The Single Market Review

EUROPE

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Volume 2:

Pharmaceutical products

The Single Market Review

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EUROPEAN COMMISSION

The Single Market Review

IMPACT ON MANUFACTURING

PHARMACEUTICAL PRODUCTS

The Single Market Review

SUBSERIES I: VOLUME 2

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This report is part of a series of 39 studies commissioned from independent consultants in the context of a major review of the Single Market. The 1996 Single Market Review responds to a 1992 Council of Ministers Resolution calling on the European Commission to present an overall analysis of the effectiveness of measures taken in creating the Single Market. This review, which assesses the progress made in implementing the Single Market Programme, was coordinated by the Directorate-General 'Internal Market and Financial Services' (DG XV) and the Directorate-General 'Economic and Financial Affairs' (DG II) of the European Commission.

This document was prepared for the European Commission

by

REMIT

It does not, however, express the Commission's official views. Whilst every reasonable effort has been made to provide accurate information in regard to the subject matter covered, the Consultants are not responsible for any remaining errors. All recommendations are made by the Consultants for the purpose of discussion. Neither the Commission nor the Consultants accept liability for the consequences of actions taken on the basis of the information contained herein.

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ABDA	Bundesvereinigung Deutscher Apothekerverbände
ABPI	Association of the British Pharmaceutical Industry
AESGP	European Proprietary Medicines Manufacturers' Association
AGIM	Association générale de l'industrie du médicament (General Association of the Medicines Industry)
AIDS	acquired immune deficiency syndrome
ANDA	abbreviated new drug application
B	Belgium
BAH	Bundesfachverband der Arzneimittel-Hersteller (Federal Association of Pharmaceutical Manufacturers – Germany)
Belg-Lux	Belgium-Luxembourg
BPI	Bundesverband der Pharmazeutischen Industrie (Federation of the Pharmaceutical Industry – Germany)
BSE	bovine spongiform encephalitis
CD-ROM	compact disc-read only memory
CH	Switzerland
Chap.	chapter
CMR	Centre for Medicines Research
CPMP	Committee for Proprietary Medicinal Products
Co.	Company
CR	controlled release
CSO	Central Statistical Office (UK)
D	Germany
DK	Denmark
DKR	Danish crown
DM	Deutschmark
DNA	deoxyribonucleic acid
E	Spain
EAG	Economists Advisory Group
EC	European Commission
ECR	European Court Reports
ECU	European currency unit (used as a monetary symbol)
EEC	European Economic Community
Ed.	Edition
EFPIA	European Federation of Pharmaceutical Industries' Associations
EFTA	European Free Trade Association (Stockholm Convention) – Austria, Finland, Iceland, Liechtenstein, Norway, Sweden and Switzerland.
e.g.	for example
EIU	Economics Intelligence Unit
EMEA	European Medicines Evaluation Agency
est.	established
et al.	and others
EU	European Union
EUR–12	total of the countries of the EC (before 1 January 1995)
Eurostat	Statistical Office of the European Communities
F	France
FDA	Food and Drug Administration (USA)
FDI	foreign direct investment
FICI	Federation of Irish Chemical Industries
FT	*Financial Times*
GATT	General Agreement on Tariffs and Trade (UN)
GDP	gross domestic product
GDR	German Democratic Republic
GIRP	Groupement international de la répartition pharmaceutique
GMP	good manufacturing practice
GP	general practioner

GR	Greece
HB	hepatitis B
HMSO	Her Majesty's Stationary Office (UK)
I	Italy
ibid.	*ibidem* – in the same book or passage, etc.
ICI	Imperial Chemical Industries
i.e.	that is
IFT	intra-firm trade
Inc.	incorporated
IR	infringement proceedings by the European Commission
IRL	Ireland
IRS	Internal Revenue Service (US tax authority)
J&J	Johnson & Johnson
JETRO	Japan External Trade Organization
kg	kilogram
L	Luxembourg
LIF	Läkemedelsindustriforengen (Swedish Association of the Pharmaceutical Industry)
LSE	London School of Economics
Ltd	limited
M&As	mergers and acquisitions
MCA	monetary compensatory amount
MC	Monaco
MEFA	Foreningen af danske Medicinfabrikker (Association of the Danish Pharmaceutical Industry)
METS	minimum efficient technical size
mg	milligram
MNE	multinational enterprise
n/k	not known
n.a.	not available
NACE	general industrial classification of economic activities within the European Communities
NAS	new active substance
NCE	new chemical entity
NDA	National Drugs Authority
NDA	new drug application
Nefarma	Nederlandse Associatie van de Farmaceutische Industrie (Dutch Association of the Pharmaceutical Industry)
NHS	National Health Service
NL	Netherlands
No	number
NTBs	non-tariff barriers
OECD	Organization for Economic Co-operation and Development
OJ	Official Journal of the European Communities
op. cit.	work previously cited
OTC	over the counter
P	Portugal
p.	page
pa	per annum
pan-EU	pan-European Union
Pharma	pharmaceutical
PhRMA	Pharmaceutical Research and Manufacturers of America
pp.	pages
PPP	purchasing power parities
PPRS	Pharmaceutical Price Regulation Scheme (UK system to control prices of pharmaceuticals)
R&D	research and development
S	Sweden
SIC	standard industrial code
SITC	Standard international trade classification
SNIP	Syndicat national de l'industrie pharmaceutique (French Association of the Pharmaceutical Industry)

SMP	Single market programme
SPC	Supplementary protection certificate
Tab.	table
TNCs	transnational corporations
UK	United Kingdom
UN	United Nations
UNIDO	United Nations Industrial Development Organization
US	United States
USA	United States of America
USD	United States dollar
v	*versus* – against
VA	value added
VAT	value-added tax
Vol.	volume
Washington DC	Washington District of Columbia
WHO	World Health Organization (UN)

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1. Summary

1.1. The role of the European Union

The European Union (EU) market for medicines has hitherto been fragmented by national controls. The Union has therefore taken action to bring about a single market.

The bases on which medicines are admitted to national markets have been harmonized (Section 3.2.1). A Community system for granting marketing authorization has been in place since January 1995. Intended to make the process cheaper and quicker, early experience suggests that the centralized procedure is working well, but there are reservations about the decentralized procedure.

The prices of medicines differ widely between member countries, in part as a result of national controls (Section 3.2.2). Concessions have sometimes been offered as a reward for local investment. The Transparency Directive of 1989 was intended to make such regulation more open (89/105/EEC). Its effects have been modest. Attempts to extend its scope have been shelved, and member nations remain in control of their expenditure policies. Decisions by the European Court of Justice have encouraged a parallel trade in medicines.

The 'rational use of medicines' Directives 92/26/EEC, 92/28/EEC, 92/27/EEC and 92/25/EEC of 1992 have harmonized the classification of medicines into prescription and non-prescription products, the advertising of medicines, the information to be provided for patients, and pharmaceutical wholesaling (Section 3.2.3). The first two are seen as particularly helpful to the self-medication sector, though problems still arise from national variations in interpretation.

Additional protection for intellectual property has been provided in the form of patent life extension and marketing exclusivity (Section 3.2.4). There is general agreement that these measures have benefited the research-based sector but handicapped the generic producers.

Horizontal measures such as those concerning product liability, trade marks, public procurement and competition policy have had a lesser but in some cases appreciable effect on the sector.

1.2. The impact of single market measures on the performance of the pharmaceutical sector of the EU

The short-term impact on pre-production costs has been limited (Section 4.1.1). Since 1985 the costs of innovation have risen sharply, but this has been a global trend. The measures taken to harmonize marketing authorization have had a generally beneficial but largely indirect effect on the time taken for approval. The saving in costs is relatively small and is mainly of benefit to the generic and self-medication sectors. Production costs appear to be slowly falling as a proportion of the total, but this is mainly a response to downward pressures from buyers.

Cross-border sales of medicines have increased (Section 4.2). The EU market is somewhat more unified in terms of companies and products than formerly; trade has risen as a proportion

of consumption and local production by foreign firms decreased. The evidence suggests that single market measures contributed to this development. The parallel trade in medicines has slowly increased in importance but is still quite small and limited to those countries where prices are generally high. Nevertheless, the research-based sector of the industry is extremely anxious about this development. Cross-border marketing, especially of self-medication products, has, however, been slow to develop because national controls over what may be sold and in which ways remain a barrier. Distance selling is illegal in most member countries. Concentration among wholesalers is in progress, prompted in part by commercial reasons and in part by the desire to exploit a unified European market.

Scale and scope effects exist in pharmaceutical operations (Section 4.3). They are mainly – but not entirely – to be found in production, where past national policies have led to an unnecessary multiplication of plants, many of which worked at well below capacity. A slow tendency towards the concentration of facilities is evident during the past decade, limited by a wish to avoid political repercussions. Taking the industry as a whole, the number of companies has remained roughly constant but their size has increased. A two-tier industry is emerging, composed of a small number of large research-based firms and a large number of small companies. The single market programme (SMP) *per se* has contributed little directly to this process, though easier trade may have facilitated it.

Foreign direct investment has been a feature of the sector for many years (Section 4.4). American companies have played a major role. Currently they are concentrating their facilities. They favour one member country rather than another mainly on grounds of national resources, policies and incentives, France and the UK being preferred. In this respect their policies are essentially unchanged over the past decade. Transnational mergers within the research-based sector in particular have been in progress for a number of years and are currently accelerating. They are a response to the rising cost of innovation and world-wide pressures from buyers. Once again, the SMP has not played a large part.

Pharmaceutical companies buy in many of their raw materials and intermediates (Section 4.5). Sourcing patterns have not greatly changed. The Union has not become more self-sufficient. The abolition of frontier controls within the EU has facilitated the concentration of specialized treatment processes and thereby reduced production costs.

As far as sales by individual companies are concerned, there has been a slow process of concentration since the 1970s, although national markets are still fragmented (Section 4.6). As with transnational mergers, factors other than the SMP are responsible. Research-based firms have increasingly diversified into generics and self-medication products, often by acquisition. Trends in competition present a complex picture. Within the research-based sector it is declining as mergers take place; the barriers to entry are prohibitively high. Generic competition is rising; it has been both encouraged (Section 4.6.1) and discouraged (Section 4.6.2) by Union actions. Competition in the self-medication sector is on balance increased by the Classification Directive and the new methods of granting access to markets.

Productivity has risen sharply within European industry (Section 4.7). This is due to detailed improvements in operations, enabling companies to maintain profit margins in a situation of dynamic equilibrium between incomes and costs. The distribution of competitive strengths

has remained much the same for a considerable period, with American companies in the lead, followed by those of the Union and those of Japan. UK firms have improved their position, German companies have held their own and French firms have declined.

Employment as a whole within the pharmaceutical sector rose by 18% between 1983 and 1992; that in R&D rose by 50% (Section 4.8). These trends were very similar to those in the USA and Japan. Increasing overall productivity meant that employment grew considerably more slowly than output. The decline since 1993 is very largely due to the current wave of mergers between global companies.

As already noted, the prices of medicines vary between member countries of the Union (Section 4.9). Both manufacturers' prices and distributors' margins are subject to official controls in most of them. In the case of prescription products, the price elasticity of demand is low; downward pressures come from health care systems, not patients. Price sensitivity is higher with self-medication products where the consumer pays the entire bill. Various measures suggest that on balance prices have not converged in recent years. The effects of the Transparency Directive have been modest.

