

Annexe D

Global overview of the pharmaceutical industry

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EXECUTIVE SUMMARY

This annexe considers the global nature of the pharmaceutical industry and the factors that influence pricing and investment decisions within it. It also identifies some high level conclusions for the principles that the UK should follow in negotiating pharmaceutical prices.

Global pharmaceutical sales totalled US \$602 billion (circa £309 billion) in 2005. This follows a period of rapid growth in the sector. UK sales make up some 3.5 per cent of total global sales, Europe combined some 30 per cent and the US over 45 per cent. The top therapeutic areas of recent world pharmaceutical expenditure have been cholesterol and triglyderide reducers, antiulcerants, cytostatics and antidepressants. In recent years, there have been around 30 annual launches of New Chemical Entities (NCEs) per year, but this represents a significant fall from the 1990s, which saw between 35 and 50 NCE launches per year.

A portion of pharmaceutical company costs are global, in the sense that they can be carried out anywhere in the world. R&D and most manufacturing costs fall into this category, and comprise about 65 to 70 per cent of total costs.

Price-setting within an individual country is the outcome of bargaining between global pharmaceutical companies – which may have market power in particular therapeutic areas – and major health purchasers – which may be able to exercise considerable buyer power in that market.

It is important to understand that much of a drug's production process is international in nature; it can be located anywhere in the world where a suitable environment exists and is not dependent on where the drug is sold. If any one country accounts for a small proportion of global sales, then sales in that country will have little direct effect on the level of global pharmaceutical R&D. It is therefore theoretically possible for some countries to 'free ride' on the R&D investment incentives provided elsewhere in the world.

Despite the fact that UK pharmaceutical sales make up only a small proportion of global sales, UK prices can nevertheless have a significant impact on global R&D investment incentives. This is because UK prices are referenced in the price-setting process of a large number of other countries, including Japan, France, Italy and Canada. In total, countries totalling some 25 per cent of global demand link the prices of some of their pharmaceutical products to those in the UK. In addition, we have heard that UK prices are sometimes used implicitly in price negotiations in other countries, even where they are not used for formal reference purposes.

The UK is therefore constrained in its ability to free-ride on global R&D, and should take into account the effect that the prices it sets have on incentives for R&D globally. In particular, it should look, through its pricing system, to provide incentives to invest in areas of the greatest clinical need.

A further important aspect of global interactions not discussed here concerns the extent to which prices affect the location of R&D investment. This is discussed in detail in Annexe E. The practicalities and mechanics of the price-negotiating process can be found in Annexe L.

1 INTRODUCTION

- 1.1 The UK pharmaceutical sector cannot be considered in isolation; a robust analysis needs to take account of the industry's global nature. This annexe aims therefore to give an overview of the global pharmaceutical industry. It considers the interactions between governments and firms to set drug prices and identifies the impact UK prices have within a global context.
- 1.2 The importance of the international dimension of the pharmaceutical sector is illustrated by the following:
- multinational pharmaceutical companies with turnover of tens of billions operate across national boundaries
 - the costs of research and development (R&D) of new drugs, and of manufacturing drugs, are incurred at a global level. That is, they are not tied to the country of sale
 - furthermore, once a company has undertaken R&D for a drug somewhere in the world, it can launch the drug elsewhere without having to incur the costs again, and
 - drug prices in one country can influence prices in other countries, partly because some governments use international price comparisons in regulating pharmaceutical prices.
- 1.3 Given this backdrop, any analysis of UK pharmaceutical policies needs to consider how global factors may affect and constrain the UK and what can be achieved through price-setting in the UK internally or in a more global context. The remainder of this annexe is structured into four chapters.
- 1.4 Chapter 2 gives a **global overview of the pharmaceutical industry**, covering:
- the global pharmaceutical industry - provides background on global demand and the world's leading pharmaceutical companies
 - the lifecycle of a drug - describes the various stages of a drug's lifecycle 'from patent to patient'
 - R&D costs – covers the level of R&D expenditure per successful drug and trends over time, and
 - Cost structure - focuses in particular on size of cost elements like R&D which are international in their nature.
- 1.5 Chapter 3 assesses the factors that influence pharmaceutical **pricing and investment in a global market**. This section discusses at a theoretical level the way in which pharmaceutical prices are set through the bargaining relationship between multinational pharmaceutical companies and national governments. It discusses in turn:
- objectives of firms and subsequent pricing incentives, and
 - government objectives and subsequent pricing incentives.

- 1.6 Chapter 4 applies this analysis to a consideration of **the importance of UK prices**, in particular their impact on ensuring patients have access to drugs today and that companies have adequate incentives to invest in new drugs for the future.
- 1.7 Chapter 5 draws some conclusions.
- 1.8 A further important aspect of global interactions not discussed here in any detail concerns the extent to which prices affect the location of investment. This is discussed in Annexe E.

2 THE GLOBAL PHARMACEUTICAL INDUSTRY

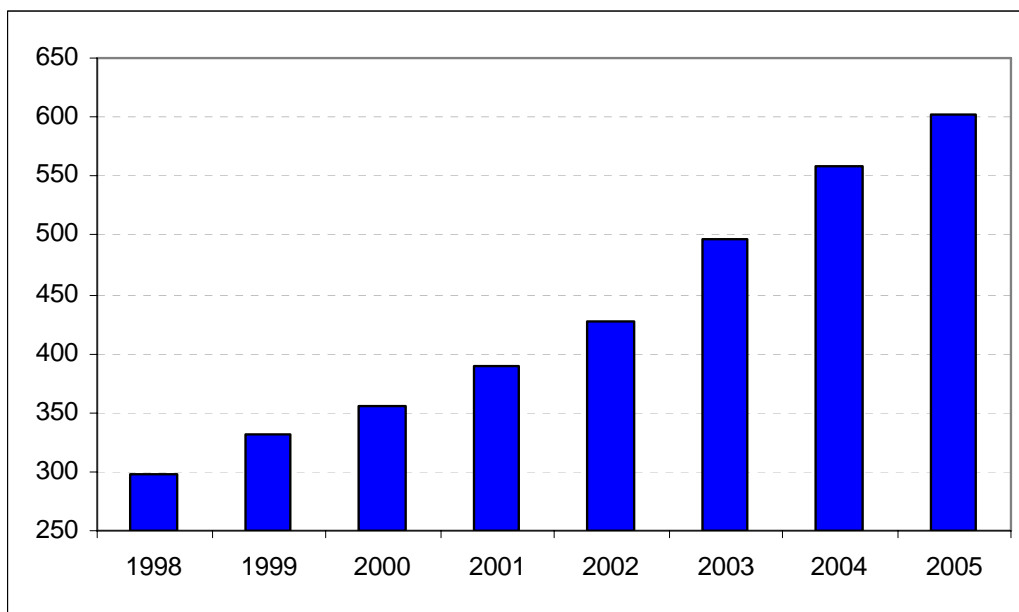
2.1 This chapter provides background information on the global pharmaceutical industry. It has four sections:

- the first section provides background on the world's leading drugs and pharmaceutical companies
- the second section describes the various stages of a drug's lifecycle 'from patent to patient'
- the third section illustrates the level of R&D expenditure per successful drug and trends over time, and
- the fourth section focuses on the cost structure of the pharmaceutical industry, including the significance of cost elements like R&D which are international in their nature.

Background

2.2 IMS estimates suggest that 2005 global pharmaceutical sales totalled US \$602 billion, a growth of seven per cent from the previous year (sales US \$550 billion). As shown in Figure 2.1 below, the market has grown rapidly in recent years, with growth rates varying between seven and 12 per cent per year. Total sales are projected by IMS to continue to grow between five and eight per cent over the next few years. These figures include sales of both branded drugs and generics. Brands continue to account for the bulk of global sales by value. IMS suggest 2005 sales of generics represented about 12 per cent of sales value in the main (audited) markets and expect generics sales to experience double digit growth over the next five years.

Figure 2.1: Global pharmaceutical sales (US \$billion)

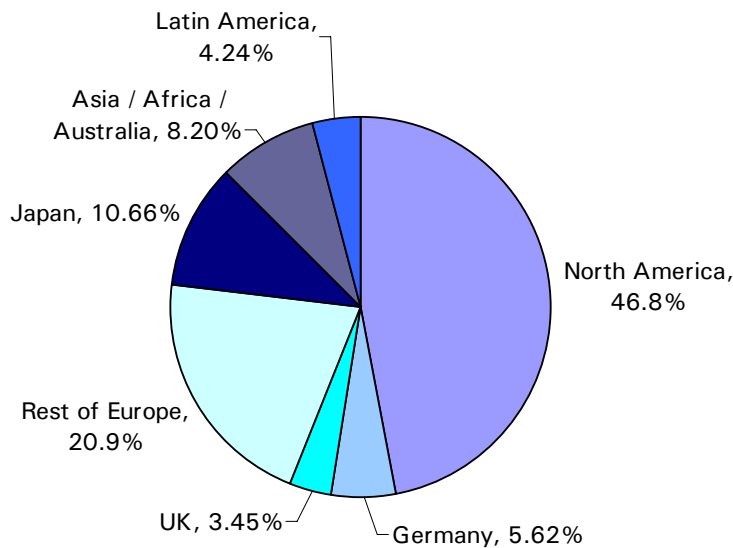


Source: IMS, 'Global Pharmaceutical Perspectives 2005', IMS Health Total Market Estimates and Global Pharma Forecasts (total sales include IMS audited figures and IMS estimates for unaudited markets);

2.3 Growth has been strongest in North America at 12.6 per cent per year compared to 9.3 per cent in Europe and only 2.9 per cent in Japan. Forty per cent of this growth in the top ten markets was attributed to the launch of NCEs; 32 per cent to increases in volumes and 28 per cent to price.

2.4 Figure 2.2 below shows global sales in 2005, broken down by world regions. North America accounts for the largest proportion of the world market (46.8 per cent). The UK on its own accounts for circa 3.45 per cent of world pharmaceutical sales, down from an estimated 3.9 per cent in 2004. Europe as a total (including the UK and Germany) accounts for 30.6 per cent of total sales.

Figure 2.2: Breakdown of pharmaceutical sales by region in 2005¹



Source: IMS, 'Global Pharmaceutical Perspectives 2005' and OFT calculations².

2.5 We can see from this figure that the UK has a relatively small share of the global pharmaceutical industry, accounting for less than four per cent of sales. It might be inferred from this that the UK's regulation and pricing policy can only have very limited effects on the pharmaceutical industry as a whole, but, as discussed in more detail later on, this is not necessarily the case.

2.6 Tables 2.1(a) and 2.1(b) show the top ten brands and the top ten therapeutic classes by global sales in 2005. We observe that the best-selling products are those which treat chronic conditions where the patient takes medicine on an ongoing basis. The best-selling drugs in 2005 were Lipitor and Plavix, the first treating high levels of cholesterol, and the second preventing heart attacks and strokes by targeting blood platelets. The two biggest selling drugs in 2004 were Lipitor and Zocor, both of which are cholesterol-reducing drugs. All of these drugs are widely used by a great number of

¹ These figures are based on the IMS world audited market rather than the total world market.

² Rest of Europe (all other European Countries except the UK and Germany).

patients in every country. The patent of Zocor has expired in most countries over the last three years.

