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Economic and Monetary Affairs

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**Environment, Public Health
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Industry, Research and Energy

Internal Market and Consumer Protection



**DIFFERENCES IN COSTS
OF AND ACCESS TO
PHARMACEUTICAL
PRODUCTS IN THE EU**

ENVI



DIRECTORATE GENERAL FOR INTERNAL POLICIES
POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

DIFFERENCES IN COSTS OF AND ACCESS TO PHARMACEUTICAL PRODUCTS IN THE EU

STUDY

Abstract

This report reviews the differences in the prices of pharmaceuticals among Member States. It presents an overview of the prices for pharmaceuticals protected by patents as well as those for off-patent pharmaceuticals subject to competition from lower-priced “generic” versions. The report reviews the approaches that Member States have used to regulate the pharmaceutical market on both the supply and demand sides, and assesses evidence regarding the impact of these different approaches on pharmaceutical prices, cost-containment, industry innovation. The report also considers the implications for patient access to pharmaceuticals. The report considers policy options to strengthen coordination among Member States and exchange best practice.

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AUTHORS

Panos Kanavos
Sotiris Vandoros
Rachel Irwin
Elena Nicod
Margaret Casson
Medical Technology Research Group – LSE Health
London School of Economics and Political Science
Prepared under a framework contract held by Milieu Ltd

RESPONSIBLE ADMINISTRATOR

Marcelo Sosa-Iudicissa
Policy Department Economic and Scientific Policy
European Parliament
B-1047 Brussels
E-mail: Poldep-Economy-Science@europarl.europa.eu

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ABOUT THE EDITOR

To contact the Policy Department or to subscribe to its newsletter please write to: Poldep-Economy-Science@europarl.europa.eu

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LIST OF ABBREVIATIONS

ASMR	Amélioration du Service Medical Rendu
CEA	Cost-Effectiveness Analysis
CEPS	Economic Committee for Health Care Products
CBA	Cost-Benefit Analysis
CMA	Cost-Minimisation Analysis
CNS	Central Nervous System
CUA	Cost-Utility Analysis
DDD	Defined Daily Dose
DH	Department of Health (UK)
DTCA	Direct to Consumer Advertising
EAEPIC	European Association of Euro-Pharmaceutical Companies
ECJ	European Court of Justice
EDQM	European Directorate for the Quality of Medicines and HealthCare
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
GDP	Gross Domestic Product
GNI	Gross National Income
HAS	French National Authority for Health
HTA	Health Technology Assessment

ICER	Incremental Cost Effectiveness Ratio
IMI	Innovative Medicines Initiative
INN	International Non-proprietary Name
JPMA	Japan Pharmaceutical Manufacturers Association
LYG	Life Years Gained
LYS	Life Years Saved
MoSA	Ministry of Social Affairs
MU	Monetary Units
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
OTC	Over-the-Counter
PhRMA	Pharmaceutical Research and Manufacturers of America
PPRS	Pharmaceutical Price and Reimbursement Scheme
QALY	Quality Adjusted Life Year
QoL	Quality of Life
POM	Prescription Only Medicine
RCT	Randomised-Controlled Trial
ROCE	Return on Capital Employed
R&D	Research and Development
SAM	State Agency of Medicine
SMR	Service Medical Rendu
SPC	Supplementary Protection Certificate

TFEU Treaty on the Functioning of the European Union

TLV Dental and Pharmaceutical Benefits Board

VAT Value Added Tax

VBP Value Based Pricing

WTP Willingness-to-pay

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EXECUTIVE SUMMARY

This report has been prepared at the request of the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament. It aims to contribute to a better understanding of why pharmaceutical prices and public pharmaceutical expenditures vary across Member States.

While Member States have the primary role in providing health care for EU citizens, the 2009 Lisbon Treaty has given the European Union a greater role in the area of public health, including in the exchange of best practice regarding Member State activities.

Pharmaceutical prices are a key issue for health care, as medicines represent the third most important cost component in Member States' health care budgets. These costs are substantial and are rising faster than Member States' GDP, mainly due to an ageing population and the increasing cost of developing new pharmaceutical technologies.

At the same time, the regulation of pharmaceutical prices will affect an industrial sector that is a major component of Europe's economy in terms of employment, manufacturing, and research and development (R&D).

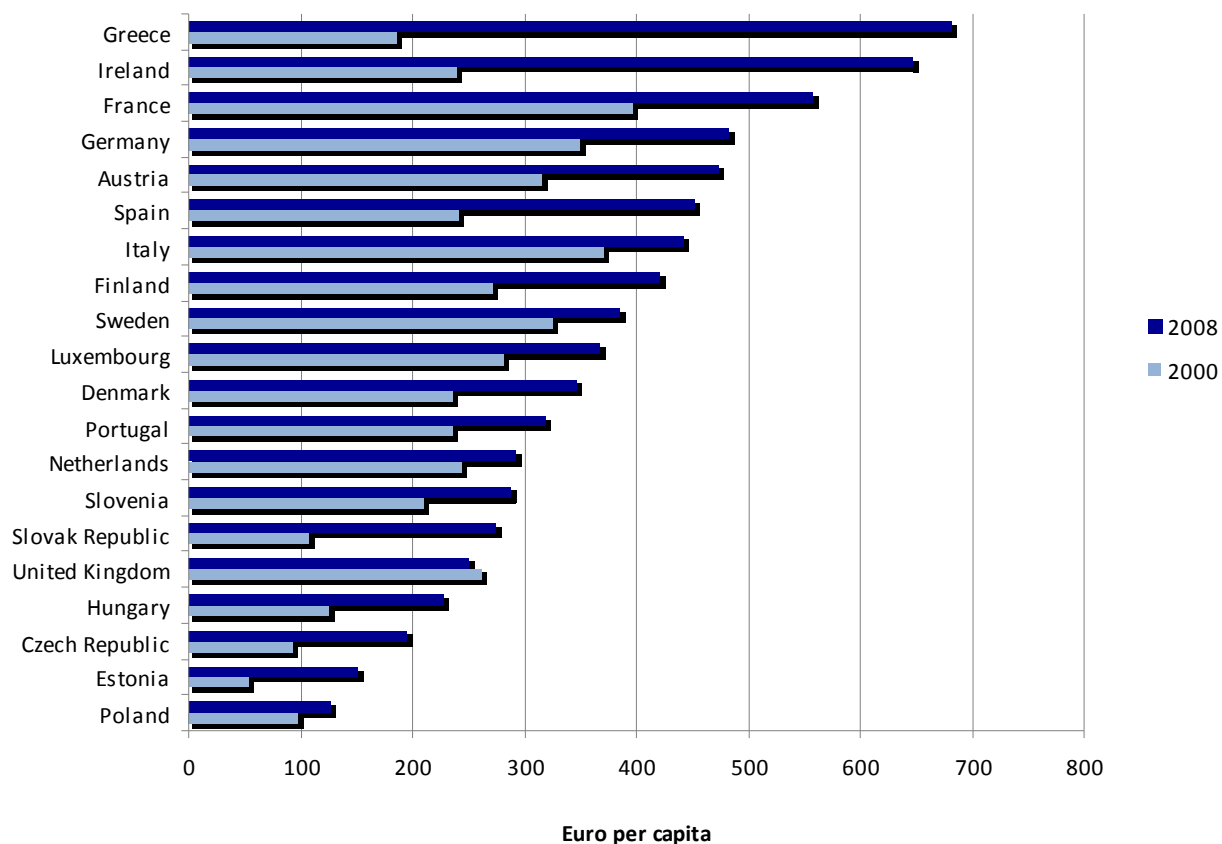
This report reviews the differences among Member States in terms of several key areas:

- Expenditure on pharmaceuticals that are reimbursed by health systems
- Prices of pharmaceuticals
- Pharmaceutical production and research

The report then studies possible reasons for the differences in pharmaceutical prices. It discusses the complexity of interactions among different regulatory measures used by Member States and their impact on pricing, cost-containment, innovation and access to pharmaceuticals.

Differences in pharmaceutical prices and expenditures across Member States

Member State spending per capita on pharmaceuticals varies significantly (see Figure 1 below). This appears to be due to a range of factors: the amount of pharmaceuticals that are consumed; the mix of pharmaceutical products (brands versus generics); and their prices; as well as the share of the price that is reimbursed by national health systems.

Figure 1: Total Pharmaceutical expenditure per capita (Euros), 2008 compared to 2000

Source: OECD Health Data 2010 - Version: June 2010

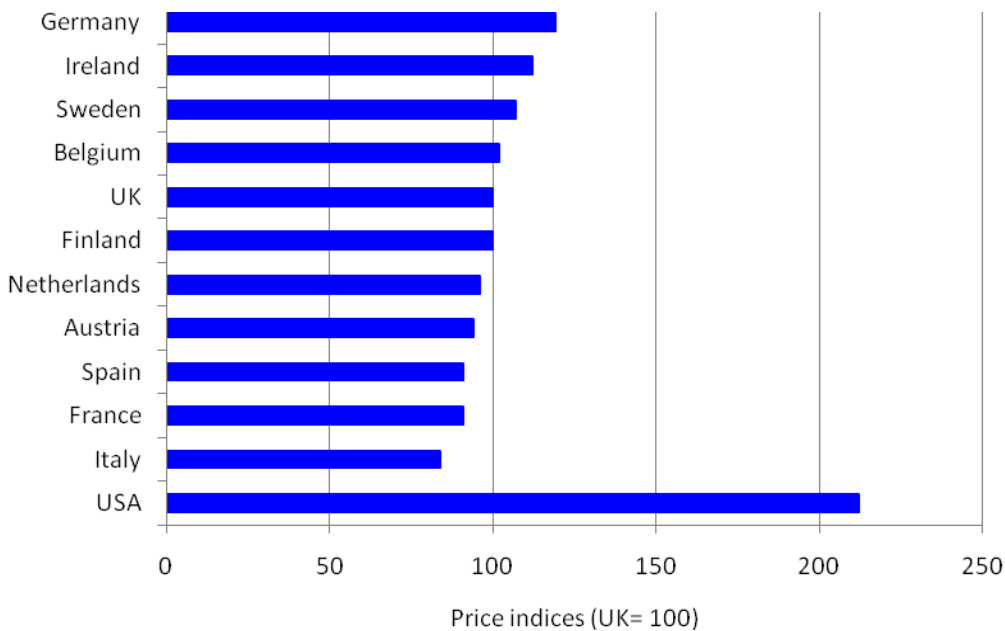
Note: 2009 data for Greece (from local health insurance sources); 2006 data for Portugal; instead of 2000 data for the Netherlands and Poland, 2002 data are used. The reduction in the UK is attributable to the sterling depreciation against the Euro.

The prices of the pharmaceuticals themselves also vary across Member States. A recent review of the prices for 150 pharmaceuticals shows that the average price for this "basket" among 11 Member States found a 25% difference between the lowest and highest Member States (UK Department of Health, 2009), as shown in Figure 2, below. (Prices in the USA are significantly higher than any of the 11 Member States.)

Price variation for an individual pharmaceutical product can be even greater. A key distinction is between pharmaceuticals that are covered by patents and related forms of intellectual property rights (including market exclusivity periods and supplementary protection certificates) and pharmaceuticals that are not: in the former, the manufacturers hold a monopoly. For pharmaceuticals covered by patents, variations in price among Member States of up to four to one for a single product have been observed (Kanavos and Costa-Font, 2005).

For price variation assessment purposes, "orphan" medicines, i.e. those for rare diseases, can be assimilated to patent-protected medicines.

Figure 2: Price comparisons among EU Member States (and with the US) for a basket of 150 pharmaceutical products; 2008 price index with UK=100



UK Department of Health, 2009

For pharmaceuticals no longer covered by patents, “generic” versions can compete with those produced by the original manufacturer. Generic versions can cost much less, typically one-quarter of the price of the original, “branded” pharmaceutical. In this market, the variation in price can be even greater: the difference between the highest and lowest prices for one generic medicine for hypertension was found to be 16-fold (Kanavos and Casson, 2011 forthcoming). This is important, as a large share of the medicines consumed across the EU-27 is no longer covered by patents. However, the share of generic pharmaceuticals purchased also varies across Member States: it is over 50% of the total volume of pharmaceuticals consumed in the UK, Germany, Denmark and Sweden, but lower in most other Member States.

Pharmaceutical production and research

The level of pharmaceutical prices (and the methods for price regulation) will affect the pharmaceutical sector, which directly employs 633,100 people across Europe and spends in excess of €26 billion annually on research and development (R&D). Production takes place in several Member States, but the bulk of manufacturing is accounted for by only a few: France, Germany, Ireland, Italy, Spain and the UK. The location of manufacturing can be explained in part by the size of domestic markets; another important factor has been the business environment.

Research and development is a critical component of the pharmaceutical sector, and the EU is the world leader in terms of pharmaceutical R&D spending, slightly ahead of the United States.

Basic and discovery research is concentrated in several Member States: on a per capita basis, Denmark and Belgium are leaders, followed by Sweden, the UK, France and Germany. Developmental R&D (including clinical trials) is carried out across the EU. Member State policies regarding the pricing and reimbursement of new pharmaceuticals clearly have an impact on the industry and its incentives for devoting resources to innovation.

Key factors influencing the differences in pharmaceutical prices

The important price differences across Member States can be explained by a number of factors.

One broad factor is national income per capita: in general, prices of in-patent pharmaceuticals seem to be proportionally higher in Member States with higher levels of per-capita income. In addition, higher-income Member States appear to spend more on pharmaceuticals.

A second key factor relates to Member State national (and, sometimes, regional) regulatory approaches. Member States use a variety of tools, both on the supply side (for determining both prices as well as the share of prices that are reimbursed) and on the demand side. The latter can include policies to encourage physicians to prescribe and pharmacists to dispense lower-priced generic pharmaceuticals, as well as requirements that patients pay a share of pharmaceutical costs.

On the supply side, Member State health systems usually negotiate prices with manufacturers based on a range of methods and criteria, and this is a factor in the price differences for pharmaceuticals, both those covered by patent and those for which the patents have expired.

A widely used tool (by 24 out of the 27 EU Member States) for determining prices is external price referencing. Under this mechanism, a Member State sets a pharmaceutical's price based on a comparison with prices in other Member States. This approach can lead to lower pharmaceutical prices, in particular when a Member State makes decisions based on the lowest comparison prices rather than an average. There are concerns, however, that it ignores other aspects, such as health priorities for each country, and moreover that it can create uncertainty for innovative sectors of the industry.

Tendering for off-patent pharmaceuticals in primary care (i.e. outpatient care) has been used in a few Member States, including the Netherlands and Germany, where it has led to a significant reduction in prices. Some Member States have also used price caps for generic pharmaceuticals, but a review suggests that price levels are lower in Member States that do not use this approach (Puig-Junoy 2010). Internal reference pricing is also used extensively to promote generic use and, through that, achieve savings for health systems.

Reimbursement decisions also affect price. Member States can establish a formulary that lists pharmaceuticals that are reimbursed by health care insurance (or a negative formulary, for those that are not reimbursed). A key method for reimbursement decisions in the context of in-patent pharmaceuticals is Health Technology Assessment (HTA): it is increasingly used to appraise the additional clinical benefit of new pharmaceuticals against existing ones, in relationship to their respective costs.

Its results are used primarily to make reimbursement decisions. However, as Member States have different ways of accepting evidence and interpreting it, variations exist in the application of HTA appraisals and these can result in different prices as well as diverging coverage decisions for the same pharmaceutical across different Member States.

The level of value added tax (VAT) will also affect prices: the rate for pharmaceuticals varies across Member States from zero (e.g. UK and Sweden) to 25% in Denmark. Some Member States such as Greece have recently raised VAT rates for pharmaceuticals.

Another factor influencing pharmaceutical prices is the margin taken by wholesalers and retailers: this too differs greatly across Member States. Government policies can influence these margins, can set requirements for the number of pharmacies and can encourage or limit the consolidation of companies in the wholesale and retail markets. In those Member States where allowed, some manufacturers have put in place direct sales to pharmacies, or chosen to work with a restricted number of wholesalers, methods that can indirectly reduce the overall cost of distribution.

The EU single market allows distributors and other market actors to purchase pharmaceuticals in Member States with lower prices and re-sell them where prices are higher. The market share of parallel-traded pharmaceutical products in the main importing Member States stands between 1.7% in Finland and 16.5% in Denmark (EFPIA, 2010). This practice, which has been reviewed and upheld by the European Court of Justice, has been cited as a mechanism that can reduce prices in the sales markets. Overall, however, it appears that the final sale prices of pharmaceuticals have not been significantly reduced by parallel trade. In other words, most of the difference in price accrues to the intermediaries (Kanavos and Costa Font, 2005; Kanavos and Vandoros, 2010). Manufacturers have turned to direct sales methods as a response to parallel trade.

Access to medicines

The different Member State approaches regarding pharmaceutical prices and reimbursement have consequences also for patient access to medicines in terms of both availability and affordability. HTA appraisals for new pharmaceuticals covered by patent may be different in one Member State from those in another. As a result, the access that patients have to such medicines varies across the EU. In particular, access to certain categories of in-patent pharmaceuticals tends to be negatively correlated with market size and per capita GDP.

In some cases a low price for a new product in one national market can lead manufacturers to refrain from launching the product in other markets, since the low price might jeopardise their pricing prospects elsewhere due to the wide application of external price referencing.

A different problem is seen regarding generic medicines: here, manufacturers of generics may decide not to enter smaller markets. As a result, health systems and patients in these markets may not have access to these lower priced alternatives. Small markets face similar problems for new orphan medicines.

Parallel trade has also raised concerns regarding access to pharmaceuticals, as it has been associated with shortages in exporting Member States (Kanavos and Costa-Font, 2005, Gainsbury, 2009; Taylor, 2010).

Policy options

The Lisbon Treaty has established a more important albeit limited role for the EU in health care policy. The EU can organise and further the exchange of best practice and carry out monitoring and evaluation of Member State health care systems.

One option could be to strengthen the sharing of information and policy experience among Member States on mechanisms used to purchase pharmaceutical products. This could be done by building on existing initiatives such as the network of Competent Authorities on Pricing and Reimbursement. An exchange of information could be used to identify good practices at the Member State level. Approaches to Health Technology Assessment (HTA) could be a key topic of further discussion, given that a growing number of Member States use this approach, but their results in terms of reimbursement decisions often vary. Clinical cost-effectiveness is one of the factors considered in HTA analysis. Here, EU institutions could foster stakeholder discussions to help define the value of innovation for patients, health systems and the EU pharmaceutical industry and its role in the European economy.

Deeper coordination among Member States in the field of biomedical innovation could avoid duplication in research efforts by national competent bodies. Setting research priorities in accordance with unmet medical needs at EU level would likewise be desirable.

EU policies can also encourage greater and earlier use of generic medicines, which could lead to significant price reductions in a number of markets.

Parallel trade also deserves further study and exchange of information at EU level.

Other options for attention include the problem of small markets, which face lower competition from generic pharmaceuticals and thus higher prices, as well as the problems related to the lack of availability of certain products in individual Member States. The EU could seek to identify mechanisms to address these issues.

GENERAL INFORMATION

Across the EU, health care is publicly financed and provided by health insurance systems based on solidarity and universal access.

While Member States have the primary role in providing health care for EU citizens, the 2009 Lisbon Treaty has nonetheless given the European Union a greater role in the area of public health. The Treaty on the Functioning of the European Union (TFEU) states that EU action "...shall complement national policies..." (Article 168(1)). Among the roles at EU level, the European Commission may:

"...take any useful initiative to promote such coordination, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation..." (Article 168(2)).

The TFEU also affirms the primary responsibility of Member States in the provision of health care, as stated in its Article 168(7):

"Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them..."

Member State governments face substantial and rising costs for the provision of health care (average costs are rising at a faster rate than GDP), mainly due to Europe's ageing population and the increasing cost of new medical technologies. Pharmaceutical costs are the third most important component in EU Member States' health care budgets.

At the same time, health is a high priority for Europe's citizens.¹ In addition, the pharmaceutical industry is a major component of Europe's economy in terms of employment, manufacturing, and research and development.

Member State governments take a strong role in regulating national pharmaceutical markets and thus in influencing prices.

They do so because the pharmaceutical market is different from that in other sectors of the economy. First, patients with the same disease may respond differently to a given treatment. Second, in a normal market, consumers in principle weigh costs and benefits of alternatives and make an informed decision. In the pharmaceutical market, patients have insufficient information on their health needs and largely rely on physicians to make the treatment decision on their behalf. A further element is that patients do not usually pay directly for their health care, including most pharmaceuticals, which are covered by national health systems.

¹ Despite rising concerns about the economic situation, health and healthcare remained in the top five concerns of EU citizens in 2009 Eurobarometers (e.g. No. 71 Spring 2009, No. 72 Autumn 2009). See for example: http://ec.europa.eu/public_opinion/archives/eb/eb72/eb72_en.htm.

On the supply side, the costs to develop a new product are difficult to assess as they result from years of multidisciplinary research involving multiple projects. Manufacturers that develop new pharmaceuticals are protected for a fixed period by patents, whereby their product is granted market exclusivity for a defined period of time.

Governments have introduced regulatory measures aiming at containing pharmaceutical costs by targeting price, volume, or both. These regulatory measures target either the demand side (i.e. physicians, pharmacists or patients), or the supply side (i.e. prices and market exclusivity of pharmaceuticals). Once patents expire, regulatory measures encouraging the market entry and uptake of lower-priced "generic" versions of pharmaceuticals can promote more efficient use of healthcare resources. Such cost-containment measures are aimed at cutting down inefficient expenditure while enabling access to other efficient, often more expensive, treatments.

The report is divided into three sections. The first section reviews differences in expenditure on health care and on medicines, as well as differences in the price of medicines that are reimbursed by health care systems. It also outlines the main features of the pharmaceutical sector in Europe. The second section analyses the effects of regulatory measures on pharmaceutical pricing and on access to pharmaceuticals.

The last section presents key findings and formulates policy options.

1. OVERVIEW OF EU HEALTH EXPENDITURES AND OF THE EU PHARMACEUTICAL SECTOR

KEY FINDINGS

Member State spending on health care and pharmaceuticals:

- Pharmaceutical spending is the third largest component of Member State health budgets. Health and pharmaceutical expenditures continue to rise as a percent of GDP throughout the EU. This raises issues of sustainability; there is an imminent and ever-increasing need to contain growing health care costs, including those associated with pharmaceutical spending, and to spend scarce resources efficiently.
- Per capita GDP and health spending per capita are strongly correlated. While per capita GDP and per capita pharmaceutical spending are also correlated, some of the Member States that spend the most on medicines do not have the highest overall health care costs.
- The level of per capita pharmaceutical spending varies greatly across the EU: in a review of 20 Member States, the highest level of spending per capita is more than three times the lowest level.

Price differences among Member States

- The prices of pharmaceuticals vary across EU Member States: for a basket of 150 medicines, the national averages differ by up to 25%.
- For individual pharmaceuticals sold across the EU, price differences are even higher. For patent-protected individual pharmaceuticals, differences as high as 4:1 have been observed between the highest and lowest prices.
- Price differences appear even greater for pharmaceuticals whose patents have expired, as generic versions increase market competition. For these medicines, differences as high as 16:1 have been observed among Member States for individual generic pharmaceuticals

The European pharmaceutical sector

- The pharmaceutical sector is a significant contributor to Europe's employment and manufacturing, directly employing 633,100 people, and a key contributor to R&D investment.
- The pharmaceutical sector in Europe spends in excess of €26 billion on pharmaceutical R&D (basic, discovery and development research).
- While aggregate data on public spending on pharmaceutical R&D is not readily available, public funding of pharmaceutical and biomedical R&D is estimated to be comparable in volume to that of the private sector.

This section provides an overview of Member State health care and pharmaceutical expenditures. It then reviews pharmaceutical prices in the EU. It also presents a brief review of the role of the pharmaceutical sector in the EU economy, identifying the Member States where this sector is concentrated.

