory agency.

New molecular entity (NME): see *new chemical entity*.

Non-prescription medicine: see *over-the-counter pharmaceutical*.

Off-patent pharmaceutical: *original product* whose patent has expired.

Off-patent product: see *off-patent pharmaceutical*.

On-patent pharmaceutical: an *original product* whose patent is still in force.

Open formulary: a *pharmaceutical* benefit design that provides coverage for drugs on the *formulary* (if any) as well as other drugs not specifically listed.

Original preparation: see *original product*.

Original product: the first version of a *pharmaceutical*, developed and patented by an originator pharmaceutical company which receives exclusive rights to market the product for a specified period of time. An original product has one or more trade names used for marketing purposes, its so-called *brand* names.

Original substitution: see *generic substitution*.

Orphan drug: a *pharmaceutical* which only has a limited target population or which treats a rare disease thus limiting its commercial and financial potential.

Out-of-pocket payments: payments made by a health-care consumer that are not reimbursed by a *third-party payer*. This includes all forms of *co-payments*, co-insurance and deductibles as well as payments for non-covered services and informal payments for health-care services.

Over-the-counter pharmaceutical (OTC): *pharmaceuticals* which may be dispensed without a doctor's prescription being submitted and which are in some countries available via self-service in pharmacies and/or other retail outlets (*e.g.* drug stores, supermarkets).

Parallel import: see *parallel trade*.

Parallel trade: the act of importing *pharmaceuticals* into one country (the "import" country) from another (the "export" country) and placing them on the market outside the formal channels authorised by the product's *manufacturer* or licensed distributors.

Pharmaceutical: any *active ingredient* or a combination of two or more active ingredients in a product which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a pharmaceutical.

Positive list: see *formulary*.

Pharmaceutical form: the pharmaceutical-technological form in which an *active substance* is made available. *Pharmaceuticals* may be administered in solid form (*e.g.* tablets, powders), in semi-liquid form (*e.g.* ointments, pastes), in liquid form (*e.g.* drops, injectables, infusions) or in gaseous form (inhalation).

Pharmaco-economics: see *pharmaco-economic evaluation*.

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Pharmaco-economic evaluation: assessment of the relationship between costs and outcomes for a given product, and, possibly, comparisons to costs and outcomes of alternative treatments, pharmaceutical or not.

Pharmacist: a person trained and licensed to prepare and distribute medicines and to give information about them.

Pharmacy margin: the gross profit of pharmacies expressed as a percentage of the *retail price*.

Pharmacy mark-up: the gross profit of pharmacies expressed as a percentage of the *pharmacy purchasing price*.

Pharmacy purchasing price: the price charged by wholesalers to the retailers (usually pharmacies). It includes any *wholesale mark-up*.

Positive list: see *formulary*.

Preferred drug list (PDL): a term sometimes used as an alternative to *formulary*, but more precisely refers to a list of preferred medicines within selected drug classes on a formulary for which a patient's co-payment is lower and/or prior authorisation is not required.

Prescribing budget: the maximum amount of money to be spent on *pharmaceuticals* in a specific region or for an individual physician or a group of physicians, for a specified period of time, fixed ex-ante. Prescribing budgets are a cost-containment measure used by *third-party payers*.

Prescription Fee/Charge: a set amount to be paid by a patient for each item prescribed by a physician and dispensed at the expense of a *third-party payer*, *i.e.* a form of fixed *co-payment*.

Prescription-only-medicines (POM): *pharmaceuticals* that may be dispensed only on a doctor's prescription.

Price-volume agreement: the price of a pharmaceutical is agreed to between a *third-party payer* and a pharmaceutical *manufacturer* based on a forecasted volume of sales. If the actual sales volume exceeds the forecast, the price of the *pharmaceutical* may be revised downwards or the manufacturer asked to pay a *rebate*.

Pricing: the act of setting a price for a *pharmaceutical*.

Pricing policy: plan or course of actions used by government authorities, or *third-party payers,* to influence the amount paid by purchasers or the amount received by sellers (*e.g. free pricing*, regulated pricing – see *regulated price*).

Prior authorisation: formal agreement from a *third-party payer* for the *reimbursement* of a treatment, prior to the purchase of the treatment.

Procurement: the act of purchasing a *pharmaceutical* by a public authority.

Product life-cycle management: refers to a range of practices used by *manufacturers* of *originalproducts*, including but not limited to patent-related strategies, intended to limit or delay competition by *generics*.

Rebate: a partial refund following a purchase.

Reference price: a maximum *reimbursed amount* set by a *third-party payer* for a defined group of *pharmaceuticals* judged to be similar. Usually, one reference price is set for all products in a given *ATC*-4 and/or *ATC*-5 level group. See *reference price system*.

Reference price system: a scheme used by *third-party payers* to set a common *reimbursement price* for a defined group of *pharmaceuticals* judged to be similar. Patients buying a pharmaceutical that is part of a group for which a *reference price* has been set must pay the difference between that price and the *retail price* of the pharmaceutical in question, in addition to any fixed or percentage *co-payments*.

Registration: see *market(ing) authorisation*.

Reimbursement: the share of costs (for a service or a *pharmaceutical*) which the *third-party payer* pays. One-hundred per cent reimbursement means that the third-party payer accepts 100% of the costs for a *pharmaceutical* or healthcare service.

Reimbursed amount: the actual sum paid by a *third-party payer* to an insured person or seller of a *pharmaceutical*. May be equivalent to the full *reimbursement price* (as in Austria) or set as a percentage share of the reimbursement price (as in Denmark).