Table 2.1(a): The top 10 brands by global pharmaceutical sales 2005 and 2004

	Leading brands (2005)	Type of drug	Global Sales 2005		Global Sales 2004	
			\$bn	%	\$bn	%
1	Lipitor (atorvastatin)	Cholesterol-regulating drug	12.9	2.3	12.0	2.3
2	Plavix (clopidogrel)	Antiplatelet drug	5.9	1.0	5.0	1.0
3	Nexium (esomeprazole)	Ulcer-healing drug	5.7	1.0	4.8	0.9
4	Seretide/Advair (fluticasone + salmeterol)	Bronchodilator /corticosteroid	5.6	1.0	4.7	0.9
5	Zocor (simvastatin)	Cholesterol-regulating drug	5.3	0.9	5.9	1.1
6	Norvasc (amlodipine)	Calcium-channel blocker	5.0	0.9	4.8	0.9
7	Zyprexa (olanzapine)	Antipsychotic drug	4.7	0.8	4.8	0.9
8	Risperdal (risperidone)	Antipsychotic drug	4.0	0.7	--	--
9	Ogastro/Prevacid (lansoprazole)	Ulcer-healing drug	4.0	0.7	3.8	0.7
10	Effexor (venlafaxine)	Antidepressant drug	3.8	0.7	3.7	0.7
	TOTAL	Leading 10 Brands	\$56.9	10.1	\$53.6	10.3

Source: IMS, 'Global Pharmaceutical Perspectives 2005 and 2004'

Table 2.1(b): The top 10 therapy classes by global pharmaceutical sales in 2004

Ranking	Therapy class	Global sales in 2004	
		US\$bn	% global sales
1	Cholesterol & triglyceride reducers	30.2	5.8
2	Antiulcerants	25.5	4.9
3	Cytostatics	23.8	4.6
4	Antidepressants	20.3	3.9
5	Antipsychotics	14.1	2.7
6	Antirheumatics, nonsteroidal	13.1	2.5
7	Angiotensin-2 inhibitors	12.0	2.3
8	Calcium antagonists, plain	11.6	2.2
9	Erythropoietin products	11.4	2.2
10	Antiepileptics	11.3	2.2

Source: IMS, 'Global Pharmaceutical Perspectives 2004'

2.7 Looking at Table 2.2, however, one can observe that the best selling drugs (in terms of value) are not those that contribute most to growth in the pharmaceutical sector. As mentioned above, new chemical entities have contributed the most to pharmaceutical growth. Oncology drugs (for cancer patients) and Angiotensin-2-Inhibitors (antihypertensive drugs) are thus the two therapeutic classes that contribute the most to growth.

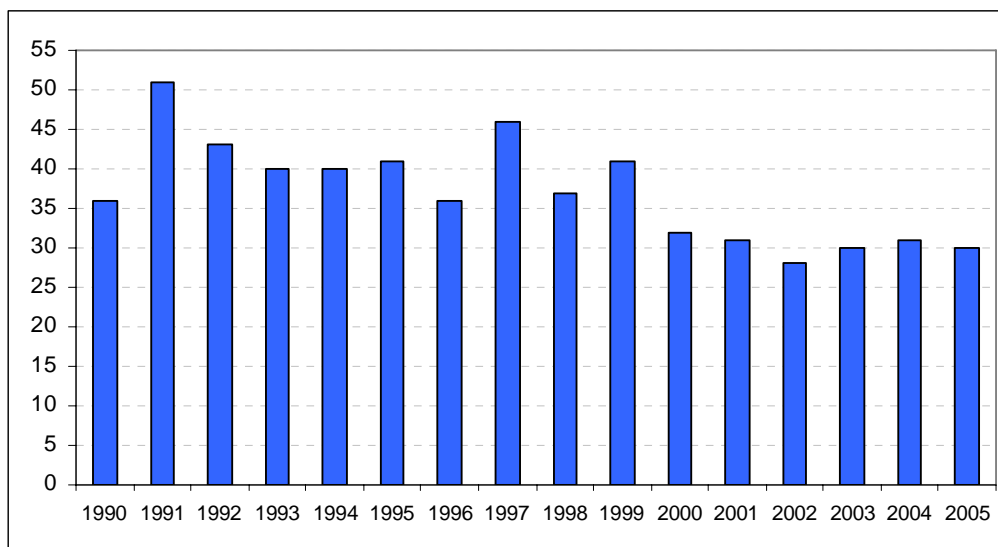
Table 2.2: The top 5 therapy classes by contributions to dollar growth in 2005

Ranking	Therapy class	Global sales US\$bn	Absolute growth const \$bn
1	Oncology Therapies	28.6	4.4
2	Angiotensin-2-Inhibitors	14.2	2.1
3	Atypical Antipsychotics	15.3	1.6
4	Antirheumatic agents, specific	5.7	1.6
5	Statins	28.2	1.3

Source: IMS, 'Global Pharmaceutical Perspectives 2005'.

2.8 In 2005, 30 NCEs³ were launched globally (compared to 30 in 2003 and 31 in 2004). Annual launches have remained around this figure since 2000, but this represents a significant fall from the 1990s, which saw between 35 and 50 NCE launches per year. The trend is shown in the table below.

Figure 2.3: New molecular entities (NMEs) first launched worldwide 1990-2005



Source: EFPIA Annual Report (2005) based on CMR International data, 2003-2005 figures based on IMS 'Global Pharmaceutical Perspectives 2005 and IMS Global Pharmaceutical Perspectives 2004'.

2.9 However, after the initial launch, not every NCE will become available in every national market (reasons for this will be discussed in further detail later). A study by Lanjouw (2005) on patents, price controls and access to new drugs⁴ shows that the number of countries in which NCEs are launched varies considerably. The data analysed covered 300 NCEs which were first launched in the period 1982-1988 and found that 18 per cent of new drugs are marketed in just a single country. The mean number of countries reached by NCEs is 20 and the median number of countries is nine.

³ Figure from IMS 'Global Pharmaceutical Perspectives 2005'

⁴ Lanjouw (2005), 'Patents, price controls and access to new drugs: how policy affects global market entry'.

Leading companies

2.10 The following table shows the size and share of global sales of the ten largest pharmaceutical companies. Pfizer is the largest company in the world and accounts for around ten per cent of global sales. The top ten companies combined account for 48 per cent of global sales.

Table 2.3: The top 10 corporations by global pharmaceutical sales in 2005

Ranking	Company	US \$bn	% Global Sales 2005	% Global Sales 2004
1	Pfizer	47.6	8.4	9.8
2	GlaxoSmithKline	34.7	6.1	6.3
3	Sanofi-Aventis	30.0	5.3	5.2
4	Novartis	28.5	5.0	4.4
5	Johnson & Johnson	25.3	4.5	4.7
6	AstraZeneca	24.0	4.3	4.2
7	Merck & Co	23.5	4.2	4.6
8	Roche	19.8	3.5	3.4
9	Abbott	15.7	2.8	--
10	Bristol-Myers Squibb	14.7	2.6	3.0
Total	Top 10 Corporations	\$ 264.0	46.7	48.4

Source: IMS, 'Global Pharmaceutical Perspectives 2005 and 2004'

2.11 The size of these companies can be put into context by noting that their individual global sales turnover will exceed the size of the entire pharmaceutical market in many individual countries. For example, seven of the firms shown in the table have a global turnover greater than the size of the UK prescription drug market. Later in this chapter we explore this further when we discuss the bargaining relationship between multinational pharmaceutical companies and national governments.

2.12 Apart from the big global players on the pharmaceutical market, there are also a substantial number of smaller biotechnology companies on the market with a number of products in their pipelines. This suggests that the biotechnology sector⁵ is likely to play an increasingly important role in the future⁶.

⁵ Biotechnology can be defined as the application of knowledge about living organisms (and their components) to industrial products and processes; examples of applications of biotechnology include: gene therapy, in which genetic material is introduced into an individual cells, or modifications are made to an individual's genetic material, to achieve a therapeutic or preventative objective; the development of antibody-based drugs (protein-based molecules which play an important role in the immune system); the development of new types of vaccine – for example, using genetic engineering to disable a virus or bacterium; genomics, which involves finding genes which are associated with particular diseases; and bioprocessing, in which living cells are used to manufacture healthcare products.

⁶ The European Commission has stated that whereas around 20 per cent of NMEs (New Medical Entities) launched on the world market are derived from biotechnology, over 50 per cent of those under development are biotech-derived.

The lifecycle of a drug

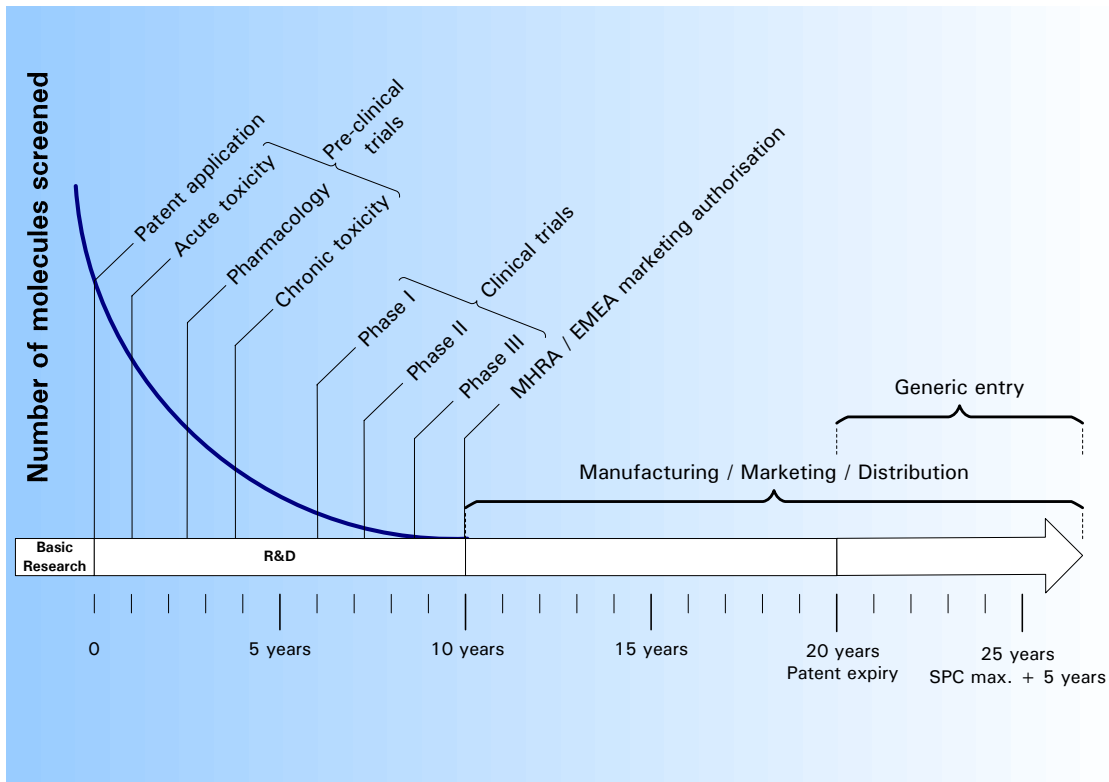
Patent system

- 2.13 The patent system plays a crucial role in the pharmaceutical industry because of the importance of product innovation and the substantial R&D costs involved in developing a new drug. Patents give their owners the legal right to exclude others for a time from making, using or selling a product or process arising from an invention, and are typically granted for a period of 20 years.
- 2.14 In the pharmaceuticals sector, companies can acquire patent protection once basic research has led to the identification of a promising NCE. A patent is then filed and may be granted, but the drug might typically be halfway through its patent period by the time it has progressed through the various stages of research and development and is ready to be launched onto the market.
- 2.15 Patent protection may allow a firm to exercise market power to some degree in pricing a drug. The profits that can potentially be earned during the patent period are crucial in providing incentives for pharmaceutical firms to undertake R&D, given the large amount of expenditure and the long lead times involved in new drug development.
- 2.16 Within the European Union, pharmaceutical companies in some countries may be able to obtain Supplementary Protection Certificates (SPCs) once the original patent has expired. SPCs have a maximum term of five years. They are intended to compensate for the length of time required to obtain regulatory approval for products, by allowing firms up to a maximum of 15 years of marketing exclusivity.
- 2.17 Once a drug's patent and any SPC have expired, other manufacturers are permitted to enter the market and sell copies of the original drug (referred to as 'generics'). Provided the generic market is competitive, this can lead to significant price reductions.