1.1 Health Care and Pharmaceutical Expenditure Trends in EU Member States

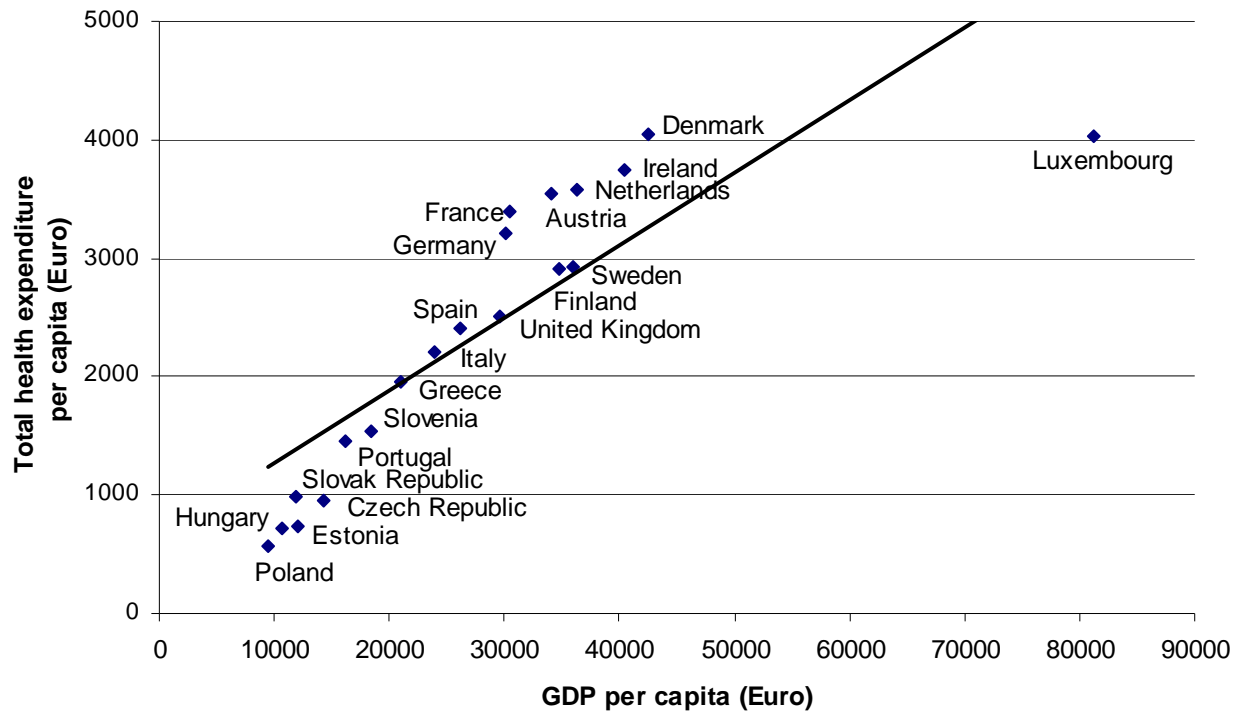
1.1.1. Finance and organisation of health services in EU Member States

Article 152 of the EC Treaty enables EU Member States to organize and finance their own social security systems based on their distinct philosophies and population needs. Health care systems in the EU are mostly publicly funded and are characterised by universal access and coverage extended to their entire populations, subject to modest or moderate co-payments depending on the type of good or service used. The two dominant forms of health care financing in the EU are general taxation and social insurance, and there is also a certain percentage of private health insurance financing (Mossialos et al, 2002).

Both tax and insurance-based systems face issues of sustainability and an imminent and ever-increasing need to contain growing health care costs, including those associated with pharmaceutical coverage and funding, and to spend scarce resources efficiently. Challenges to sustainability include population ageing, lifestyle choices (diet, alcohol consumption, exercise) and their impact, technical innovation, inappropriate variation in clinical practice, resource constraints and increasing public expectations. Both types of systems require procedures for prioritization and efficient use of scarce resources. Despite obvious differences in the organisation and delivery of health care at member state level, pharmaceutical funding and coverage issues across Member States are largely common and, broadly speaking, relate to achieving efficiency in resource allocation and obtaining value for money given the investments made, improving evidence-based policy-making, optimising pharmaceutical regulation and ensuring that the best possible outcomes are achieved for patients.

1.1.2 Member State expenditures on health care and pharmaceuticals

Member State expenditures on health care per capita vary greatly, though they are closely correlated with GDP per capita. There is a positive relationship between health expenditure per capita and GDP per capita. Higher-income Member States such as Austria, France, Germany and Sweden spend, on average, more on health given their GDP per capita. Figure 3 below shows this relationship for 20 Member States.

Figure 3: Health expenditure per capita and GDP per capita, 2008

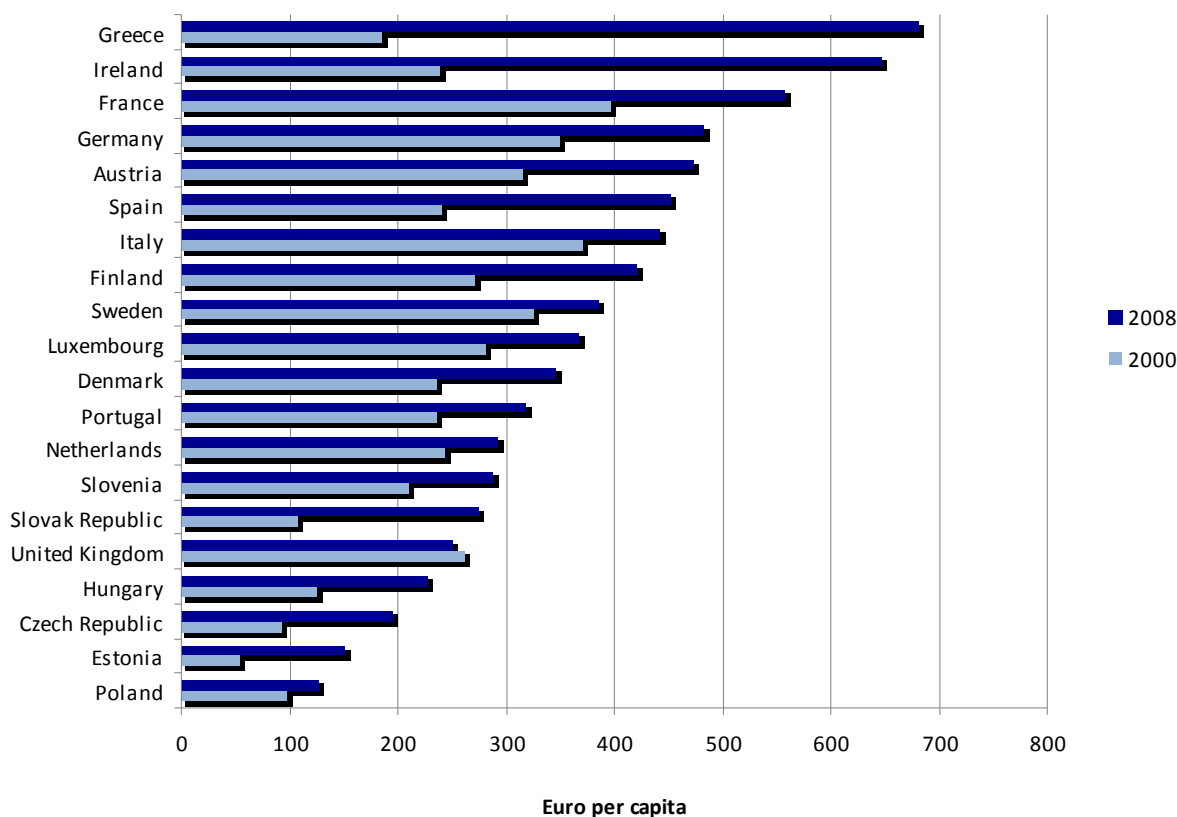
Source: OECD Health Data 2010 - Version: June 2010.

Note: The line shows the average relationship between GDP and total health expenditure for those Member States considered.

Total expenditure on health has risen considerably over the past twenty years across EU Member States, both in absolute terms and as a share of GDP (OECD Health Data, 2010). The level of total health expenditure steadily increased during the 1990s and early 2000s across all Member States. This growth continues today, to varying extents in each Member State, accounting for between 6.8% (Luxembourg) and 12% (France) of GDP, which represents an increase of between 4.7% (Czech Republic) and 10% (France) since the early 1990s. Health expenditures are increasing at a faster rate than GDP across EU Member States, and it is predicted that this growth will continue in the coming years due to the ageing population, more expensive technologies and rising expectations for health care services.

1.1.3 Pharmaceutical expenditure

Pharmaceutical expenditures are the third largest component of health expenditures, following hospital and ambulatory care spending (European Commission, 2009). Pharmaceutical expenditure as a proportion of total health expenditure currently ranges from less than 10% in Denmark to almost 25% in Greece.

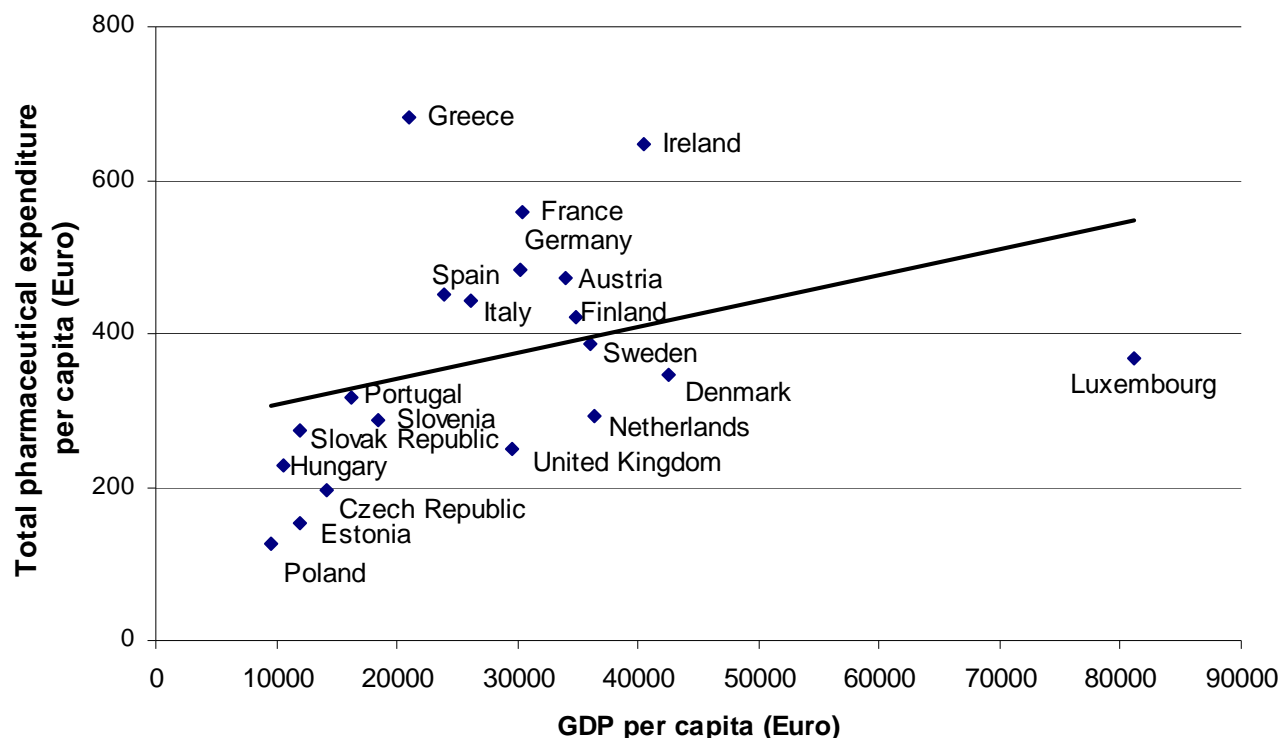
Figure 4: Total Pharmaceutical expenditure per capita (Euro), 2008 compared to 2000

Source: OECD Health Data 2010 - Version: June 2010; 2009 data for Greece (from local health insurance sources).

Note: 2009 data for Greece; 2007 data for Denmark; 2006 data for Portugal; instead of 2000 data for the Netherlands and Poland, 2002 data are used. The reduction in the UK is attributable to the sterling depreciation against the Euro.

Member State expenditures per capita on pharmaceuticals vary greatly. A review of 20 Member States shows that there is a more than three-fold difference in per capita pharmaceutical spending between the highest- (Greece, with €682 per capita) and the lowest-spending Member State (Poland, €127 per capita) in this group (see Figure 4).

There seems to be a similarly positive relationship between pharmaceutical expenditure per capita and GDP per capita (OECD Health Data, 2010), however, this is less strong than for health care expenditure (see Figure 5). Greece, Ireland, France, and Germany, for example, are among the Member States that spend proportionally more on pharmaceuticals in per capita terms as share of GDP (i.e. above the regression line), while the Netherlands and the UK are among those that spend proportionally less (i.e. below the regression line).

Figure 5: Pharmaceutical expenditure per capita (Euro) and GDP per capita, 2008

Source: OECD Health Data 2010 - Version: June 2010.

Note: The line shows the relationship between GDP and total health expenditure for those Member States considered.

In absolute terms, pharmaceutical expenditures are increasing, and this increase is more pronounced in some Member States, including Greece, Ireland, Germany, France, the Czech Republic, Estonia and Spain. In some cases – including France, Germany and Sweden – the rise in pharmaceutical expenditure is matched by the overall rise in health care.

Pharmaceutical expenditures are one of the most identifiable components of health expenditure. Governments therefore implement a variety of regulatory measures targeting pharmaceutical expenditures for the purpose of controlling overall health care costs.

1.1.4 Links between GDP, health and pharmaceutical expenditure

The following sections in this part of the report explore two central components of national pharmaceutical markets and associated policies: (a) market structure and industrial policy, and (b) supply- and demand-side regulation. Supply side policies include pricing and reimbursement policies, while demand-side policies include those policies targeted at physicians, pharmacists and patients.

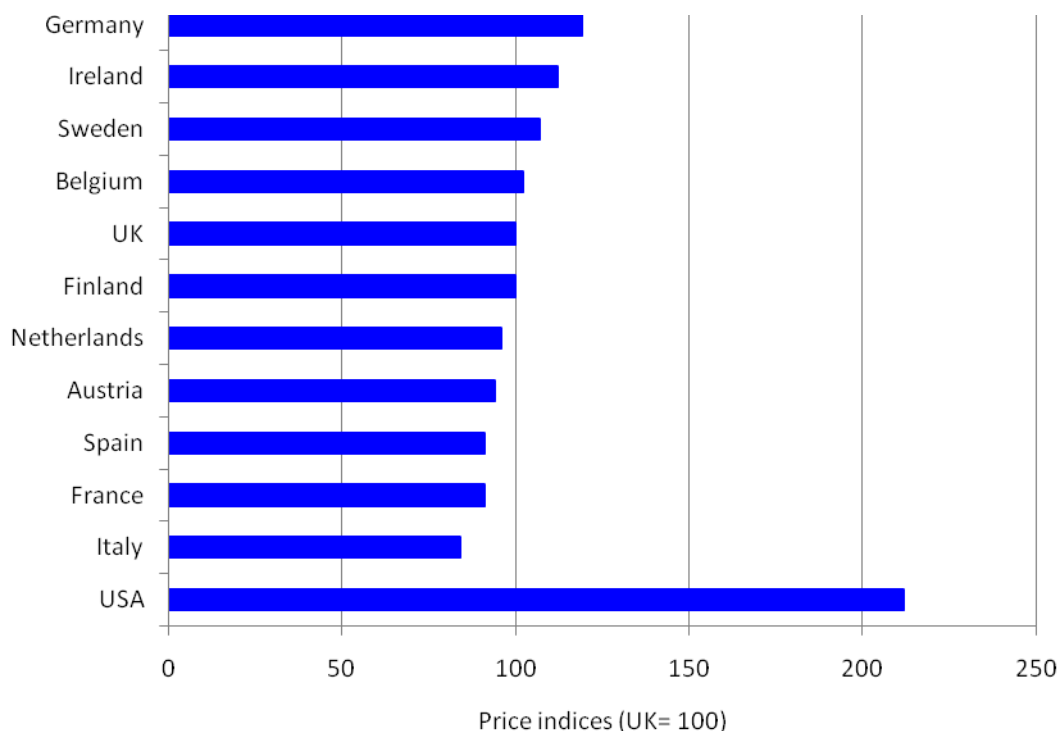
1.2 Differences in pharmaceutical prices

The prices for pharmaceuticals vary across EU Member States. This section provides a brief review of price differences for pharmaceuticals covered by patents, and then for off-patent pharmaceuticals.

It should be noted that several approaches have been used to examine drug prices². One issue is whether prices are considered at the factory gates (ex-factory prices), at wholesale level or at retail level: this section focuses on retail prices.

An overview of the price variation for in-patent pharmaceuticals can be seen in a review of the 11 most developed pharmaceutical markets in the EU. Figure 6 below compares prices of branded medicines in the UK with prices in 10 other EU Member States (and also with prices in the USA). It is based on an annual exercise carried out by the UK Department of Health, which compares the prices of the top 150 branded medicines in the UK with those in other Member States (the analysis compares matching preparations of the pharmaceuticals).

Figure 6: Price comparisons among EU Member States (and with the USA) for a basket of 150 products; 2008 price index with UK=100



Note: Price index uses 5-year average exchange rates.

Source: UK Department of Health, 2009.

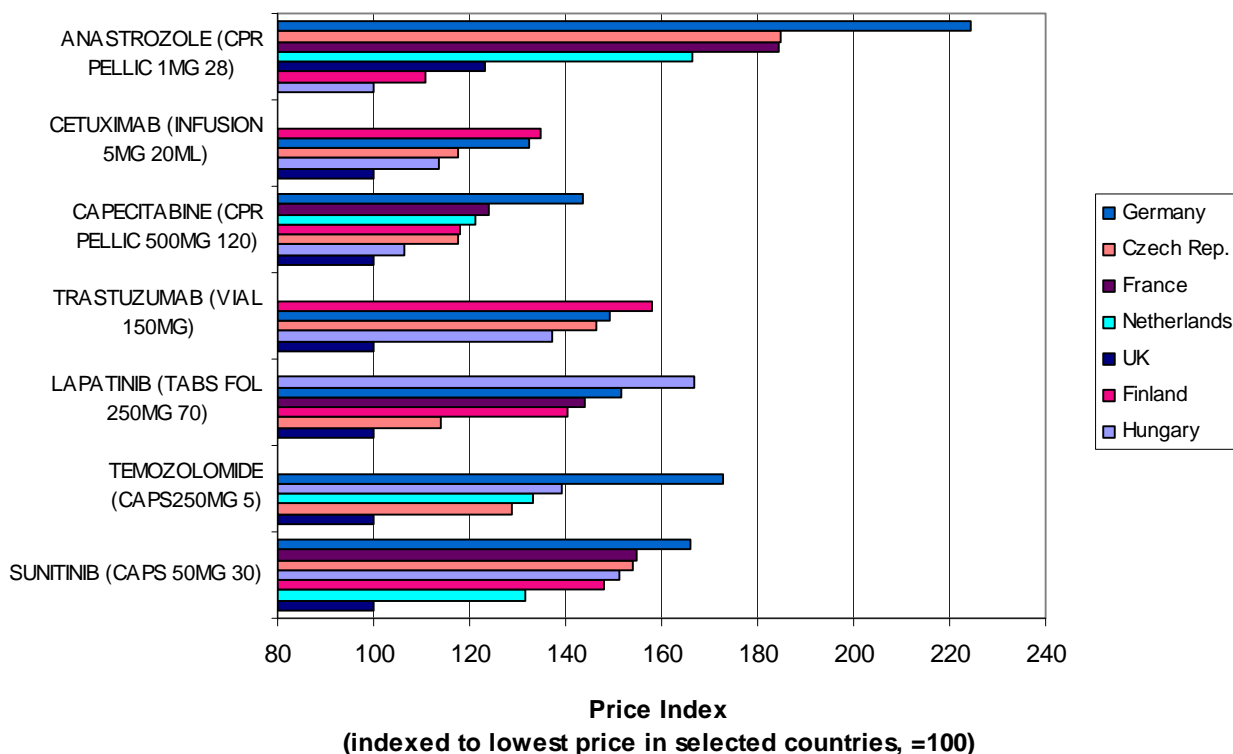
² See, for example: Danzon and Chao 2000, Danzon and Furukawa 2008, Roughead et al 2007, Kanavos and Vondoros 2011

Prices are indexed to the UK price (=100) for comparability. However, it is important to note that international price comparisons can be significantly affected by the relative level of sales in each country, movement in exchange rates and the proportion (and mix) of pharmaceutical expenditure included in the analysis (UK Department of Health, 2009). Among the EU Member States analysed, Germany, Ireland and Sweden were among those with higher average prices in 2008; Spain, France and Italy had lower prices. The USA is an outlier, as prices of branded medicines have been consistently higher than in Europe, with over twice the price level of the UK in 2008. It is however unclear whether these prices are reimbursed by health insurers or relate to the private non-insurance market, therefore not being directly comparable with the European price indices, which reflect reimbursed prices.

1.2.1 Price differences in pharmaceuticals covered by patents

When comparing the five largest EU pharmaceutical markets (Germany, UK, France, Italy and Spain), Germany has the highest retail prices for in-patent drugs (23% higher than the average of the five countries), followed by the UK (exactly at the 5-country average), Spain (5% lower), Italy (6% lower) and France (14% lower) (Kanavos and Vandoros, 2011).

Figure 7 Prices of selected cancer medicines across Europe, June 2009



*Price indexed to the price in the country with the lowest price (=100). The UK is the index for all medicines except Anastrozole, where the lowest price is observed in Hungary.

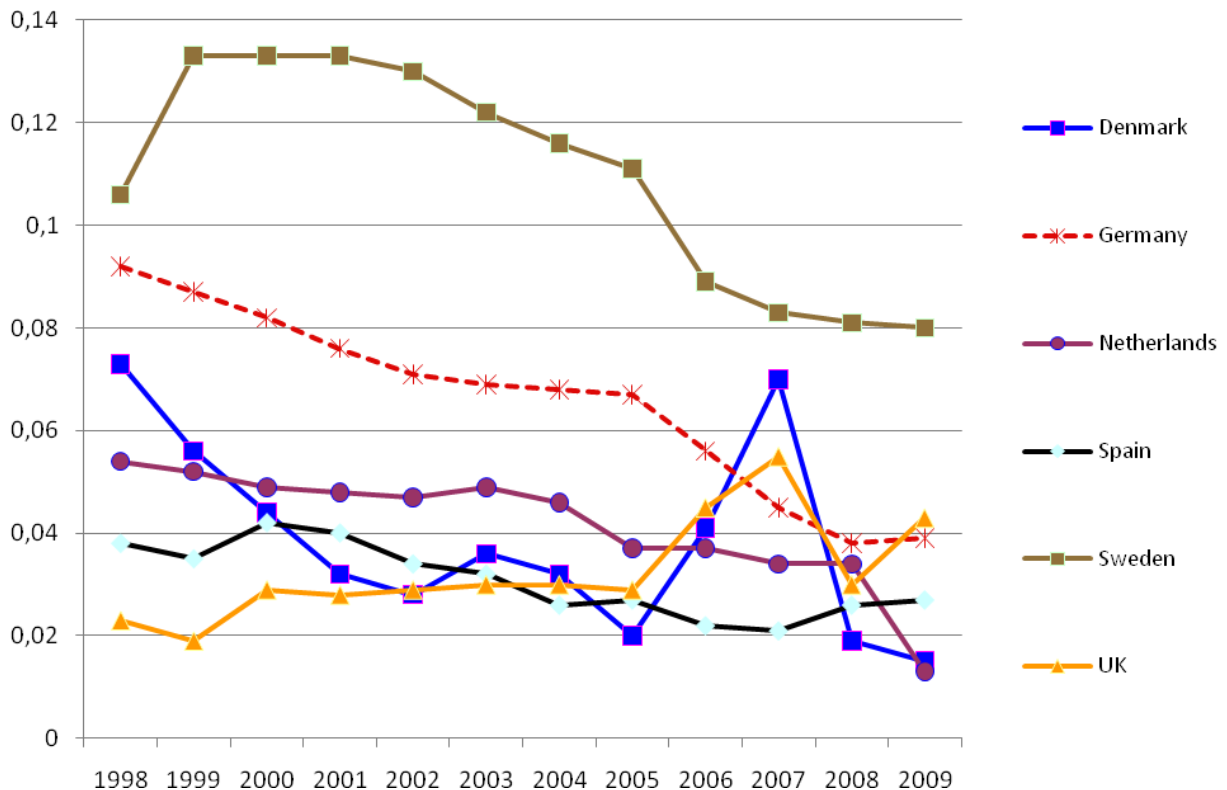
Notes: Range in actual prices (€): Anastrozole (55.8€ in Hungary to 125.2€ in Germany); Cetuximab (159.2€ in UK to 214.3€ in Finland); Capecitabine (295.6€ in UK to 424.2€ in Germany); Trastuzumab (408.1€ in UK to 645.5€ in Finland); Lapatinib (805.7€ in UK to 1343.45€ in Hungary); Temozolomide (850.0€ in UK to 1467.5€ in Germany); Sunitinib (3368.7€ in UK to 5596.8€ in Germany)

Source: Kanavos and Vandoros (2011).

Differences can be even greater when considering individual pharmaceuticals. Figure 7 (above) presents price differences for a selection of prescription pharmaceuticals, drawn from the oncology area. It shows that significant price variability exists across countries and products in the in-patent market: in this sample, the greatest price differences for individual medicines vary by 50-60%. For these pharmaceuticals, no country demonstrates consistently higher prices for all products (Kanavos and Vandoros, 2011). Further evidence of price differentials is provided in Appendix 7, for a range of widely used older products, a large number of which are still in-patent, where price differentials are significantly higher and, from highest to lowest, they can be four to one.

Despite the significant price differentials, there appears to be some price convergence for in-patent pharmaceuticals across EU countries, as price differences across Member States have been decreasing (Kanavos and Vandoros, 2011). This is likely to be due to the mechanism of external price referencing (see section 3), which has become the most common price setting measure for in-patent pharmaceuticals in EU Member States (Kanavos and Vandoros 2011). Price convergence, however, does not appear to be taking place among off-patent (generic) medicines.