Reimbursement level: the share of total charges for a service or a *pharmaceutical* which the *third-party payer* pays. For example, an 80% *reimbursement level* means that the third-party payer assumes 80% of the costs for a pharmaceutical or healthcare service.

Reimbursement price: the basis for *reimbursement* of pharmaceuticals in a health care system, *i.e.* the maximum amount that a *third-party payer* will pay for a particular *pharmaceutical*. See *reimbursed amount*.

Retail price: the price charged by retail *pharmacists* or other retailers to the general public.

Switch: reclassification of the dispensing status of a *pharmaceutical* from *prescription-only* to *over-the-counter*.

Supplementary Protection Certificate (SPC): gives originators (see *original product*) a complementary period of market exclusivity beyond patent expiry to compensate for delays of marketing in the *pharmaceutical* sector. SPCs are available in EU countries. Similar protection exists in other countries.

Therapeutic group: *pharmaceuticals* from the same pharmacological class, such as statins.

Therapeutic referencing: see *internal reference pricing*.

Third-party payer: any entity, public or private, that pays or insures health or medical expenses on behalf of beneficiaries or recipients of the coverage.

Unbranded generic: see *generic*.

Value-added tax (VAT): a tax levied on the sale of goods and services (compulsory for EU Member States). The VAT rate for pharmaceuticals in the EU is often lower than the standard minimum VAT-rate of 15%.

Wholesale margin: gross profit of wholesalers, expressed as a percentage of the *pharmacy purchasing price*.

Wholesale mark-up: gross profit of wholesalers, expressed as a percentage of the *ex-factory price*.

Wholesale price: see pharmacy purchasing price.

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Various sources were used to compile this glossary. The following sources were consulted most frequently or were used to extract a verbatim definition:

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List of Abbreviations

ADR	Adverse Drug Reactions
AMP	Average Manufacturer Price
ANAFAM	Asociación Nacional de Fabricantes de Medicamentos
ASMR	Amélioration du Service Médical Rendu
ATC	Anatomic Therapeutic Chemical Classification
BP	Best Price
BPAs	Blanket Purchase Agreements
CBO	Congressional Budget Office
CBS	Centraal Bureau voor de Statistiek (Netherlands)
CEPS	Economic Committee for Health Products
CME	Continuing Medical Education
CP	Centralised Procedure
DALY	Disability Adjusted Life Year
DDD	Defined Daily Dose
DoH	Department of Health
DP	Drugs Payment
DP	Decentralised Procedure
DRA	Deficit Reduction Act
DRG	Diagnostic-Related Group
DTC	Drug and Therapeutic Committees
DTCA	Direct-to-Consumer Advertising
DTI	Department of Trade and Industry
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industry Associations
EGA	European Generics Manufacturers Association
EMEA	European Medicines Evaluation Agency
EPC	European Patent Convention Treaty
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
FTC	Federal Trade Commission
GAO	General Accounting Office
GDP	Gross Domestic Product
GP	General Practitioner
HD	Health Data
IOM	Institute of Medicine
IPR	Intellectual Property Rights

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LFN	Sweden's Pharmaceutical Pricing Agency
LOOP	Law of One Price
LTI	Long Term Illness
MAGR	Mean Annual Growth Rate
MCC	Marginal Cost of Capital
MPA	Medical Products Agency
MRP	Mutual Recognition Procedure
MRR	Marginal Rate of Return
NAS	New Active Substances
NCE	New Chemical Entities
NCU	National Currency Unit
NHS	National Health Services
NICE	National Institute of Clinical Excellence
NME	New Molecular Entities
ÖBIG	Austrian Health Institute
OOP	Out-of-pocket
OTC	Over-the-counter (non-prescription) drugs
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Pharmaceutical Benefits Management
PDL	Preferred Drug List
PDP	Prescription Drug Plan
PICTF	Pharmaceutical Industry and Competitiveness Task Force
PMPRB	Prescription Medicine Prices Review Board
POM	Prescription-only medicine
PPP	Purchasing Power Parity
PPRI	Pharmaceutical Pricing and Reimbursement Information
PPRS	Pharmaceutical Price Regulation Scheme
R&D	Research and Development
RBP	Rémunération basée sur les prestations
ROI	Return on Investment
SKK	Slovak koruna
SPC	Supplementary Protection Certificate
TRIPS	Trade-Related Aspects of Property Rights
USC	Uniform System of Classification
USP	US Phamacopeia
VA	Veterans Affairs
VAT	Value Added Tax
VFA	Verband Forschender Arzneimittelhersteller e.V.
VHA	Veterans Health Administration
VISN	Veteran Integrated Service Network

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Pharmaceutical pricing policies are designed with national objectives in mind, but are the transnational implications always taken into account?

Pharmaceutical policy making raises particular challenges in reconciling key objectives for health policy, such as ensuring affordable access to the latest effective drugs, with other important policy considerations, such as providing support to a valuable national industry. Unusually among health policy issues, it also raises international considerations that further complicate decision making, particularly as the nature and extent of such considerations are not well understood. How do national pharmaceutical pricing policy decisions affect innovation in the pharmaceutical sector? How do such decisions affect prices paid for pharmaceuticals, or access to pharmaceuticals, in other countries?

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This publication presents an analysis of comparative price levels, making use of a unique dataset to construct the most comprehensive pan-OECD pharmaceutical price index to date. It also draws upon original case studies of pharmaceutical pricing and reimbursement policies in six OECD countries to provide specific examples of the impacts of policies on health system performance.

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