Drug lifecycle

- 2.18 The diagram below shows the typical length of time that it takes for a new drug to go through the various stages of its life cycle.

Figure 2.4: Lifecycle of a drug: from patent to patient



Source: OFT

- 2.19 It is possible in the diagram to distinguish between components of the production process that can be considered 'international' (namely can be located anywhere in the world for supply to any given country) and those that are 'national' (that is need to be located in the country in question). As the diagram moves from left to right and becomes lighter, so the activities become increasingly 'national' in scope.
- 2.20 More formally, the term 'international' is used to denote those stages of a drug's lifecycle for which:
- the activity can be located anywhere in the world where a suitable environment exists
 - once the costs of that activity have been incurred somewhere in the world, they do not have to be incurred again in order to make the product available in other countries.
- 2.21 R&D is an 'international' activity in this sense of the term, as it can be located wherever a suitable research environment exists, and once a drug has been developed the R&D cost does not need to be incurred again to make the drug available in other

countries.⁷ In addition, some of the costs of global manufacturing facilities may also represent an 'international' cost element.

- 2.22 The different stages shown in the chart above normally follow the patent application and are described in the next few paragraphs. Even before patent application a considerable amount of time and money may have been spent on basic research to identify suitable entities for investigation, although much basic research is carried out in universities and publicly-funded institutes.
- 2.23 **Pre-clinical trials** precede any testing on humans, and involve rigorous testing of selected NCEs in laboratories and animals. There are very high attrition rates⁸ at this stage of development: less than one per cent of compounds successfully make the transition from pre-clinical trials to clinical studies in humans.⁹
- 2.24 **Clinical trials** are carried out in humans. Three stages are carried out before drugs receive marketing authorisation, namely:
- Phase I: trials in 20-100 healthy adults to test the drug's safety. 70 per cent of investigational new drugs (INDs) proceed successfully through Phase I
 - Phase II: trials in 100-300 patient volunteers to determine the safety and efficacy of the drug. A third of INDs make it through both Phase I and II, and
 - Phase III: trials on larger groups of patients (typically 1,000–3,000), to gain further data on safety and efficacy. Around 25 per cent of INDs progress through all three phases to a regulatory review.
- 2.25 **Marketing authorisation** must then be obtained before drugs can be launched onto the market. Within the EU, there are two main routes for obtaining marketing approval:
- a centralised procedure run by the European Medicines Agency (EMA): new drugs may be granted a single marketing authorisation valid throughout the EU. (This procedure is compulsory for all new biotechnology products and orphan drugs)
 - a mutual recognition procedure: firms first seek marketing authorisation in one Member State, but can then expect rapid authorisation in other Member States in the absence of any specific objections.
- 2.26 After the drug reaches the market, Phase IV **pharmacovigilance trials** begin. These seek to identify any adverse drug reactions and continue throughout the lifetime of the drug.
- 2.27 As discussed earlier, generic manufacturers are able to enter the market and sell **generic copies** of the drug after a drug's patent (and any supplementary protection certificate) has expired.

⁷ An exception would be where countries stipulate that clinical trials must be carried out within the country concerned.

⁸ The rate at which investigational drugs fail to progress to the next stage of testing.

⁹ ABPI: www.abpi.org.uk/amric/tried_&_tested.pdf

Table 2.4: Success rates at different R&D stages

R&D stage	Phase I	Phase II	Phase III
Probability of success	71%	44%	68%
Example: number of products at end of stage starting with 100 products	71.0	31.4	21.5
Mean length of phase (years)	1.8	2.1	2.5

Source: DiMasi et al (2003).

- 2.28 Even after the preclinical stage, with its high attrition rate, only a small proportion of drugs proceed successfully to marketing approval. Using data on drugs first tested on humans between 1983 and 1994, DiMasi et al (2003)¹⁰ estimate that on average only 21.5 per cent of drugs entering clinical trials reach marketing approval (see Table 2.4).
- 2.29 In general it is clear that only a small fraction of drug entities will on average achieve a stage where commercialisation is valuable. For each new successful drug, there are many which prove unsuccessful.

R&D costs per approved drug

- 2.30 It is often reported that the costs of R&D per approved drug have risen considerably over the past 30 years. This section explores available data relating to this assertion.
- 2.31 R&D is not only a lengthy process but also a costly one. DiMasi et al (2003) calculated R&D costs for a sample of 68 drugs first tested on humans between 1983 and 1994 (taken from a confidential survey of R&D by ten pharmaceutical companies, accounting for 42 per cent of pharmaceutical industry total R&D). The results are shown in Table 2.5 and Figure 2.5 below: total 'out of pocket' expenditure on R&D (including the cost of R&D on drugs that did not successfully make it to marketing approval) averaged \$403 million per approved new drug. Adding in the cost of capital between the time of R&D expenditure and the time of marketing approval increases this substantially—the capitalised value of R&D expenditure averages \$802 million per approved new drug.¹¹

¹⁰ DiMasi et al (2003), *The Price of Innovation: New Estimates of Drug Development Costs*, Journal of Health Economics 22 (2003), 151-185;

¹¹ In calculating capitalised costs, DiMasi et al (2003) used a real cost of capital of 11.0 per cent, based on their estimates of companies' actual costs of capital during the 1980s and 1990s, when the R&D was being carried out.

Table 2.5: R&D spend at different stages (constant 2000 dollars)

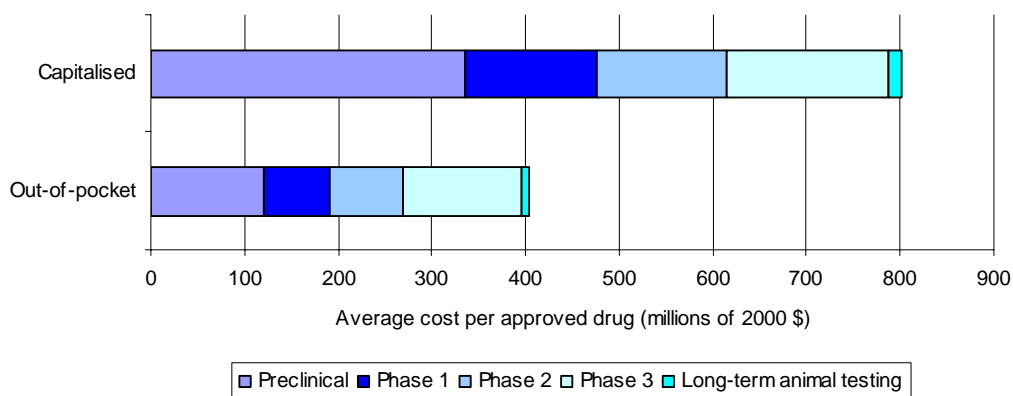
R&D stage	Preclinical	Phase I	Phase II	Phase III	Total*
'Out of pocket' R&D spend (\$m)	121	71	78	126	403
'Out of pocket' R&D spend (% of total)	30%	18%	19%	31%	100%
Capitalised R&D spend† (\$m)	335	142	137	174	802
Capitalised R&D spend† (% of total)	42%	18%	17%	22%	100%

* Total exceeds sum of preclinical and phases I to III because it includes spend of \$8 million (capitalised spend of \$14 million) for long term animal testing.

† Capitalised cost includes cost of capital between the time of R&D expenditure and the time of marketing approval.

Source: DiMasi et al (2003).

Figure 2.5: Breakdown of R&D spend



Source: calculated from DiMasi et al (2003)

2.32 DiMasi et al (2003)'s estimates suggest about 42 per cent of total capitalised expenditure on R&D is incurred in the preclinical phase (see Table 2.5 and Figure 2.5) but only about 21.5 per cent of drugs making it through the preclinical phase are successfully marketed (see Table 2.4). This illustrates the importance of unsuccessful R&D expenditure.

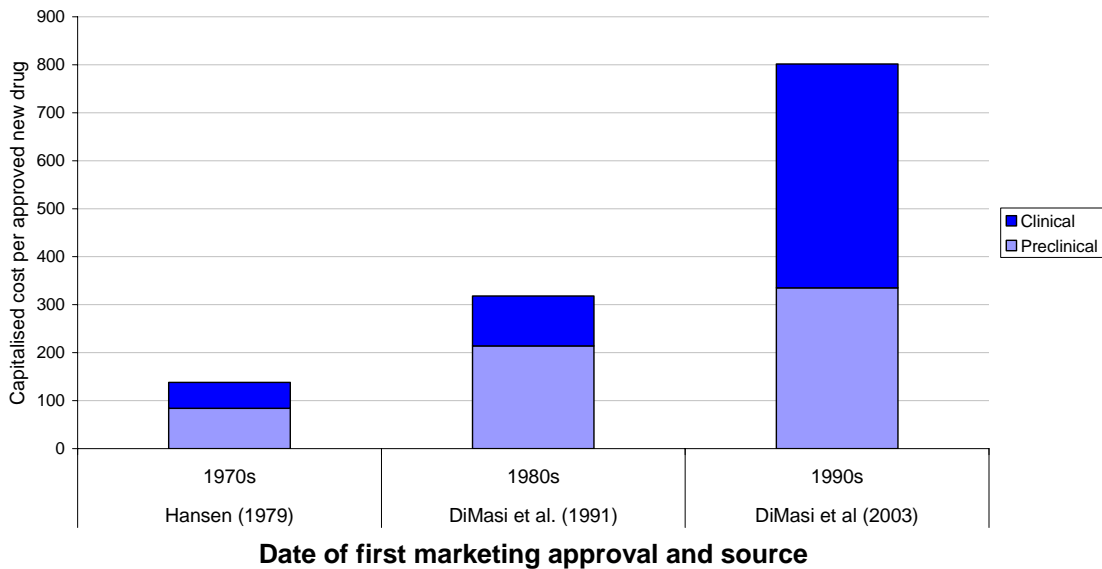
2.33 The cost estimates of DiMasi et al have been criticised because they are derived from confidential proprietary data. Light and Warburton (2005) suggest 'readers cannot know how each company collected its data, or what was counted as research costs, and no independent verification of the accuracy of the information is possible', implying the estimates overstate R&D costs. However, DiMasi et al (2005) respond that their data was cross-checked against other sources and point out that similar estimates from their earlier study (Di Masi et al, 1991) were accepted in a major analysis by the US Office of Technology Assessment (OTA, 1993). Adams and Brantner (2006) carry out an analysis using publicly available data which suggests the cost of R&D per each additional drug is at least as high as the average cost estimated by DiMasi et al (2003).