Figure 8: Metformin generic price differences, 1998 - 2009, (average Euro price)



Source: Authors' compilations.

1.2.2 Price differences for off-patent pharmaceuticals

A pharmaceutical is exposed to competition following the expiry of its patent by “generics”, which are replicas. Generics need to prove bio-equivalence to the original molecule prior to entering the market. The generics typically sell for significantly lower prices than the original manufacturer’s “branded” version. Although the regulatory aspects governing authorisation of generics have been standardised, several country-specific policies remain that determine generic drug entry and uptake (European Commission 2009).

A review of prices for pharmaceuticals no longer covered by patents has found even greater differences among Member States. In the case of another drug, Ramipril, whose generic prices vary by 16:1 gap between highest (Greece) and lowest (The Netherlands) (see Appendix 8). One reason is that there are differences in patent expiry dates between Member States. A later patent expiry in France and Italy, for example, is related to higher generic prices in a given year (e.g. 2008 and 2009).

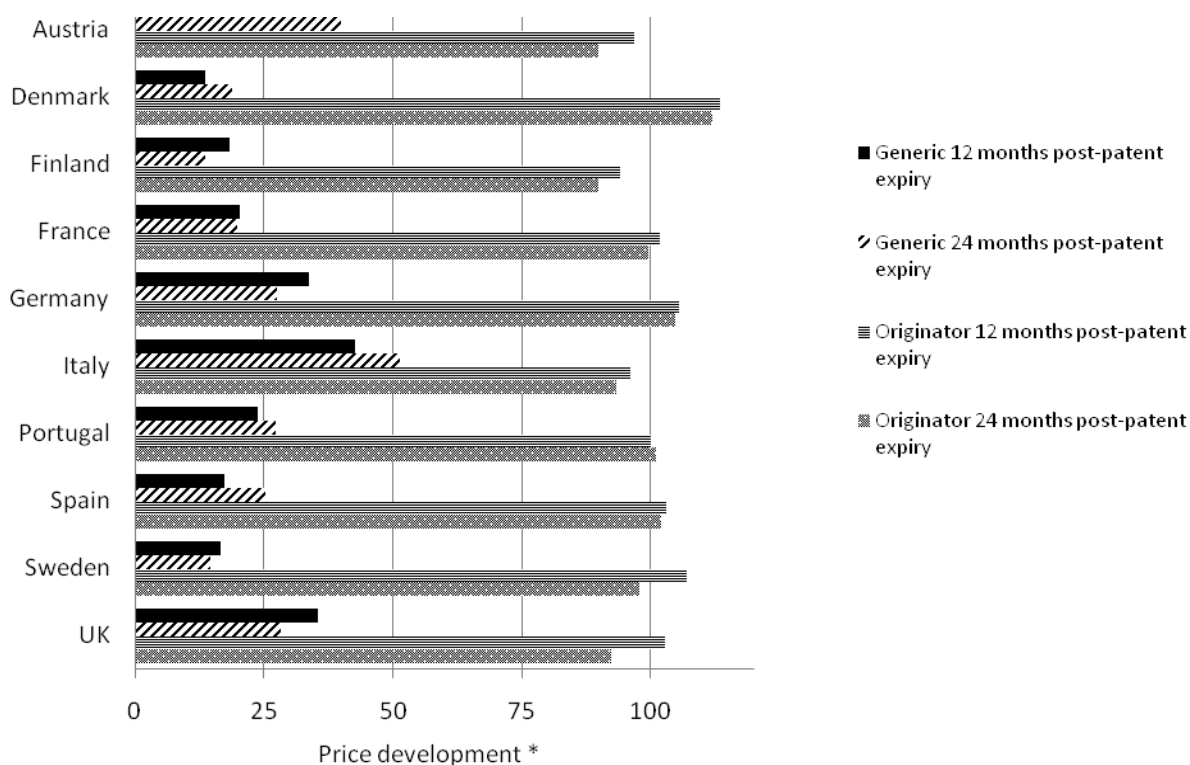
The exceptions are Greece and Portugal, where the price of generic Ramipril remains high relative to other Member States. While this is an extreme case, a broad review of pharmaceuticals has found that prices vary significantly across the EU for a wide selection of products (Kanavos and Casson, 2011 forthcoming).

Moreover, there are differences in the evolution of prices. For metformin, an old but widely used oral anti-diabetic medicine, some Member States have seen a price decline over time (Sweden, France, Germany), while in others generic prices are relatively stable (Finland, Portugal, Italy). These trends are presented in Figure 8, above.

Generic prices average about 25% of the originator price, 12 and 24 months following patent expiry. Such a generalisation, however, masks significant differences between Member States.

One difference is that the evolution of the prices for generic competitors shows greater variation among Member States than that of the original product that was previously covered by patent (called the “branded” version or the “originator”). In some Member States, the average price for generic competitors increases from 12 months to 24 months following patent expiry of the originator (France, Italy, Spain, the Netherlands and Portugal), while in others it decreases (the UK, Germany and Austria in particular and to a lesser extent Sweden, Greece and Finland). These trends are presented in Figure 9, below.

Figure 9: Average generic price development in 10 EU Member States (from originator patent expiry to 24 months post-patent expiry)



Source: Kanavos and Casson, 2011 (forthcoming).

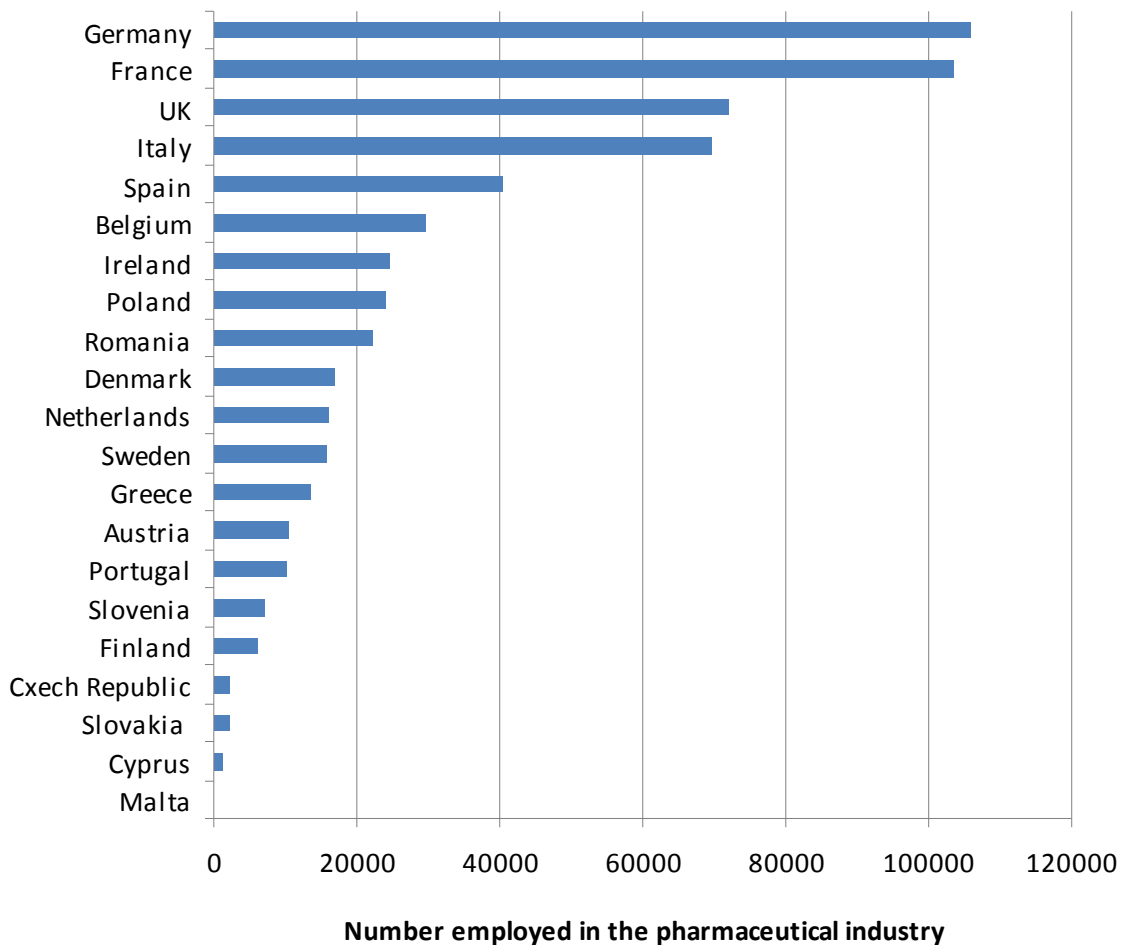
*Price is indexed to the price of the originator product 12 months pre-patent expiry (=100)

1.3 Market Structure and Industrial Policy

Pharmaceutical prices will affect the industry. This section provides an overview of the market structure of the pharmaceutical industry across the EU, in areas including employment, and research and development.

1.3.1 Manufacturing activities, employment and trade

The pharmaceutical sector is of great relevance for the EU's manufacturing and knowledge-based economy. It accounts for approximately 3.5% of total EU manufacturing value added and for 17% of total private sector research and development investments (EFPIA 2010).

Figure 10 Employment (individual full-time equivalent) in the pharmaceutical industry, 2008

Source: EFPIA, The Pharmaceutical Industry in Figures- 2010 Edition.

Moreover, the sector directly employs approximately 633,100 people in 2008, up from 500,000 in 1990. The sector employed 113,400 in research and development (R&D). Germany and France employ the most followed by the UK and Italy (see Figure 10). These numbers, however, do not include the thousands of researchers in universities, hospitals and other clinical settings who work closely with the pharmaceutical industry (EFPIA 2010).

The United States, by comparison, employs a total of 686,422 directly, with 90,712 people in R&D, including support staff.³ Japan employs almost 120,000.

The EU is one of the leading producers of pharmaceuticals globally. Pharmaceutical manufacturing activities can be divided into medicines covered by patent protection and those whose patents have expired: for the later, competing manufacturers produce “generic” versions.

³ US figures from PhRMA (2010) and there may be slight methodological differences in assessing numbers of those directly and indirectly involved in the industry.

Manufacturing of in-patent originator products takes place in several Member States and the majority of Member States have elements of manufacturing facilities or facilities enabling packaging and labelling of finished products with a view to distributing them in the country where these activities take place.

There is a significant amount of manufacturing in Member States that provide low business taxation regimes (e.g. Ireland). Although there is little evidence currently linking manufacturing activities to prices of medicines in a particular Member State, input from different stakeholders interviewed in this context suggests a certain level of correlation.

In contrast with the manufacture of patent-protected pharmaceuticals, generic manufacturing takes place in most Member States. Local manufacturing value-added and contribution to employment play some role in the treatment of generic medicines and pricing strategies for generics at national level, although, again, this is not a direct and fully transparent link.

1.3.2 Expenditure on pharmaceutical research and development in the different Member States

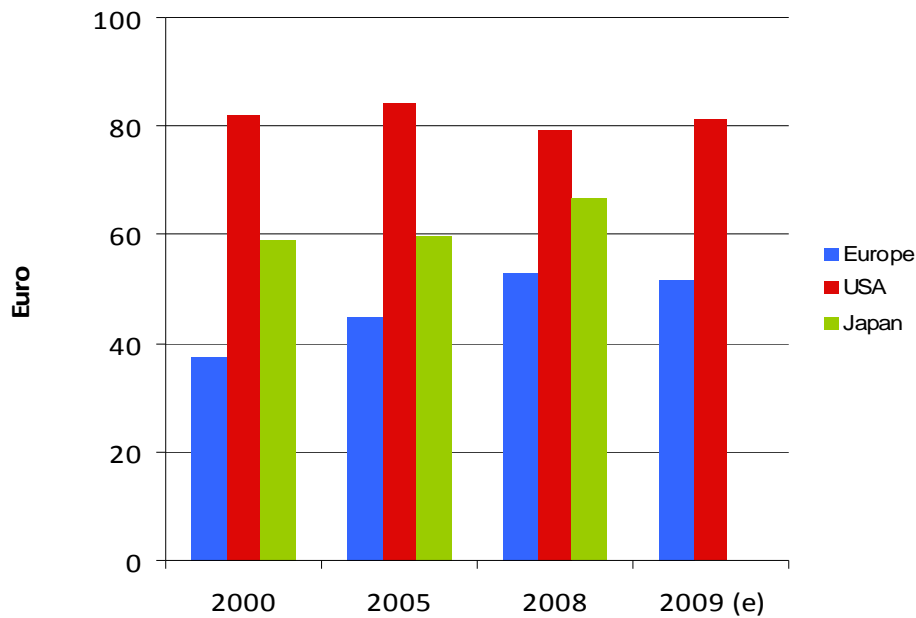
Aggregate expenditure on pharmaceutical R&D has grown considerably over the past 2 decades. Europe (including Norway and Switzerland) spends slightly more on pharmaceutical R&D than the United States and significantly more than Japan (€26 billion versus €24 billion in the USA and €8.5 billion in Japan), though in per capita terms, the European figure, which includes Switzerland, is 40% lower than that of the USA and 20% than that of Japan (see Figure 11).

While the individual EU Member States spending the most on R&D are the UK, France and Germany (each spending approximately 5 billion Euros per year), on a per capita basis Denmark and Belgium have the highest spending levels, followed by Sweden (see Figures 11 and 12).

R&D activities – particularly basic and discovery research – are concentrated in those Member States that have the infrastructure, scientific critical mass, provide additional funding mechanisms and a range of direct and indirect financial and non-financial incentives for these activities. Available finance to commercialise intellectual property is also crucial, particularly in the early stages of developmental research. All these factors are necessary requirements to ensure an enabling business environment that stimulates innovation.

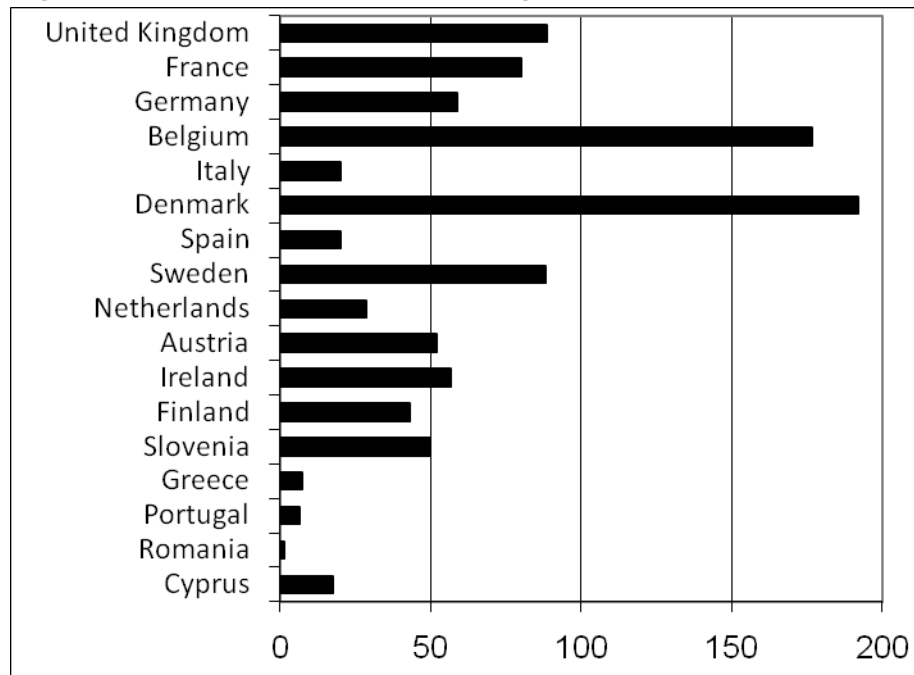
Other Member States participate in development research activities through clinical trial networks. There is no apparent direct link between location of R&D activities and prices of pharmaceuticals, perhaps with the exception of the UK, where the local regulatory scheme – the pharmaceutical price regulation scheme (PPRS) – indirectly links financial incentives for R&D with rate of return on capital employed and, thus, indirectly, with the price of medicines.

Figure 11 Pharmaceutical R&D Expenditure per capita in Europe, Japan and the USA (Euros)



Sources: Adapted from EFPIA, The Pharmaceutical Industry in Figures- 2010 Edition (NB: Europe includes Norway and Switzerland); OECD Stat Extracts, ALFS summary tables on "population"
 NB. 2009 data not available for Japan

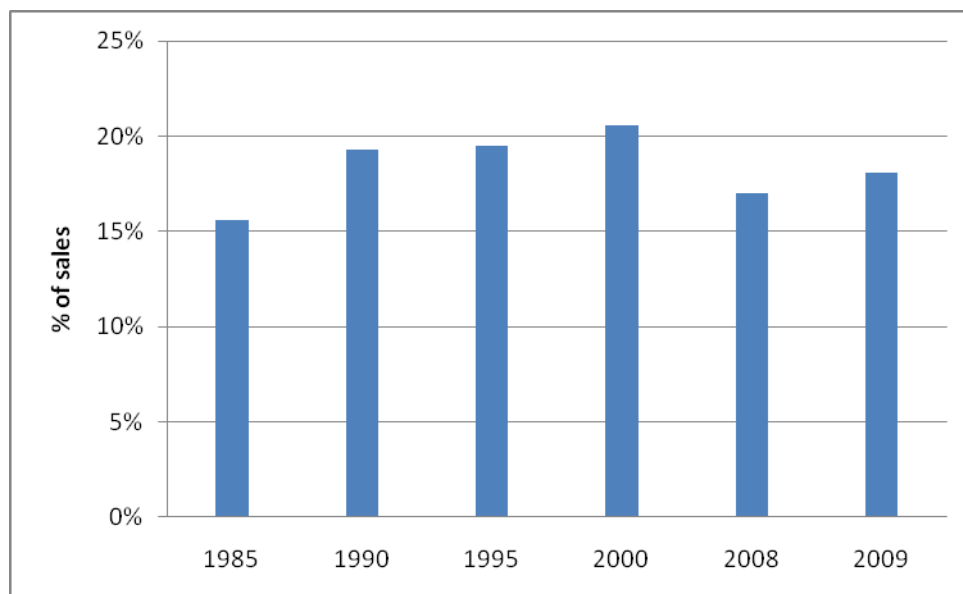
Figure 12 Per capita R&D Spending per Member State in 2008, Euros



Source: EFPIA, The Pharmaceutical Industry in Figures- 2010 Edition.
 NB: 2007 data used for Austria, Cyprus, Denmark, France, Netherlands, Romania and Slovenia.

The proportion of R&D as share of pharmaceutical sales in Europe rose steadily from 1985 to 2000. In 2008 and 2009, however, it dropped below the 1990 level (see Figure 13).

Figure 13 Pharmaceutical R&D expenditure as a share of pharmaceutical sales in EU Member States, 1985 – 2009.



Source: EFPIA, The Pharmaceutical Industry in Figures- 2010 Edition.

1.3.4 Impact of sales and marketing on prices

Pharmaceutical manufacturers extensively promote their products to prescribing physicians. (Direct advertising to consumers is not allowed in the EU, unlike a few other markets, notably the US.) Promotional activities in the EU include direct information and sample distribution to physicians as well as sponsorship of healthcare professionals. Member States regulate the extent of these promotional activities and codes of practice exist at EU and national level through the European (EFPIA, 2004) and national industry associations.

The concerns regarding advertising and its effect on prices are two-fold: first, promotional activities could inappropriately affect physician prescribing behaviour, thus unnecessarily driving up pharmaceutical costs. For example, a physician could prescribe a high-priced branded medication instead of a generic version, or may prescribe a medication unnecessarily. The second concern is that the funds spent on promotional activities could be better spent on R&D, although a precise account of how much is spent on promotion is not available.

There is little evidence on the effects of pharmaceutical marketing in the European context, although research on one class of medicines (statins, used for control cholesterol levels) suggest that promotional activities may affect the level of daily doses prescribed by physicians (Walley et al 2005).

2. THE IMPACT OF MEMBER STATE REGULATION ON DIFFERENCES IN PHARMACEUTICAL PRICES AND ON ACCESS TO MEDICINES

KEY FINDINGS

The impact of regulation on price differences

- The main factors leading to price differences include income levels; national (and sometimes regional) regulatory policies for pricing and value assessment of pharmaceuticals; approaches to regulating wholesale and retail distribution; and taxation of pharmaceuticals, in particular VAT.
- Member States use a range of mechanisms to regulate pharmaceutical prices and reimbursement rates. External price referencing, which is used by 24 of the 27 Member States, bases pharmaceutical prices on those in other Member States. External price referencing can be either applied at the launch of new medicines, where it usually follows an average price rule, or on an ongoing basis, where the use of a lowest price rule can result in price reductions over time.
- Health Technology Assessment (HTA) is increasingly used to appraise new pharmaceuticals in relation to comparable existing ones. As different Member States have different ways of accepting evidence and interpreting it, variations exist in the application of HTA appraisals, and these can result in diverging coverage decisions for the same pharmaceutical across different Member States.
- The main regulatory approaches for pharmaceuticals no longer protected by patents and subject to competition from “generics” include: internal reference pricing, tendering for out-patient medicines, and price capping linking generic prices to those of originator prices. These policies can allow health systems to achieve some savings on their pharmaceutical budgets through the purchase of lower-priced generic medicines.
- Another important factor is the level of VAT rates, which vary across Member States and have risen in recent years in some of them.
- Differences in distribution systems and their regulation account for a share of the differences in the cost of medicines across Member States.
- “Parallel trade” practices have developed to take advantage of the differences in prices among Member States. There is intense debate about the extent to which parallel trade can reduce or eliminate price differences between Member States. Evidence suggests that a large share of the surplus generated by parallel trade is captured by intermediaries, and does not accrue to patients or health systems. Parallel trade does not appear to be significantly reducing pharmaceutical prices in those Member States where they are high.
- Demand-side policies targeting patients, physicians, and pharmacists have shown to be effective in promoting cost-effective use of medicines.

Access to pharmaceuticals

- Differing HTA appraisals can mean that patient access to a pharmaceutical will vary across the EU.

- Some Member States are unable to meet the high cost of some treatments, notably some of the costly new treatments for cancer or the “orphan” treatments for rare diseases.
- A different problem is seen where a low price in one national market for a new product can lead manufacturers to refrain from launching the product in other markets, since the low price might jeopardise their pricing prospects elsewhere due to the wide application of external price referencing.
- The availability of some generic medicines may be related to the size of geographical or product markets. In small national markets, the expected return from the sales of generic medicines may not exceed the entry cost. The same may hold for small product markets. In such cases, generics are not available for one or more medicines. The result is often more expensive choices for patients and health systems.
- One important concern is that parallel trade might potentially lead to shortages in exporting Member States.

It appears that price differences of pharmaceuticals across the EU are linked to two main factors: differences in expenditure on health (associated with GDP); and differences in pricing policy and regulation. This section of the report focuses on the different types of pricing policy and regulation and the way these affect the price of pharmaceuticals.

2.1 GDP per capita and pharmaceutical prices

Pharmaceutical expenditure is associated with per capita GDP levels as well as total health expenditure, and is influenced by demographics and domestic policy priorities. These factors also affect demand, and, ultimately, can have an impact on both pharmaceutical prices and the overall availability of pharmaceutical products in different Member States.

On the one hand, prices of pharmaceuticals, particularly in-patent, seem to be proportionally higher in Member States with higher levels of per capita income.

On the other hand, richer Member States appear to spend more on pharmaceuticals. This may be due to either higher average pharmaceutical prices or higher per capita consumption in volume terms (or a combination of both). Manufacturers, in turn, have greater incentives to launch and market products in Member States with high reimbursement levels and comprehensive coverage, as it is more likely that there will be sufficient demand to ensure their profitability. Higher-income Member States are thus better placed to ensure access to new and expensive pharmaceuticals. Conversely, smaller Member States, especially those with lower per capita GDP may be unable to afford widespread coverage or high reimbursement levels, and will therefore have a smaller market with which to attract manufacturers. As a result, access to certain categories of pharmaceuticals tends to be negatively correlated with market size and per capita GDP.

2.2 Overview of Pharmaceutical Regulation

As any market, the pharmaceutical sector is characterised by a *supply side*, composed of the producers of pharmaceutical products, and a *demand side*, comprising patients, prescribers (i.e. physicians) and dispensers (i.e. pharmacists) of pharmaceuticals.

On the supply-side, patents protect pharmaceutical inventions for a nominal period of 20 years plus a further 5 years maximum through the Supplementary Protection Certificate (SPC). A period of market exclusivity of up to 11 years also applies. During this period, protected inventions benefit from market exclusivity and monopoly or quasi-monopoly power.