The environmental impact of the pharmaceutical industry is lower than that of most parts of the chemical industry. National requirements have so far determined company attitudes. There is no sign that firms have relocated to countries with low standards.

1.3. Business strategy

The conclusions reached in earlier sections are reviewed in terms of Porter's typology (Chapter 5).

The bargaining power of buyers is high where public health care systems are concerned. Less certainly, that of wholesalers may have been increased *vis-à-vis* manufacturers by the trend towards concentration. The bargaining power of suppliers is low. These features of the competitive situation have been little affected by the SMP. The threat of new entrants depends on the type of pharmaceutical firm. Among research-based companies it is small and declining. Elsewhere, barriers to entry are much lower, and the actions of the Union may encourage new entrants among generic and self-medication enterprises. Competition between the research-based and other pharmaceutical firms has been increased by the steps taken.

The strategic responses of companies were also considered in terms of Porter's typology. It is expected that research-based companies would seek competitive advantage primarily via product differentiation, generic firms and wholesalers via cost leadership, and self-medication firms by niche strategies. The strategic responses of major firms were explored through interviews undertaken in 1990 and 1995. Attitudes towards the outcomes of the SMP were broadly favourable where admission to markets and aspects of European operation were concerned. National controls over prices and reimbursement are seen as a major problem and the area where the Union had made least progress. Parallel trade arouses great anxiety. The global frame of reference and the world-wide rather than regional preoccupations of the research-based sector were repeatedly emphasized.

Asked about strategic issues in the near future, respondents identified in particular the need for a coherent European industrial policy for the sector, the possibilities of pan-European selling, relations with wholesalers, the need to maintain a critical mass in research and development, the further rationalization of production facilities and vertical integration into disease management.

2. Method

The study was undertaken by REMIT Consultants Limited, London, together with Economists Advisory Group Limited, London (EAG) and PLS Consult, Copenhagen.

Three main sources of information were used:

(a) published reports and data which are referenced throughout the report;
(b) previous relevant non-confidential work undertaken by the three consultancies. In particular, REMIT's work for the American Pharma Group (1994-95) provided useful insight into incentives for investment in different European countries, and the perceptions of non-European companies towards the EU. REMIT's work for the British Pharma Group (1995) contributed useful data on pharmaceutical prices in EU countries. The chapter on business strategy was based on EAG's analysis of its work for the UN Centre on Transnational Corporations published in 1994 and field research conducted in 1990 and 1995 by P. Chaudhry, the 1995 research being financially supported by EAG specifically for the present study;
(c) interviews undertaken specifically for the present study. A total of 40 companies, trade associations and public sector bodies were interviewed. Wherever possible, these interviews were conducted through personal meetings arranged in advance and using structured interview guides. A mailed questionnaire was sent to all the major trade associations in the EU but with disappointing results. Most of these associations were subsequently interviewed in person. A list of all organizations interviewed is included in Appendix A. Slightly different interview guides were developed and used for the various types of organization interviewed: research-based companies, generics companies, self-medication companies, wholesalers and trade associations. One is included in Appendix A as an example.

For the case studies, at least two full days were spent within the companies profiled, and for the larger companies two consultants worked together to assist with collecting and analysing data. Several functional areas (e.g. marketing, R&D, legal, intellectual property, manufacturing) within the company were visited so that we gained the widest possible perspective on the impact of the single market. Much of the material gathered during the case study research was provided in confidence and has therefore been used together with the confidential information from the main interview programme, as supporting evidence throughout the text.

3. Effectiveness of measures taken to complete the single market

The salient characteristics of the European pharmaceutical industry are described in Appendix B. At this point we are concerned with the impact of national controls upon it and of the measures taken under the SMP. Detailed references to Community legislation etc. are listed in Appendix D.

3.1. National regulation of the pharmaceutical sector

The pharmaceutical sector has for many years been subject to a considerable degree of regulation by the Member States (Table 3.1). Until 1995 national authorities controlled the admission of new medicines to national markets. They continue to regulate pharmaceutical expenditure under public health care schemes by a variety of means. They license pharmaceutical manufacturers, inspect their premises and monitor imports for quality. They decide whether particular drugs may be sold with or without prescription, who may sell them and how they may be marketed. They determine what information should be given to consumers and in what form. They may choose to encourage investment in the national pharmaceutical industry either directly or indirectly.

In all these respects the pharmaceutical sector differs markedly from manufacturing industry in general. Some of the reasons are obvious. Medicines have powerful physiological effects and must be used with care. Almost all of them have side-effects in some patients. It would be irresponsible to allow new products on the national market unless it was first established that they are both safe and effective. For the same reason, the conditions under which they are made and supplied to patients have to be strictly controlled. High standards of purity and cleanliness are vital. Similarly, some drugs will be suitable for self-medication, but most must be used under professional guidance. All member countries agree that such regulation is necessary.

Other reasons are basically economic. The state is heavily involved in financing health care throughout the Union. Expenditure on this account is steadily rising and there is a general consensus among national administrations that it must be restrained. Spending on medicines is a significant part of the total. Official controls over such expenditure are therefore general, although the forms that they take vary widely. At the same time, governments often see the pharmaceutical sector as a national asset, creating wealth and providing high-quality employment. In such cases, they may offer subsidies or other concessions. A certain tension between these divergent aims is often apparent.

Clearly such regulations have the potential to fragment the EU market for medicines and to distort patterns of trade. In the past they have done so, and it is this fact which has promoted the single market measures, to which we now turn.

Table 3.1. Ways in which EU Member States regulate the pharmaceutical sector

Activity	B	DK	F	D	GR	IRL	I	NL	P	E	UK
Innovation											
Patent legislation	All varying to extents										
New products need marketing authorization	Yes										
Manufacture											
Manufacturer licensed	Yes										
Premises inspected	Yes										
Marketing											
Drugs classified as prescription-only or non-prescription	Yes				No	Yes					
Restrictions on advertising	Yes										
Labels, patient information need approval	Yes										
Restriction on expenditure	No		Yes		No						Yes
Reimbursement											
Admission controlled	Yes										
Prices of prescription medicines controlled	Yes	No	Yes	No	Yes	No	Yes	No	Yes		No
Profits controlled	No										Yes
Generics encouraged	No	Yes			No			Yes	No	Yes	
Prices of non-prescription medicines controlled	Yes	No							Yes		No
Retail distribution											
Permitted outlets restricted	Yes										
Margins controlled	Yes	No	Yes								
Local investment											
Subsidies	No					Yes		No			
Other encouragement	No	Yes		No		Yes		No		Yes	

Source: National sources.

3.2. Sector-specific Union legislation and its impact

Legislation aimed specifically at the pharmaceutical industry is summarized in Table 3.2.[1] The two 'framework' Directives passed in 1965 and 1975 set out the basic approach of the Union (65/65/EEC, 75/319/EEC). The White Paper of 1985 on the completion of the single market specified further measures seen as necessary as far as the pharmaceutical sector was

[1] European Commission. 'The rules governing medicinal products for human use in the European Union', *The rules governing medicinal products in the European Union*, Vol. I, 1995, and earlier issues.

concerned.[2] By the end of 1994 they had all been enacted by the Union and almost all been incorporated into the national law of member countries.

Table 3.2. Principal rules governing medicinal products within the EU

Measure	Date	Main provisions
Measures intended to remove obstacles to a single European market in human pharmaceutical products		
Concerning marketing authorization		
Directive 65/65/EEC	26.1.1965	All medicines for human use require marketing authorization by a competent national authority. Information to be supplied by applicant specified. Grounds for refusal of authorization laid down.[1]
Directive 75/318/EEC	20.5.1975	Specified analytical, toxicological and clinical standards and protocols for testing medicinal products.[2]
Directive 75/319/EEC	20.5.1975	Extended Directive 65/65/EEC. Requires expert reports in support of applications. Creates system of mutual recognition by national authorities under Committee for Proprietary Medicinal Products (CPMP).[3]
Directive 83/570/EEC	26.10.1983	Modified system of mutual recognition laid down by Directive 75/319/EEC.
Directive 87/21/EEC	22.12.1986	Allows abbreviated applications for copy products.
Directive 87/22 /EEC	22.12.1986	Created concertation system for products based on biotechnology or high technology (repealed by Directive 93/41/EEC, replaced by Regulation (EEC) No 2309/93).
Directive 93/39/EEC	14.6.1993	Made provisions for binding decisions under the system of mutual recognition laid down by Directive 75/319/EEC.
Regulation (EEC) No 2309/93	22.7.1993	Established binding centralized system of marketing authorization for the Union; authorized European Medicines Evaluation Agency (EMEA) incorporating the CPMP.
Concerning prices and price controls		
Directive 89/105/EEC	21.12.1988	Price and profit controls must be transparent and based on clear and objective criteria. Timetables for approval/disapproval of proposed prices laid down; reasons for disapproval must be given.
Concerning manufacturing		
Directive 75/319/EEC	20.5.1975	Manufacturers require authorization, as do imports from countries outside the Union.
Directive 78/25/EEC	12.12.1977	Regulates colouring materials used in medicines.[4]
Directive 91/356/EEC	13.6.1991	Principles and guidelines for good manufacturing practice specified.
Concerning marketing and distribution		
Directive 92/25/EEC	31.3.1992	Wholesalers must be authorized; minimum requirements specified.
Directive 92/26/EEC	31.3.1992	Medicines to be classified as subject to prescription or otherwise on admission to the market; principles and practice of classification specified.
Directive 92/27/EEC	31.3.1992	Information to be given on the outer package of medicines and in the user leaflet specified.

[2] European Commission. *Completing the Internal Market*, COM(85) 310 final, 1985. It should be noted that as well as the specific measures identified in Table 3.2, further unspecified action 'to complete work eliminating obstacles to the free movement of pharmaceutical products' was foreseen.

Table 3.2. Principal rules governing medicinal products within the EU (continued)

Directive 92/28/EEC	31.3.1992	Public advertising restricted to non-prescription drugs; all forms of advertising to be controlled in specified ways.

Concerning intellectual property

Directive 87/21/EEC	22.12.1986	Provides a period of protection from time of marketing authorization of a novel medicinal product against copy products without prejudice to patent protection.
Regulation (EEC) No 1768/92	18.6.1992	Provides for additional protection for novel medicines for up to 15 years from the time of first marketing within the Union.

Other measures

Directive 83/189/EEC	28.3.1983	National technical regulations and standards concerning medicines must be notified to a standing committee of the Commission.[5]
Directive 87/18/EEC	18.12.1986	Non-clinical testing of medicines must be carried out according to the principles of good laboratory practice.
Directive 88/320/EEC	9.6.1988	Procedures for inspecting laboratories to ensure good laboratory practice are specified.[6]
Directive 90/219/EEC	23.4.1990	Specifies measures for the contained use of genetically modified micro-organisms in medical applications.[7]
Directive 90/220/EEC	23.4.1990	Specifies measures concerning the deliberate release of genetically modified micro-organisms into the environment.
Directive 90/679/EEC	26.11.1990	Specifies measures needed to protect workers against risks from exposure to biological agents at work.
Directive 86/609/EEC	24.11.1986	Regulates the use of animals in scientific and experimental work.