2.34 Not only is a high proportion of R&D unsuccessful (in the sense that it is spent on drugs that are not ultimately approved for marketing) but, even for those drugs successfully marketed, a high proportion of revenue and cash flow is accounted for by a small number of 'blockbuster' drugs. Grabowski et al (2002) analysed global cash flows (sales value less production, distribution and marketing costs) through the life

cycle for 118 new drugs entering the market between 1990 and 1994. They found that the single best selling drug (Zocor, the originator brand of simvastatin) accounted for nine per cent of the present value of cash flows and the top ten per cent of drugs accounted for 52 per cent of present value of cash flows.

2.35 Comparison with earlier similar work suggests that R&D costs per approved drug are increasing rapidly (see Figure 2.6). On the basis set out above (capitalised R&D costs per successful drug including unsuccessful R&D and the cost of capital), DiMasi et al (2003) estimate a compound annual growth rate of about 9.4 per cent between the 1970s and the 1980s, and about 7.4 per cent between the 1980s and the 1990s.

Figure 2.6: Trends in capitalised spend¹² per approved new drug



Source: Di Masi et al (2003);

2.36 The rapid increase in R&D spend per successful new drug shows that the productivity of expenditure has been falling. This reflects two trends. First, the absolute amount of R&D expenditure by the pharmaceutical industry has been rising rapidly over time. Second, the number of NCEs receiving approval has not been increasing and indeed has shown a steady decrease in recent years. The annual growth rate of R&D carried out by member companies of PhRMA¹³ has averaged about ten per cent in the last ten years.

¹² Notes: These estimates include the cost of unsuccessful R&D. Preclinical costs include discovery research as well as preclinical development.

¹³ PhRMA: Pharmaceutical Research and Manufacturers of America. PhRMA data quoted here reflects global R&D and sales of US-owned members of PhRMA plus R&D and sales of US subsidiaries of foreign-owned members of PhRMA. Consequently, it does not include R&D and sales of non-US companies unless attributable to their US subsidiaries.

Industry cost structure

2.37 This section summarises available data on the overall cost structure of branded pharmaceutical companies.¹⁴ First, however, we consider the nature of costs incurred by pharmaceutical companies, as this is important for the analysis in the following chapters of this report.

Types of costs

2.38 The costs involved in developing, producing and marketing a drug can be assessed according to where they are incurred and whether they vary with the volume of sales and/or the countries in which the drugs are sold:

- R&D is an international activity in the sense that it can be located wherever a suitable research environment exists. Moreover, once a drug has been developed, the R&D cost does not need to be incurred again to make the drug available in other countries (R&D is a globally common activity). The amount spent on R&D does not depend on the number of countries in which the drugs developed are ultimately sold.¹⁵ The costs associated with R&D include current R&D spending, the capital expenditure required (for example on laboratories) and any associated overheads
- manufacturing also can be located anywhere in the world (although some transport costs are involved in getting products to different markets around the world), and economies of scale usually mean that manufacturing of each drug is in fact concentrated in a small number of locations. Selling a drug in an additional market causes some additional manufacturing costs to be incurred – for example the variable costs of materials and labour. The relevant costs here include manufacturing costs, capital expenditure required and the associated overheads
- the remaining costs are mostly incurred in the country of sale and are specific to the country in which they are carried out. These include some distribution costs and the costs associated with marketing, provision of information and similar activities (including interactions with government pricing and reimbursement agencies) as well as the working capital associated with making sales in the country concerned and the overheads necessary to operate there.

Evidence on cost structure

2.39 Since R&D is an international cost, it is only meaningful to consider it on a global basis.

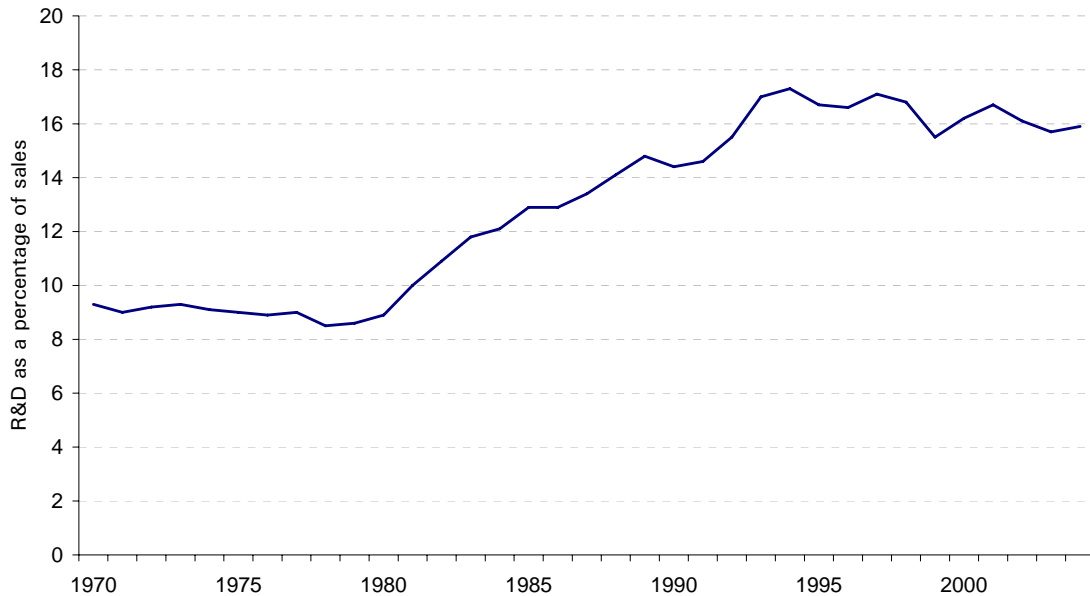
2.40 Figure 2.7 below shows trends through time in R&D as a percentage of sales – or 'R&D intensity' – for pharmaceutical companies belonging to PhRMA. This ratio was relatively stable in the 1970s, at around nine per cent, but grew steadily throughout

¹⁴ We are concerned with branded pharmaceutical companies since these companies carry out R&D and finance it from sales of branded drugs.

¹⁵ An exception would be where countries stipulate that clinical trials must be carried out within the country concerned. Japan had been mentioned to us as such a country but no further information on this has been gathered.

the 1980s and early 1990s to reach a level of 17.3 per cent in 1994. Since then the ratio has declined very gradually and currently stands at around 16 per cent. This implies that in recent years the rapid growth in R&D expenditure has been matched by a broadly equivalent rate of growth in sales revenue.

Figure 2.7: Trends in R&D to sales ratio



Note: The data is based on PhRMA member companies.
Source: PhRMA, 'Pharmaceutical industry profile 2005'

2.41 Data in the DTI's R&D scoreboard suggest an average R&D intensity of about 15 per cent for pharmaceutical and biotech companies in the top 1,000 global companies for R&D¹⁶. It is possible that both estimates slightly understate global R&D intensity, albeit for different reasons (PhRMA estimates because they include the sales of US subsidiaries of non-US companies but may exclude most of the underlying R&D of such companies if done outside the US¹⁷, DTI scoreboard figures because they represent group totals which may include activities with lower R&D intensity than pharmaceuticals). Moreover, it is important to be aware that R&D intensity can be much higher for small research-based pharmaceutical or biotech companies¹⁸.

2.42 The simple R&D intensity of 16 per cent, or slightly more, reflects current R&D spending as a percentage of current sales. However, it does not necessarily reflect the economic cost of R&D contributing to current sales since current sales result from past

¹⁶ DTI 2005 R&D scoreboard data.

¹⁷ PhRMA figure also show the US R&D of PhRMA members was 18 to 19 per cent of US sales. However, this is likely to overstate global R&D intensity of US-owned companies if they do most of their R&D in the US, and there is no obvious reason why this precisely offsets any understatement of R&D intensity of non US-owned PhRMA members.

¹⁸ In particular, some companies in this category may have low sales revenue because they currently have few products on the market, which in some cases may mean that R&D is actually higher than sales. The 2005 R&D scoreboard published by the DTI includes 26 pharmaceutical and biotech companies in the top 1,000 global companies for R&D which report higher R&D than sales. These companies all have sales in the range £0 to 60 million.

R&D. By investing in R&D years before revenues are likely to accrue, investors forego other opportunities of earning returns on their capital during this period. Hence, the simple R&D intensity does not reflect the cost of capital foregone.¹⁹ Nor does it reflect the fact that R&D costs per drug have increased over time, with the result that current R&D exceeds the R&D which contributed to current sales. Although these factors go in opposite directions the cost of capital exceeds the rate of growth in R&D costs, and hence the net effect is that the economic cost of R&D as a percentage of sales exceeds current R&D intensity.

- 2.43 Grabowski et al (2002) combine their estimates of cash flows with DiMasi et al (2003) figures on R&D costs to estimate the economic profitability of drugs entering the market between 1990 and 1994. Based on a 'contribution margin' of 45 per cent²⁰, they estimate a life cycle IRR for these drugs of 11.5 per cent. At their estimated cost of capital, this implies the economic cost of R&D represents around 36 per cent of sales value).²¹ The economic cost of R&D as a percentage of sales value is however highly sensitive to the contribution margin and the cost of capital. Reducing the cost of capital to ten per cent (in line with our estimate for the UK, see Annexe H), with the same contribution margin of 45 per cent, would reduce the economic cost to around 32 per cent.
- 2.44 Grabowski et al (2002) do not disaggregate non-R&D costs between production, distribution, marketing and other areas, although they do quote an estimate of 14 per cent for marketing expenditure as a percentage of sales during the 1996 to 2000 period. Evidence from analysts' reports quoted by Reinhardt (2001) suggest manufacturing costs represent about 27 per cent of sales value with sales, general and administrative costs accounting for 35 per cent. This gives total non-R&D costs of 62 per cent, rather more than Grabowski et al (2002)'s estimate of 55 per cent, although closer to the earlier estimate of Grabowski and Vernon (1994) which was 60 per cent.
- 2.45 A further relevant estimate is that of Danzon (1997)²², who estimated the breakdown of economic costs across the lifetime of a typical drug, taking into account the cost of capital. Danzon's figures show each cost category as a percentage of total economic costs, rather than of sales, but this would not make a big difference unless economic profits or losses are a large percentage of sales (which Grabowski et al (2002) and Grabowski and Vernon (1994) suggest is not the case). Danzon's figures suggest that R&D accounts for roughly 30 per cent of total lifetime cost of a drug, manufacturing (including capital expenditure) around 29 per cent, marketing 24 per cent, general and

¹⁹ DiMasi et al (2003) estimates in Table 2.5 suggest capitalised costs at the time of marketing approval are double 'out of pocket' costs but there is an additional cost of capital foregone between the time of marketing approval and the average time at which sales are made.