Governments in EU Member States play a key role in the markets for pharmaceutical products, both as purchasers and regulators. More generally, their interventions can be classified in three major groups:

- Supply-side interventions: methods to determine the prices of pharmaceuticals (in particular those in patent)
- Supply-side interventions through pharmaceutical reimbursement policies
- Demand-side actions, including policies affecting physicians, pharmacies and patients

Government action on the supply-side focuses primarily on the regulation of pharmaceutical prices, both in-patent and off-patent (generic medicines). Specific measures in this context include controls of pharmaceutical prices through different regulatory schemes (i.e. price regulation, fixed reimbursement levels, profit or rate-of-return regulation, among others), and encouragement of price competition by lowering the barriers to entry in pharmaceutical markets. Supply-side action on volume relates to making entry into pharmaceutical markets easier, for instance, by enabling faster entry of generics onto the market place. Action on the demand-side primarily targets volume by implementing policies on physician prescribing (e.g. through financial and non-financial incentives), pharmacy dispensing (e.g. regulation of margins, policies on generic substitution) and patient behaviour (e.g. cost-sharing arrangements for different types of medicines).

Member States use a range of methods. Table 1 on the next page presents an overview of the main approaches, together with examples of Member States where they are used. The following sections describe each of the key methods and discuss their impacts on pharmaceutical prices, based on current research results.

2.3 Supply-side regulation

2.3.1 Pricing methods for in-patent pharmaceuticals

Differences in national pricing policies and regulations are partly responsible for observed price differentials in both in- and off-patent markets for several reasons. First, there are fundamental differences between free-pricing and price-controlled systems which allow different stakeholders, with different interests to control initial price setting.

Free-pricing systems, which allow pharmaceuticals to be priced without restriction at launch, are likewise regulated through other means such as profit control (UK) (Mrazek and Mossialos, 2004), or reimbursement regulation through internal reference pricing and/or use of HTA.

Table 1: Pharmaceutical regulation in Europe (overview)

Regulatory mechanism	Examples of Member States employing each mechanism
SUPPLY-SIDE: Methods to determine prices of in-patent pharmaceuticals	
Price controls: administrative or statutory pricing	All Member States except Germany, UK and, to a certain extent, Sweden
External reference pricing	All Member States except UK, Germany, Sweden
Rate of return regulation	UK
Negotiations and price-volume agreements	France, Italy, Austria
Direct expenditure controls: payback	France, Portugal, Austria
Direct expenditure controls: price-volume agreements	France
Cost-plus pricing	Elements are used in Spain indirectly
SUPPLY-SIDE: Methods to determine prices of off-patent pharmaceuticals	
Tendering for generics pharmaceuticals in primary care	The Netherlands, Germany
Price capping for generics and linking these to the originator price	Italy, Greece, France
SUPPLY-SIDE: Reimbursement methods	
Positive and negative formularies	All Member States
Internal reference pricing	Germany, the Netherlands, Czech Republic, Italy, Spain, France, Hungary
Health Technology Assessments (HTA)	UK, Sweden, the Netherlands, Hungary, Poland, Finland, Estonia, Latvia, Lithuania. In France only assessment of clinical benefit
Innovative pricing and reimbursement schemes	Italy, Germany, UK, Finland
DEMAND-SIDE: Policies towards physicians	
Clinical practice guidelines	All Member States
Compulsory generic prescribing	UK, Denmark, Estonia
Financial incentives	Some elements in France, UK
Prescription monitoring and audit	Belgium, UK, the Netherlands, France, Denmark, Sweden, Estonia
DEMAND-SIDE: Policies towards pharmacies	
Control of remuneration (e.g. margins, fees) including contractual arrangements	All Member States
Generic substitution	France, Italy, Spain, Sweden
DEMAND-SIDE: Policies towards patients	
Cost-sharing	All Member States
Encouraging use of over-the-counter medicines and "de-listing"	UK, Germany, Sweden, the Netherlands

* Definitions from PPRI Reports.

Source: The authors from the literature.

Fixed pricing, also referred to as direct price controls, amounts to the setting of fixed maximum prices, which may apply broadly to all medicines whether or not they are reimbursed, or to specific groups of products (for example, reimbursed, inpatient/outpatient, on-patent/off-patent). While the aim is to set prices at a reasonable or affordable level, definitions thereof differ across as well as within countries. The way in which prices are set i.e. through negotiations (Austria, France, Italy, Portugal, Spain) or unilaterally by the national authority, affects prices to wholesalers, patients and ultimately to health insurers/governments. Direct price controls may slow price increases or induce lower prices altogether. However, the influence on overall pharmaceutical expenditure may be overshadowed by increases in expenditures due to volume and innovative drugs (Mrazek and Mossialos, 2004).

Second, within price-regulated systems, the specific features of individual policies as well as the mix of regulatory measures vary significantly across Member States. Pricing policies and regulatory approaches reflect national priorities in both health and industrial policy, such as containing overall pharmaceutical expenditures or promoting R&D, employment and trade. Third, pricing regulation may be implemented at various stages along the distribution chain, from manufacturer to wholesaler to pharmacist and individual consumer or hospital. Moreover, in several Member States, the type and strength of regulation differs between in-patent and off-patent markets.

The following is a discussion of how the main types of pricing methodologies can affect prices of pharmaceuticals in EU Member States.

a) External price referencing (EPR)

Member States using external price referencing (EPR) (also known as international reference pricing) create a basket of other countries whose prices they wish to use as benchmarks to set national pharmaceutical prices. This approach is used extensively in 24 EU countries (all except the UK, Germany and Sweden). The number of countries included in the basket may range from 3 (e.g. Slovenia) to 26 (e.g. Latvia and the Czech Republic). The lowest price, or an average of the lowest prices in the basket, is defined as the reference price. EPR is used as a means to set a maximum price for a pharmaceutical product. The table in Appendix 1 shows Member States using EPR, the countries used for benchmarking (basket definition) and prices taken into account for price setting purposes.

Although EPR can help cost-containment by reducing prices, there are concerns arising from the fact that it is an arbitrary measure targeting prices that ignores other aspects of the market, the particular health priorities in each country and creates uncertainty for the innovative segments of the industry, especially due to the impact of exchange rate fluctuations on reference prices.

EPR can contribute to lower pharmaceutical prices. Price reduction becomes even steeper as most countries adopt the lowest price of all countries in their basket, or the average of the lowest, combined with periodic adjustments, which typically take place annually or, in some cases, more frequently.

In addition, when using EPR, prices are affected by exchange rate fluctuations, which put further downward pressure on prices, rather than have a neutral effect in the long run (Kanavos and Vandoros 2010). Among the unintended consequences of EPR is the reality that manufacturers are likely not to launch a product in a certain country if that country's price influences third countries, or it is likely to be too low and, therefore, encourages parallel exports.

b) Rate of return regulation

Rate-of-return regulation is used in the UK to determine pharmaceutical prices. The PPRS (Pharmaceutical Price Regulation Scheme) is essentially a "profit control" or "rate of return on capital employed" (ROCE) scheme and a voluntary agreement between government and industry, targeting manufacturers' profits on sales to the UK National Health Service (NHS) beyond a certain threshold, whilst allowing pricing flexibility up to that threshold. The ROCE used is limited to 21% plus a margin of tolerance. Any excess must be paid back to the UK Department of Health (DH), or prices must be reduced (PPRS, 2009; OFT 2007). Producers can modulate prices based on their portfolio such that any changes are neutral. The UK government has announced it will abandon the PPRS after the current term expires at the end of 2013, in favour of value-based pricing (VBP), a system whereby the price is determined as a function of the value it provides to patients and society at large and which involves the use of economic techniques (described later in this section).

The relative price freedom assumed by the scheme could mean that prices are higher than would otherwise be the case, although re-negotiations of the scheme are usually associated with price cuts. Assessments of the scheme in the UK based on periodic reports submitted to the UK Parliament, suggest that it ensures reasonable prices for the UK National Health Service and a stable and predictable environment for the industry to operate (PPRS 2009). UK prices are found to be close to average European prices. Over the past two years, they have been below that average, notably due to the depreciation of the sterling vis-à-vis the euro.

c) Negotiations

Negotiations have been a common way of setting reimbursement levels of new medicines. In this case, payers (health insurance) and manufacturers reach an agreement on the reimbursement price. A manufacturer holding a patent is a monopolist for the particular pharmaceutical, but monopoly power cannot be exercised to a large extent because public health insurance also has market power, due to its status as a monopsonist (single purchaser on behalf of patients). Therefore, the price agreed upon is not expected to be unreasonably high or low: negotiation outcomes are not expected to cause excessive strain on health insurance, or set a price that is extremely low for the manufacturer and discourages future investment in R&D. This way of pricing may implicitly take into account clinical evidence and the therapeutic value of the medicine. Frequently, prices are fixed based on volume projections (price-volume agreements) and if agreed volumes are exceeded, a payback clause may exist whereby manufacturers return the excess revenue to health insurance institutions and/or re-negotiate prices.

2.3.2 Supply-side regulation: pricing methods for off-patent pharmaceuticals

The policies that affect the prices of generic pharmaceuticals vary across the EU. A summary of national generic policies is presented in Appendix 2. A brief discussion of two key policies follows: (a) tendering for pharmaceuticals consumed in primary care and (b) price caps.

a) Tendering

Tendering is a common measure for the procurement of hospital pharmaceuticals, and it has recently been used for out-patient pharmaceuticals (i.e. those consumed in primary care) in the Netherlands and Germany (Kanavos, Seeley and Vandoros, 2009b). A tender is issued and the lowest price bidder wins the tender and thereby the right to supply the whole market. The terms of the tender and whether a single product can supply the entire market or competitors that can supply at the tender price also have this right are laid out by the body issuing the tender.

Table 2 The effects of tendering on prices in the Netherlands (Top 10 packs by sales, May-June 2008)

Pharmaceutical Product	Preferred supplier	Pharmacy purchase price (Euros)		Change
		May 2008	June 2008	
1. Omeprazole tablets/capsules, 20mg	Ratiopharm	€ 0.36	€ 0.05	-88%
2. Alendroninezuur tables, 70mg	Centrafarm	€ 4.99	€ 0.36	-93%
3. Omeprazole tablets/capsules, 40mg	Centrafarm	€ 0.65	€ 0.09	-86%
4. Paroxetine tablets, 20mg	Ratiopharm	€ 0.37	€ 0.07	-82%
5. Simvastatin tablets, 40mg	Actavis	€ 0.27	€ 0.04	-84%
6. Pravastatin tablets, 40mg	Focus Farma	€ 0.54	€ 0.13	-76%
7. Simvastatin tablets, 20mg	Ratiopharm/Actavis	€ 0.17	€ 0.03	-85%
8. Tamsulozine tablets/capsules, 0.4mg	Centrafarm	€ 0.34	€ 0.07	-80%
9. Amlodipine tablets, 5mg	Ratiopharm	€ 0.19	€ 0.03	-85%
10. Citalopram tablets, 20mg	Ratiopharm	€ 0.34	€ 0.04	-88%

Source: Stichting Farmaceutische Kengetallen (SFK), quoted in Kanavos, Seeley and Vandoros, 2009.

Tendering can be very effective in reducing pharmaceutical prices in out-patient markets. In the Netherlands, tendering has replaced other approaches, such as internal reference pricing, for part of the market. Tenders initially (2005) applied to three widely consumed drugs.⁴ In 2008, tenders were expanded to 33 off-patent products. In the 2008 tendering, prices decreased as much as 95% following the implementation of tendering (selected examples are presented in Table 2). This can lead to immediate price cuts and savings for health insurance, but, as the initial evidence from the Dutch setting suggests, these savings must be balanced against losses in the distribution chain, which the Dutch authorities have had to rectify because of the Dutch retail system's reliance on discounts from (generic and other) manufacturers. Tendering does not pose a threat to innovation, as the substances subjected to tendering are already patent expired. However, there are concerns that tendering could drive out competition in the long run, especially if it is used for a large variety of products and in many EU Member States.

⁴ omeprazole for peptic ulcer, simvastatin and pravastatin for dislipidemia and prevention of heart disease

Some generic producers will not be able to sell their products if they do not win any tenders; exit from the market is then the only option. A decrease in the number of generic producers could lead to an increase in generic prices, not necessarily to the level prior to tendering, but part of the price reduction is expected to be offset because of less competition. This could be of some concern to governments, not only from a pricing perspective, but also as part of the EU's industrial strategy and the future of the European generic industry.

b) Price caps for generic pharmaceuticals

Price capping policies in the off-patent pharmaceutical market refer to regulation which sets price ceilings on generic and originator products following originator patent expiry. These policies mirror the situation in the originator market, where maximum prices are established, but also apply in generic markets once the originator product patent has expired. In this case, the regulator is making an assumption about what the price of the generic on the market should be. In principle, price capping aims at containing costs by limiting high drug prices and encouraging generic drug use (Brekke et al. 2007). Acceptable price levels differ between countries depending on a range of factors including prescribing behaviour, utilisation trends and budget limits (Mrazek 2002). Price caps are often linked to the price of the originator. The use of price caps, and prices linked to originators, is not consistent across the EU. For example, generic price caps are explicitly linked to originator prices in the UK, Austria, Finland, France, Greece and Portugal (ÖBIG 2009). In Austria, the price of the first generic must be at least 48% lower than the price of the originator product on the market, the price of the second generic must be reduced by 15% compared to the first one; and the price of the originator must also decrease by at least 30% within three months of the inclusion of the first generic (ÖBIG 2009). In contrast, in Portugal, the price of the first generic competitor must be at least 25% below the price of original product, and the second follower needs to reduce its price by 25% compared to the first follower (ÖBIG 2009).

Price caps are set as a method of controlling the prices of both branded and generic pharmaceuticals. In many cases price caps on generics are set according to the price of the originator or branded price. Fixing prices has the potential to provide an alternative to simple cost-based regulation, but is controversial in that the practice of setting fixed prices is subject to bias and may not be completely transparent (Mrazek 2002). There remains debate as to whether price caps have successfully facilitated cost-containment as there is mixed evidence on the influence of price fixing on both in-patent and generic drugs (Danzon and Chao 2000; Garattini and Tediosi 1999). For example, a meta-analysis of current literature on the effect of pricing policies found that that generic prices level is higher when price capping regulations are instituted, than without such policies (Puig-Junoy 2010). Moreover, the European Commission's report on pharmaceutical industries in the EU (2009) concludes that those Member States that have not enforced price caps have seen faster uptake of generic medicines and over time see the prices of these generics decrease to a greater extent.

2.3.3 Supply-side regulation: reimbursement methods

Member States use a range of methods to determine which pharmaceuticals are reimbursed and at what price. An important consideration for reimbursement policies at EU level is that they adhere to the Transparency Directive⁵, which lays down harmonised provisions to ensure the transparency of national provisions regulating the pricing and reimbursement of medicinal products.

Due to the scarcity of resources in healthcare, with budgets that are limited and fixed in advance, and the increasing cost of new healthcare technologies (CBO 2006), Member State governments have recognised that not all new pharmaceuticals can be reimbursed and have introduced regulatory mechanisms for reimbursement decisions. These mechanisms determine which pharmaceuticals are covered and at what price. As a result, some pharmaceuticals may not be reimbursed; others may only be partially reimbursed and a proportion of the drug's price is borne by the patient (though complementary insurance and other schemes may cover part of this share).

Of the multiplicity of measures regulating reimbursement, four are discussed in this section: 1) *positive/negative formularies*, 2) *internal reference pricing*, 3) *health technology assessments*, and 4) *innovative schemes, such as risk-sharing agreements*. These instruments are complementary to the pricing mechanisms discussed earlier, and are designed to influence the sales volume, as well as the pricing of the pharmaceuticals considered (McGuire et al. 2002).

A positive formulary is a list of all pharmaceuticals that health insurance will reimburse and by how much; HTA is a method to determine whether a new product provides value for money in relation to existing comparators and, therefore, can be reimbursed; internal reference pricing sets a maximum reimbursement ceiling among inter-changeable products, by promoting cheaper generics; and risk sharing attempts to reduce the uncertainty for health insurers, particularly in expensive new products, for instance by only reimbursing manufacturers for all cases where the product proves effective.

The advantages and disadvantages of each of these schemes are discussed here, as well as their impact (direct or indirect) on pricing, cost-containment and innovation. It is important to keep in mind the principles for an effective reimbursement policy: 1) it is transparent, 2) it allows flexibility to ensure rapid access to new treatments, 3) it is robust in evaluating the drug's clinical benefit and economic impact, and 4) it has common principles that apply across players.

a) Positive and negative formularies

A national formulary contains information on the drugs selected for reimbursement by health insurance. It also includes other related information about the drug, namely the indication or population it is intended for, the different doses and ways of administration, or the circumstances under which the drug is covered or not covered and the relevant co-payments. Formularies can be positive or negative.

⁵ Directive 89/105/EEC relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems

A positive formulary lists the drugs that are fully or partially covered by the health insurance. It is the most common type of formulary used in Europe. In contrast, negative formularies list the drugs that are not reimbursed. These can be found in a few EU Member States such as Germany or the UK. The rationale for establishing positive and negative lists is to regulate the use of pharmaceuticals, by discouraging physicians from prescribing ineffective drugs, or drugs that are more expensive than other treatment alternatives providing the same level of effect.

b) Internal Reference Pricing for off-patent pharmaceuticals

Internal reference pricing is a commonly employed policy in EU Member States (as well as Canada and Australia) to regulate off-patent drug prices; in doing so, health insurance uses generic prices within a product market – usually the lower-priced generics – to set a maximum reimbursement level for a particular product that has generic alternatives. This maximum reimbursement level is called the reference price. Products whose price exceeds the reference price are either not reimbursed, or the patient has to pay the difference between the reference price and the actual price of the product out of pocket. Usually reference prices are determined at the chemical substance level. This means that the originator and all generics are grouped together. The reference price is usually the lowest or the average of the lowest prices of the group. In some Member States (e.g. Germany and the Netherlands), a reference price applies to a therapeutic class, rather than a single pharmaceutical. This means that more products are included in the reference group, some of which may be still covered by patents. This is used to prevent costs occurring from dispensing so-called “me-too drugs” with very similar therapeutic effects, which are considered to be interchangeable, that are in-patent and are priced much higher than generics of other off-patent pharmaceuticals of the same therapeutic class.

Internal reference pricing is effective in reducing generic prices in the first instance. However, once a price has been set, the producers of generics tend to set their prices at or around the reference price, so there is no incentive for further price reductions. This can be observed in Germany, France or Italy (Kanavos, Costa-Font, and Seeley 2008).

c) Health Technology Assessment (HTA)

Traditionally, reimbursement decisions were based mainly on the drug’s efficacy, safety and quality; other criteria included budget impact, severity of illness and, occasionally, industrial policy considerations discussed in a process of negotiation with manufacturers. Pharmaceuticals were then included accordingly in the positive or negative formularies.

An increasing number of Member States have introduced health technology assessments (HTAs) to assess the value of a drug for a specific indication from a medical, economic, and social perspective. Agencies that carry out HTAs can be either regulatory bodies responsible for coverage decisions, or advisory bodies making recommendations on coverage to decision-makers (i.e. Minister of Health).

Health technology assessment is increasingly being considered in pricing and reimbursement settings, whereby the costs and benefits of the new drug are weighed against those of an existing therapeutic alternative.⁶ Thus, economic techniques are used to derive the value of new therapies compared with older ones. In recent years, the term “value-based pricing” has been used to describe the use of economic techniques (e.g. cost-effectiveness) in defining the value of a new therapy. Based on the drug’s cost-effectiveness (i.e. whether it is more or less cost-effective than its comparator), the price premium over its comparator may be determined and used to set the pharmaceutical’s price. In other words, this method enables health systems to determine the value of a drug by assessing the drug’s clinical value in relation to costs and against one or more pre-defined comparator drugs. Based on this value assessment, manufacturers are rewarded for the level of innovation they bring to market. These methods are being used explicitly to inform pricing and reimbursement decisions in an increasing number of Member States: Sweden, Finland, the Netherlands, the UK, Estonia, Latvia, Lithuania, Poland, and Hungary use an assessment of costs and clinical benefits, whereas France uses an assessment of clinical benefits only to inform its pricing and reimbursement decisions.

Pharmacoeconomic analysis is used to determine a pharmaceutical product’s cost-effectiveness in relation to a defined set of comparator treatments (pharmaceutical or other). To do so, it encompasses several methods: 1) cost-effectiveness analysis, 2) cost-benefit analysis, 3) cost-utility analysis, and 4) cost-minimisation analysis (Appendix 3). The choice of the appropriate method depends on the outcome measures to be evaluated, but generally the use of one method does not necessarily exclude the other. The incremental cost-effectiveness ratio (ICER) then enables to determine whether a drug is cost-effective, as well as its level of therapeutic benefit in relation to its comparator(s) (Appendix 4). A “cost-effectiveness threshold” or “willingness-to-pay threshold” may be set in this context setting out the upper limit of individual health care systems’ affordability and willingness to pay. Such thresholds determine the maximum additional amount the system is willing to pay for an additional unit of benefit. In Sweden, the willingness-to-pay threshold increases with the severity of the disease.

In some instances, costs are not used in assessing the value of a drug. For example in France, value is assessed according to the relative clinical benefit of a drug compared to existing alternatives based on evidence from clinical research (i.e. randomised-controlled trials, observational studies, etc.). The drug’s overall clinical benefit (SMR) is thus assessed and measured against a series of comparators. The drug’s relative benefit is then ranked on a 5-level scale according to its “level of improvement of the clinical benefit (ASMR)”, which is used to inform the level of reimbursement (Appendix 5).

d) Impact of reimbursement decisions on pricing of pharmaceuticals

While cost-effectiveness analysis is predominantly used to determine reimbursement levels, in some cases it is also used to set prices; in others, the reimbursement decision can influence prices.

⁶ A therapeutic alternative is a drug that can be used to treat the same condition. In this case it is used as the comparator. Different types of comparators exist, such as the current best practice, the cheapest alternative, or the most frequently used.

In Sweden, the Dental and Pharmaceutical Benefits Board (TLV), considers the reimbursement application together with the proposed price set by the manufacturer. If a drug is deemed *cost-ineffective*, it is probably because the price was set too high and, since no price negotiations take place, the manufacturer may have to resubmit its application with a lower price (ISPOR Sweden 2009). Other Member States follow slightly different approaches: in France, for example, the HTA agency (HAS - Haute Autorité de Santé) recommends the reimbursement of a drug only if it provides an improvement of medical service or cost-savings. The reimbursement prices are then set according to their ASMR level by the CEPS (Economic Committee for Health Care Products), after negotiation with the manufacturer (usually through price/volume agreements) (PPRI France, 2008).

As a result, in some cases (Sweden), HTA processes are used as a tool for price setting and reimbursement; in other cases (France), they may influence price levels but only indirectly; while in other instances (UK), prices are set according to a different regulatory scheme (i.e. the rate-of-return regulation) combined with HTA appraisals for new and expensive medicines and those that are likely to have significant resource implications for the health service.

In an ongoing study, HTA outcomes between 2007 and 2009 across six agencies have been compared (Euro Observer 2010). A small sample of the study drugs were selected to determine whether HTA appraisals, in their assessment of a drug's clinical benefit and cost-effectiveness, have an impact on the price levels of these drugs. To do so, the relative prices of the study drug and its comparators were calculated to determine whether a correlation between the ASMR ratings issued in France (representing the level of innovation) and the drug's price premiums over their therapeutic alternatives exists. Evidence suggests that price premia vary significantly according to the level of innovation: in cases where the drug has a low or medium ASMR rating the variation is almost inexistent (i.e. erlotinib with an ASMR V rating, was priced approximately 1.2 times higher than its comparator docetaxel in Germany, the UK, and Sweden), whereas substantial price premiums were reflected in drugs with important or major levels of innovation (i.e. imatinib, with an ASMR I-II rating, was priced approximately 100 times higher than its comparator bufulsan) (Nicod and Kanavos, 2011).

The same study also found that 76% of the drugs and indications had differing HTA outcomes. Such differences may also have direct or indirect implications on price levels and possibly explain a proportion of the price differentials. But this will depend on the role of HTA agencies in pricing and reimbursement within each country.

e) Cost-effectiveness pricing and value assessment

One of the main issues with cost-effectiveness pricing is the difficulty in assessing the real value of a treatment to patients and to society. This "value" may vary depending on which method was used for its assessment, which costs were included (direct and indirect), and how the benefits were measured.

National requirements on the preferred methods used for cost-effectiveness analysis vary across as well as within Member States. Thus, it appears that the value of a drug is subjective, because it depends on many considerations including the method and the perspective (i.e. the insurer's or societal perspective) used for its assessment, as well as the types of costs and benefits considered. As a result, the assessed value may vary accordingly and hence affect pricing and reimbursement decisions.

f) Innovative schemes: Performance-based and risk-sharing agreements

In some cases, especially for new and expensive medicines, it may be difficult to perform satisfactory health technology assessments due to the limited amount of available evidence. The regulator can then decide not to reimburse this drug. However, this may prevent patients from accessing certain promising drugs.