[1] Modified in detail by Directives 83/570/EEC, 87/21/EEC, 89/341/EEC, 92/27/EC and 93/39/EEC; extended to cover immunological products (Directive 89/342/EEC), radiopharmaceuticals (Directive 89/343/EEC), products derived from blood or plasma (Directive 89/381/EEC), and homeopathic medicines (Directive 92/73/EEC).
[2] Modified in detail by Directives 83/570/EEC, 87/19/EEC, 89/341/EEC, 91/507/EEC and 93/39/EEC.
[3] Modified in detail by Directives 83/570/EEC, 87/21/EEC, 89/341/EEC and 93/39/EEC.
[4] Modified in detail by Directive 81/464/EEC.
[5] Modified in detail by Directives 88/182/EEC and 94/10/EC and Commission Decision 90/230/EEC.
[6] Modified in detail by Directive 90/18/EEC.
[7] Modified in detail by Commission Decision 91/448/EEC and Directive 94/51/EEC.
Source: European Commission. 'The rules governing medicinal products for human use in the European Union', *The rules governing medicinal products in the European Union*, Vol. I, 1995 and earlier issues.

3.2.1. Marketing authorization

The aim of marketing authorization is to ensure that a new medicine is safe, effective and of good quality before it is put on sale. Such permission is also required for a new use of an existing product, a copy of one already on the market or a medicine intended for self-medication.

Until 1 January 1995 the ultimate responsibility rested with the national authorities of the Member States. These bodies were autonomous, free in principle to make their own binding decisions without reference to what happened elsewhere. Originally they had widely differing approaches and requirements and varied considerably in the speed with which decisions were made. A number of untoward consequences resulted. Companies were obliged to make separate applications to each state, so raising the cost of introducing a new medicine. Delays in approval reduced effective patent life, and denied access to new drugs to consumers. There was an obvious potential for discrimination in favour of local companies.

Early legislation

The first Union initiatives in this area were directed towards the approximation of national regulations.

Formal marketing authorization was made mandatory for all new products, with evidence of safety, quality and efficacy required. The latter were the only grounds on which authorization might be refused; thus, considerations of price, need or the number of similar products already on the national market were excluded. Common standards were adopted for pharmacological and toxicological tests in animals and for the conduct of clinical trials together with common forms of documentation. Detailed, though non-binding guidance to applicants was provided. A uniform 120-day period for decision – plus 90 days in exceptional circumstances – was laid down.[3]

By the mid-1980s a good deal of agreement about common practice among the member countries had been attained. However, some national differences in evaluation persisted, while no member country then met the 120- or even 210-day limit laid down.

Mutual recognition and concertation

In view of these problems, new methods for granting marketing authorization were introduced at Community level.

The first of these was a form of mutual recognition, usually referred to as the multistate procedure by the countries involved. This came into force in 1978 and in modified form from 1986. Under the later variant, a company which had obtained authorization in one member country – the *rapporteur* nation – could have this fact taken into account by others to which it applied. Given the full dossier and the assessment and expert reports, the latter were obliged to grant authorization within 120 days unless a 'reasoned objection' was made. If such an objection was made, the application would be referred to the Committee for Proprietary Medicinal Products (CPMP). This body has a member from each of the national authorities of the Member States and one from the Commission. The CPMP would consider the issue and issue a non-binding opinion. The Member States involved would then be obliged to accept or reject the application within a further 60 days.[4]

A more centralized approach was introduced for medicines based on biotechnology and other specified high-technology procedures. The company involved applied to the appropriate national authority, who then notified the CPMP, acted as *rapporteur* for the product and prepared the documentation. The company simultaneously submitted a summary of the documentation to all other Member States, who were invited to provide any drug monitoring reports to the CPMP. The CPMP then prepared a non-binding opinion for the national authorities who were obliged to give a decision within 30 days. This 'concertation' procedure

[3] As laid down in Directive 75/318/EEC and subsequently modified (see Table 3.2). The guides for applicants have been published since 1986. The latest editions are European Commission. 'Notice to applicants for marketing authorization for medicinal products for human use in the European Union', 'Guidelines on the quality, safety and efficacy of medicinal products for human use', *The rules governing medicinal products in the European Union*, respectively Vol. II and Vol. III, 1989, Addendum No 1, 1990, Addendum No 2, 1992, Addendum No 3, 1995.

[4] As laid down by Directives 75/319/EEC and 83/570/EEC. Initially, the procedure was confined to cases where application was made to at least five Member States; from 1986 onwards the number was reduced to two.

was mandatory for biotechnological products and optional for other high-technology medicines.[5]

How successful were these initiatives? The multistate procedure came into force in 1979. Between then and 1985, when it was modified, it attracted only 41 applications. Between 1986 and the end of 1994, 355 applications had been made, which were equivalent to 2,319 individual national applications. Throughout this period the popularity of the procedure rose steadily. Generics predominated, but the system was also used to obtain marketing authorization for a number of new active substances. The concertation procedure also proved increasingly attractive, with a total of 93 applications between 1987 and 1994, 36 coming in the last two years. Applications on behalf of high-technology rather than biotechnology products formed a rising proportion of the whole.[6]

Thus, these procedures were successful in that they were increasingly used for a wide range of medicines. However, national agencies proved reluctant to cede ultimate control. No application under the multistate procedure failed to attract 'reasoned objections' which revoked the case to the CPMP. Even when the CPMP had given its opinion – more than 90% of which were favourable – prolonged delays often followed before the final decision was made at the national level. Of 245 opinions given by the CPMP between 1986 and 1994, 74 had still not resulted in a final decision by all the states involved by the end of the period. Moreover, the decisions reached by national authorities sometimes differed. Similar problems also arose with the concertation procedure.

Future systems

A general consensus rapidly emerged that these procedures were less than totally adequate. After prolonged negotiation they were superseded by the so-called 'future systems' for marketing authorization, which have been in force since 1 January 1995. Three procedures are laid down.

(a) A centralized procedure, under which applications are made to a central body, the European Medicines Evaluation Agency (EMEA), in effect a strengthened version of the CPMP which it now incorporates. This route is mandatory for biotechnological products, replacing the concertation process, and is optional for other high-technology medicines and those which contain a new active substance (NAS).[7] The evaluation is

[5] The concertation process was authorized by Directive 87/22/EEC and repealed by Directive 93/41/EEC, when it was replaced by the centralized procedure specified by Regulation (EEC) No 2309/93. The procedure was mandatory for products based on recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokariotes and eukariotes, and hybridoma and monoclonal antibody methods. It was permitted for medicinal products developed by other biotechnological process, which incorporate new delivery methods, contain a new substance or refer to an entirely new indication, are based on radioisotopes or which employ in their manufacture a novel process, provided that 'in the opinion of the competent authority [they] constitute a significant innovation'.

[6] Details of the use of the multistate and concertation procedures are given in European Commission: Report on the operation of the Committee for Proprietary Medicinal Products, 1991, 1992 (SEC(93) 771), 1993, 1993-94 draft, 1996. The British agency was particularly cautious in its initial attitude, as reflected by their taking longer to respond to CPMP opinions than any other Member State during the period 1987-90 (*Scrip*, No 1644, 21.8.1991, p. 2).

[7] Regulation (EEC) No 2309/93 and Directive 93/39/EEC. The EMEA is given discretion to decide which new products, other than those for which the centralized procedure is mandatory, may use the procedure. For the time being, the classes of product which may qualify are those specified in Directive 87/22/EEC (see note 5 above), together with medicines derived from human blood or plasma. As before, the criterion that such products constitute a 'significant innovation' applies.

delegated to a *rapporteur*, chosen from the membership of the CPMP, and individual experts drawn from lists provided by Member States.

(b) For products not reserved for the centralized procedure a company would have the alternative of a mutual recognition system, in effect a strengthened version of the existing multistate recognition procedure.

(c) Finally, the national systems of authorization will remain in place for the time being. After 1998, however, applications to more than one country will be automatically transformed into mutual recognition applications since Member States will be bound by the decisions of other Member States.

Decisions reached through the centralized procedure will be binding on all 15 Member States, but those reached through the decentralized procedure will apply only to the countries involved. Timetables for each stage in both procedures are specified. Decisions must state in detail the reasons on which they are based and must be communicated to those involved.[8]

These new measures provide for decisions which are ultimately binding on EU Member States. However, the role of the EMEA is advisory and not executive. Once it has given its opinion, the Commission prepares a draft decision for submission to Member States. If the latter do not oppose it, the decision becomes law. If one or more object on scientific grounds, a further round of discussions with the EMEA takes place. If the objections are on non-scientific grounds, the matter is referred to the standing committee of the Commission. Failure to achieve a qualified majority vote means referral to the Council of Ministers who will decide by a qualified majority vote.

Current trends

The EMEA is still developing its administrative procedures and otherwise settling down. Nevertheless, its first year has been encouraging.

During 1995 the EMEA received 30 new applications under the centralized procedure, representing 26 new active substances, and took over 18 more which were pending under the former concertation procedure. Significantly, 21 of the new applications were for products for which the procedure is optional. By January 1996 the EMEA had given 13 positive opinions concerning both converted concertation and new applications, and five Union marketing authorizations have been issued. The requirement that an opinion should be reached within 210 days – the clock being stopped if additional information is required – has been generally respected.[9]

The use of the decentralized procedure is less clear because no definitive pan-European figures are available. The UK Medicines Control Agency reported that 20 new products had completed the process during 1995 and had reached the market in at least some member countries. Some 150-200 variations of licence had been dealt with. Generic and self-medication products were among the applications as well as those containing new active substances. However, the industry attitude is cautious, fearing the possibility that the process of arbitration might be triggered if Member States do not agree with the CPMP decision. So far, this has happened in only one case.

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[8] As specified by Regulation (EEC) No 2309/93 and Directive 93/39/EEC.

[9] Information from the EMEA and the UK Medicines Control Agency.

The impact of the new systems on the costs of the industry is considered in Section 4.1.

3.2.2. Prices and price controls

Price differences and their effects

The prices of medicines vary widely between one member country and another. In part, these variations reflect variations in national income and therefore in average price levels. In part, however, they are due to the measures taken by national governments to control expenditure on medicines by their public health care systems.

The right of Member States to take such measures, subject to certain conditions, was confirmed by two decisions of the European Court of Justice, both of which turned on the interpretation of Article 30 of the Treaty of Rome. In the *Roussel* case, it was decided that price regulations, including price freezes, might be imposed provided that they did not discriminate against imported products or in favour of local firms.[10] In the *Duphar* case, it was decided that reimbursement might be refused to particular medicines in order to protect the financial stability of the public health insurance system. Once again, however, this was contingent upon such decisions being non-discriminatory and based on objective and verifiable criteria.[11] Thus, exceptionally, the prices of self-medication products are also regulated in Belgium, Portugal and Spain.

Price controls may have the following effects:

(a) access to national markets may be delayed while admission to reimbursement or permitted prices are agreed;
(b) prices may be fixed at relatively low levels;
(c) where differences between national prices exceed a certain level, a parallel trade in medicines may develop;
(d) price controls may be used to encourage or reward local activities.