²⁰ The 'contribution margin' represents sales value less production, distribution and marketing costs (including depreciation) as a percentage of sales value.

²¹ These figures were interpolated from Table III of Grabowski et al (2002) and assume cost of capital on non-R&D plant and equipment and working capital (including inventory) represent five per cent of sales value, which appear broadly consistent with the assumptions in Grabowski et al.

²² Danzon, P. (1997), *Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU*, International Journal of the Economics of Business, Vol. 4, No. 3, 1997;

administration 12 per cent and working capital (including inventory) six per cent.²³ Danzon's estimate of the R&D share is somewhat below suggested by Grabowski et al (2002) — possibly because Danzon's analysis derives from the earlier 1991 work of DiMasi et al (2003), which shows a lower level of R&D cost (see Figure 2.5).

- 2.46 Data on costs incurred in the UK can be obtained from companies' annual financial returns to DH under the PPRS. These suggest total sales promotion and information costs average about 18 per cent of sales value (see Annexe H).²⁴ These returns also show that distribution costs average about three per cent and general and administrative costs about 12 per cent of sales value—but information on these categories is more difficult to interpret since the costs relevant to UK sales may in part be incurred in other countries.²⁵

Conclusion

- 2.47 Summing up this section, the costs of supplying branded pharmaceuticals can be divided into three main categories:
- R&D, which can be carried out anywhere in the world and, once incurred, does not need to be incurred again to make the drug available in other countries (representing perhaps around 35 per cent of global total costs)
 - manufacturing can also be carried out anywhere in the world (given transport costs are low) but manufacturing costs do vary, at least to some extent, with the volume of sales and hence do increase when sales are extended to an additional country (manufacturing and associated costs perhaps represent around 30 to 35 per cent of global total costs)
 - other costs (including marketing and information costs)—these mostly are incurred in the country of sale and may or may not vary with the volume of sales (these other costs perhaps represent around 30 to 35 per cent of total global costs).
- 2.48 An understanding of the cost structure of pharmaceutical companies is crucial to understanding the interaction between companies and major public health purchasers in setting drug prices and in assessing the potential importance of UK pharmaceutical prices on global investment decisions. We assess both of these issues in the following two chapters.

²³ Percentages of discounted present value at launch (after 46 per cent corporate tax plus R&D and possessions tax credits) based on ten per cent cost of capital.

²⁴ Maximum allowable sales promotion costs under the PPRS profit control are substantially less than companies' actual sales promotion costs but, as discussed in Annexe H, this is of limited significance since the PPRS profit control is not binding on most companies.

²⁵ As discussed in Annexe H, data from companies' returns does not provide useful information on R&D and manufacturing costs.

3 PRICING AND INVESTMENT IN A GLOBAL MARKET

- 3.1 The previous chapter presented an overview of the global market and examined the life cycle and cost structure of drugs. We have discussed how large multinational pharmaceutical companies operate across national boundaries, in some cases having a global sales turnover which exceeds the size of the pharmaceutical market in many individual countries. We also found that a substantial proportion of the lifetime cost of a drug typically is accounted for by R&D, which cannot be directly attributed to drug sales in any individual country.
- 3.2 In this section, we consider price-setting within an individual country as the outcome of bargaining between:
- global pharmaceuticals companies (which may have market power in particular therapeutic areas), and
 - major health purchasers – typically national governments (which may be able to exercise buyer power when purchasing pharmaceuticals, for example through the PPRS in the case of the UK).
- 3.3 This chapter has two sections:
- in the first section, we consider bargaining from a firm's perspective
 - in the second section, we consider bargaining from a government's perspective.
- 3.4 The discussion first examines the likely objectives of firms and governments engaged in this bargaining process. Secondly, it analyses the resulting pricing incentives for firms and governments in a static and dynamic context. Finally, the analysis is extended to incorporate the price linkages that exist between countries due to parallel trade and international reference pricing.

Firm's objectives

- 3.5 A reasonable assumption is that pharmaceutical firms will seek to set prices in order to maximise profits. We take this as our starting point in this analysis.
- 3.6 For newly launched drugs, pharmaceutical companies are typically able to acquire a patent, granting them temporary rights to be the sole producer of that drug. In this case they will wish to maximise revenues, subject to a two types of constraints:
- the range of demand side measures in place within the country concerned, including pricing and reimbursement policies adopted by the public buyer (which are likely to bite to a greater extent if therapeutic substitutes are available
 - international linkages, in particular the extent to which parallel trading and international reference pricing constrains the discretion the company has in setting prices in any individual country.
- 3.7 For drugs whose patents have expired, pricing is constrained further through competition from generic manufacturers. In the absence of other structural or regulatory distortions, free competition between off-patent drugs should lead to

significant drops in price. In the following analysis, we focus on patented drugs for which pharmaceutical firms may have market power.²⁶

Pricing incentives

- 3.8 Given that they have market power, it will be useful to identify pricing strategies that pharmaceutical companies are likely to adopt in different national markets so as to maximise profits.
- 3.9 Typically, firms with market power will engage in price discrimination if they can segment their market into buyers with different degrees of price sensitivity, that is, by charging mark-ups above marginal cost in inverse proportion to the price-sensitivity of buyers. In this way, companies can extract as much rent as possible from buyers who are willing to pay higher prices, whilst not losing sales from buyers with a lower willingness to pay.²⁷
- 3.10 In the context of the pharmaceutical sector, this could mean charging different prices in different countries, depending on the price sensitivity of the national buyer or buyers. Generally, we might expect that countries with a lower national income per capita might be more price sensitive. In this instance, we would expect pharmaceutical companies to vary prices in relation to income per capita in each country.
- 3.11 It is worth noting at this point that such pricing behaviour may be beneficial for society overall (considered from a global rather than a national perspective), as well as being in the commercial interest of firms.
- 3.12 In order to understand why this might be the case, the starting point is to remember that R&D is a globally common cost and forms a substantial proportion of the lifetime cost of a drug. In order for firms to have an incentive to engage in R&D, they must have an expectation that they will be able to recover the cost of R&D, at least on average across all drugs. This means that they have to be able to charge prices (somewhere in the world) which are above the marginal cost of manufacturing and marketing drugs. The relevant question is, therefore, what pattern of mark-ups across countries represents the fairest and most efficient way of allowing firms to recover R&D costs.
- 3.13 Some have argued that this form of price discrimination may represent the best solution:
- on efficiency grounds, setting differential prices based on the price sensitivity of national buyers allows firms to recover R&D costs in a way which minimises any effect on the take-up of drugs, and

²⁶ The ability to profitably raise prices above marginal costs of production.

²⁷ This is often described as 'Ramsey pricing', which is applicable where there are common fixed costs associated with sales to different segments of a market. In such circumstances, an efficient way to recover these fixed costs is to set prices for each customer group such that the mark-up above marginal cost varies inversely with the elasticity of demand.

- on equity grounds, if income per capita is the key driver of differences in price sensitivity between buyers in different countries, then price discrimination by firms will tend to have the effect that rich countries contribute more to the cost of R&D than poor ones.
- 3.14 For this outcome to be efficient, however, mark-ups over marginal cost must be limited on average across all drugs to what is necessary to recover R&D costs.²⁸ More importantly, the prices of drugs must reflect the value they bring to patients.²⁹ The pricing and reimbursement systems employed by major purchasers are a key tool in sending these signals.

Parallel trade

- 3.15 Pharmaceutical companies may be constrained from price discriminating effectively by parallel trading. Where significant price differentials exist between countries, there is an incentive for parallel trade (that is for third parties to engage in arbitrage by buying drugs in low-price countries and reselling them in high-price countries, after suitable repackaging or re-labelling).
- 3.16 Parallel trade is permitted within the single market of the European Economic Area (the EU plus Norway, Iceland and Liechtenstein). Kanavos and Costa-Font (2005) show 2002 wholesale prices of 19 branded products in 11 members of the EEA. The differences between countries with the highest and lowest price varied between 67 per cent and 736 per cent. The simple average between highest and lowest wholesale price for the 19 products was 199 per cent.³⁰ Thus there are substantial differences between prices in EEA countries, creating incentives for parallel trade.
- 3.17 Figure 3.1 below shows estimates for 2002 of the level of parallel imports/exports for some selected EU Member States. The UK is a significant parallel import country³¹ whereas drugs are generally exported from low price European countries such as Greece or Spain (not shown in graph).

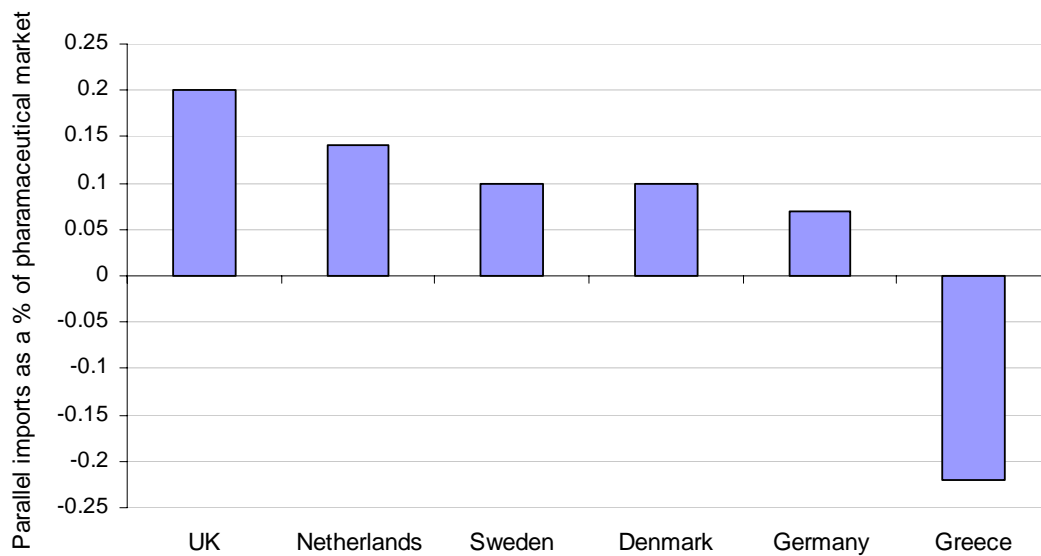
²⁸ R&D costs might still be over- or under- recovered on individual drugs, because some drugs will be commercial successes and others will be failures.

²⁹ In formal terms, dynamic efficiency requires that investment, including R&D, is made up to the point where the present value of the total benefits to all patients (for whom the benefit exceeds the marginal cost) is greater than the present value of total costs.

³⁰ Within this sample, the highest priced countries were Netherlands and UK (6 products each), Germany (5 products), France and Norway (1 product each). The lowest priced countries were Greece (12 products), Spain (5 products), Denmark and Sweden (1 product each).

³¹ More recent data suggest the UK's parallel import penetration was about 18 per cent in 2005 (see Annexe J).

Figure 3.1: Estimates of parallel imports/exports in selected EU countries, 2002



Source: Kanavos, P., Gross, D. and Taylor, D. (2005), *'Parallel Trading in Medicines: Europe's Experience and Its Implications for Commercial Drug Importation in the United States'*.