In this context "risk-sharing" or "performance-based" agreements are fairly new mechanisms addressing this problem. These schemes intend to protect insurers, while enabling patients to have access to these innovative medicines under certain circumstances. They can also be used in cases of uncertainty about the appropriate doses or indications exist, or when there is a possibility to offer larger patient access (Espin 2009). Under these circumstances, insurers typically seek to minimise risks and (a) ensure that patients receive a relevant treatment, (b) hedge against uncertain clinical value, (c) address low cost-effectiveness, and (d) ensure that a fixed budget is not exceeded.

A number of currently existing performance-based schemes exist, enabling reimbursement to take place under certain conditions:

- *Risk-sharing agreements* are the most commonly used. The reimbursement level is set in different manners:
 - *Coverage with evidence development.* The product is reimbursed when it is used under controlled circumstances, while developing evidence. For example, the drug can be reimbursed within randomized-controlled trials, or can be recorded in evidence-providing registries. In this case, health insurers are primarily concerned about (a) insufficient knowledge about who are precisely the right patients for the product, (b) uncertainty surrounding the value of the product at the time of reimbursement application and (c) low cost effectiveness. As a result, the conditions for reimbursement of the drug are very tight and relate to use under controlled circumstances, thus restricting the number of patients benefiting thereof.
 - *Conditional coverage.* Under this scheme, the drug is temporarily covered until it is able to provide evidence on its effectiveness based on a pre-defined set of criteria. If it is unable to achieve the set targets, the manufacturer will incur price changes or rebates. As in the previous case, concerns about the overall value of the product exist, and it can thus be reimbursed only in some cases; in which case a budget may also be fixed. If the latter is exceeded, the manufacturer is liable for returning the excess.
 - *Outcome guarantee.* When pre-defined outcomes are not realised for individual patients, the manufacturer will bear the full costs or partial costs. In this case, there are concerns about the overall value of the product and it can be reimbursed only for those who respond best to treatment. Unlike the previous case, budget criteria need not apply.

- *Price and volume (budget) agreements.* If these agreements are not respected, a penalty to the manufacturer will be foreseen. In this case, the primary consideration is to ensure that budgets are not overspent, irrespective of the type of patient benefiting from the product(s) in question.
- *Portfolio deals* entail a trade-off negotiated between the price or reimbursement price of one product, and the prices of other products in the same company's portfolio. The trade-off can also take the form of discounts on joint volumes.
- *Disease management* is the case when the manufacturer becomes responsible for the management of a disease of certain patients or of a sub-group of the population, and guarantees budget savings in return of favourable pricing and coverage.
- *Through targeting out-of-pocket payments of patients,* where the manufacturer offers solutions to decrease the out-of-pocket burden of prescription drugs.

2.4 Demand-side regulation

The pharmaceutical market on the demand side has certain particularities that need to be addressed. First, patients or consumers do not have the expertise or the knowledge to make choices on the most appropriate treatment, but rely on physicians to make this decision on their behalf ("agency relationship"). Second, since patients usually do not bear the full cost of their treatment, they may tend to acquire a higher amount of more expensive drugs ("moral hazard"). Third, cultural issues in prescribing by physicians and in consumption by patients, can lead to a deterioration of the moral hazard problem: evidence suggests that over 87% of all patient visits to physicians results in a prescription in Spain, Italy and France, but this percentage is lower (less than 75%) in the UK, Sweden and the Netherlands (Kanavos, 2008). Fourth, depending on the type of remuneration pharmacists receive, it may be in their advantage to dispense more expensive drugs even if cheaper alternatives exist. Finally, patients are willing to pay more if they believe that a treatment is better than another.⁷

All these peculiarities may result in resources being used inefficiently when purchasing pharmaceuticals, for instance, by prescribing more expensive treatments when cheaper and equally good alternatives exist. In order to avoid this, different regulatory mechanisms targeting patients, physicians, and pharmacists have been introduced. The first two are discussed in this section. Policies regarding pharmacists are discussed in the next section, together with the distribution chain overall.

2.4.1 Policies targeted at prescribing physicians

Demand for pharmaceuticals is dictated to a large extent by physician prescribing. Prescribing behaviour and decision-making are influenced by several factors including individual characteristics of the physician and patient, industry advertising, and financial and non-financial incentives at work. While studies have found that changing prescribing patterns is difficult and requires a multi-dimensional approach, several policies exist to shape prescribing practices.

⁷ This is referred to as the price elasticity of demand, which is known to be low for the healthcare market, whereby an increase in the price of a good will result in a comparatively smaller increase of the demand for that good.

Three important components of pharmaceutical prescribing are outlined and discussed below and summarised in Appendix 6: generic prescribing, financial and non-financial incentives and prescription monitoring and audit.

A range of policies exist to increase generic market entry and diffusion, including those which encourage or require generic prescribing at the physician level and generic substitution and dispensing at the pharmacist level. The level and scope of generic prescribing policies varies across the EU. For example, while generic prescribing may be mandatory in some Member States, it is simply allowed or encouraged in others. Prescribing procedures also vary in terms of how doctors are allowed to prescribe pharmaceuticals; e.g. whether they are to use the International Non-proprietary Name (INN), the generic name or only the branded name. Most physicians will prescribe using the brand name unless specifically instructed to use INN, as is the practice in the UK. However, in some Member States, INN prescribing is compulsory in order to minimise the dispensing of branded medicines.

Both financial and non-financial incentives exist to influence prescribing behaviour and encourage the prescription of the most cost-effective treatment option. Financial incentives include monetary rewards for achieving prescription targets and remaining within prescription limits. Financial penalties may be enforced for missing targets or exceeding limits. The incentive or penalty structure, as well as the degree of monitoring and the level of enforcement vary between Member States. The German experience is a commonly cited example of the use of pharmaceutical budgets as a method of influencing drug prescription and controlling pharmaceutical costs. In 1993, following negotiations with the German government, sickness funds and physicians' associations, it was agreed that if a regional pharmaceutical budget exceeds a maximum expenditure threshold, the physicians would be responsible for the deficit (Ess et al. 2003). While the number of prescriptions initially declined following the implementation of budgetary restrictions, the number began to rise again in 1995. The law was eventually abolished in 2001, following consistent opposition from physicians. In the UK, the fundholding experiment offers interesting insights on the way financial (budgetary) incentives were implemented at the individual general practitioner (GP) level over the 1991 – 1997 period (Chaix-Couturier et al, 2000; Delnoij D and Brenner, 2000); the current UK government aims to empower GPs so that they can make most purchasing decisions directly, by delegating in excess of 75% of the UK NHS budget to them.

Another measure for general cost-containment is the use of prescription monitoring and auditing systems alongside the use of clinical practice guidelines and evidence-based medicine to ensure appropriate prescribing. The goals of monitoring or publishing prescribing behaviour include increasing prescribing efficiency, encouraging generic prescribing and, in some cases, verifying adherence to guidelines. Most Member States monitor pharmaceutical prescribing to some extent, but there is variation in the level, frequency and intensity of monitoring. For example, prescription data may be used to compare physician practices and regions within a country, or simply used by individual physicians to monitor their own prescribing habits. In Austria, for example, the most common form of prescribing monitoring is to compare individual prescribing behaviour with regional averages (ÖBIG 2006). In the UK, prescribing behaviour is compared to national and regional levels. Specifically, data on prescription volume and costs for individual GP practices is collated on a national level and statistics are disseminated quarterly to encourage awareness of prescription volume and costs. Individual physicians are notified if they exceed regional averages.

Similar systems exist in France, Germany, the Netherlands, Sweden and Italy. Prescription monitoring systems rely on comprehensive electronic medical records, or internet-based databases, such as Denmark's Oridprax, which allow for comparisons at the regional level (ÖBIG 2006).

The influence of demand-side policies on physician performance in many EU Member States is limited and complicated by several factors including: 1) generic prescribing and financial and non-financial incentives are relatively new in many Member States, or have undergone significant changes since their initial implementation, 2) prescribing policies vary significantly across Member States, 3) such policies are often implemented simultaneously with other organisational re-structuring or supply-side policies, and 4) the evaluation is constrained by a lack of comprehensive information systems tracking prescriptions.

The evidence available from the UK, Germany and France, provides a basis for some broad conclusions and further research in the area. In the UK, studies have found that while the introduction of fundholding and financial incentives led to containment in the overall prescribing costs, it was not accompanied by similar improvements in the quality of prescribing. Conversely, financial incentives could be directly linked to increased quality and appropriateness of prescribing. The size of financial incentives is not correlated with the magnitude of change or improvement in costs or quality of prescribing. Therefore further research is needed to clarify the relationship between the size, and character of incentives, which are required to effectively alter prescribing behaviour (Ashworth 2002). In Germany, budgetary restrictions implemented in 1993 initially caused a substantial decline in the number of prescriptions. Prescription levels quickly returned to their previous levels, following sluggish policy implementation and enforcement, although it is suggested that they led to a 10% savings on the drug budget (though this cannot be attributed to demand-side policies alone, especially considering studies suggesting that physicians may have shifted costs by referring more patients to hospitals (Bloor and Freemantle, 1996). In France, surveys suggest that the system of guidelines attached to small financial incentives or penalties has reduced prescribing of certain drugs, even though more rigorous analysis is still required.

The evidence, albeit limited, indicates that incentives work, but that several components require further study. It is therefore suggested that the following areas be investigated further: first, the aims and targets of each demand-side policies and the desired impact on performance must be clarified; second, more comprehensive follow-up systems must be implemented to accurately record change in prescribing costs and behaviour; and third, transparent measurement tools must be developed to assess physician performance. This research is necessary to identify both the intended and unintended impact of demand-side policies on physician behaviour.

2.4.2 Policies targeted at patients

Policies targeted at patients include information provision and cost-sharing. Patient autonomy and empowerment is gaining greater relevance in healthcare decisions, while exclusive reliance on physicians is weakening in relative terms. Patients need to have access to sufficient, reliable, comprehensible and adequate information to provide an informed consent for a treatment (Bradley et al. 2002).

The internet has become the main source of information to European patients. A number of national health authorities maintain some web sites providing pharmaceutical and other health information. Other web sites are regulated and quality-assured. Nonetheless, some web sites are not controlled and can lead to misinformation.

Member State governments have put in place economic mechanisms that influence patient decisions concerning pharmaceuticals (in some cases, notably reimbursements, a key stated goal is to reduce health care costs). The reimbursement decisions set cost-sharing or out-of-pocket (OOP) payments, which refer to the proportion of healthcare and/or pharmaceutical costs borne by the patient. Cost-sharing mechanisms, such as co-insurance⁸, fixed fee⁹, deductible¹⁰ and reference pricing¹¹, have been introduced mainly for two reasons: a) to ease the public expenditure burden on health, and b) to address the problem of moral hazard, namely unnecessary or frivolous use. However, the introduction of cost-sharing may generate adverse effects for which appropriate measures need to be implemented. For example, cost-sharing may reduce equity in access if people cannot afford their co-payments. The proportion of OOP as total expenditure on health varies greatly across Member States, since different cost-sharing schemes exist in each country (Figure 14), but remains small, with average effective co-payment rates under 10%. Significantly higher variations exist in the new Member States, where co-payments are unaffordable in some cases (Kanavos et al, 2009a).

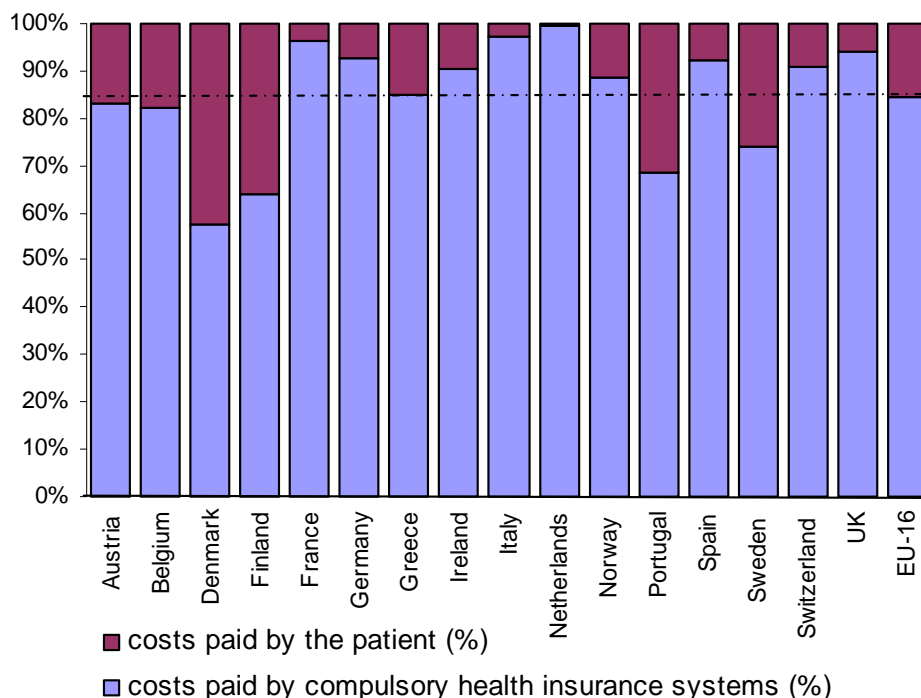
⁸ Patients pay a proportion of the cost of all or most medicines, determined by health insurance. Typically, this is determined by the severity of the illness they treat. For instance, life threatening diseases, such as diabetes, carry a 0% co-insurance. This exists in France, Spain, and Greece.

⁹ Patients pay a fixed amount per prescription, irrespective of the cost of medicines they consume. Exemptions typically exist for the chronically ill. This exists in the UK. A variation of this fixed fee per prescription exists in Germany, where patients pay a fixed fee per pack of medicines.

¹⁰ Under a deductible, patients pay out of pocket the entire prescribing costs (e.g. the first €300 or €400) in any given year, before their insurance coverage covers anything on top of that. In some form this exists in Sweden, but the level of the deductible is low.

¹¹ A system, whereby health insurance fixes the maximum reimbursement price, based on a generic medicines (assuming it is available) and if patients desire a higher cost medicine (e.g. the originator) the need to pay the difference out-of-pocket (as is the case in Spain, France, Germany, the Netherlands, the Czech Republic, among others), or, in some cases, they pay the entire cost out-of-pocket, should they opt for the more expensive option.

Figure 14 Proportion of pharmaceutical costs paid by the health insurance and by the patient in 17 Member States



Source: Kanavos et al, quoted in WHO, 2009.

Another economic mechanism is to establish over-the-counter pharmaceuticals (OTC)¹², which are those available without a prescription. In principle, OTC products are not reimbursed; however, if they also exist in a positive formulary and if they are prescribed by a physician, they are reimbursed. The classification of medicines as prescription-only or OTC remains the competency of each Member State, although harmonisation initiatives across Europe exist. Between 2007 and 2009, the OTC drugs accounted for 15.8% of total pharmaceutical expenditure in Europe (AESGP Facts & Figures, 2010).

Several reasons exist to classify medicines as OTC: a) to shift certain costs from statutory health insurance to the individual; 2) to empower individuals and their responsibility in self-treatment; 3), to widen access to medicines; and 4) to extend product life when they are near patent expiry (Bond et al. 2002). OTCs are not without risks, notably irrational use, though this risk also exists among prescription drugs. Member State approaches to OTCs vary greatly.

¹² The WHO definition of an OTC: "An OTC is a pharmaceutical product, drug, or medicinal specialty whose dispensing or administration does not require medical authorization, and it can be used by the consumers under its own initiative and responsibility to prevent, relieve or to treat symptoms or mild diseases and that its use, in the form, conditions and authorized dosages are safe for the consumer" (WHO & Pan American Organization).

2.5 The distribution chain

In considering the differences in the retail prices of pharmaceuticals, it is important also to look at the role of wholesalers, retailers and other stages of the supply chain in the final price. The make-up of these different costs also varies greatly across the EU, both for “branded” pharmaceuticals as well as generics.

2.5.1 The impact of the distribution chain on prices

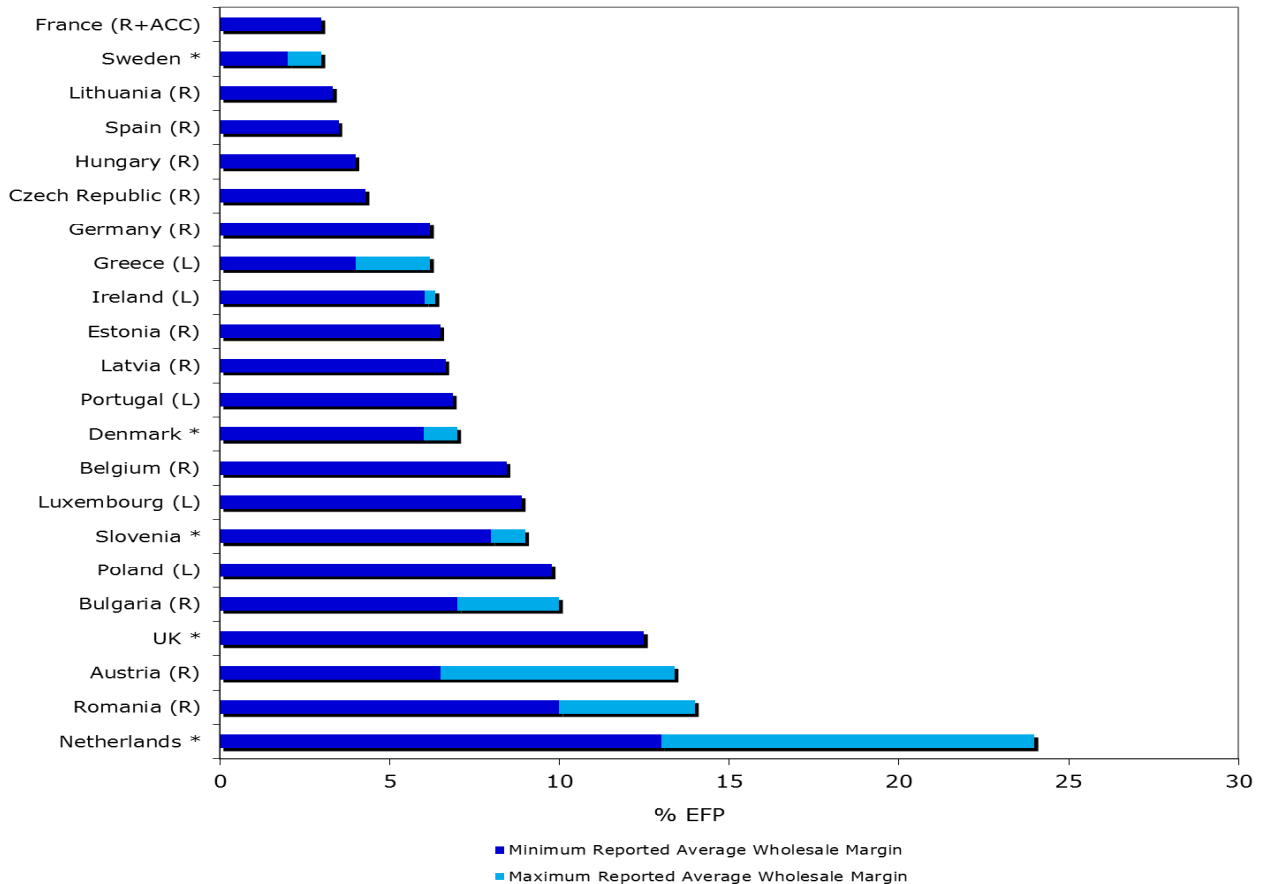
Despite recent reductions in distribution margins, the impact of distribution in different Member States can be as high as 50% of a drug’s retail price (i.e. the price payable by health insurance). The proportional impact of margins on retail prices is often higher for generics (which have lower prices) than it is for branded medicines.

One factor is that national patterns for distribution vary greatly. This is in part a reflection of historical patterns. Italy has 193 pharmaceutical wholesalers and Spain has 99, while Germany has only 16 and the UK, less than 9. Moreover, the top three wholesalers in the UK control 85% of the market. Finland and Sweden have only two wholesalers each. In a similar vein, the density in retail distribution via pharmacies varies significantly across Member States with some of the southern Member States (such as Portugal, Spain, Italy and Greece) having the highest density of pharmacy networks; in comparison, some northern Member States have a much lower pharmacy network densities.

Some Member States have seen the introduction of new approaches, such as manufacturers that sell pharmaceuticals directly to pharmacies or, in certain cases, directly to dispensing physicians. Another approach for manufacturers is to use a small number of wholesalers in a national market.

Figure 15: Average wholesale margins as a share of retail prices in selected EU Member States

Average Wholesale Margins presented across EU27 Countries. Greater than one source (2007-2010) creates minimum and maximum values. Countries with * have private negotiations, 'R' denotes regressive margins and 'L' denotes linear markups.



Source: Kanavos (Pharmaceutical Policy, 2010, lecture 9)

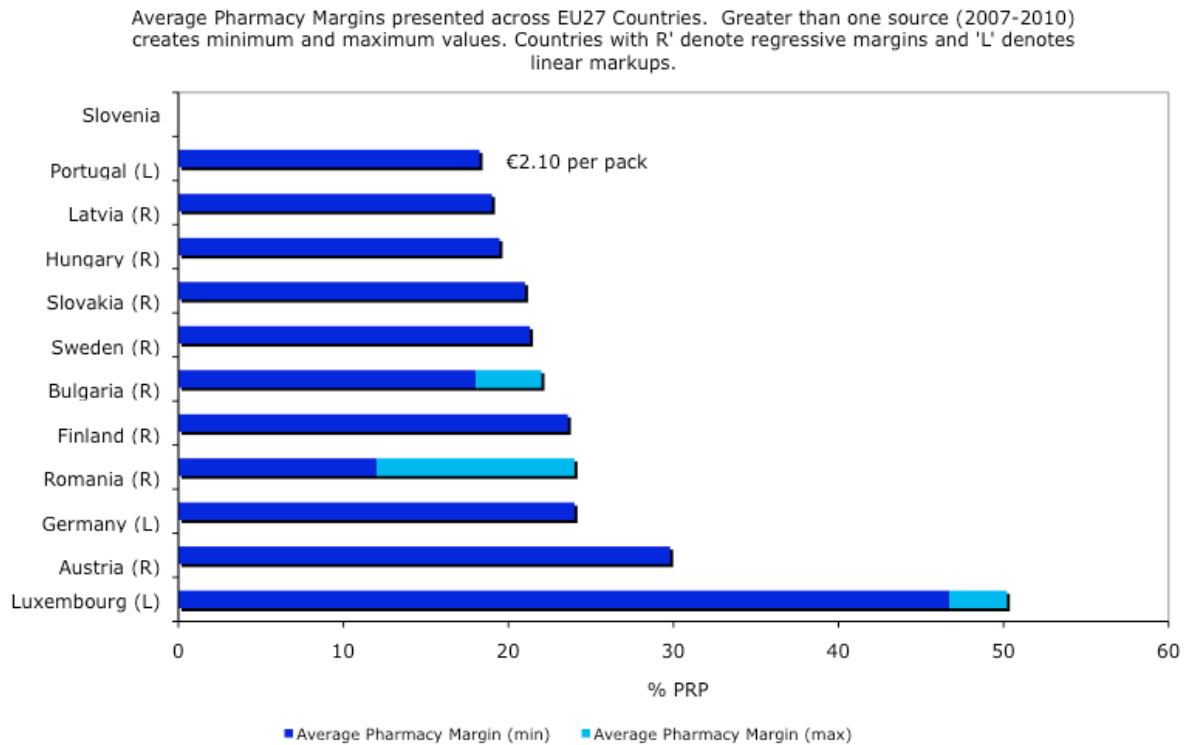
Regulations can have a major effect, through controls on remuneration of the distribution chain, licensing of pharmacies on the basis of population criteria as well as decisions whether pharmacies or wholesalers can combine, either horizontally or vertically.

Demand-side policies can target all stakeholders within the distribution chain, notably manufacturers, wholesalers and retailers, for example through regulatory interventions that include controlling wholesale and retail margins, allowing generic substitution and monitoring price discounts where possible.

Wholesale and retail margins may be progressive, regressive, a fixed percentage of the relevant price or a flat fee. The current practice in the EU nowadays consists of applying either regressive or fixed fee margins. Depending on how they are structured, regressive margins can encourage generic use.

As a result, both wholesale and retail margins vary greatly, as shown in Figure 15 (above) and Figure 16 (below).

Figure 16: Average pharmacy (retail) margins as share of retail price in selected EU Member States



Source: Kanavos (Pharmaceutical Policy, 2010, lecture 9)

2.5.2 Policies to encourage generic pharmaceuticals

Generic substitution policies can encourage or require that pharmacists dispense the generic version of a medicine when available. Generic substitution varies from mandatory (Sweden) to voluntary (France) to “not allowed” (Austria) (PPRI 2007). These categories are not static however, as governments alter their policies over time (PPRI 2007). Generic substitution policies also vary according to the extent to which physicians and patients are allowed to refuse the substitution. In countries such as Sweden the substitution of a generic alternative can be refused by the prescribing physician, but only with medical evidence as justification. Because of the varying degrees of generic prescribing and substitution, there is varied evidence as to the influence of generic substitution on generic utilization. The European Commission (2009) concluded that those Member States that require pharmacists to dispense generic medicines when possible are more likely to have generic entry earlier and achieve higher cost-savings. Moreover, data from Sweden shows that generic substitution has facilitated a drop in market price for generics (approximately 40% since the introduction of substitution in 2002; PPRI 2007).