Delays in admission to reimbursement and in fixing prices

The majority of member countries operate positive lists, i.e. reimbursement under the national health care system is confined to those medicines that have been specifically approved. In such countries, admission to reimbursement – which normally involves agreement on a permitted price – is separate from and usually subsequent to marketing authorization. Elsewhere admission to reimbursement is automatic except for certain products or classes of product that have been specifically excluded in a negative list.

Given that national health care systems pay for the majority of the medicines bill, pharmaceutical companies find it highly desirable for their products to be admitted to reimbursement. During the 1980s delays in admission and in agreeing a price were common,

[10] Case 181/82 *Roussel Laboratories and others* v *Netherlands* [1983] ECR 3849.

[11] Case 238/82 *Duphar and others* v *Netherlands* [1984] ECR 523. Examples of objective and verifiable reasons were 'the existence of other less expensive products having the same therapeutic effect, the fact that the preparations in question are freely marketed without the need for any medical prescription, or are products excluded from reimbursement for reasons of a pharmacotherapeutic nature justified by the protection of human health'.

usually ranging from three to six months, but sometimes amounting to a year or more.[12] Moreover, once fixed, official permission was required to change a price in response to increased costs, inflation and so on. Such permission was often refused, with the result that in real terms the price of a medicine tended to fall during its life-time. Price freezes were common. Finally, the bases of official decisions were far from clear.

The EC responded with the so-called Transparency Directive of 1989,[13] intended to make the processes of admission to reimbursement and determination of prices more transparent, while also imposing timetables for the processes involved. As far as admission to reimbursement is concerned, inclusion on a positive list must be decided within 90 days of application. Refusal to include a product or group of products for reimbursement must be supported by a statement of 'objective and verifiable' reasons. The national authorities must publish and inform the European Commission of the criteria used to make such decisions. Similar provisions apply to negative lists. In addition, the national authorities must publish a list of excluded medicines every six months.

As far as prices are concerned, the Directive requires that Member States must both make decisions about the prices of new medicines and communicate them to applicants within 90 days of the application. If the responsible body fails to do so, the applicant may market the product at the price proposed in the application. If the application is rejected, the authority must provide reasons based on 'objective and reliable' criteria. Applications for price increases are subject to similar provisions. Price freezes must be reviewed annually. Where profitability is controlled, as in the UK, the authorities must publish the range of target profits permitted, the criteria used to assign targets to particular companies and the extent to which firms may exceed these targets.

The effects of the Directive have been modest. There is no industry consensus as to whether or not it has reduced the time taken for admission to reimbursement, although the majority feeling is that the processes involved have become somewhat more transparent.[14]

Relatively low prices

Controls over the prices of medicines have never been popular with the pharmaceutical industry. The major research-oriented companies have complained for many years that prices among the Member States of the Union not only vary but are often too low. In their eyes, their own continued ability to develop new products is therefore compromised.

There is much controversy about such statements. Critics point to the continued prosperity of the international sector. Furthermore, it is rare for a company to refuse to market a widely-used product even if the price is low; provided that it can cover its direct costs and make some contribution to overheads, that is sufficient. In any case, low prices only concern the Commission if they inhibit intra-Union trade; this could be the case if, for example, they made

[12] Information from Interpharma and the British Pharma Group in 1991. In 1990 delays in member countries of the Union were reported to be as follows: Belgium 10 months, France 2-5 months, Greece 5 months, Italy 12 months, Portugal 6-12 months, and Spain 30 months.

[13] Directive 89/105/EEC.

[14] Interpharma, op. cit., note 12. In 1991 delays had become as follows: Belgium 5 months, France 2 months, Greece 3 months, Spain 48 months.

imports unprofitable. This is difficult to prove. The European Commission failed to do so in a case which it brought against Belgium before the European Court of Justice.[15]

Parallel trade in medicines

Parallel trade takes place when a good has significantly different prices in two or more different markets. Traders buy in the low-price market and sell in the high-price markets. It is a form of arbitrage and helps prices to converge. The only unusual feature of the parallel trade in medicines is that the price differences that make it worthwhile may result from the actions of governments rather than manufacturers or distributors.[16]

Parallel trade in medicines began in the 1970s. To no small extent it owed its rise to decisions by the European Court of Justice. It was laid down that parallel trade was legal even when price differences were the result of government action;[17] that governments could not exclude a product for which the importer was unable to produce the necessary documentation from the manufacturer;[18] and that repackaging was permissible provided that the condition of the product was not affected.[19] Neither patent rights nor trade mark legislation could be invoked to prevent the trade. In all these cases Article 30 of the Treaty of Rome was given preference over other articles and other considerations.

The development of this trade is discussed later in Section 4.2.2.

The use of price controls as incentives for local investment

To control prices or profits is to create opportunities for official pressure to be brought to bear on companies. A local firm may be treated more favourably. In return for admitting a new product to reimbursement or agreeing a better price for it, a foreign company may be expected to increase its local activities.

In the past incentives of this kind were common.[20] They were offered in Belgium, France, Italy and Spain and possibly elsewhere in Europe. In the UK the permitted rate of return on capital under the Pharmaceutical Price Regulation Scheme (PPRS) varied – and varies – according to 'the scale and nature of the company's relevant investments and activities [in the UK] and the associated long-term risks'. This had something of the same effect. In Denmark, Germany and the Netherlands, however, prices have never been controlled in ways that might lend themselves to this purpose. Ireland successfully encouraged the development of an export-oriented pharmaceutical sector by means of subsidies and tax concessions, but differential pricing played no part.

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[15] Case 249/88 *Commission* v *Belgium* [1991] ECR I-1275. For comments see *Scrip*, No 1598, 13.3.1991, pp. 8-9; ibid., No 1604/5, 3-5.4.1991, p. 4; ibid., No 1610, 24.4.1991, p. 4.

[16] This section is based primarily on Ranson, P. *Parallel imports and the law*, Richmond-on-Thames, PJB Publications, 1988; and Burstall, M. L. and Senior, I. S. T. *Undermining innovation – Parallel trade in prescription medicines*, London, Institute of Economic Affairs, 1992.

[17] Case 15/74 *Centrafarm BV and others* v *Sterling Drug* [1974] ECR 1147; Case 16/74 *Centrafarm BV* v *Winthorp* [1974] ECR 1183.

[18] Case 104/75 *de Peijper* [1976] ECR 613.

[19] Case 102/77 *Hoffmann-La Roche* v *Centrafarm BV* [1978] ECR 1139; Case 1/81 *Pfizer Inc.* v *Eurimpharm* [1981] ECR 2913.

[20] Burstall, M. L. and Reuben, B. G. *The cost of fragmentation in the European Community's pharmaceutical industry and market*, 1988, pp. 84-86 and 99-100; Burstall, M. L. and Wallerstein, K. R. B. *American pharmaceutical companies in Britain and Europe*, London, Economists Advisory Group Ltd, 1988, pp. 77-95.

To connect prices with local investment is clearly undesirable in a single market. Facilities were unnecessarily multiplied, and production costs in 1984 were 1.6-2.7% more than would otherwise have been the case.[21] At that time, most international companies felt that although the cost penalties were appreciable, they had no choice but to acquiesce to national policies. Local investment had been the entry fee to a number of commercially attractive markets. Firms felt that to withdraw might permanently sour relations with local authorities and damage their prospects for the future. Nevertheless, signs that the concentration of facilities had reached the strategic agenda were already apparent.

Several existing policies which openly related prices to investment were struck down by the European Court of Justice.[22] However, less formal arrangements which do not offer a definite *quid pro quo* remain. The French system of contracts is an example. Companies provide detailed information about current and future sales, investments and costs. Reimbursement prices are fixed with reference to the strategy of the firm and the therapeutic value of the products in question. The aim is to assure value for money without prejudicing the competitive position of the French industry. Similarly, in southern Europe international companies report that local activities count in their favour, even where there are no legal requirements.[23]

Major firms are therefore cautious about rationalizing their facilities, desirable as this may be on cost grounds. This conclusion is further explored in Sections 4.3 and 4.4.

Extending the Transparency Directive: the limits of Union action?

The Transparency Directive included a provision for further action 'leading to the abolition of any remaining barriers or distortions of the free movement of proprietary medicinal products so as to bring this sector closer into line with the normal conditions of the internal market'.[24]

Accordingly the Commission circulated a discussion document in 1991,[25] followed by a draft Directive, which, modified after extensive discussions, was put forward in August 1992. The draft was concerned in part with technical modifications but also contained a Recommendation to Member States to be followed when drug price controls or reimbursement systems were modified. It suggested that the use of direct price controls should be reduced wherever possible. Controls over admission to reimbursement should be the preferred way to regulate public spending on medicines. Free pricing should apply to products which were not reimbursed, which should include those for self-medication. Significant patient co-payments should be imposed. The use of generic equivalents should be encouraged. The central thrust was towards freer pricing, higher patient co-payments and a more restrictive approach to

[21] Burstall, M. L. and Reuben, B. G., op. cit., p. 108.

[22] Case C-249/88 *Commission v Belgium* [1991] ECR I-1275; Case 56/87 *Commission v Italy* [1988] ECR 2919.

[23] REMIT Consultants. *American pharmaceutical companies in the UK and Europe*, Part 2, London, 1995. It may be noted that the position of the PPRS is not dissimilar. It has never been challenged in the courts. A senior official of the UK Department of Health told the author that it was thought to be legal because (1) the permitted rate of return was not a strict *quid pro quo*, and (2) it was a chance to reach the specified rate and not a guarantee that it would be possible to do so.

[24] Article 9 of the Directive required the Commission to submit further proposals within two years of the Directive becoming law.

[25] European Commission. *Preliminary draft for measures aiming at modifying and completing Directive 89/105/EEC concerning the pricing and reimbursement of medicinal products for human use* (III/3749/91).

reimbursement. From the standpoint of the Union, they would have reduced the scope for covert subsidies and encouraged the development of a price-sensitive pharmaceutical market.

Both the Directive and the Recommendation were abandoned at the end of 1992.[26] Opposition from Member States to further central regulation of their health care finance systems was the major reason. The subsequent Communication on a possible industrial policy for the pharmaceutical industry[27] strikes a cautious note. The Commission is 'prepared to address with Member States the impact of direct price control on competition and the management of health care expenditure'. In the case of 'medicinal products which are available without prescription and which are not reimburse[able] ... it seems that the market is often competitive enough to ensure an affordable price level'. Furthermore, 'in the case of reimbursed ... products it could be interesting to consider other cost containment measures'.

Thus, price controls and reimbursement systems remain firmly in the hands of Member States.

3.2.3. The rational use of medicines

In 1992 the Commission adopted a package of four Directives (92/25-28/EEC), commonly referred to as the Rational Use of Medicines Directives. They were intended to eliminate actual or potential barriers to intra-Union trade while ensuring that patients were thoroughly protected against dangerous or misleading practices. Before 1992, these matters had been left to the individual Member States, whose regulations had varied appreciably.

The classification of medicines

With the exception of Greece,[28] all Member States have, for many years, distinguished between medicines that require a doctor's prescription and those that do not and may therefore be bought freely. They varied considerably in where they drew the line, and so products might differ in their availability. Moreover, the Advertising Directive (92/28/EEC) and the forthcoming centralized procedure for obtaining marketing authorization required clarification of the legal status of pharmaceuticals.