- 3.18 The existence of parallel trade will tend to weaken the ability of pharmaceutical companies to charge different prices across different Member States of the EU, because if they seek to do so they risk losing revenue from sales in high price countries to parallel imports.
- 3.19 In response to this, pharmaceutical firms may have an incentive to delay launch or avoid launching altogether in low price countries, so as to prevent them becoming a source country for parallel trade. Moreover, since average prices may be lower and parallel traders incur costs and earn profits from their activities, parallel trade may reduce returns to the innovating companies, undermining incentives to invest. This point is made for example in Danzon (1997) and Danzon and Towse (2003).
- 3.20 Parallel trading thus imposes a constraint on pharmaceutical companies' ability to price discriminate, with potential implications for their willingness to market drugs in low price countries and their incentive to innovate.

Government's objectives

- 3.21 In their role as healthcare providers, we would expect national governments to be interested in maximising health outcomes for their citizens within the constraints of their health budget.³²
- 3.22 There are three principal objectives that governments might have in bargaining on pharmaceutical prices:
- *achieving reasonable pharmaceutical prices.* If governments can purchase existing volumes of drugs at lower prices, this will release some of the healthcare budget for spending on higher drug volumes or on other healthcare treatments
 - *ensuring that drugs are made available in their country.* Clearly, there is a constraint on price-minimising. Governments have to offer pharmaceutical companies a price which is sufficiently high that they are willing to continue to supply the drug in that country. At a minimum, the price would need to cover the 'national' element of drug costs, and
 - *ensuring that there are adequate incentives for R&D on valuable new drugs.* In a longer-term context, governments' overall objective could be restated as maximising health outcomes for their citizens, both now and in the future, within the constraints of current and future health budgets. Within this longer-term framework, governments will wish to see new drugs being developed which will be of benefit to their citizens in the future. In negotiating drug prices, there should therefore be consideration of the implications for the incentives for pharmaceutical companies to invest in R&D.
- 3.23 In practice, any pricing approach will involve a trade off between these objectives.
- 3.24 In addition, there may be other non-healthcare objectives of importance to some governments in negotiating pharmaceutical prices, such as industrial policy objectives. In particular, they may wish to use high drug prices to attract footloose pharmaceuticals' R&D and production to locate in their country. However, given the international nature of R&D costs, such a policy is unlikely to provide incentives for firms to locate R&D in a specific country. A more detailed discussion about governments' industrial policy objectives and the role of price can be found in Annex E.
- 3.25 Since national governments are the principal purchasers of pharmaceuticals in most countries, they are almost certain to have buyer power in the market for pharmaceuticals—that is, they will be able to influence the prices at which they buy drugs. We now consider how a government could use its buyer power to achieve the policy objectives outlined above.

³² This assumes that the healthcare budget is fixed. An alternative would be to view national governments as wishing to minimise healthcare expenditure for a given level of health outcomes. In practice, of course, it would be possible for the government to steer a middle course between these two approaches. For example, a saving in pharmaceutical expenditure could be used partly to increase other health spending and partly to reduce the overall health budget.

Reasonable prices

- 3.26 Typically, if a firm has buyer power, it is able to take into account the effect that the quantity it buys has on the price of the product it is buying. The buyer will therefore buy a lower quantity at a lower price than would be the case in the absence of buyer power. If a single buyer is buying in a competitive market, where many suppliers compete on price, use of buyer power would lead to a loss of overall welfare if the costs of supply increase with total output (that is, there is a rising supply curve).
- 3.27 In this case, however, the market from which the government buys is unlikely to be competitive, given that patents grant pharmaceutical firms temporary rights to be the sole producer of a particular drug. In order to analyse the government's best use of its buyer power, the starting point (or counterfactual) should in this case be taken as a monopoly,³³ where a single firm is able to exert its seller power by taking into account the effect the quantity it sells has on the price. As long as demand is not completely price inelastic, a monopolist will sell a lower quantity at a higher price than in a competitive market, leading to a loss of overall welfare.
- 3.28 If there is a single seller and a single buyer operating in one market, there are a range of possible outcomes consistent with either side using their market power. Market outcomes (prices and quantities) may be determined as a result of negotiation between the two parties. Where two firms, both with monopolies, are involved, one might expect them to agree on a quantity that maximises joint profits³⁴ and then negotiate on a price. In this case, the quantity produced will be the same as in the outcome where there is only one monopolist, but the buyer may be able to negotiate a lower price, reallocating profits from the seller to the buyer.³⁵ In principle, it may be possible in this way for national governments to use buyer power to negotiate lower drug prices (although, as discussed further below, one might also expect a government, concerned with its citizens health, to try to induce the monopoly to supply a higher quantity than that which maximises profits).

Ensuring that drugs are made available

- 3.29 Of course, in practice, governments are constrained in the extent to which they can push down prices by the threat that companies have not to supply the drug in question if a price cannot be agreed. Governments in turn can threaten to withhold reimbursement status. Hence the price bargaining process is best analysed strategically, with prices being agreed in the context of:
- the threat of withholding reimbursement from government, and

³³ In the case of the market for a drug, the existence of close therapeutic substitutes may mean that there are in fact several sellers of differentiated products: the case of a monopoly is presented for simplicity.

³⁴ Including both the monetary profits of the seller, and the 'surplus' (non-pecuniary excess benefits) of the buyer.

³⁵ See OFT Research Paper 16 'The Welfare consequences of the Exercise of Buyer Power' for a more thorough exposition.

- the threat of pharmaceutical companies withdrawing the supply of a drug to a particular country

3.30 The factors that influence this bargaining relationship and their implications for pricing and reimbursement arrangements are set out in Annexe L.

Incentives to invest in valuable drugs

3.31 The use of buyer power can also have effects on incentives to invest. Please refer to OFT's study *'Assessing the impact of public sector procurement on competition'* (2004) for a more detailed discussion of public sector buyer power.

3.32 In the context of pharmaceutical pricing, the long-term objective of maximising health outcomes for people into the future implies that governments will wish there to be adequate incentives for R&D into new drugs. Ensuring that there are adequate incentives for R&D therefore forms a constraint on governments using their buyer power to negotiate as low drug prices as possible. The optimal set of drug prices from a government's perspective will therefore be the one that maximises all health outcomes (now and in the future), taking into account the effect that these prices will have on incentives for R&D into new drugs.

3.33 However, the global nature of R&D costs means that the effect of prices in any one country (particularly a small one) on investment is less clear. This is taken up in the following section.

Globally common costs and 'free riding'

3.34 R&D is a globally common cost. If a country accounts for a small proportion of global sales, sales in that country will have little effect on companies' global return from R&D. As a consequence, prices in such countries are likely to have little direct effect on the level of R&D and hence on the pace of pharmaceutical innovation. This is more relevant to the UK and other European countries, which individually account for less than six per cent of global pharmaceutical sales, than to the US (which accounts for 47 per cent of global pharmaceutical sales).³⁶

3.35 This could affect the incentives governments have in exercising buyer power. In particular, governments may face an incentive to 'free ride' on global R&D by paying prices which do not contribute to this cost element. In order to ensure the national supply of a drug, a government may seek to negotiate prices that cover only national costs and avoidable international costs, leaving the globally common costs to be paid for by other countries. Where governments seek to free ride in this way, companies may respond by delaying launch of a drug in that country, or even not launching at all (evidence on launch delays is considered in Chapter 4 of this Annexe).

³⁶ Japan is the second largest national market and accounts for 10.7 per cent of global sales (see Figure 2.2).

- 3.36 Furthermore, although free riding may be rational for an individual country, if many governments successfully adopt this approach then there would be significant aggregate effects on global returns to R&D and hence on companies' incentive to develop new drugs. In the light of this, governments may recognise their common interest in allowing higher prices that incentivise the development of new drugs. The objectives of the PPRS specifically refer to promoting an industry 'capable of such sustained R&D as should lead to the future availability of new and improved medicines' while our international survey of pharmaceutical pricing and reimbursement schemes (see Annexe K) suggests a number of countries do not just seek to set as low a price as possible but, for innovative drugs, seek to negotiate prices that reflect a drug's cost effectiveness.
- 3.37 In principle, the solution to this problem would be to coordinate price setting between countries, ensuring that each paid its 'fair share' (possibly according to some measure of ability to pay). In practice, concerns to retain national sovereignty over drug pricing mean that such an approach is not likely to be implemented in the near or medium term.
- 3.38 The incentive to free-ride may, however, be dampened by the practice of international reference pricing, which has the effect of linking prices in different countries. If prices are linked, an individual country may have a greater effect on global returns to R&D than the size of that country's pharmaceutical market might initially suggest. Therefore, these countries will have a greater incentive to take account of long-run effects on innovation when exercising their buyer power. As discussed in the next chapter, UK prices play a particularly important role in this respect.

4 THE IMPORTANCE OF UK PRICES

- 4.1 The discussion above describes at a general level the objectives a government may have in bargaining on drug prices, how it may best use its buyer power to achieve them. This chapter considers the specific importance of UK prices in this global context and hence assesses which objectives could realistically be targeted through a UK pricing scheme.
- 4.2 The objectives we consider are essentially those discussed above:
- achieving reasonable pharmaceutical prices
 - ensuring that drugs continue to be supplied, and patients are given rapid access, and
 - ensuring that there are adequate incentives for R&D on valuable new drugs.
- 4.3 As noted, a separate objective that is often ascribed to the PPRS – that of attracting investment in the UK – is discussed in Annexe E.

Reasonable pharmaceutical prices

- 4.4 A UK pricing scheme clearly has an impact on the extent to which medicines are supplied to the NHS at reasonable prices. Annexe M provides some evidence that this may not be the case for some of the largest selling drugs in the NHS.
- 4.5 The focus of this study is not, however, on the overall size of the drugs bill, but how effectively it is used. Annexe F gives an overview of comparisons of UK prices with those in other countries. While prices in the UK have historically been higher than those in other European countries, the disparity has reduced with the seven per cent price cut introduced in 2005. In general, however, we would not suggest undue weight be put on price comparisons, given the considerable methodological and data difficulties encountered in conducting them.