Internal reference pricing systems (discussed above) and generic substitution are methods by which the government encourages the dispensation of generic drugs over more expensive branded medicines. Within the structure of these policies, pharmacists still have considerable market power in the absence of price differences between comparable drugs. Wholesalers or manufacturers, therefore, provide discounts to pharmacies in exchange for dispensing their product, incentivising the pharmacist to dispense the product with the greatest discount. The difference between the reimbursement price set by the health insurer and the discounted price offered by the wholesaler or manufacturer may be considerable, and the greater the margin between prices, the greater the incentive for pharmacists.

Discounting practices are particularly important in the generic market because the level of discount offered can distinguish one generic from another in a pool of directly comparable, reimbursable drugs. While there are legislated limits on the discounts wholesalers and manufacturers may offer pharmacies, the level and scope of discounts is kept confidential. In a study of the French generic market, for example, it was found that while discounts are related to price, the discounts exchanged are greater than the discount ceilings placed by the government (Kanavos and Taylor 2007). In a response to discounting practices, and as a method of capitalising on the cost-saving potential of generic discounts, governments recalculate margins in order to claw back at the pharmacy level discounts.

2.5.3 Direct delivery chains

Of significant interest is the development of direct delivery to pharmacy from the pharmaceutical manufacturers, using wholesalers as logistics providers or restricting the number of wholesalers used to distribute their products. Whereas the majority of pharmacy sales continue to originate from (full-line) wholesalers, in a number of Member States the proportion of pharmacy sales originating directly from the manufacturer is over 10% (e.g. in Denmark, Greece, Ireland, Luxembourg, the Netherlands, the UK) and can be over 20% (e.g. in the Czech Republic, France, Italy). In Austria, locally manufactured medicines can be delivered directly to pharmacies, and in Bulgaria most manufacturers have their own wholesaling (via own development or acquisitions). In Hungary, a manufacturing license also incorporates a wholesaling license. In France, direct delivery occurs particularly for high turnover products, and in Italy manufacturers are allowed to deliver directly to the regions to discharged hospital patients and outpatient clinics (e.g. for oncology patients). In the UK, direct distribution occurred particularly for generic medicines (PPRI Country Reports 2006-2008; OBIG 2006) until recently, but, currently, this trend appears to be on the wane.

Agency distribution relates to Direct-to-Pharmacy (DTP) arrangements (or Direct to Dispensing Doctor, where these operate). In this case, manufacturers sell direct to their customers with exclusive or limited wholesalers acting as distributors or logistics service providers only. The wholesalers never own the stock and so are in no position to offer any discount on it. DTPs tend to be chosen by the larger firms. In the UK, there has been a significant uptake of DTP arrangements over the past 3 years. GSK was first, Pfizer second (now including Wyeth). With just Astra Zeneca and Eli Lilly these cover over 30% of the market. There are also optional offers by some companies to sell direct or via mainline wholesalers, e.g. Roche and Bonviva via Williams, Takeda and Prostep via Clarity DTP. Some companies distribute lines that tend to be low volume and high cost directly themselves, e.g. Novartis supply ten low volume lines for dispensing GP in the UK, which include Sandimmun and Roche two such (product) lines.

Very often, DTP arrangements are complementary to other schemes, such as Reduced Wholesaler Model Schemes (RWM). In RWM (or Reduced Wholesaler Agreements, RWA), pharmaceutical manufacturers use a very small number of wholesalers (1-3) in the traditional manner to distribute products. In this case, wholesalers purchase the stock and can thus offer a discount. In the UK a number of companies follow this scheme, namely, Sanofi Aventis, Novartis, Janssen-Cilag, Roche, Novo Nordisk and Bayer Schering, which, if put together, account for about 20% of the market.

In principle RWMs do not violate the “public service obligation”, but restrict its remit to a limited number of players on the market. Agency arrangements, on the other hand, exist where this obligation is not part of the wholesaling arrangements, notably the UK.

DTP and RWM arrangements have implications for integration within the supply chain in the sense that selective agreements between manufacturers and wholesalers may force some of the latter to consolidate in order to face the emerging type of competition. At the same time, these arrangements imply in themselves a different type of vertical integration, whereby manufacturers bypass the traditional chain to supply direct to pharmacy (DTP) or select which wholesalers to work with (RWM), or even create their own distribution vehicle. In the DTP arrangements the discounting ability by wholesalers to pharmacy is removed, whereas in the RWM arrangements, it is maintained but may be influenced by the agreement between the manufacturer and the wholesaler.

The changing nature of distribution and the advent of the agency and the reduced wholesaler models are beginning to have a significant impact in some countries. In principle, changes in the distribution model should make the process of delivering medicines from factory gates to the patient bed-side more efficient and cost-effective. Yet, there seem to be some concerns about the availability of medicines; manufacturers’ activities in streamlining supplies and managing stock, coupled with the ever-fragmented nature of distribution, can lead to shortages in some markets (Kanavos and Costa-Font, 2005). More recently, exchange rate fluctuations have led to a deterioration of this problem in some countries (e.g. UK) (Gainsbury, 2009; Taylor, 2010).

Clearly, there are different incentives and disincentives from different stakeholders’ perspective (manufacturers, wholesalers, retailers) in this process, but these do not seem to be aligned at all times. Health insurance institutions find little reason to step in unless patient access to medicines is significantly affected or shortages are shown to be having an impact on care and outcomes. At the same time, breaches from the public service obligation do not necessarily occur in situations where a reduced wholesaler model operates.

An important factor influencing retail price variability is the type and amount of remuneration of the supply chain. Wholesalers and pharmacists are subject to various mark-up types across Europe, which directly reflects on retail prices.

2.6 Differences in VAT levels

Another important factor is that VAT rates on pharmaceutical products vary significantly across Member States (Table 3), with some (the UK and Sweden) exempting these products from VAT. In contrast, Denmark charges a 25% VAT rate.

VAT rates for pharmaceuticals have recently increased in several Member States, including Greece, Hungary and the Baltic States.

Table 3 VAT rates for outpatient prescription medicines, 2009

UK	0%
Sweden	0%
France	2.1%
Spain	4%
Netherlands	6%
Italy	10%
Germany	19%
Denmark	25%

Source: UK, Sweden, France, Netherlands, Italy, Germany, Denmark: PPRI country reports; Spain: Vogler, Espin, Habl 2009.

2.7 Access to Pharmaceuticals

In addition to affecting price levels, government regulations and market conditions also influence patient access to pharmaceuticals. Access is determined by two factors: 1) the affordability of medicines, which is the extent to which health insurance covers the (pharmaceutical) needs of patients in an adequate manner and at an affordable cost; and 2) the availability of prescribed medicines (or the medicines of choice) at appropriate outlets. The implications of these two dimensions and their relevance to prices are examined below.

2.7.1 Affordability

a) The influence of co-payment requirements

The affordability of pharmaceuticals varies across Member States as a result of the variance in national GDP, GDP per capita and available health budgets. The affordability of a drug at the patient level is dependent on the extent to which a drug is covered by the health insurer, combined with the cost-sharing burden placed on the patient. Patient co-payments for pharmaceuticals are a form of direct cost-sharing meant to mediate demand and/or generate revenue for the health system.

The introduction of co-payments may reduce demand for health services, while pharmaceutical co-payments may reduce the demand for essential drugs, and even more so for discretionary or symptomatic drugs (Rubin and Mendelson 1995; RAND Health Experiment 1970). The same studies found, however, that cost-sharing systems reduce the demand disproportionately amongst the poor. As a response, there are exemptions for various groups including children, the elderly and those with low-income. Moreover, because the burden of co-payments will be most disenfranchising for those with lower levels of health, there are further exemptions for certain types of pharmaceuticals.

For example, in Spain, while co-payments may reach 40% of the drug sale price, the co-payment is reduced to 19% (with a maximum annual charge) for drugs treating chronic and fatal diseases (Ess et al. 2003).

Evidence on the likely impact of co-payments on affordability from an EU perspective is scarce, but there are indications that it exists. A recent WHO study suggests that high co-payments are restricting drug affordability and availability (Kanavos et al, 2009a). Specifically, effective prescription-only medicines (POM) co-payments in Estonia seem to be higher (43%) than in most other EU Member States and are posing an affordability barrier; the majority of medicines dispensed are subject to some form of co-insurance and about 50% of all prescriptions dispensed are subject to a 50% co-insurance. Treatments for a number of chronic diseases are subject to a 25% co-insurance (75% coverage), whereas differential co-payments also exist depending on the provider visited (whether the patient visits a GP or a specialist) (Kanavos et al. 2009). Interviews with stakeholders suggest that high prices of (new) medicines pose a significant affordability problem to health insurance systems in several EU Member States and can also expose patients to high and unaffordable co-payments.

The use of co-payments as a cost-containment method remains an issue of debate considering its potential influence on affordability and thus access to pharmaceuticals, especially for vulnerable populations. Co-payments must be set at a level that does not restrict access but which promotes rational drug use. It is suggested that a reduction in the level of co-payments could be achieved by promoting rational drug use, cost-effective prescribing and patient awareness of cheaper therapeutic options at the pharmacy (Kanavos et al. 2009).

b) Coverage decisions

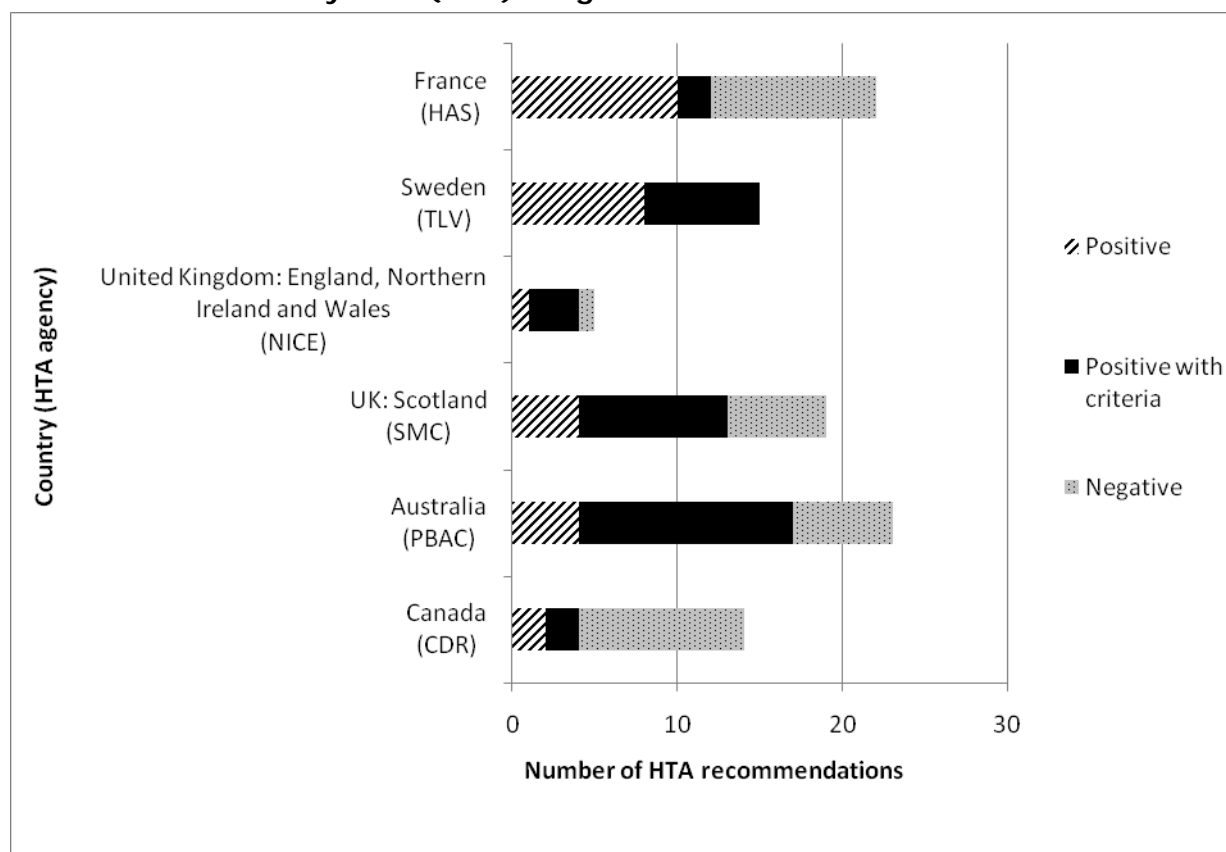
National decisions on pricing and reimbursement levels influence not only the access and affordability of these treatments, but also whether pharmaceutical companies seek to market their products in a given country. Because Member States often base pricing and reimbursement levels on those in other Member States, it is advantageous for companies to market their product first in a Member State that can afford the highest price or reimbursement level. This results in significant variation in market access across the EU, with high-income Member States such as the UK and Germany gaining access earlier than smaller market Member States. By doing so, pharmaceutical companies also intend to achieve higher prices in the countries launched subsequently, by putting forward the (higher) prices already approved in the countries where the product has already been launched.

Reimbursement decisions determine the level and scope of coverage, including the level of co-payments borne by the patient to gain access to these treatments. Within the EU, coverage decisions are increasingly based on health technology assessments (HTA). The national formularies then list whether the drug is reimbursed or not. In case where a treatment receives a negative coverage decision, the patient is likely to bear the full cost to gain access to this treatment, thus limiting the affordability and access to this treatment.

In theory, HTAs should be more or less homogeneous across EU Member States. In reality, substantial variations in recommendations across countries have been identified, thus impacting on the affordability and access to these treatments for those with negative or delayed coverage decisions, as well as on price levels depending on whether HTAs are used directly or indirectly as a price setting or reimbursement scheme.

HTA outcome records compiled between 2007 and 2009 from six different agencies illustrate these differences, with a special focus on central nervous system (CNS) drugs, cancer drugs, and “orphan” drugs (those for rare diseases). In the case of CNS treatments for example, only 24% received consistent recommendations from all six agencies, while the remaining 76% got a mix of positive and negative recommendations¹³. The number of drugs and the indications appraised also varied across countries (Figure 17). The same trend was identified in cancer treatments as well as in orphan drugs.

Figure 17: HTA outcomes in three Member States and two comparison countries for 25 Central Nervous System (CNS) drugs



Note: In the case of France, a negative recommendation is ASMR V, which essentially says that the drug has no *additional* therapeutic benefit in relation to comparators.

Source: Kanavos et al, Euro Observer 2010.

¹³ HTA recommendations per drug and per indication are divided into three levels: 1) positive recommendation, where the treatment is reimbursed as applied for, 2) positive recommendation with criteria, where the treatment is reimbursed with restrictions (i.e. to a subgroup of the population, or when prescribed by a specialist), 3) negative recommendation, when the treatment is rejected for reimbursement.

Several reasons exist for these variations. First, the selection criteria of the drugs for which an HTA is conducted differ across agencies. In the UK for example, all drugs are potentially reimbursable once they receive a market authorization; of the drugs that are approved each year, only a fraction are appraised based on a series of selection criteria, including need and likely high impact on NHS resources. In contrast, all drugs are appraised in France, and all newly licensed drugs and new indications are appraised in Scotland. In countries where not all drugs are appraised periodically, a risk exists that some of the drugs reimbursed that have not been appraised are not cost-effective.

Second, the duration of HTA processes may delay access to certain treatments, especially in Member States where these processes are longer (i.e. 32 to 56 weeks in the UK versus 17 to 18 weeks in Sweden). Negative recommendations may cause additional delays, since most often the manufacturer will appeal against the decision and/or re-submit its application. When price negotiations are included in the HTA process, additional delays may also be incurred. However, the timeliness of HTAs may on one hand give patients faster access to promising technologies, but on the other may be based on earlier evidence that may induce uncertainties in the appraisals. It is important that balance is maintained in this regard.

Third, there is limited amount of evidence available, and, in particular, a lack of long term data resulting in uncertainties and gaps in the evidence. In the case of cancer drugs, HTA agencies may respond in a number of ways when faced with these uncertainties, all of which can vary across countries: 1) by focusing on a sub-group population or a narrowed-down indication for which the evidence is more certain, 2) by including indirect comparisons or expert opinions to supplement the evidence, 3) by deferring the decisions until further evidence is available, 4) by rejecting the application, 5) by pressuring the manufacturer to decrease its prices, or 6) by implementing risk-sharing agreements (Pomedli 2010 in Euro Observer, 2010).

In other cases, as seen mostly in cancer and "orphan" drugs (those to treat rare diseases), positive recommendations (including positive with criteria) were granted in particular cases, although there was a high level of uncertainty in the evidence. This was often seen in cases where few or no other alternative treatments exist, when patient need is high and the severity of the disease is significant (Pomedli 2010; Van den Aardweg 2010 in Euro Observer, 2010).

Diverging interpretation of the same evidence has also shown to cause differences in HTA outcomes. For example, when assessing the efficacy of a treatment against schizophrenia, different weights and permutations of the type of evidence considered were identified. Some agencies considered mainly the primary clinical endpoint, whereas others chose the primary and secondary endpoints, the latter including a measure for quality of life. Moreover, different economic models and comparators were used for a same drug and same indication. As a result, considering all the above in addition to the uncertainties emerging from cost-effectiveness pricing discussed earlier, many reasons for diverging interpretations of the same evidence may exist resulting in possible differing HTA outcomes (Nicod 2010 in Euro Observer 2010).

Fourth, the lack of transparency in the processes may also impair manufacturers in their applications, for whom the submission requirements may not be clear, resulting in possible negative appraisals. Moreover, the level of stakeholder involvement has also shown to be limited, with potentially negative impacts on HTA decisions or recommendations (Drummond et al. 2008).

Finally, the effective implementation of HTA recommendations also appears to be variable depending on the advisory or regulatory role of the HTA agency. In the case of Sweden, where the national HTA agency is a regulatory body whose decisions are to be adopted by the county councils, not all county councils are able to afford all reimbursement decisions, thus resulting in national differences as far as reimbursed treatments are concerned.

It can thus be concluded that health technology assessments are complex processes with many stages and involving many stakeholders. One should keep in mind that at each stage different factors may influence HTAs outcomes, thus affecting the affordability and accessibility of these treatments.

Different initiatives have been implemented at international and EU level to work on improving health technology assessments. In Europe, the EUnetHTA collaboration is an initiative launched in 2008 aiming to develop an effective and sustainable HTA collaboration in Europe, through: 1) reducing duplications of efforts and improve the efficiency in the use of resources; 2) increasing the impact of HTA in EU Member States; 3) strengthening the link between HTA and health care policy-making; and 4) supporting countries with little experience in HTAs (EUnetHTA Project 2009). These initiatives intend to harmonize or standardize the HTA processes so to improve their level of transparency, quality and comprehensiveness, and facilitate the extraction of relevant information that can then be transferred cross-border.

2.7.2 Availability

The availability of medicines is dictated by supply and demand-side factors, such as levels of drug use, overall expenditure on medicines, drug prices, as well as more wide-ranging factors including market structure, regulatory policies, and cultural practices. As a result of variation in these factors, drug availability varies between Member States.

In this context it is important to distinguish between the number of authorised pharmaceuticals and the number of authorised pharmaceuticals actually available on the market. In many Member States, notably Portugal, Greece and Austria, the number of available pharmaceuticals is smaller than the number of authorised pharmaceuticals (PPRI 2007). Interviews with stakeholders have also revealed this is the case in many of the new Member States, where new products are not being launched by manufacturers. Such differences between authorised and available pharmaceuticals may be the result of three factors: 1) drug companies apply for drug authorisation but do not market the drug in each country, fearing that price regulation by means of EPR will jeopardise their pricing strategies elsewhere and could also lead to parallel trade; 2) for generic products, several applications for the same product are often submitted by business consultancies, in order to be sold to generic companies once authorisation is received, and 3) not all forms and sizes of pharmaceutical products will be marketed in each country.

While data availability issues complicate direct comparisons, the EURO-Medicines project (2001) found that the number of medicines available varies across the EU, with the greatest number available in Germany and the UK, with the least available in the Scandinavian countries (Folino-Gallo et al. 2001). Three main concerns for drug availability, relate to the availability of drugs in small market Member States, the potential for parallel trade and the availability of generic alternatives.

a) Access to pharmaceuticals in small markets

Approximately 2/3 of the EU pharmaceutical market is held by the five largest markets (France, Germany, Italy, Spain and the UK). While there has been considerable growth in pharmaceutical markets across Europe (3-4% per year), growth has been particularly fast in the newest EU Member States (EU12) (13% per year). Despite this growth, overall access to pharmaceuticals is significantly lower in smaller markets (Kanavos et al, 2009a; European Commission, 2009). Such limited access is a result of several factors influenced by historical context, national budgets, and reimbursement policies on the supply-side, as well as local market size, and national language on the demand-side. For example, the additional costs of translation of information and labelling of medicinal products, may not in the long-term, appear profitable enough for pharmaceutical companies to apply for, or renew, their market authorisation. EU regulations stipulate that regulatory bodies are not in a position to force manufacturers to market any medicinal products, nor are there legal instruments which allow them to handle and solve such situations (Kanavos et al. 2009a).

Issues of pharmaceutical availability due to expired market authorisation can be overcome by policies which allow physicians or professional bodies to request and procure drugs from other Member States, for individual patients. While this is a likely solution there are two significant barriers: first, the application process is cumbersome and time consuming and second, the affordability of the drug may be compromised as unauthorised drugs may not be considered for reimbursement and the patient will have to pay out-of-pocket (Kanavos et al. 2009a).

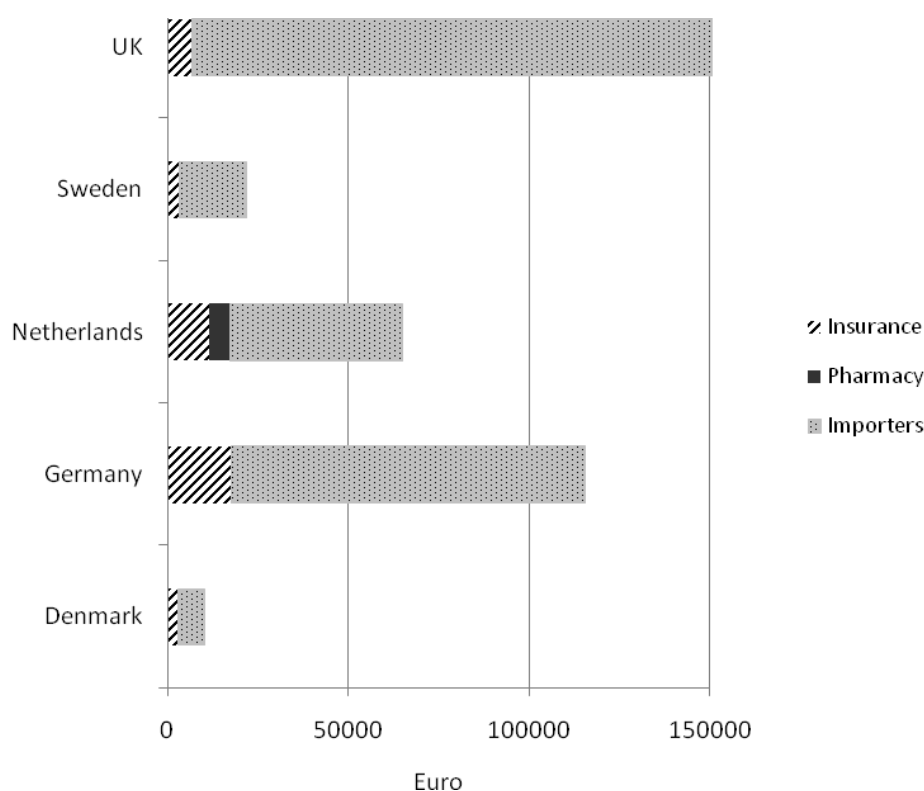
b) Parallel Trade

Pharmaceutical price regulation has led to significant price differences across EU countries. In the EU single market, the free trade of goods has created arbitrage opportunities in the pharmaceutical market. Pharmaceuticals have been purchased in Member States with low prices and re-sold in higher-priced Member States through parallel trading activities. The market share of parallel-traded pharmaceutical products in the main importing countries stands between 10% and 20% (Kanavos and Kowal 2008). The European Court of Justice (ECJ) has ruled on numerous occasions on a variety of aspects of parallel trade, e.g. repackaging, relabeling, dual pricing, and overall has upheld the practice.

Parallel trade has been perceived as a cost-containment mechanism by policy makers in some Member States, and this practice has in some cases been encouraged (West and Mahon 2003, Kanavos and Costa Font 2005). In the Netherlands, health insurance would share any price difference between locally sourced and parallel traded products with pharmacists; in Germany quotas were used to force pharmacists to sell parallel-traded drugs, although this is no longer the case.