Directive 92/26/EEC required national authorities to classify medicinal products at the time of marketing authorization. Prescriptions were to be required for products that were likely to present dangers if used without medical supervision, those which were frequently used incorrectly, those based on substances that need further investigation or those given by injection. Other medicines were to be classified as non-prescription products. Member States were to compile lists of prescription and non-prescription products, update them annually and communicate them to the Commission and other Member States. The Commission was to report by 1996 on the operation of the Directive and, if necessary, make further proposals.

Enquiries showed that the self-medication sector had welcomed the Directive, which was seen as encouraging the transfer of medicines from prescription-only to non-prescription status. However, it was widely noted that, as yet, classification remains in the hands of individual

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[26] This was made clear by Sir Leon Brittan, then Vice-Chairman of the European Commission at a Conference organized by the Institute of Economic Affairs in Brussels (1 December 1992). The remarks by Mr Strachan Heppell, Deputy Secretary of the UK Department of Health, are also highly relevant.

[27] European Commission. *Communication from the Commission to the Council and the European Parliament on the outlines of an industrial policy for the pharmaceutical sector in the European Community*, COM(93) 718 final, 1993.

[28] In Greece all medicines require a prescription in principle.

governments whose behaviour varies. A product available for self-medication in one country may be available only on prescription in another. Some member countries, such as the UK, have a liberal attitude to transferring medicines to non-prescription status; others, such as France, have a more conservative attitude.

Firms mainly active in the prescription-only market felt that the Directive was only of marginal interest to them.

Advertising medicines

An earlier Directive[29] forbade misleading advertising in general, but until 1992 the regulation of pharmaceutical advertising was again left to the Member States.

The new Directive 92/28/EEC prohibits all forms of advertising to the public of medicines that are available only on prescription. Such products may be advertised to health care professionals subject to certain specified restrictions. Most – though not all – inducements to prescribers are forbidden. Sales staff must be adequately trained and are obliged to report adverse reactions to their superiors. Non-prescription drugs may be advertised to the public, provided that the material does not mention the treatment of diseases which are not suitable for self-medication, make unfounded claims, compare the product with other alternatives, suggest that it is superior because it is natural or use a number of other specified stratagems.

Once again, Member States have the responsibility for the regulation of advertising. Their methods, attitudes and controls differ widely. All forbid general advertising for prescription-only medicines. Where non-prescription medicines are concerned, a majority favour self-regulation, but Belgium, France and Portugal have official bodies for this purpose. Moreover, in France, Italy, Portugal and Spain, reimbursable medicines may not be advertised even if they do not require a prescription. These variations together with differences in classification are seen by the self-medication sector as a barrier to the unification of the European market.

Labelling and patient information

From the beginning of Union legislation about pharmaceuticals, provision was made for the regulation of package labelling and patient information.[30]

Directive 92/27/EEC extended and elaborated this earlier legislation. The information to be provided on the outer packaging is specified in detail, including the name, form and strength of the medicine; its composition; the method of administration; the unit dose; the expiry date; the name and address of the holder of the marketing authorization; and the manufacturer's batch number. The patient information leaflet must identify the product; the indications for which it is to be used; the information necessary before it is taken, including on persons or circumstances when caution is necessary; the instructions for use; and an account of the possible side-effects and the action that should be taken. The languages used must be those of the countries in which the product is to be marketed. Samples of the packaging and leaflets

[29] Directive 84/450/EEC. Under Directive 89/552/EEC television advertising of prescription-only products was already forbidden.

[30] The information to be supplied on the medicine's package was laid down by Directive 65/65/EEC and that to be contained in patient information leaflets – if those were to be provided – in Directive 75/319/EEC. The inclusion of patent information leaflets was made obligatory by Directive 92/26/EEC, unless it could be conveyed on the packaging itself.

must be submitted when applying for marketing authorization; for this reason the EMEA has jurisdiction over products applied for through the centralized system of approval and Member States over those applied for through the decentralized or national procedures. Member States must refuse such authorization if the packaging or labelling does not comply with the Directive.

The Directive has had its most immediate impact in the UK where original pack dispensing and patient information leaflets were not mandatory for prescription medicines. Its provisions are now being phased in. As yet, pan-European packs have not appeared, perhaps because 11 languages are spoken in the 15 member countries.

Wholesale distribution

Making and selling medicines are separate activities. Drugs are typically sold by manufacturers to wholesalers, by wholesalers to retail pharmacists, and by retail pharmacists to final consumers. These operations are subject to different types of official regulation.

Directive 92/25/EEC is concerned with pharmaceutical wholesaling, where one company may supply several member countries. It requires that wholesalers be authorized by the Member State where they are located; once authorized, they may operate in other Member States. A timetable is specified for dealing with applications for authorization. Successful applicants must meet specified minimum requirements in terms of premises, equipment and qualified personnel. They must satisfy the authorities that they have plans to recall products from the market should this be required. They must keep specified records for a period of five years. They must also comply with the principles and guidelines of good distribution practice for medicines.[31]

Major wholesalers feel that the Directive reflected their own long-standing policies rather than imposing new requirements. More generally, the Union has not as yet considered retail distribution, although this activity is subject to official regulation in all Member States and the controls applied arguably differ more considerably than those which apply to pharmaceutical wholesaling.

3.2.4. Intellectual property

The research-based pharmaceutical sector has always attached great importance to patent protection for new medicines. Moreover, there is a particular problem attached to patents for pharmaceutical products. To be allowed onto the market, it must be shown that a new medicine is safe, efficacious and of good quality. To prove that this is the case, extensive and prolonged testing in animals and humans – often lasting many years – is unavoidable. While this work is carried out, patent protection is necessary, since many persons and organizations other than the innovator are involved. In consequence, when a medicine reaches the market, much of the patent life may already have been consumed.

The basis of patent legislation in the Union is the European Patent Convention of 1973. Products, processes and uses are covered, and 20 years of protection are given from the date on which the application is filed. Application may be made to a national agency for protection in that country; alternatively, the office in Munich is empowered to award a bundle of national

[31] European Commission. *Guidelines on good distribution practice of medicinal products for human use* (94/C 63/3).

patents giving protection in all the countries that have signed the Convention. The Convention is independent of the Union, and several non-EU countries – notably Switzerland – adhere to it.[32] By 1981, all the then Member States had subscribed to the Convention, and it was made a condition of the Accession Treaties under which Greece, Portugal and Spain joined the EU that they should also do so. Thus, barriers to trade due to differences in the type and extent of protection had in principle been eliminated well before the single market came into being.

The Convention is a general one which covers all forms of product and process and is not in any way confined to medicines. Hence, further action was needed to solve the problems already indicated. This was clearly best done at Union level, so as to avoid the creation of new obstacles to trade.

Marketing exclusivity

This was a by-product of Directive 87/21/EEC, which was essentially concerned with abridged applications for marketing authorization for copy products. The applicant with an essentially similar product was allowed to omit the normal pharmacological, toxicological and clinical evidence if:

(a) the originator gave permission for his own data to be used; or
(b) the applicant was able to show that the published literature demonstrated that the constituent or constituents of the product have a well-established medicinal use with recognized efficacy and an acceptable level of safety; or
(c) the applicant was willing to wait for six years – under certain circumstances ten years – from the date of first licensing of the product, after which the applicant could refer to the originator's data without his or her consent.

In effect, this conferred on the originator a minimum of six years' protection against a second application for marketing authorization, since he or she was not obliged to supply the necessary information to a competitor. This period was extended to ten years for products developed by biotechnology or high technology. Member States were allowed to extend the six-year exclusivity period for all products to ten years at their discretion, and Belgium, France, Germany, Italy, the Netherlands and the UK did so. However, again at their discretion, they were also at liberty not to apply the six-year limit beyond the expiry of the patent, and Denmark took the decision not to do so. Ireland, Luxembourg, Greece, Portugal and Spain kept the six-year limit for medicines not based on high technology or biotechnology.

Supplementary protection certificates

In 1984 the USA passed legislation allowing patents for pharmaceuticals and certain other products to be extended by up to five years in order to allow for the time used in testing for safety and efficacy and for the Food and Drug Administration to decide upon marketing authorization.[33] Japan followed suit. Several European countries considered similar measures

[32] The introduction of a Union patent was agreed by the Member States of the Union in 1989 but is yet to come into force.

[33] The US Patent Office grants protection lasting 17 years from the time of grant. The extension allowed to drugs under the Waxman-Hatch Act of 1984 is the time taken by the Food and Drug Administration to review the completed application plus half the time required to conduct clinical studies of safety and efficacy. The extension, however, must not exceed five years and effective lifetime of the patent must not exceed 14 years.

and France put forward concrete proposals. Faced with pressure from the European industry for some form of additional protection and faced with the possibility that action by the individual Member States might well fragment the EU market, the Commission proposed a common solution which came into force in 1993.

Under Regulation (EEC) No 1768/92 a supplementary protection certificate (SPC) comes into force when a patent expires. It provides further protection for up to five years, provided that the total period of protection by patent and SPC is not more than 15 years. For example, consider a product for which the patent was applied for on 1 January 2000 and for which the first marketing authorization was received on 1 January 2007; the SPC would provide an additional two years protection. However, take a product for which the patent application was made at the same time but which did not receive approval until 2012; the SPC would give five years extra protection, but the total would nevertheless be only 13 years.

Because this measure is a Regulation it came into effect immediately and did not have to be incorporated into national law. Furthermore, an application for an SPC cannot be opposed. However, separate applications have to be made in each member country. Transitional arrangements were made for products already on the market and in patent in 1993, but here some discretion was left to the Member States. In most of them SPCs are available for all products which received marketing authorization on or after 1 January 1985; in Belgium and Italy the corresponding date is 1 January 1982 and in Denmark and Germany 1 January 1988.

The advent of SPCs is a definite benefit to the research-based industry but an obvious blow to the generic drug sector. In this connection, an issue which has recently emerged concerns the point at which a generic company may start to develop its products in order to introduce its version of a medicine as soon as protection expires. The US legislation to which reference has already been made allows this – by the so-called Bolar Roche clause – to begin before the end of the patent. There is no such provision in the EU Regulation, which is a cause for concern to the European generic companies.

Biotechnology patents

The extent to which inventions developed by biotechnology are patentable has raised ethical and political questions which have proved difficult to resolve. So far the limits have been established through *ad hoc* decisions by national authorities and by the European Patent Office. Significant variations between member countries are emerging and could have an impact on marketing authorization. Given the rising importance of biotechnological innovation, new barriers to intra-Union trade might emerge. For this reason, the Union attempted to harmonize the protection of products developed in this way by means of a proposal for a Directive.[34] After a prolonged gestation period and repeated modification, this measure was rejected by the European Parliament. The new proposal[35] tabled by the Commission in 1995 has taken on board the European Parliament's concerns and is likely to be adopted at the earliest in 1997.

[34] Legal protection of biotechnological inventions COM(88) 496; COM(92) 589.

[35] COM(95) 661.

3.3. Horizontal measures and their impact

The pharmaceutical industry may also be affected by general measures taken to create the single European market. The areas in question and their potential effects are summarized in Table 3.3. Certain of them call for a more extended treatment.