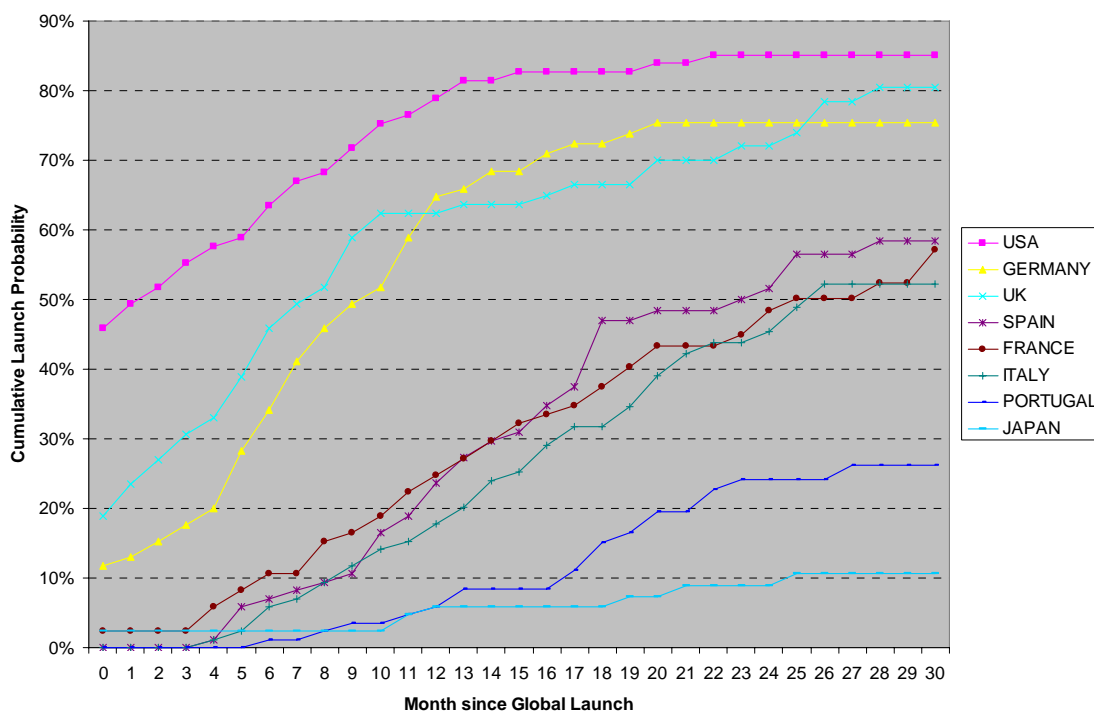
Launch and uptake of new drugs

- 4.6 Pricing and reimbursement schemes can also have an impact on the timing of drug launch and subsequent uptake of drugs.

Drug launch

- 4.7 Drugs are generally launched in the UK before most other countries. Figure 4.2 below illustrates the UK's performance in terms of the probability of NCEs being launched in the country. It can be seen that, after the US, the UK has the next highest probability of early launch with around 50 per cent probability of a new entity being launched within seven months after global launch. This is broadly on a par with the position in Germany.

Figure 4.2: Cumulative launch probability for selected countries



Source: Danzon P, (2006) 'Drug Pricing in A Diverse World', BIO Conference June 2006, based on Danzon, Wang and Wang (2005).

- 4.8 For drugs that are eventually launched in a particular country, the speed with which they become available will reflect a combination of strategic decisions by the company (when they seek marketing approval) and the time required to go through administrative processes and price negotiations. The choice of pricing regime can affect both of these factors.

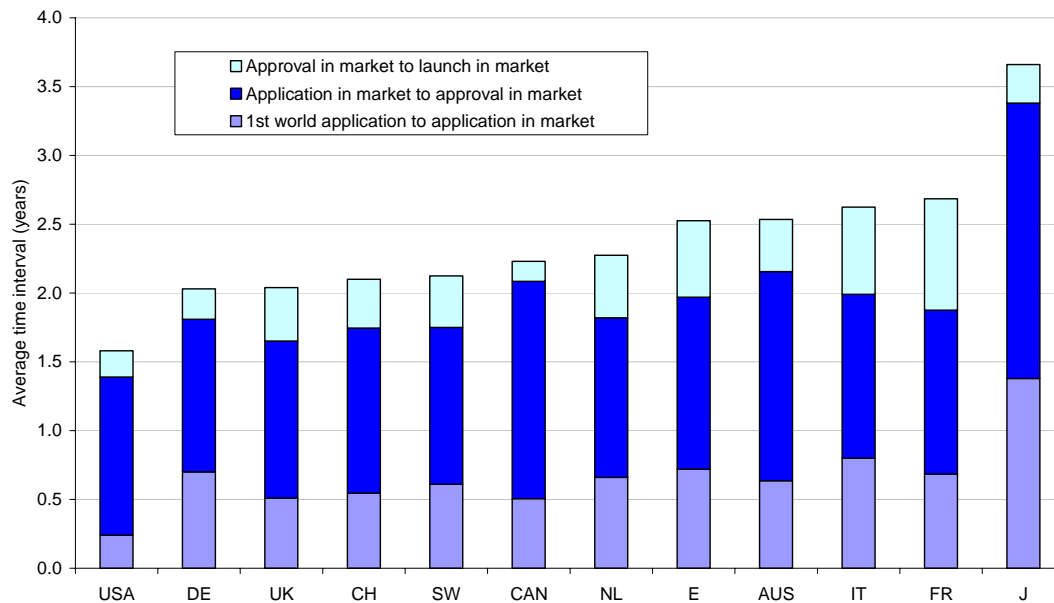
- 4.9 The hypothesis that pricing regimes can affect companies' choice over the timing of drug launch receives some empirical backing in academic literature.³⁷ The main consideration here in a European context is parallel trade, which will give pharmaceutical companies an incentive to delay launches of drugs in countries with lower than average EU drug prices. Therefore, if governments wish to ensure that particular drugs are launched within their countries, they are constrained from setting prices which are too low. However, as long as its drug prices remain within the upper half of European countries, it seems unlikely that an EU country is in danger of becoming a parallel exporter with consequences on the launch of drugs.

³⁷ Lanjouw (2005) finds that in rich countries extensive price control lowered the probability of market entry by new drugs. Danzon, Wang and Wang (2005) present evidence that fewer drugs are launched in countries which reduce pharmaceutical prices, and that there tends to be a longer time delay for those drugs which are launched. Kessler (2004, funded by PhRMA) reviews the empirical literature on the effects of government drug price controls. He finds (among other things) that price regulation is typically held to delay drug launches.

4.10 The relative contribution of strategic and administrative effects on launch timing can be analysed using the data shown in Figure 4.3 below. This shows the average time interval between the first application of a drug for market authorisation somewhere in the world and market launch in each specific country, broken down into the following three components:

- **interval between a first application anywhere in the world and application in the particular market.** This is likely to reflect commercial decisions about the order and timing of applications in different national markets but also the fact that a country where a clinical trial for a particular product has been undertaken is more likely to receive this particular drug at an early stage
- **delay between application in the market and approval in the market.** We would expect this to reflect the time required to go through the purely regulatory process on health and safety evaluation, and
- **interval between approval in the market and launch in the market.** This is likely to reflect the delays required in some countries to go through pricing and reimbursement procedures. It may reflect, in certain cases, a company's commercial decision about how quickly to launch a product.

Figure 4.3(a): Average time interval between first application somewhere in the world and launch in each country



Note: The data relates to 1999-2003.

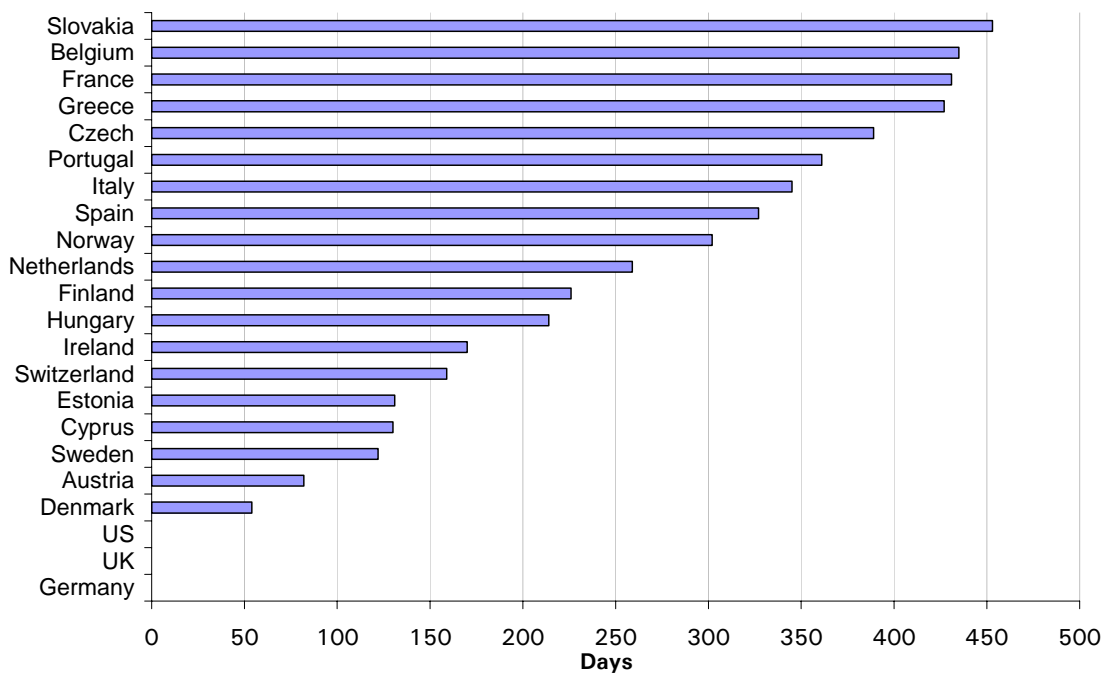
Source: PICTF, 'Competitiveness and Performance Indicators 2005'. Spreadsheets containing the charts shown in the report were supplied by the DH.

4.11 The figure shows the average delays due to application (time between the first application in a national market and the first application anywhere in the world), and due to the approval process (time between market application and market approval). It can be observed that overall delays in the UK are comparatively short, with the UK average application delay for new drugs being only six months and (as in most European countries) the approval delay also being relatively short. The relatively rapid

marketing approval process reflects the fact that European countries coordinate their licensing procedures and are thus able to recognise respective decisions. Interestingly the time between approval and launch is not particularly short in the UK compared with other European countries. Presumably this reflects companies' strategic decision-making, since, as discussed below, there is no requirement in the UK for a pricing and reimbursement decision to be made before a product can be sold to the NHS.

4.12 In countries where prices must be agreed by Government, or an official authority before launch, the pricing and negotiation process can contribute to approval delays. Information on the delays caused by pricing and negotiation procedures is shown in Figure 4.4 below, supplied to us by ABPI. The absence of any delays in the UK and Germany reflects freedom of launch pricing in these countries.

Figure 4.4: Average pricing and reimbursement delay



Note: data covers EMEA and non-EMEA approved molecules granted marketing authorisation between 30 June 2000 -2004.