Evidence suggests that parallel trade does not lead to significant savings for health insurance, as parallel traded products are usually priced at the same level or very close to the corresponding locally sourced ones (Kanavos and Costa-Font 2005; Kanavos and Kowal 2008). In practice, profits accrue to the supply chain, and little or no savings accrue to health insurance (Kanavos and Kowal 2008). It has also been shown that parallel trade does not necessarily trigger competition; therefore, locally sourced products are not priced at lower levels as a result of parallel trade (Kanavos and Vandoros 2010). The distribution of financial benefits from pharmaceutical parallel trade on stakeholders is illustrated in Figure 18. Importers receive the vast majority of the financial benefit of parallel trade followed by insurance companies. In Sweden, Denmark and Germany, where margins are fixed by regulation, pharmacists have no explicit financial incentive to dispense a parallel-imported medicine, but are legally obliged to do so. In Germany they incur financial penalties if they do not. Pharmacists are also clear beneficiaries in Member States where pharmacy margins are not determined by regulation (e.g. the Netherlands) or where a financial incentive is provided to them to dispense a parallel-imported medicine (the Netherlands, Norway) (Appendix 9).

Figure 18 Distribution of benefits associated with parallel trade in selected countries



Source: Kanavos and Costa-Font 2005.

One of the unintended consequences of parallel trade is that it can lead to shortages in exporting countries, due to medicines being exported to higher priced countries (Kanavos and Costa-Font, 2005; Gainsbury, 2009; Taylor, 2010). Yet, there is little evidence on the impact this is having on availability and access.

Further, it has been suggested that it can be a threat to innovation and lead to significant welfare losses (Danzon 1998; Bordoy and Jelovac 2003; Rey, 2003; Ganslandt and Maskus 2004; Szymanski and Valletti 2005), as parallel trade reduces the expected profits from an innovative product.

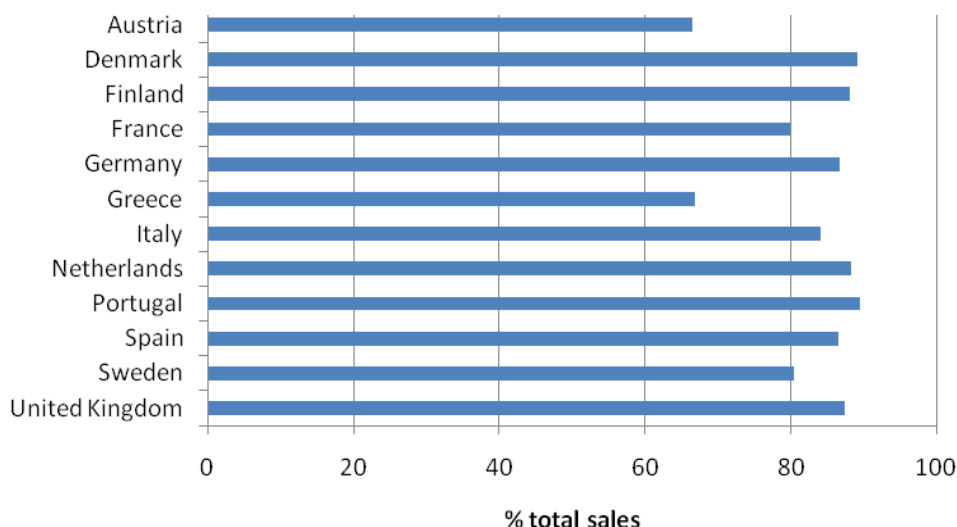
A further issue arising from parallel trade is the risk of counterfeiting. Parallel traders often repackage medicines in order to help sell them in the destination countries. However, this practice can give the opportunity to criminals to disguise counterfeit medicines (Davies and Taylor 2009). Counterfeit medicines have been seized in various European countries over the past few years and some of these counterfeit medicines were related to parallel trading (Davies and Taylor, 2009 and references therein).

In recent judgements, the EU Court of Justice has questioned some of the legal principles underpinning the EU policy on pharmaceutical parallel trade and this suggested that there might be scope for policy change; however, how and to what extent changes should take place remained partially unclear (Desogus, 2010).

c) Delays in pricing and reimbursement negotiations

Delays in pricing and reimbursement negotiations can act both as a disincentive for innovation and as a barrier to access by leading to differential availability between Member States. Within in EU, the time elapsing between EU market authorisation and accessibility (date of completion of pricing/reimbursement) ranges from 101 to 403 days (EFPIA 2009)¹⁴ and can have an impact on access in many Member States. This issue is currently under discussion in the revision of the EU Transparency Directive.

Figure 19: Generic drug availability by proportion of total sales (for pharmaceuticals facing generic entry within 24 months post patent expiry)



Source: Kanavos and Casson, 2011 (forthcoming).

¹⁴ Excludes Germany and the UK

d) Generic drug availability

Overall access to and affordability of pharmaceutical treatments is influenced by the availability of cheap generic alternatives to expensive branded drugs (figure 19 compares availability across 12 Member States).

Generic availability can be examined by the level of generic competition, the time delay to generic entry and demand for generics as dictated by physicians and pharmacies. Very frequently the cheapest alternative is not available at the pharmacy; under these circumstances, a more expensive medicine will be dispensed, at a higher cost to the patient and, possibly, health insurance.

Ongoing research analysing pharmaceuticals whose patents expired between 2000 and 2008, suggests that there exist significant differences in generic availability, entry and competition in 12 EU Member States (Kanavos and Casson, 2011, forthcoming). The availability of generic drugs is measured through the number and proportion of pharmaceuticals with generic entry within the first 24 months following originator patent expiry, as well as the proportion of total sales facing generic entry over the same period. The findings clearly indicate that substantial differences exist in the generic markets, as for example, the number of products facing generic competition ranges from 34% in Greece (66% of total sales) to 57% (89% of total sales) in Denmark (Figure 19).

In addition to the proportion of pharmaceuticals and sales facing generic competition, another component of the generic market that influences availability is the time delay to market entry; that is the time elapsed between originator patent expiry and patient access to a generic alternative. The European Commission's Inquiry into the Pharmaceutical Sector (2008) concluded that it takes on average seven months for generic medicines to become available, which, if reduced, could result in an additional 20% savings on pharmaceutical expenditure. While time delays are influenced by several factors, the role of pharmaceutical companies and some of the strategies they employ may inhibit early entry and delay generic penetration. These strategies include the creation of "patent clusters" (strategic patenting), prolonging patent litigation and lodging complaints to national authorities claiming patent right violations (European Commission 2009).

3. CONCLUSIONS AND POLICY OPTIONS

KEY FINDINGS

Assessment of Member State approaches and policy options

- Systematic evaluations of pharmaceutical policies and measuring the performance of individual policy measures could benefit national health systems.
- Risk sharing and other payer-related schemes can offer insights into payer and supplier behaviour, while enabling access to costly treatments.
- Evidence suggests that significant savings can be achieved through policies that increase the use of generic pharmaceuticals. There is considerable room for faster generic drug entry and uptake in all Member States. This may be achieved with a combination of supply- and demand-side measures, notably by supplementing pricing and reimbursement policies with targeted physician or pharmacist incentives to increase demand for generic alternatives. More research, however, would be desirable to quantify the influence of financial and non-financial incentives on physician and pharmacist behaviour.
- Action may be considered at the Member State level in order to improve the conditions for entry of pharmaceuticals on the market. Launch delays, often due to regulation, jeopardise timely access to medicines. The timing and length of Health Technology Assessments (HTAs) also seem to be affecting access.
- Key actions for stimulating innovation in the pharmaceutical sector include simplifying and shortening the market authorisation and market access procedures, adopting simpler pricing and reimbursement regulation mechanisms and ensuring greater EU-level coordination amongst the trade, health and research sectors.

Policy options at EU level

- EU institutions can play an important role in facilitating the exchange of best practices and improving coordination among Member States.
- Notably, EU institutions can promote further exchanges of information among Member States on different policy mechanisms and their results, with a view to further harmonising methods such as HTA and, more generally, reducing price differences and improving access.
- Further encouraging biomedical innovation at EU level could have important spill-over effects in the European economy. Deeper coordination among Member States could avoid duplication in research efforts by national competent bodies. In addition, setting research priorities based on unmet medical needs at EU level would be desirable.
- Expanded use of HTAs can improve transparency of price-setting mechanisms and reimbursement decisions. Greater coordination would be desirable at EU level, particularly on HTA methods, the production of comparative effectiveness evidence, and broad guidance on appraisals in order to avoid diverging interpretation of the same body of evidence by national competent authorities.
- EU policies can also encourage greater use of generic medicines, which could lead to significant price reductions in a number of markets.
- Parallel trade in pharmaceutical products continues to raise concerns and deserves further study and policy discussion at EU level.

3.1 Price differences across EU Member States and their impact on pharmaceutical budgets

3.1.1 Reimbursement

Reimbursement mechanisms are closely linked to the price of a drug. As a result, it is important to understand the dynamics between pricing and reimbursement regulatory schemes, as well as their impact on the access and affordability of drugs. Occasional delays are observed in achieving reimbursement status based on available indicators (EFPIA, 2010). Delays may often be exacerbated by HTAs requiring thorough reviews of the clinical evidence and the associated economic costs of new treatments relative to comparable existing ones. There also seems to be discrepancy between the type of evidence requested to manufacturers by regulatory authorities such as European Medicines Agency on the one hand, and national HTA and/or reimbursement agencies on the other hand.

Policy option at EU level

Efforts could be undertaken to harmonise and disseminate these evidence and information requirements. Such efforts would ideally be coordinated at EU level, with the participation of EMA, a number of competent authorities and representatives of the pharmaceutical industry.

One option could be to strengthen the sharing of information and policy experience among Member States on mechanisms used to purchase pharmaceutical products. This could be done by building on existing initiatives such as the network of Competent Authorities on Pricing and Reimbursement. An exchange of information could be used to identify good practices at the Member State level.

3.1.2 Formularies

Formularies, lists of pharmaceuticals that are either eligible or excluded from reimbursement, are an effective way to regulate drug utilisation and encourage rationale use in terms of the choice of the appropriate treatment, dosage, form for a patient, and adequate use). Formularies encourage efficient use of healthcare resources and may lead to cost savings.

Policy options for Member States

Decision-makers at Member State or regional level could consider keeping clinically and cost-effective treatments on formularies, while removing treatments that are obsolete and less efficacious compared to new ones. Where formularies exist, a more pro-active stance regarding their management could help optimise costs and improve efficiency.

Comprehensive guidelines detailing the different scenarios and appropriate treatments to be used (e.g. in terms of sub-population, indication, and dosage) could increase transparency in processes and thus enable manufacturers to better identify R&D priorities.

In turn, this could encourage innovation, increase the number of available drugs and consequently foster price competition. Patient and physician input in formulary design would help reduce discrepancies between recommendations and user behaviour.

Concerns regarding the lack of flexibility of formularies could be addressed through more frequent reviews. Some Member States currently do so on a monthly (Belgium, France) or fortnightly basis (Denmark), to ensure that effective and cost-effective treatment options are timely available.

3.1.3 Innovative pricing and reimbursement schemes

Innovative pricing and reimbursement schemes and risk-sharing practices tend to enable earlier access for patients, while protecting the payer and allowing manufacturers to prove the value of their product. However, little evidence exists to date as to the impact and benefits of such schemes. It is thus important to monitor them and conduct further research to better understand their performance and implications, namely in terms of implementation and administrative costs.

Policy options at EU level

It might be worthwhile for treatments that have not proved their value to be brought onto a European list (e.g. a registry) to create the mid- to long-term knowledge required, drawing on a wider patient population at EU level for a determination of value.

Transparency may contribute to successful implementation of these schemes; e.g. by publishing the results of negotiations between the coverage entity and the manufacturer.

3.2 External price referencing and cross-country comparisons

External Price Referencing can lead to significant uncertainty and cascade effects on prices of prescription medicines, often due to the unintended consequences of factors such as basket design and exchange rate volatility.

Policy options for the Member States

While pricing is an issue of national competence, Member States may want to consider the EU-wide implications of pricing strategies relying on cross-country comparisons. To that end: (a) the average of all countries in the basket can be used for the determination of the reference price, rather than lowest or average of lowest; (b) adjustments for exchange rate fluctuations or altogether excluding non-Eurozone currencies from the basket could help ensure price stability and exclude factors that are exogenous to pharmaceutical price determination; (c) launch delays, due to strategic considerations arising from the knock-on effect of external price referencing ought to be studied, and their extent identified; policies could then be put in place that discourage such practices, while improving access to medicines.

3.3 Health Technology Assessment (HTA)

HTAs are most often based on the treatment's clinical-cost-effectiveness. Measurement of costs and effects determines the HTA outcome. The impact of a negative HTA recommendation is substantial in terms of pricing, R&D incentives and access to a given treatment. Substantial differences in terms of coverage recommendations and decisions from HTAs have been reported. Minimising such differences in recommendations across Member States requires significant effort.

HTA agencies do not assess all the drugs reimbursed. Since their role is to identify ineffective and cost-ineffective treatments as well as appraise new ones, it is important to understand how many of these "cost-ineffective" treatments are still being reimbursed and to what extent the amount spent on these treatments is used inefficiently.

Policy options for the Member States

It could be useful to assess all drugs that are reimbursed, either periodically or each time a new treatment in the same therapeutic class comes onto the market (although the latter option would be somewhat costly).

Efforts could be made to understand costs from both a health service and a societal perspective, by taking into account the direct and indirect costs from the treatment. When measuring effects, aspects such as effect on the quality of life of the patient or the severity of the disease could be considered in addition to efficiency.

Policy options at EU level

Co-operation at EU level could harmonise the evidence requirements for HTA across Member States. This would help manufacturers to prepare evidence more efficiently. The strengthening of HTA processes and shared learning across borders may be valuable in this respect.

Early communication and collaboration between HTA agencies and manufacturers may help to improve the reimbursement application and result in better HTA outcomes.

In a similar direction, a pan-European observatory to monitor potential launches of new medicines (horizon scanning) could be of value to EU governments as well as institutions by providing knowledge and understanding of the types of treatments that are likely to emerge in the mid- to long-term.

Gauging the long-term clinical impact of new treatments is most important for European society and, probably an issue of supra-national competence. Whereas the evidence on which marketing authorisation and coverage are decided rests on efficacy, it is important to understand how treatments work in the community (i.e. effectiveness). In a number of priority areas, where additional evidence may be required, European institutions could foster EU-wide registries to help inform the process of decision-making in the Member States. For this to take place, initiatives regarding methodologies and priority areas would be beneficial. EUNetHTA, the collaborative agreement among national HTA bodies, could be used as a vehicle for coordinating a number of initiatives in this area.

3.4 Transparency

In some cases, HTA appraisals may raise concerns with regard to the Transparency Directive¹⁵, particularly in terms of the time limits for approval of new medicines and their availability (and whether they are reimbursed by health insurance or not). This is delaying access to new treatments in several Member States. Another concern relates to the submission and assessment processes.

Policy options at EU level

A number of issues can be addressed at EU level and are part of the current debate on the revision of the Transparency Directive. One specific issue identified in this study is the need for clear, common guidelines on HTA procedures, which can improve the quality of the clinical and economic evidence as well as manufacturer compliance, thus reducing information costs. Further, transparency in the appraisals is likely to encourage stakeholder compliance with associated recommendations.

3.5 Access to new medicines in EU Member States

Access to new medicines in EU Member States is often hindered or delayed by slow HTA processes. Processes in some agencies are longer (i.e. 32-56 weeks in the UK) than in others (17-18 weeks in Sweden). Rapid completion of HTAs and speedy implementation of the recommendations will enable faster access to promising treatments. This can also result in potentially large savings, by a faster and more efficient allocation of resources. When price negotiations are included in the HTA processes, this may create further delays. Conversely, HTA recommendations that are issued earlier rely less evidence, which increases uncertainty as to the value of a given treatment. Striking the right balance involves enabling fast access to treatments as well as the production of sufficient evidence for reliable HTA.

Both availability and affordability are influenced by explicit decisions to fund (or not) a particular medicine based on the medicine's cost and willingness-to-pay by competent health authorities in a Member State. Several Member States examining precisely the same clinical and economic evidence may come up with opposite funding/reimbursement decisions. Varying eligibility criteria also seem to be creating a differential rationing situation, which affects patient access on affordability grounds.

Availability and affordability may also depend on decisions made at regional level, following initial guidance or recommendation to fund a particular treatment at national level. Based on this, it is possible for certain regions in one Member State to adopt a new treatment that has received a positive HTA recommendation, while others reject it, thus creating an uneven playing field within a Member State. Differential outcomes of this type may need to be carefully examined.

¹⁵ Directive 89/105/EEC relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems

Policy options at EU level

EU institutions can assist in standardising some of the methods used to arrive at coverage decisions and could therefore contribute to more consistent outcomes across Member States.

Innovative payer schemes also have the potential to improve access to treatments, encourage manufacturers to develop innovative technologies and protect the payer, but more research on the impact of such schemes may be required. Exchange of information on their performance at EU level may prove valuable to that regard.

3.6 Access to generic medicines in EU Member States and the benefits of generic competition

3.6.1. Access and generic use promotion

Access to cheap generic medicines is a function of their availability and affordability. Availability is often problematic in small Member States and this is further exacerbated by the relative size of Member States' budgets and domestic markets.

There seems to be considerable room for increased generic drug availability and penetration, particularly in terms of faster launch and uptake of generic alternatives after patent expiry. If Member States are to fully capitalise on the availability of generic alternatives, it is essential that market entry takes place immediately after patent expiry. Evidence suggests that the optimal window of opportunity to capitalise on generic availability is the period 1-3 years after patent expiry, beyond which alternative therapeutic options may attract the interest of practising physicians.

Policy options for the Member States

Governments and pharmaceutical companies could seek agreements to increase the incentive and decrease costs for manufacturers to launch and market generic medicines in these markets, while setting price and reimbursement levels that match the Member States financial capabilities.

Policy options at EU level

Encouraging generic use is the competence of Member States. Yet, it is important to note that policy options such as mandatory generic prescribing have different uptakes among EU Member States. Member States may draw benefits by learning from each other's experience in this field in order to generate further savings from "genericisation". Critical policies in this respect are (a) mandatory INN prescribing, (b) extensive generic substitution rights, (c) experimentation with differential (or 'tiered') co-payments in circumstances where generics are available; (d) monitoring and audit of prescribing patterns in real time (rather than ex-post) through the use of information technology.

3.6.2. Encouraging generic competition

Generic prices average about 25% of the originator price 12 and 24 months following originator patent expiry. There are, however, considerable differences in generic pricing between Member States, even for the same medicines. This demonstrates the room for further reductions in generic prices and/or optimisation of generic policies, which may be achieved through increased generic competition and greater generic penetration.

Policy options for the Member States

Generic penetration is greater in countries with free pricing systems, yet all Member States could benefit from employing both demand- and supply-side policies to reduce generic prices and decrease the time to generic entry. Relaxing supply-side regulation on generic medicines, particularly in large markets, may also contribute to price reduction.

3.7 Parallel Trade

The differences in pharmaceutical prices across Member States create arbitrage opportunities for stakeholders involved in parallel trade. The market share of parallel-traded pharmaceutical products in the main importing Member States stands between 1.7% in Finland and 16.5% in Denmark (EFPIA, 2010). No formal permission from the products' rights holder is required for parallel trade to take place, apart from a parallel trade licence in the importing Member State.

Despite numerous European Court of Justice rulings, parallel trade remains controversial. Disputes are often associated with re-packaging and relabeling. Concerns surrounding parallel trade have risen due to some cases of counterfeit drugs discovered in the supply chain (Davies and Taylor, 2009 and references therein). Shortages have been reported in a variety of contexts and different countries (Kanavos and Costa-Font 2005; Gainsbury, 2009; Taylor, 2010).

Parallel trade has often been perceived by policy makers as a cost-containment mechanism. Although some country-specific evidence exists in favour of this argument (Ganslandt and Maskus 2004, West and Mahon 2003), empirical evidence suggests that, on the whole, savings for health insurance systems are very low or non-existent, as rents are mainly captured by the supply chain (Kanavos and Costa-Font 2005, Kanavos and Kowal 2008, Kanavos and Vandoros 2010). Previous studies have also shown that parallel trade can lead to significant welfare losses (Danzon 1998, Bordoy and Jelovac 2003, Rey 2003, Ganslandt and Maskus 2004, Szymanski and Valletti 2005).

Several Member States have implemented policies encouraging parallel trade. In particular, in the Netherlands health insurance shares any savings due to parallel trade with pharmacists, while in Germany parallel trade minimum quotas are implemented. Clawbacks (present in the UK and the Netherlands) may also implicitly encourage parallel trade because they create incentives to seek cheaper-sourced drugs.

The effect of these policies is ambiguous as they may offer temporary price concessions to health insurers, but they do not necessarily lead to sustainable price reductions over time. The fact that a continuous supply of parallel imported product from other Member States cannot be guaranteed contributes to this. At the same time, exporting Member States have reported shortages on parallel-exported products from their territory, leading to access problems.

Direct-to-pharmacy supply of drugs on behalf of the pharmaceutical industry can lead to a decrease in the market share of parallel traded products; however, this will be a slow procedure and depends heavily on the industry's willingness to create alternative distribution links on a large part of the market.

Policy options at EU level

In light of this multi-faceted evidence and resulting ambiguity, the subject of parallel trade deserves further EU-level study to properly evaluate its impact on prices, access and availability of medicines in exporting as well as importing Member States.

3.8 The changing nature of the distribution chain

In recent years, a new distribution model seems to be emerging in many Member States, whereby the traditional manufacturer – wholesaler – pharmacist model seems to be supplemented by direct agency and reduced wholesaler arrangements. While national and European regulation and legislation enable these arrangements, they can lead to potential concerns, including shortages of essential medicines in some Member States.

Policy options for Member States

Competent authorities may find it useful to carry out inspections to identify whether manufacturers or wholesalers are in breach of their legal duties to maintain an adequate supply of medicines. Similarly, greater accountability by pharmacists and doctors could be beneficial.

The standards required for wholesaling operators may need to be overhauled. Additional measures such as the establishment and updating of a list of drugs exposed to supply difficulties may need to be considered in that context. Best practice guidance for dispensing doctors, pharmacies, wholesalers and manufacturers would help manage supply problems more efficiently. Finally, options to reinforce the duty of manufacturers and wholesalers to ensure that stocks are sufficient may need to be explored. The same applies to the feasibility of establishing requirements for buffer stocks to be held by wholesalers, to convey greater flexibility to the supply chain.

3.9 The impact of demand-side policies on physician performance

Member States are increasingly using financial and non-financial incentives to encourage physicians to make cost-effective prescriptions.

Policy options for Member States and at EU level

Further research is required: 1) to clarify the goal of each demand-side policy and the desired impact on performance; 2) to allow for more comprehensive follow-up systems to be implemented, so as to accurately track change in prescribing costs and behaviour; and 3) to develop transparent measurement tools to assess physician performance.

3.10 Competitiveness and the future of the sector and of biomedical research

The European pharmaceutical sector is a major contributor to the European economy in terms of manufacturing, employment and R&D, and it is important that it retains its competitive edge.

Policy options for Member States and at EU level

To foster an innovative and competitive industry, policy-makers at both national and EU levels may want to support actions to:

- Incorporate value-based pricing into reimbursement schemes to encourage innovation
- Shorten approval and market access times and simplify procedures; the creation of performance-based agreements can also shorten market approval and access times, hence encouraging innovation.

Other valuable actions go beyond pharmaceutical regulation. These can include:

- Further investments in science education and encourage collaborations with academic and other research institutions.
- Linking research and development to unmet medical needs, through policies to better focus R&D on areas requiring attention.

3.11 Summary of policy options at EU level

In light of the current environment, which is characterised by fragmentation in national pharmaceutical policies and markets, the following policy options at EU level could be considered:

- They could provide a continuous and sustainable forum for Member States to share information and policy experience in a number of areas, for example: (a) The mechanisms Member States use to purchase pharmaceutical products; (b) Their approaches for HTA (with an eye towards greater harmonisation or approximation where this is used); (c) Sharing HTA results and other research among Member States; (d) Collaboration on standardised methods for HTA; (e) Discussion of issues related to parallel trade. Strengthening existing initiatives could contribute to this.

- EU institutions might also encourage better practices in the Member States. For example, EU institutions could support greater transparency in negotiations between health administrations, manufacturers and other stakeholders, including the publication of agreements and their accessibility by all interested parties. Greater use of generic medicines can also be encouraged and solutions still need to be found to the small market issue and the non-availability of products in some Member States. This latter point will probably require joint action by Member States and EU institutions.
- Parallel trade is an important issue to be addressed and probably an area that merits further study given that it raises difficult questions about the interactions between the EU single market and national health policies.
- As decisions are increasingly taken based on clinical cost effectiveness, EU institutions could support coordination for the definition of the value of innovation. Better understanding of different national and stakeholder perspectives would be helpful in this regard.
- Encouraging biomedical innovation further at EU level could have spill-over effects in the European economy. Further coordination may be needed to avoid duplications in the research effort; in addition, continuing to set research priorities based on unmet medical need at EU level would be desirable.