Table 3.3. Horizontal legislation of immediate, potential or indirect significance to the pharmaceutical sector, 1985-93

Area	Legislation	Effects
	Immediate relevance	
Product liability	Directive 85/374/EEC	Imposes strict liability; allows development defence.
Intellectual property	Directive 89/104/EEC	Approximates national law on trade marks.
	Regulation (EEC) No 40/94	Creates Community trade mark.
Public procurement	Directive 93/36/EEC	Consolidates earlier directives of 1971 and 1977 and amendments governing public supply contracts.
	Potential relevance	
Genetically modified organisms	Directive 90/219/EEC	Controls contained use of such organisms.
	Directive 90/220/EEC	Controls release of such organisms.
Taxation	Directive 90/435/EEC	Common system for taxation of parent companies and subsidiaries.
Competition policy	Articles 85 and 86 of Treaty of Rome	Continued interpretation by European Court of Justice sets limits on European and national controls.
	Regulation (EEC) No 4064/89	Controls mergers over a certain size.
State aids	Article 92 of Treaty of Rome	Continued interpretation by European Court of Justice sets limits on European and national controls.
	Indirect relevance	
Free movement of goods	Article 30 of the Treaty of Rome	Continued interpretation by European Court of justice sets limits on European and national controls.
		Abolishes border controls within the EU.
	Directive 88/379/EEC	Approximates national regulations on classifying and packaging dangerous chemicals. Medicinal products are excepted but raw materials may not be.
Free movement of capital	Directive 88/361/EEC	Implements Article 67 of the Treaty of Rome in creating a liberalized capital market.

3.3.1. Measures of immediate relevance to the pharmaceutical sector

Product liability

By their very nature the use of medicines carries a risk. The large majority of them have untoward side-effects in certain patients, even though the number may be small. Their use is justified because in general their benefits outweigh the risks. Medicines also carry development risks – those that could not have been foreseen when the product was marketed. Particularly after the thalidomide disaster, cases with claims for compensation for injuries

caused by drugs became more common. They were dealt with under the laws of the individual Member States which varied considerably.

As part of the programme to remove internal barriers to trade and to create a single market for goods and services, the EU adopted a general Directive on product liability.[36] This imposed strict liability, i.e. the question at issue is whether or not a product is defective. If so, the producer is liable. The burden of proof lies on the plaintiff. The possible defences for a producer are specified. For a pharmaceutical manufacturer the most important is the development risk defence, i.e. that the state of scientific knowledge at the time the product was put into circulation was not such as to enable the existence of the defect to be discovered. The Member States were allowed to choose whether or not to incorporate this defence as they transposed the Directive into national law. All did so. However, a number of other factors, including levels of damages, procedures and limitation rules were not harmonized.

Trade marks

The situation as regards pharmaceutical patents has already been outlined, from which it will be remembered that patent protection in Europe has developed largely outside the institutions of the EU.

However, patents are not the only form of intellectual property. Trade marks are also valuable, especially for the pharmaceutical industry. Most medicines are sold under brand-names and this name lasts indefinitely. Experience suggests that the goodwill attached to a brand-name is considerable and helps a product to retain a part of its market for some time after patent protection expires. The EU recently introduced the Community trade mark,[37] a single instrument of protection, obtainable by making a single application and giving the same rights everywhere. Member States are, however, allowed to continue to register national trade marks.[38]

Products seeking marketing authorization under the centralized procedure must use the same brand-name in all European countries. Although held by the Commission to promote a single market, it has aroused anxiety in the industry. To find a name suitable for pan-European use is difficult. Other problems concern national regulations. In most member countries – Germany and the UK are the main exceptions – it is not possible to use the same brand-name for the prescription and self-medication forms of the same product. In France, this is permitted, but both are then excluded from reimbursement.

Public procurement

Public authorities in most member countries own and operate hospitals, though they do not have a monopoly of these institutions. Consumption by hospitals is some 10-20% of total pharmaceutical consumption by value. There is often keen competition to supply them, because the volumes required are large and because patients prescribed a particular medicine in hospital are likely to continue with the same product after they are discharged. Medicines

[36] Directive 85/374/EEC. This account is based mainly on ed. Kendall, V. *Product liability for pharmaceuticals*. European Pharma Law Centre, 1992.

[37] Regulation (EEC) No 40/94.

[38] National laws on trade marks had already been approximated by Directive 89/104/EEC.

sold through ordinary pharmacies, however, are not involved, since wholesalers and retailers are private enterprises.

Hospital supplies, including drugs, may therefore be regulated by the Directives governing public procurement. The object of these measures is to coordinate national contract award methods for transactions above ECU 200,000 net value and to make sure that there is no discrimination against potential suppliers on the grounds of nationality. The latest Directive, which consolidates all previous legislation, specifies that calls for tenders must be published in the *Official Journal of the European Communities*, S series, lays down how the process of decision is to be carried out, together with the grounds for acceptance or rejection of a candidate, and provides for a large degree of transparency.

To date problems concerning public procurement have not emerged as a major concern of the pharmaceutical industry.

3.3.2. Measures of potential relevance to the pharmaceutical sector

Competition policy

The bases of EU action in this area are Articles 85 and 86 of the Treaty of Rome. The former prohibits all agreements between undertakings which may affect intra-Union trade or distort competition within the Union. In particular, price-fixing and market-sharing agreements are forbidden. However, such agreements are permitted if they '...contribute to improving the production or distribution of goods or to promoting technical and economic progress while allowing consumers a fair share of the resulting benefit...'. Article 86 prohibits abuse of a dominant market position by imposing unfair purchase or selling prices or limiting production, markets or technical development to the prejudice of consumers. Both articles forbid discrimination against other trading parties and the imposition of unreasonable supplementary obligations.[39]

The interpretation of these articles has given rise to a large body of case-law, much of it concerned with the meaning of and limits upon the various clauses. In practice Article 85 has been held not to prevent agreements to limit or control production where an industry is suffering from substantial over-capacity and where a temporary cartel would assist necessary structural adjustment. This was the case with, for example, the synthetic fibres sector. It has also allowed joint research and development programmes provided that the object of the work is clearly defined, that all parties have access to the results and are free to exploit them, and that joint exploitation of the research, if undertaken, relates only to results protected by patent or which constitutes significant know-how. Outside these areas the Union has been notably less sympathetic to practices that reduce competition.

Article 86 has also required much interpretation. Dominance starts to be an issue when a stable market share reaches 30-35% of the Union market or a substantial part of it, although the definition of the market is often difficult to determine. Abusive conduct has been taken to include excessive prices, refusal to supply particular distributors, and discrimination in pricing between different Member States. Pressure by a dominant undertaking on its customers to fulfil most or all of their requirements from itself is also an abuse. Thus, rebates offered to customers are generally illegal if used by a dominant firm. So are policies in which

[39] This section is based mainly on Goyder, D. G. *EEC competition law*, Oxford, Clarendon Press, 1988.

expressions of related technologies are unreasonably bundled together rather than sold separately. Once again, some of these practices are difficult to prove.

Finally, mergers are subject to the condition that they must not infringe Articles 85 and 86. A recent Regulation controls their formation.[40] The Commission must be notified in advance of any merger where the combined world-wide sales of the companies concerned exceed ECU 5,000 million and where the sales within the Union of at least two of these companies exceed ECU 250 million. Companies which achieve more than two-thirds of their sales within one and the same Member State are, however, left to the control of that state. A merger which does not create or strengthen a dominant position which would reduce effective competition within the Union or a substantial part of it is permissible. The Commission is empowered to decide whether this is so or not and to enforce its decision subject to right of appeal to the European Court of Justice.

The pharmaceutical industry is relatively fragmented. As it is demonstrated in Section 4.6.1 no company has more than 4% of the EU market. However, concentration within a given therapeutic area may be much higher, with three or four firms – even less – dominating the market. Price competition is often limited and a substantial proportion of sales are of in-patent products. In all member countries the sale of prescription medicines to the public is confined to retail pharmacies and in a majority of them the same is true for non-prescription products.

Mergers between pharmaceutical companies have been little affected by EU law. No important merger has so far been prevented, although conditions have been imposed in some cases. Thus, Glaxo was obliged to license out an anti-migraine drug then under development when it merged with Wellcome; the degree of overlap between products appears to be the crucial factor.

State aids

State aid to industry is permitted by the Treaty of Rome under certain conditions. Article 92 forbids such aid in so far as it affects trade between Member States unless it promotes the development of areas which are unusually poor or where unemployment is high, is intended to remedy a serious disturbance in the economy of a Member State, facilitates the development of certain activities or areas without adversely affecting trade, or is otherwise approved by the EU. All schemes must be approved by the Commission, and once again an impressive body of case-law has developed. In effect approval depends on the scheme in question being selective, transparent, temporary and of an appropriate nature. A large number have been rejected on one or other of these grounds.

In the past the pharmaceutical industry often benefited from regional incentives to investment, which most commonly took the form of grants or soft loans. As permitted by Article 92, the areas in question were those where economic growth was slow or where unemployment was high. Ireland provided – and provides – subsidies and tax concessions to a range of high-technology industries. Until 2011 the maximum corporate tax rate is 10% while generous capital and R&D grants are also available. The pharmaceutical industry has benefited among others and Ireland is a major centre for the production of active substances. Italy also provides grants to encourage research in Italy; the pharmaceutical industry is the largest single recipient.

[40] Regulation (EEC) No 4064/89; see also Regulation (EEC) Nos 2367/90 and 3384/94.

Generally, however, such incentives are of declining importance.[41] They were a significant factor in the past, especially when major firms were considering where to manufacture their products. By now most companies are more concerned to rationalize rather to expand their operations.

[41] REMIT Consultants: *American pharmaceutical companies - R&D and manufacturing investment in Europe*, 1995.

4. The impact of the single market measures on the performance of the pharmaceutical sector of the EU

The previous chapter has surveyed the actions taken by the EU to bring about a single market in pharmaceuticals and has indicated their nature, scope and limitations. We now turn to the impact of these measures on the pharmaceutical sector. Many of the activities of the sector have been under official regulation. At the beginning of the SMP such regulation was almost entirely national in character and generally differed from one member country to another. Such controls often amounted to barriers to trade. Markets were segmented and operations fragmented. In an effective single market such barriers would be absent. Other things being equal, trade in medicines should rise. A genuine pan-European market should emerge in place of a series of national markets. Production would be concentrated where it was most effective. To the extent that economies of scale are a significant factor, costs should be reduced. Competition should increase; prices and profits should fall; and marginal producers and distributors should be eliminated.

Two important reservations are necessary however. Other things are not always equal. Traditions of medical practice and attitudes to the place of medicines in health care vary widely between member countries and have a substantial effect on what is sold and in what amounts. Patterns of demand may eventually converge but only slowly. Moreover, the highly developed multinational system of operation has to some extent overcome the effects of non-tariff barriers. The effects of the SMP may then be correspondingly muted. More generally, in considering the impact of the single market measures it is clearly necessary to distinguish between markets and suppliers of different kinds and sizes.

That said, the following sections of this chapter attempt to determine what progress has been made from the 1985 *status quo* towards a single European market for medicines and to estimate the role of EU legislation in this direction. In doing so it is necessary to consider both direct and indirect effects and allow for the sometimes complex and diverse impact of these measures.