Source: IMS, supplied by ABPI

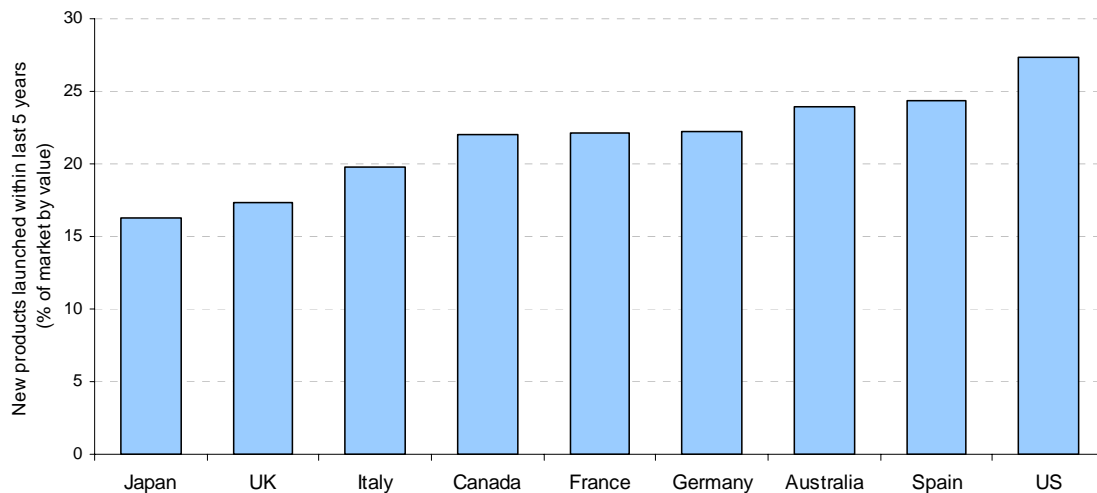
4.13 The data must be interpreted with some caution, however. For example, we have found that in the US, most purchasers negotiate with companies (on price and / or reimbursement status) before covering a drug under a particular plan. Therefore, while some individual plans will approve drugs very rapidly, it is not true to say that there is no reimbursement delay in the US. That is a function of the particular plan to which a patient has subscribed. (See Annexe K for more details.)

4.14 These data concerns notwithstanding, it is clear that, by avoiding a system in which prices need to be agreed up front, the UK pricing regime avoids an element of delay in launching a drug onto the market.

Drug uptake

- 4.15 In comparison with healthcare systems in other countries, the NHS tends to be relatively slow in taking up new medicines once they have been launched onto the market. Figure 4.1 below shows the proportion of various national markets accounted for by products launched within the last five years. New products represented only 17 per cent of the UK market by value in 2004, compared with a figure of 27.4 per cent in the US.

Figure 4.1: Proportion of national markets in 2004 accounted for by products launched in 1999-2004 (% of 2004 market by value)



Note: The data used captures all new products including new generic products.
Source: PICTF, 'Competitiveness and Performance Indicators 2005'.

- 4.16 There are many factors explaining the level of uptake in different countries, many of which are specific to the country in question, such as the degree of conservatism amongst prescribers and the extent of price sensitivity at different levels of demand.
- 4.17 In Annexes B and L we explore the hypothesis that, in the context of the UK, low uptake might at least in part be explained by the lack of a view on the clinical and cost effectiveness of a particular product (this is sometimes known as the phenomenon of NICE blight). This leads to the conclusion that, for some drugs at least, moving towards a system in which a view is taken at launch on the cost effectiveness of a product might help improve the uptake of those products.

Incentives to invest in drugs

- 4.18 A key question is whether pharmaceutical prices in the UK have any effect on the incentives of companies to invest in certain drugs. As noted above, the costs of R&D (and certain global manufacturing facilities) can be characterised as global common costs, and there may be some scope for individual countries not to remunerate such costs, thus 'free riding' on the prices paid by other countries.

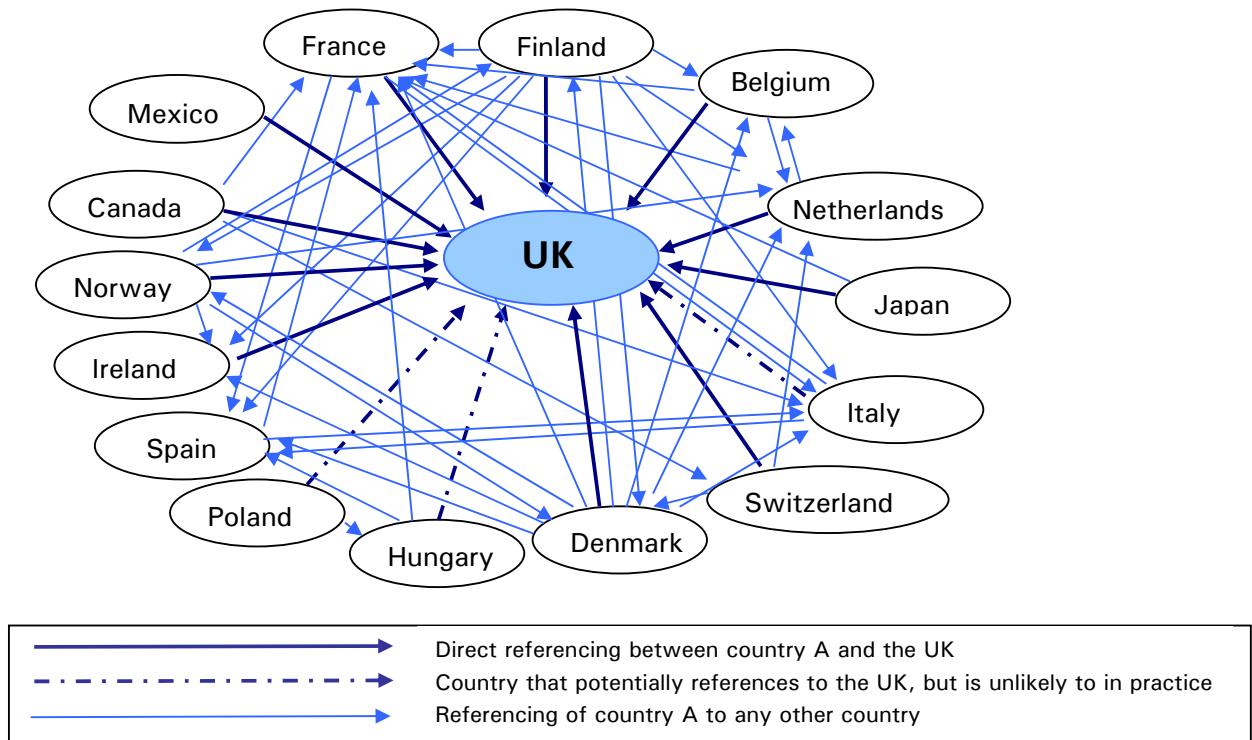
- 4.19 Pharmaceutical prices in the UK will obviously have a direct effect on the revenues that companies earn from UK sales. However, this effect is likely to be relatively small in a global context, because the UK market represents only 3.9 per cent of global sales.
- 4.20 However, some countries base their prices, in part or in full, on prices in other countries (international reference pricing). As a result of international reference pricing, a country to which other countries link their prices will have a greater effect on global returns to R&D than the size of that country's pharmaceutical market might initially suggest. The UK has a particularly important effect in this respect. We have found that:
- countries which reference pharmaceutical prices to the UK include Japan, France, Italy, Canada, Belgium, Switzerland, Poland, Netherlands, Finland, Hungary, Norway and Ireland
 - together, these markets account for around 25 per cent of world pharmaceuticals sales.
- 4.21 Table 4.1 summarises the information we have collected on reference pricing to the UK. Figure 4.2 also shows the importance of the UK as a country to which others reference their prices. Thus, the effect of UK prices goes beyond what one would expect from its market share, since many other countries' pricing and reimbursement systems reference UK prices.
- 4.22 UK prices may have further 'ripple' effects as a result of other countries which do not reference directly to the UK but do reference to one of the above countries. This can also be observed in the diagram above that shows all countries that are directly or indirectly referencing to the UK. It is difficult to arrive at a definitive view of the strength of this indirect effect. The importance of international referencing pricing in the overall pricing regime varies between these countries, as does the number of countries included in each nation's reference basket. Annexe K provides further details.
- 4.23 In addition, UK prices may be used for negotiating purposes even where they are not used for formal reference purposes.

Table 4.1: Summary of pricing regimes in countries with reference pricing

Country	Market value 2004 (ex factory prices) (\$m)	How is international reference pricing used?	How many and which countries are used as comparators?
Japan	55,500	One criteria alongside cost-plus calculations	4 US, FR, DE, GB
France	28,311	For innovative drugs	4 GB, DE, ES, IT
Italy	18,901	As one factor (among others) in pricing negotiations	EU 15, mainly FR, ES
Canada	10,500	For innovative drugs and ex-post pricing adjustment	7, FR, DE, IT, SE, CH, GB, US
Belgium	4,402	Alongside other factors	3-10, generally FR, GB, DE, NL
Switzerland	3,244	Alongside efficacy and cost-benefit analysis (ex- ante), main ex-post evaluation method	4 DK, NL, GB, DE
Poland	3,656	One of a range of factors taken into account	19 (EU 15 + HU, LT, CZ, SK) greatest importance attached to countries with similar GDP
Netherlands	4,452	Main ex-post price-setting method	4 BE, FR, DE, GB
Finland	2,101	Alongside costs and therapeutic benefit analysis	17 EU 15, NO, IS
Hungary	1,936	Main price-setting method, some price- volume agreements	15, greatest importance: FR, GR, PT, ES
Norway	1,521	Main price-setting method	3 lowest prices out of 9 countries FI, SE, DK, GB, IR, DE, NL, BE, AT
Ireland	1,625	Main initial price-setting method where comparators are available	1 to 9 GB, DE, FR, DK, NL, FI, OE, BE, ES
Denmark	1,754	Ex-post cap at average European price	13 AT, E, FI, FR, DE, EI, IT, NL, SE, UK, NO, IS, LI
Mexico	9,680	Ex-factory prices of the six countries with highest shares of sales of the product	UK (40 per cent of cases) Other countries frequently used: US, FR, ES, IT, DE, CA, AU,

Sources: OFT estimates based on World Health Organisation data, EFPIA Annual Report (2005), IMS 'Global Pharmaceutical Perspectives (2005)'.

Figure 4.2: International reference pricing



Source: OFT

4.24 From the UK's perspective (as a country extensively used as a benchmark when countries set drug prices), the impact that its prices have on global returns to R&D is likely to be large, despite the relatively low (from a global perspective) volume of sales in the UK. The UK is therefore constrained in its ability to free ride on global R&D, and should take into account the effect that the prices it sets have on incentives for R&D globally. In particular, as discussed in Annexes L and M, it should look, through its pricing system, to provide incentives to invest in areas of the greatest clinical need.

5 CONCLUSION

- 5.1 This section sets out the main conclusions on the nature of the global pharmaceutical industry, and on the basic principles that the UK should follow in negotiating pharmaceutical prices within it.
- 5.2 Large multinational pharmaceutical companies operate across national boundaries, in some cases having a global sales turnover which exceeds the size of the pharmaceutical market in many individual countries. A substantial proportion of the lifetime cost of a drug is accounted for by the costs of R&D, which cannot be directly attributed to drug sales in any individual country. Furthermore, manufacturing and R&D costs are often incurred outside the country of sale.
- 5.3 Governments' control over health budgets may mean they have significant buyer power, but the global nature of R&D may reduce the incentives for individual countries to pay for it through higher drug prices ('free riding'). However, in the case of the UK, the fact that it is used as a comparator for countries that use international reference pricing might mean reducing drug prices could significantly lower global incentives for R&D investment.
- 5.4 Within this context, the UK's central objective when negotiating pharmaceutical prices should be to maximise the health outcomes of its citizens both now and in the future. In practice this means setting prices to secure good value for money on the drugs that it buys while also ensuring that there are adequate rewards for developing new drugs.
- 5.5 While the objectives and basic incentives of government in setting pharmaceutical prices have been outlined, the practicalities and mechanics of the price-negotiating process have not been addressed. A more detailed consideration of pricing issues is found in Annexe L.