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APPENDICES

Appendix 1 External price referencing in EU Member States, 2010

	AT	BE	BG	HR	CY	CZ	DK	EE	FI	FR	DE	GR	HU	IE	IT	LV	LT	NL	NO	PL	PT	RO	SK	SI	ES	SE	CH	UK
AT		✓			✓	✓		✓	✓			✓	✓	✓		✓			✓			✓	✓	✓			✓	
BE	✓		✓		✓	✓		✓	✓			✓	✓	✓		✓		✓	✓			✓	✓		✓			
BG						✓		✓								✓						✓	✓					
CY	✓					✓		✓				✓				✓							✓					
CZ	✓		✓	✓				✓				✓	✓			✓	✓			✓		✓	✓					
DK	✓	✓			✓	✓		✓	✓			✓		✓		✓			✓			✓	✓				✓	
EE	✓		✓			✓						✓				✓	✓			✓			✓					
FI	✓	✓				✓		✓				✓		✓		✓			✓				✓					
FR	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓	✓		✓			✓		✓	✓	✓		✓	
DE	✓	✓			✓	✓		✓	✓	✓		✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓		✓	
GR	✓	✓	✓		✓	✓		✓	✓				✓			✓				✓	✓		✓		✓			
HU	✓		✓			✓		✓	✓			✓				✓	✓			✓		✓	✓					
IE	✓	✓				✓		✓	✓			✓	✓			✓			✓				✓		✓			
IT	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓			✓					✓	✓	✓		✓		✓	
LV	✓		✓			✓		✓	✓			✓					✓			✓			✓					
LT	✓		✓			✓		✓	✓			✓				✓				✓		✓	✓					
LU	✓					✓		✓				✓				✓							✓					
MT	✓					✓		✓				✓				✓							✓					
NL	✓	✓				✓		✓	✓			✓		✓		✓			✓				✓		✓		✓	
NO								✓	✓							✓												
PL	✓					✓		✓				✓	✓			✓	✓					✓	✓					
PT	✓		✓		✓	✓		✓	✓			✓	✓			✓							✓		✓			
RO			✓			✓		✓								✓							✓					

SK	✓		✓			✓		✓				✓	✓			✓	✓		✓	✓						
SI	✓			✓		✓		✓				✓	✓			✓					✓					
ES	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓				✓	✓		✓				
SE	✓	✓				✓	✓	✓	✓			✓					✓					✓				
CH								✓				✓								✓	✓					
UK	✓	✓				✓		✓	✓	✓		✓		✓		✓	✓			✓	✓		✓		✓	✓
Formula	A	A	L	A	L 4	L		L	M	L		A 3+ 1	L	A	L	L	A - 5 %	A	L3	L	A	L3	L6	L	L	A
Freq (per y)	1*	AL	2	1	0.5	1		1	1	1*	*	1	AL	AL	AL	1	1	2	1	1	1	-	2	2	1	** *

Source: Kanavos and Vadoros 2010.

Notes: A: Average; A3+1: Average of 3 lowest EU-15 and 1 lowest from EU-10; A-5%: average minus 5%; L: Lowest; M: Median; L3: Lowest 3 prices; L6: Lowest 6 prices; AL: At launch.

N.B: *Countries in top row referenced by countries in first column.*

* Most oncology drugs exempted

** Only for the first 5 years, not automatically implemented

*** 2 and 7 years after rmb patent expiry or 15 years after rmb and 2 years later

*** 3 months after each change in ref. min prices

Appendix 2 Generic pharmaceutical policies in selected EU Member States, 2010

	Internal reference pricing	Tendering		Price capping *	Reimbursement linked to originator
		System in place	Types of procured pharmaceuticals		
Austria		✓	Vaccines, pharmaceuticals as defined in pandemic plans; also pharmaceuticals for military and prisoner population	✓	
Belgium	✓			✓	✓
Cyprus		✓		✓	✓
Czech Republic	✓			✓	✓
Denmark	✓	✓	Vaccines, pharmaceuticals against communicable diseases, pandemics		✓
Estonia	✓			✓	✓
Finland	✓	✓	NA	✓	✓
France	✓	✓	NA	✓	✓
Germany	✓	✓	Pharmaceuticals in ambulatory care; mostly generics (also bio-similars), some branded ; AOK tenders for >90 molecules; tenders can be regionalized for AOK		✓
Greece	✓	✓	NA	✓	✓
Hungary	✓			✓	✓
Italy	✓	✓	NA	✓	✓
Latvia	✓			✓	
Lithuania	✓			✓	✓
Malta	✓	✓			
Netherlands	✓	✓	Currently 33 molecules; vary by insurer; possibility to extend to more molecules	✓	✓
Portugal	✓	✓	NA	✓**	✓
Spain	✓	✓	NA	✓	✓
Sweden		✓	NA	✓	
United Kingdom		✓	Vaccines, pharmaceuticals against communicable diseases, pandemics	✓	

Source: Internal reference pricing, price caps and reimbursement: PPRI 2007

Tendering: Kanavos et al. 2009

* Generics are subject to an official maximum price which cannot be more than a certain proportion of the branded price. In the UK, this is applied to only a limited number of generics, as outlined in the Maximum Price Scheme (MPS) of 1999 (Kanavos et al., 2008).

** Portugal: price control for prescription-only medicines, and therefore prescription-only generics.

Appendix 3 Pharmacoeconomic methods

- 1) **Cost-effectiveness analysis (CEA)** compares the relative costs and relative effects of two or more courses of action. Effects can be measured by, for example, years of life gained from the intervention, or number of surgical procedures avoided.
- 2) **Cost-benefit analysis (CBA)** distinguishes itself from cost-effectiveness analysis in that the treatment's effects are expressed in monetary values.
- 3) **Cost-utility analysis (CUA)** is a type of cost-effectiveness analysis, which uses quality-adjusted life years (QALYs) as the measure for the effects of each intervention. QALYs represent the number of years lived in full health added by the intervention, taking into consideration also the patient's quality of life.
- 4) **Cost-minimisation analysis (CMA)** assumes that the effect of two interventions are the same, and compares the cost of each intervention.

Source: The authors.

Appendix 4 Cost-effectiveness and incremental cost-effectiveness ratio

Cost-effectiveness is usually expressed by the *incremental cost-effectiveness ratio (ICER)*, which represent the additional cost for an additional unit of efficacy between two alternatives (Drummond et al. 2005).

$$\text{ICER} = \frac{\text{cost NEW TREATMENT} - \text{cost COMPARATOR}}{\text{effect NEW TREATMENT} - \text{effect COMPARATOR}}$$

A drug is considered cost-effective compared to another drug when 1) it provides the same clinical effect as its comparator but at a lower price, 2) if it provides a better clinical effect as its comparator at the same price, or 3) if it provides the same clinical effect as its comparator for the same price.

Source: The authors.

Appendix 5 Level of improvement of the clinical benefit (ASMR) – France

ASMR I	Major improvement
ASMR II	significant improvement in efficacy and/or reduction in side-effects
ASMR III	modest improvement in efficacy and/or reduction of side-effects
ASMR IV	minor improvement
ASMR V	no improvement

Source: ISPOR, France.

Appendix 6 Policies towards prescribers in selected EU Member States, 2010

	Prescribing and dispensing				Financial incentives	Non-financial incentives		
	INN prescribing*		Generic substitution			Budgets are controlled	Subject to prescription guidelines	Prescription habits monitored
	Allowed	Obliged	Allowed	Obliged				
Austria	✓		X			✓	✓	
Belgium	✓		X			✓	✓	
Cyprus	✓		✓**					
Czech Republic	✓		✓**		✓	✓	✓	
Denmark	✓		✓**	✓			✓	
Estonia	✓	✓	✓**			✓	✓	
Finland	✓		✓**	✓		✓	✓	
France	✓		✓**		✓	✓	✓	
Germany	✓		✓	✓	✓	✓	✓	
Greece							✓	
Hungary	✓		✓**			✓	✓	
Italy	✓		✓**	✓	✓	✓	✓	
Latvia	✓		✓**	✓	✓	✓	✓	
Lithuania	✓	✓	✓**	✓	✓	✓	✓	
Malta	✓		✓**					
Netherlands			✓**		✓	✓	✓	
Portugal	✓	✓	✓**	✓				
Spain	✓		✓		✓	✓	✓	
Sweden	✓		✓	✓	✓	✓	✓	
United Kingdom	✓				✓	✓	✓	

* INN prescribing refers to the use of the International Non-proprietary Name when prescribing a drug.

** Physicians may oppose generic substitution, though the level justification for opposition varies between countries.

X Generic substitution is not allowed in Austria, Belgium.

Source: Based on PPRI 2008, OBIG 2006 and authors' own information.

Appendix 7 Brand prices per unit in EU countries, DDD-adjusted, in €, 2005

INN name	Norway	Belgium	Germany	Sweden	Denmark	UK	Nether Lands	Spain	Portugal	Italy	Greece	France	Ireland	Austria
Atorvastatin	0.78	0.86	1.37	1.04	0.72	1.01	0.95	0.96	0.91	0.63	0.55	0.91	0.89	0.97
Pravastatin	1.25	1.08	1.63	1.00	0.98	1.67	1.04	1.58	1.11	0.91	0.66	1.07	1.55	0.92
Simvastatin	1.43	1.28	1.06	N/a	0.81	1.25	1.12	1.19	0.82	0.74	0.62	0.80	1.13	0.96
Captopril	0.48	0.62	0.28	0.21	0.46	0.58	0.54	0.26	0.56	0.30	0.38	0.61	0.50	0.77
Enalapril	0.25	0.29	0.20	N/a	0.22	0.59	0.30	0.19	0.28	0.28	0.19	0.46	0.41	0.24
Quinapril	N/a	0.76	0.45	0.49	0.37	0.38	0.88	0.19	0.36	0.37	0.27	0.53	0.75	0.43
Ramipril	0.32	0.51	0.48	0.31	0.17	0.60	0.69	0.21	0.28	0.24	0.18	0.40	0.35	0.36
Losartan	0.83	0.93	0.80	0.85	0.63	0.97	0.87	0.63	0.77	0.69	0.58	0.92	0.77	0.47
Valsartan	0.82	0.59	0.80	0.82	0.60	0.88	0.86	0.45	0.72	0.62	0.39	0.87	0.75	0.77
Clozapine	0.20	0.27	0.25	0.18	0.19	0.92	0.28	0.13	0.28	0.29	0.11	0.30	N/a	0.10
Olanzapine	4.80	5.60	5.78	5.37	3.81	5.48	5.19	3.57	3.90	3.60	3.30	4.83	6.07	5.28
Risperidone	3.98	4.23	5.54	4.08	2.68	5.21	5.47	2.87	3.22	2.93	2.25	3.65	5.03	5.23
Lansoprazole	1.37	2.01	1.84	1.15	0.85	1.33	1.93	1.07	0.90	1.53	1.05	1.68	1.66	1.57
Omeprazole	1.89	2.24	1.77	1.83	N/a	1.60	2.09	0.43	1.66	1.50	0.84	1.86	1.77	1.57
Pantoprazole	1.33	2.01	2.32	1.16	0.83	1.33	1.88	1.27	1.34	1.28	1.10	1.65	1.40	1.57
Citalopram	1.02	1.08	1.12	0.66	0.75	0.90	1.18	0.73	N/a	0.75	0.68	0.90	0.97	0.97
Fluoxetine	0.97	1.04	1.16	0.85	0.78	1.51	1.38	0.53	0.69	0.56	0.65	0.93	0.90	0.61
Paroxetine	N/a	1.31	1.16	0.90	0.91	0.93	1.11	0.80	0.86	0.77	0.69	0.90	0.90	0.56
Sertraline	1.08	1.22	1.11	1.12	0.82	0.85	1.31	0.72	0.76	0.87	0.55	0.84	1.36	0.88

Note: ¹DDD is Defined Daily Dose.

Source: Kanavos and Costa-Font 2005.

Appendix 8 Ramipril generic price differences, 2004 - 2009 (average Euro prices (absolute))

	Austria	Denmark	Finland	France	Germany	Greece	Italy	Netherlands	Portugal	Spain	Sweden	UK
Patent expiry (Quarter/Year)	Q1/04	Q1/04	Q1/04	Q1/06	Q1/04	Q1/00	Q4/07	Q1/04	Q1/04	Q2/04	Q4/04	Q1/04
2004	0.000	0.293	0.403	0.000	0.272	0.383	0.382	0.406	0.255	0.000	0.000	0.366
2005	0.192	0.022	0.176	0.000	0.192	0.386	0.345	0.317	0.367	0.249	0.000	0.291
2006	0.152	0.096	0.107	0.317	0.182	0.410	0.372	0.302	0.354	0.255	0.000	0.094
2007	0.151	0.231	0.071	0.288	0.049	0.412	0.327	0.253	0.352	0.230	0.000	0.094
2008	0.149	0.112	0.070	0.290	0.045	0.395	0.204	0.215	0.351	0.228	0.185	0.043
2009	0.149	0.042	0.068	0.237	0.038	0.467	0.150	0.029	0.229	0.212	0.187	0.048

Source: Authors' compilations.

Appendix 9 Aggregate net benefits from pharmaceutical parallel trade on stakeholders (% million), 2002

	Germany	Sweden	Denmark	UK	Netherlands	All 6
Total sales at PPP \$ million	2,208.3	353.7	138.7	1,972.3	524.9	5,394.20
Total PI penetration (%)	13.5	31	28.1	27.4	19	25
Price spread between locally sourced and PI medicines (%)	6.7	2.2	8.4	0	15.8	N/A
Total impact of PT ^a \$ million	115.7	22.2	10.4	524.9	68.8	755.6
Parallel distributor maximum revenues \$ million	98	18.4	7.4	469.0 ^b	43.2 ^b	648.4 ^b
Parallel distributor mark-ups	53	60	44	49 ^b	44 ^b	53
Health Service Savings if elasticity of demand is 0; \$ million	17.7	3.8	3	55.9 ^b	19.1 ^b	100.1 ^b
Savings as % market if elasticity of demand is 0	0.8	1.3	2.2	2.8 ^b	3.6 ^b	1.8 ^b
Health service savings when elasticity of demand is -0.33; in \$ million	23.6	5.01	4	55.9 ^{b,d}	25.4 ^b	113.9 ^b
Savings as % market when elasticity of demand is -0.33	1.1	1.4	2.9	2.8	4.8	2.1
Pharmacy revenue from parallel distribution; in \$ million	0	0	0	Positive	6.4	6.9
Pharmacy revenue as % of market	0	0	0	Na	1.2	0.1
Patients	0	N/A ^c	N/A ^c	0	0	0
Ratio of benefits to parallel distributors/health insurance savings	5.5	4.9	2.5	75.2	4.0	16.0

Source: Kanavos and Costa-Font 2005.

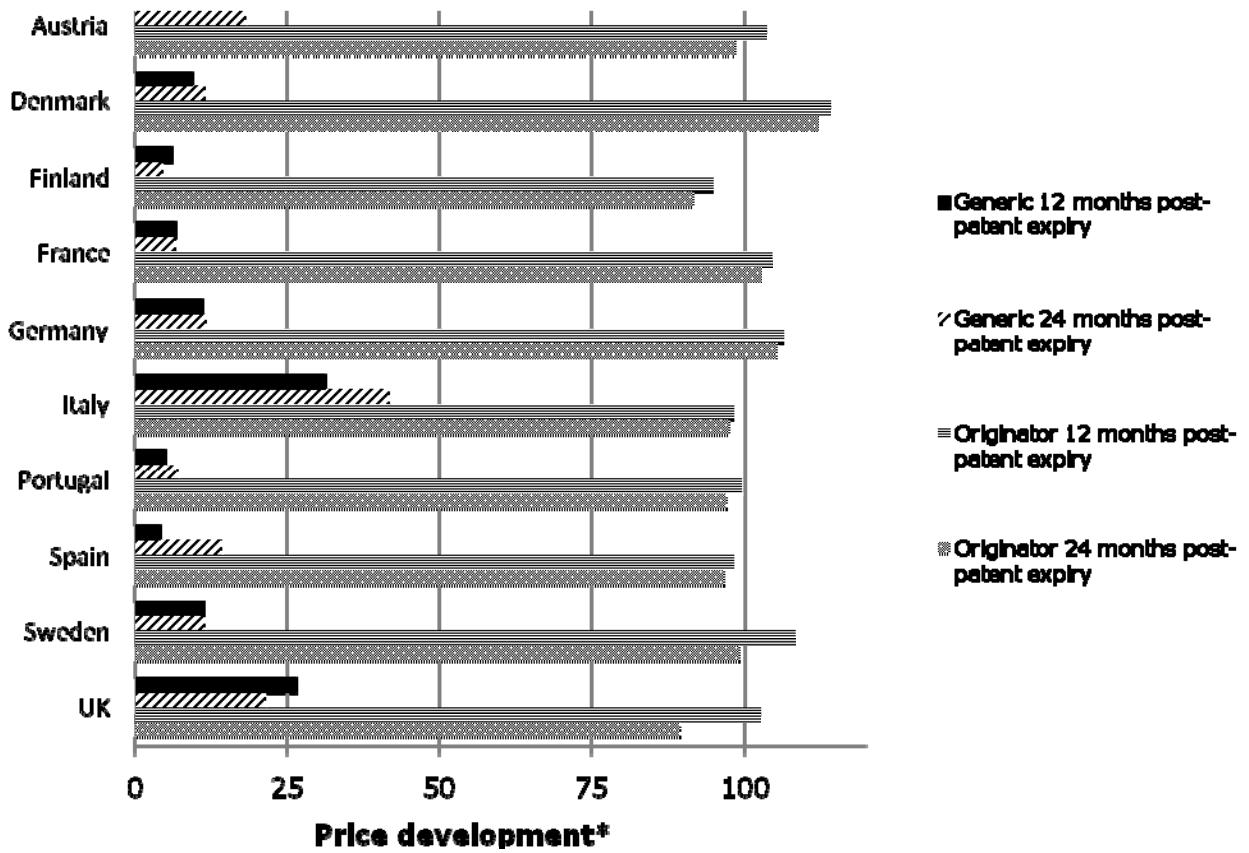
^a Or, equivalently, net loss to pharmaceutical manufacturers (producer loss)

^b Including the effect of the clawback. In the UK these are estimates only.

^c The impact on patients depends on the cost-sharing policy affecting each drug and the type of patient, i.e. whether the latter pays co-payments or is exempt due to age or illness

^d Savings are unaffected by virtue of the zero price difference between locally sourced and PT medicine. The reported corresponds to the clawback.

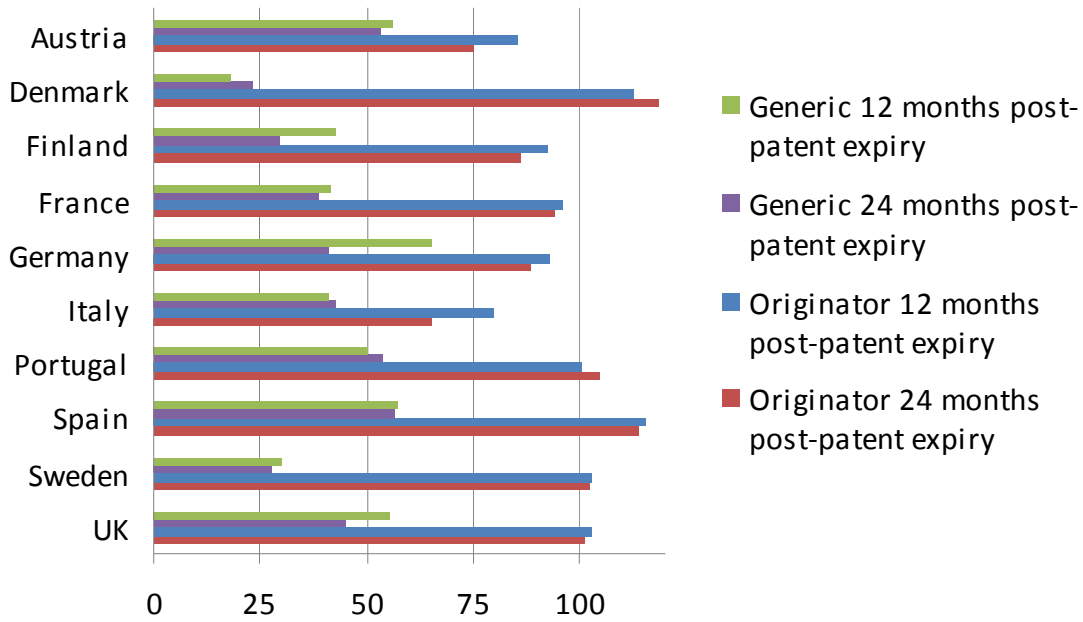
Appendix 10 Price Development (Lowest 10% of Molecules by sales value)



Source: Kanavos and Casson 2011 (forthcoming).

*Price is indexed to the price of the originator product 12 months pre-patent expiry (=100)

Appendix 11 Price Development (top 30 molecules by sales value)

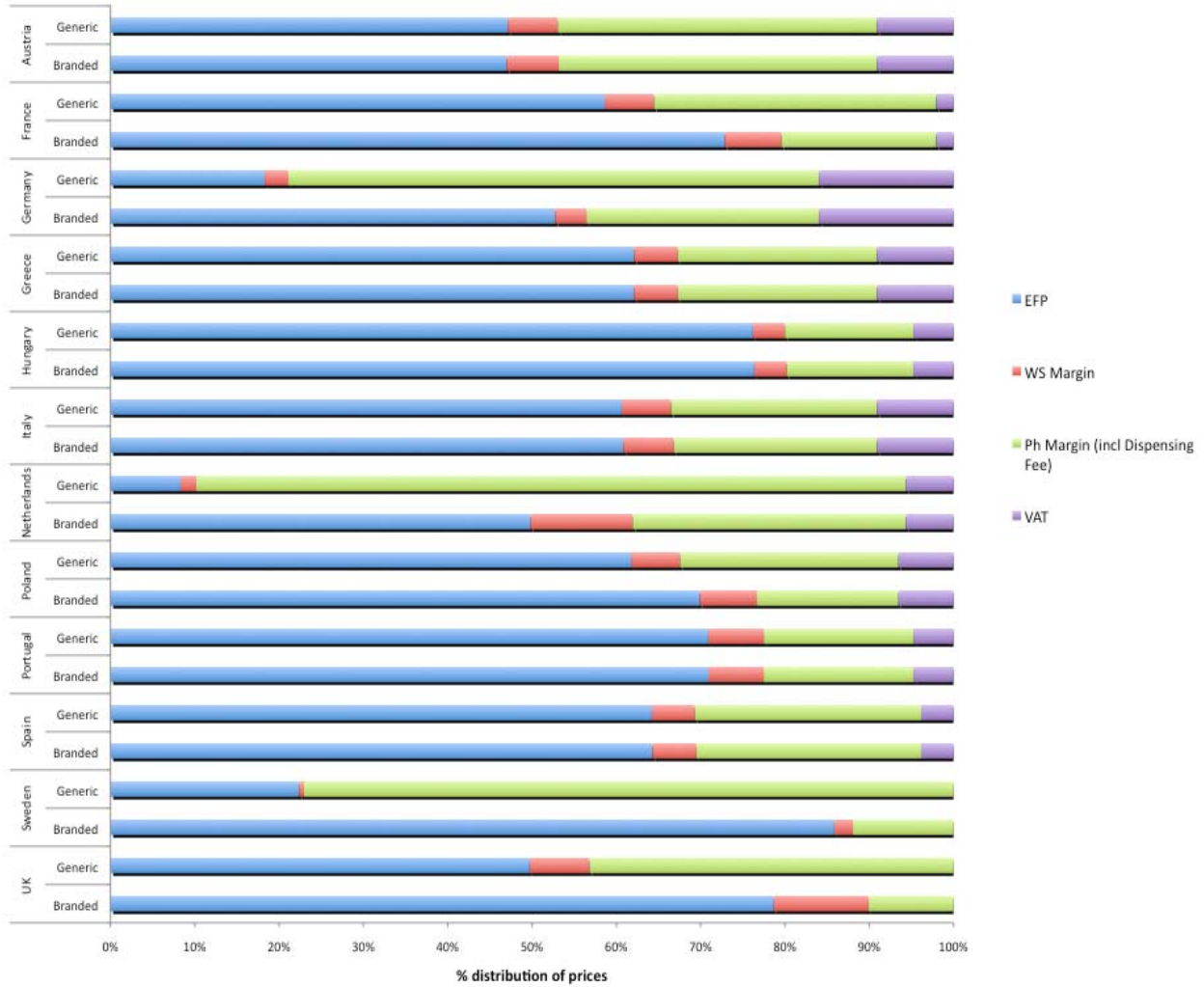


Price development*

Source: Kanavos and Casson, 2011 (forthcoming).

*Price is indexed to the price of the originator product 12 months pre-patent expiry (=100)

Appendix 12 Price build-up for branded and generic omeprazole, from ex-factory to retail price, 2008



Notes: EFP is the ex-factory price; WS margin is the wholesale margin; Ph margin is the retail margin or dispensing fee; VAT is the value added tax.

Source: Kanavos and Vondoros, 2011.

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