4.1. Direct short-term impact on production costs

The production costs of the pharmaceutical industry may be divided into pre-production costs (i.e. those incurred before a product reaches the point at which it is marketed), and actual costs incurred in the production process itself. The former are primarily those of innovation, including those of obtaining marketing authorization while the latter are the usual costs of raw materials, services, labour and capital. In the pharmaceutical industry pre-production costs are proportionately more important and direct production costs are proportionately less important than is the norm in manufacturing industry.

The SMP would be expected to affect such costs in the following ways:

(a) the costs of innovation would be reduced:
    (i) by encouraging the concentration of facilities and the exploitation of economies of scale,
    (ii) by making it possible to place facilities where they would be most effective;

(b) the costs of obtaining marketing authorization would be reduced by standardizing the information required and simplifying the process of evaluation;
(c) production costs would again be reduced:
  (i) by facilitating the concentration of production and the realization of economies of scale,
  (ii) by making available cheaper sources of materials and services;
(d) good manufacturing practice might, however, raise costs.

Economies of scale and their effects are explored in Section 4.3. Here we are concerned with the other potential effects.

4.1.1. Pre-production costs

Spending on research and development

To discover, develop and bring to the market a medicine based on a new active substance (NAS) is a prolonged and expensive process. The costs of doing so have risen substantially over the past 30 years, from 1990 ECU 90 million for drugs entering human testing in the USA in 1963-75 to ECU 200 million for those entering testing in 1970-82.[42] Figures as high as ECU 400-500 million have been suggested for the present day. These estimates include the costs of failures but also opportunity costs; the actual cash outlays were about 50% of these figures. As a proportion of output R&D expenditures rose within the EU from 9.3% in 1982 to 12.3% in 1993; growth relative to production was above the EU average in Denmark, Italy, Spain and the UK and below it in Belgium and the Netherlands.[43] For the research-based international companies the proportions of sales spent on R&D are yet higher.

Thus by any measure the costs of R&D have risen rather than fallen. However, this is a universal trend, shared by the industries of the USA and Japan. Innovation has become more difficult everywhere. It remains possible that the SMP has prevented costs rising further than might otherwise have been the case. The concentration of research facilities might have this effect. In practice such concentration was limited until the current wave of mergers described in Section 4.4.2. Moreover, R&D is already concentrated in countries which are inherently attractive for research. For example, US firms account for 17% of all pharmaceutical R&D undertaken in the EU. Of their 1993-94 spending, 36% was in the UK, 28% in France and 9% in Germany; a similar distribution has prevailed for a number of years.[44]

Our enquiries show that there is a general feeling that the efficacy of research needs to be enhanced. Organizational changes to this end are being introduced in many companies. There is agreement that some further concentration would probably be desirable. However, the continued existence of incentives for local investment (Sections 3.2.2 and 4.3.2) has inhibited action. The impact of the SMP has therefore been limited.

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[42] US Office of Technology Assessment. *Pharmaceutical R&D - Costs, risks and rewards*, Washington DC, US Government Printing Office, 1993. The studies quoted are Hansen, R. W. in ed. Chien, R. A. *Issues in pharmaceutical economics*, Lexington, D. C. Heath and Co., 1979, and Di Masi, J. A., Hansen, R. W. and Grabowski, H. G. *Journal of health economics*, No 10, 1991, pp. 107-142. The samples of drugs are those which reached the US market in the 1970s and 1980s.

[43] Authors' calculations are based on information from EFPIA, national industry associations and the Centre for Medicines Research.

[44] Information from PhRMA, Washington DC; for a more detailed description and analysis see Burstall, M. L. et al. *American pharmaceutical companies: R&D and manufacturing investment in Europe*, 1995.

Marketing authorization

About one-third of the cost of developing a genuinely new medicine is that of the clinical and toxicological studies needed to establish to the satisfaction of national licensing authorities that it is safe and efficacious. In the past there were substantial differences in the data required by Member States and still more in their interpretation. These differences have now been largely though not totally eliminated: national authorities are still reported to ask for extra data on occasion. There was also some feeling in international companies that clinical standards were higher in some member countries than in others. This is now considerably attenuated, although it remains to some extent.[45]

To this extent the actions of the EU since 1965 have been successful. However, the saving in costs is modest.[46] During the past 20 years clinical trials have become more elaborate and more focused on products for chronic disease. They have become correspondingly more expensive. Moreover, a new product must be sold world-wide if it is to recover its development costs and must have access to all major markets. International companies have therefore always worked to the highest standards which in the past were those of the US Food and Drug Administration. Moreover, within Europe they coped adequately with differing national requirements by compiling a master dossier from which the specific application was constructed.

A further problem is the time taken to grant marketing authorization. This is of importance to the research-based sector in that it ties up capital and reduces effective patent life. It is also of concern to patients since it may deny them access to better medicines. In 1990 the average time of approval was close to two years for the UK and Japan, with France more rapid and with Germany, Spain and the USA taking substantially longer. By 1994-95 France, Germany, the UK and the USA all took approximately two years to admit new medicines. A downward trend in the time taken was visible in Spain and an upward one in Italy and Japan.[47]

There is a general consensus that increased resources and the dissemination of best practice have improved the efficacy of some national authorities. The activities of the Committee for Proprietary Medicinal Products (CPMP) have played a significant part in the latter. The existence of the multistate procedure, which was used on occasion to by-pass the slower national systems, may also have been important. As yet there is insufficient evidence to show whether or not approval times for new active substances will be further improved by the centralized or decentralized procedures, although experience so far with the former suggests a cautiously optimistic conclusion (Section 3.2.1).

For generic and self-medication products patent protection is not an issue. However, factors that delay entry to the market impose opportunity costs and limit competition. The decentralized procedure should therefore benefit these sectors which view it with approval. However, problems have already surfaced. There have been reports that updated dossiers have been required for older self-medication products, despite their having been on national markets for many years. Both direct and opportunity costs have been increased. Classification

[45] Enquiries in connection with this and another study. A definite economy due to EU action is the fact that clinical data from all member countries are now more generally acceptable throughout the Union.

[46] Burstall , M. L. and Reuben, B. G. op. cit. pp. 52-67. In the mid-1980s the extra direct costs of multiple registration were estimated as a maximum of 0.16% of total industry costs. Savings to nations from the new systems of approval are negligible, since national authorities will remain in being.

[47] Information from the Centre for Medicines Research. *CMR News*, Spring 1996.

(Section 3.2.3) and trade mark issues (Section 3.2.4) are also a source of anxiety to the self-medication sector. National differences in bioequivalence requirements and marketing exclusivity handicap generic producers.[48]

4.1.2. Direct production costs

To analyse direct production costs in detail is not easy. Much depends on the operations of individual companies and the composition of the national pharmaceutical sector. Some companies are marketers who buy in what they sell; others turn bulk drugs into dosage forms and package them for retail sale; yet others make the active materials used in their products. Even among this last category there are substantial differences. Most active substances are made by complex processes and much turns on what stages are carried out within the company and what is bought ready-made. Finally, the technological basis of production may change; thus, medicines derived from biotechnology are becoming increasingly important.

German data throw some light on production costs. For the sector as a whole, they were around 40% of all costs, falling from 45% in 1980 to 39% by 1987 and remaining broadly constant thereafter. They were a bigger proportion for small companies than for large ones.[49] An OECD estimate[50] for large multinationals suggested that manufacturing had been 50% of all costs in 1973 but only 34% by 1989. An analysis of the reports of major companies suggested that the current figure was between 30 and 35% of the total and had been falling slowly for many years. In contrast, the corresponding figure for generic firms was 60-70%.

What has been the impact of the SMP on production costs? It appears to be limited. Companies are keen to cut such costs and have taken a variety of measures to this end. Production of particular medicines has often been concentrated at a single site in order to realize economies of scale. Processes have been constantly improved in detail. Cheaper sources of intermediates have been sought and often found. The impetus has come primarily from downward pressures on pharmaceutical spending, present or anticipated, rather than enhanced opportunities for economies. Good manufacturing practice guidelines are thought to present no problems for large research-based companies but arouse some anxiety among generic producers.

4.2. Development of cross-border sales and marketing

National markets within the Union are supplied by a mixture of imports from countries both inside and outside the Union, by local production by foreign companies and by local production by indigenous firms. The distribution of pharmaceuticals through wholesalers and retailers has until recently been organized on a national basis.

How might the single market measures have affected this pattern? Other things being equal, several consequences would be expected.

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[48] *Scrip OTC*, 10.1995, p. 1; *Scrip*, 2.1996, No 1999, p. 3; interviews.

[49] Bundesverband der Pharmazeutischen Industrie. *Pharma Daten*, various issues.

[50] OECD, *Globalization of industrial activities: Sector case study of globalization in the pharmaceutical industry*, Paris, 1994. It should be noted that these data refer to world-wide operations of these companies and can be used as a guide to Europe only with caution. However, Nefarma estimated that in 1991 production, quality control and distribution formed 39% of the costs of the innovative pharmaceutical industry in Europe.

(a) Competition should increase; successful medicines should be sold more widely; companies' share of their own national market should diminish.
(b) As trade becomes easier, imports of finished medicines should form a rising proportion of consumption and local production by foreign firms a declining proportion.
(c) To the extent that prices differ significantly between member countries a parallel trade in medicines should develop.
(d) Distributors should increasingly operate across national borders; distance selling should develop.

4.2.1. Consumption, trade, and local production

Patterns of consumption

How has the pattern of pharmaceutical consumption within the EU changed in the period under review?

As Table 4.1 shows, in terms of the products used, no EU market has ever been even approximately self-contained. During 1984-93 the proportion of their local markets held by local firms ranged from 45-55% in France and Germany, through 30-40% in Italy, Spain and the UK, to 10-15% in Belgium, the Netherlands and Portugal. The balance was held by companies based in other member countries of the Union and by those based elsewhere, mainly in the USA, Switzerland and, more recently, Sweden. The overall share of the Union market held by local firms selling in their own national markets declined somewhat in the period under review. This trend was most marked in France, Italy and Spain; in Germany their position was broadly stable and in the UK it increased.[51]

Further evidence comes from an examination of the best-selling products in the various member countries. Table 4.2 shows the extent to which the top 15 medicines by sales, which typically account for 10-20% of national totals by value, overlapped in 1984 and 1994. If each of the ten markets for which data are available had been completely self-contained 150 separate products would have been listed; instead there were 87 in 1984 and 76 in 1994. There are other suggestions that a modest degree of concentration has taken place: thus, the number of medicines in this category that appeared in only one country fell from 63 to 54.[52]

A tentative conclusion would be that the market has become more unified but that the effect has so far been limited. Moreover, other considerations are important. A best-selling product can have a significant impact; so may a change in the nationality of a company. Thus, the increased prominence of Swedish firms in the international market in recent years is due to both factors.[53]

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[51] Authors' estimates based on IMS information contained in Société nationale de l'industrie pharmaceutique. *L'Industrie pharmaceutique - ses réalités*, various issues.

[52] Ibid.

[53] In 1984 Swedish companies held approximately 1% of the EU market. By 1991 this had become 2.4% and by 1993 4.1%. This reflects in part the commercial success of Astra products – Losec is now the world's leading medicine – and in part the emergence through mergers of Pharmacia as a major player.

Table 4.1. Partition of the EU market between firms of different nationalities

(%)

	National firms				Other EU firms[1]				Non-EU firms[2]			
	1984	1987	1991	1993	1984	1987	1991	1993	1984	1987	1991	1993
B	9.5	10.3	10.7	9.5	38.9	41.4	44.0	42.4	52.6	46.8	43.4	44.5
D	55.9	55.3	51.9	52.5	13.9	14.1	15.7	14.0	30.2	30.4	31.1	31.9
E	35.0	35.3	31.0	29.3	34.4	35.7	36.3	36.2	30.6	28.4	30.9	33.0
F	53.6	48.8	46.0	45.0	17.2	20.1	24.1	24.0	29.2	30.7	29.2	30.1
I	40.1	43.0	38.3	33.7	29.1	24.9	29.3	29.7	30.8	31.7	31.6	36.0
NL	10.5	12.5	11.6	15.6	42.4	36.1	40.7	35.2	47.1	38.0	42.6	43.7
P	18.2	16.1	14.7	14.8	27.3	35.8	43.2	43.6	54.5	45.1	40.3	41.0
UK	32.4	33.8	39.0	36.6	18.7	16.0	17.6	16.3	48.9	39.9	36.8	41.0
EU[1]	44.8	44.6	41.2	41.0	21.5	21.1	24.6	23.7	33.5	32.6	32.4	34.3
USA[3]	80.0	74.8	70.2	69.2	10.2	14.4	14.6	15.1	9.8	10.8	8.4	8.2
Japan[3]	77.2	80.7	82.1	82.3	8.0	5.4	8.1	7.3	15.0	13.9	9.3	10.0

[1] Excluding those from Denmark, Ireland and Greece.
[2] Those based in Sweden, Switzerland, the USA and Japan.
[3] 1982 figures instead of 1984.
Source: Authors' estimates based on IMS information contained in Société nationale de l'industrie pharmaceutique. *L'Industrie pharmaceutique - ses réalités*, various issues.

Table 4.2. Numbers of medicines appearing in the top 15 by sales in ten Member States of the EU

	Present in number of member countries									
	10	9	8	7	6	5	4	3	2	1
1984	1		2	3			3	4	10	63
1994	1	1		2	1	5	1	6	5	54

Source: *Ibid.*, based on IMS. *World Drug Market Manual*, 1986 and 1994.

Patterns of supply

Changes in the ways in which EU markets are supplied are more clear-cut.

Some relevant information is presented in Table 4.3. Trade in finished medicines – those ready for retail sale – within the Union rose from 9.8% of total consumption by value in 1988 to 17.2% in 1994. Growth was above average in France, Greece, Italy and especially Spain; in all these countries imports had formerly been only a small proportion of consumption. It was below average in Belgium, the Netherlands and the UK, but except for Denmark and Portugal all member countries shared in this trend. Imports from outside the EU grew even more

rapidly, especially in the most recent years. Those from the EFTA countries rose from 3.3 to 6.1% of EUR-12 consumption and those from the USA and Japan from 0.5 to 1.1%.[54]

What of local production by foreign companies? A conflation of trade and market share data (Table 4.4) suggests, if tentatively, that this has fallen slightly in relative importance. This conclusion is supported by independent trade data. Imports of bulk drugs – those not yet made up in doses and packaged for sale – have declined from 14.7% by value of bulk plus finished medicines in 1988 to 7.25% in 1994. Since many subsidiary plants exist to convert the former into the latter this suggests a decline in their contribution. The change appears to have been greater for EU companies than for those from elsewhere; at all times American firms have accounted for the largest proportion of production in this category.

Table 4.3. Imports of finished medicines from other EU Member States as percentage of consumption, 1988-94

(%)

	1988	1989	1990	1991	1992	1993	1994
B	42.1	45.6	45.0	47.0	50.9	47.7	56.8
D	6.7	8.5	9.0	9.5	9.9	9.2	11.0
DK	39.2	38.4	37.0	41.2	46.7	32.6	43.3
E	2.6	3.8	4.2	5.1	8.5	11.5	15.3
F	4.6	5.6	6.7	7.8	8.3	8.3	8.9
GR	15.9	21.8	29.0	25.8	31.6	27.5	29.6
I	5.0	5.2	5.7	5.7	7.3	8.7	10.8
IRL	75.1	90.8	91.8	92.7	92.6	78.8	87.2
NL	53.8	58.9	58.6	59.8	62.1	61.6	82.3
P	16.0	13.8	15.3	13.7	16.6	16.7	18.5
UK	15.2	18.2	17.5	18.8	19.1	18.6	21.1
EU	9.8	11.2	11.6	12.2	13.6	13.9	17.2

Source: See note 54.

The role of the European Union

To summarize, the EU market appears to be somewhat more unified than it was a decade ago. Imports have become substantially more important as a source of supply than in the past. These findings support the hypothesis that single market measures have had a significant effect in unifying both the market and the means of supplying that market. However, other explanations are possible. The developments in question might be part of some global process; equally, they might be due to a long-term trend within the EU alone.

[54] Authors' calculations from the Eurostat NACE 257 database.

Table 4.4. Estimates of local production by foreign firms as a proportion of consumption, 1987-93

(%)

	1987	1991	1993
D	35.7	34.3	33.2
E	60.7	60.7	55.2
F	47.4	43.2	42.1
I	49.1	52.4	52.4
UK	47.2	35.7	36.3
EU	44.5	43.0	40.7

Source: Authors' estimates from the data of notes 51 and 52. It should be emphasized that they are highly approximate and should be taken simply as an indication of the situation at various times.

One way to test the first alternative is to examine the experiences of large developed countries outside the EU. Market share data suggest that the American market has become less self-sufficient during the past decade, with the proportion held by American firms falling from 80% in 1982 to 69% in 1993. In contrast, Japanese firms have kept their grasp on their national market. In both countries imports of finished drugs formed throughout a low proportion – less than 5% – of consumption; in neither did they rise systematically. Thus, trade has not followed the same trend as in the Union.

The second alternative would predict that as a proportion of consumption imports should have risen at much the same rate since, say, 1980. Long-term trends in intra-EU trade in medicines are difficult to study because of changes in the classification system in 1987-88. In particular no data for finished medicines alone are available before the latter date. However, as a proportion of consumption, the data for imports of finished medicine plus bulk drugs suggest faster growth after 1987 than before that date.

The balance of evidence therefore suggests, that the SPM has had a significant impact in promoting trade as an alternative to local production.

4.2.2. Parallel trade in medicines

Because the prices of medicines differ widely between one member country and another a parallel trade within the EU has developed. Decisions by the European Court of Justice held that this trade was legal even when the price differences that made it worthwhile were due to national regulations (Section 3.2.2).

The trade is mainly – though not entirely – between member countries where prices are generally high – Denmark, Germany, the Netherlands and the UK – and those where they are generally low – Belgium, France, Greece, Italy and Spain (Section 4.9). The products involved are mainly in-patent prescription medicines in high demand. An adequate price differential in absolute terms is necessary if the trade is to be worthwhile. Generic and self-medication products are little affected; indeed, as patent protection expires and generic competition appears, the trade often declines. The trader buys from wholesalers in low-price member countries and sells to

wholesalers or, less frequently, retail pharmacists in high-price countries. The profit is divided between them and, in recent years, the public health care system.[55] The scale of the trade is relatively small (Table 4.5). In 1994 parallel imports probably amounted to ECU 750-850 million, or about 4% of prescription drug consumption by the countries affected, though 13% of their imports of finished medicines from other member countries of the Union and one-third of their imports from those with lower prices.[56] For individual products and individual companies, however, the extent of penetration and loss of sales is much higher than these global figures suggest.

Table 4.5. Estimates of parallel trade in medicines within the EU, 1990-95, percentage of total market by value

(%)

	1990	1992	1995
D	0.8-1.0	0.5-0.8	1.5-2.0
DK	0.0	1.5-2.5	3-4
NL	4-8	7-9	10-12
UK	4-5	5-6	5 -6
EU	0.9-1.1	0.9-1.1	1.5-1.7

Source: Industrial sources.

From the standpoint of the EU the significance of the trade is that it shows that the market is not yet completely unified. If it were, then prices should have converged to the point where the trade was no longer commercially viable. The questions that might be asked are then: given that the trade within the EU has been legal for many years and that pharmaceutical prices continue to differ, often sharply (Section 4.9), why is it so small and why has it developed so slowly? Various estimates have suggested that the trade should amount to between 6 and 20% of the EU market, depending on the assumptions made about the necessary price differentials and distributors' margins.[57] What are the obstacles to the trade? Some are obvious. Importers need an official licence for each product and there have been complaints that national authorities are dilatory. Delays of several months or longer were common in Germany and the UK in the early 1990s.[58] Licences are also relatively expensive. Presentations may differ. Changes to the packaging and information leaflet will usually be necessary. Such transaction costs are significant.

There are other problems. There may be consumer resistance since the brand-names of products are not necessarily the same in all member countries of the Union. Wholesalers may be opposed

[55] The nature and development of the trade is described for the European Commission's Directorate-General IV by REMIT Consultants. *Impediments to parallel trade in pharmaceuticals within the European Community*, 1991.

[56] Authors' estimates based on recent data and on those of note 55. They are open to an exceptional degree of uncertainty; much higher levels have been quoted on occasion. For individual products the levels of penetration by parallel imports may be as high as 50%.

[57] Some estimates of potential losses under various assumptions are given in Burstall, M. L. and Senior, I. S. T. *Undermining innovation – Parallel trade in prescription medicines*, London, Institute for Economic Affairs, 1992, pp. 42-64.

[58] See op. cit. note 55.

if traders by-pass them by selling direct to retailers; this was the case in Germany. Retailers may also be reluctant to deal in parallel imports, fearing problems about quality and repercussions from wholesalers and manufacturers. It is significant that national health care systems, which stand to gain from the trade, found it necessary to provide incentives or pressure to encourage their use. In the UK the remuneration of pharmacists was reduced by 0.92% on the assumption that they were profiting by doing so; in the Netherlands they were allowed to keep 33% of the saving realized by their use; and in Germany they must be dispensed – subject to availability – if they are cheaper by DM 5 or at least 10% than the medicine obtained by the normal route. The greatest difficulty, however, is in obtaining adequate supplies. Traders suffer shortages, find it difficult to provide customers with the amounts that they need and sometimes have to make up deliveries from multiple small batches.

Parallel trade is a source of anxiety to the research-based pharmaceutical industry. The structure of the distribution chain means that their sales and profits are reduced to the extent that wholesalers or retailers can obtain their products at reduced prices. A rough estimate is that in 1990 the trade reduced output in the three countries principally affected by 1.8-2.1% and profits by 3.3-4.0%.[59] If the trade were to grow substantially the impact would be correspondingly severe. In effect parallel trade reduces the value of patent protection. These companies have responded in a variety of ways. In the 1970s they attempted to prevent the trade altogether on various grounds. Subsequently, there have been repeated allegations that manufacturers have brought pressure to bear on wholesalers not to deal with traders and have restricted supplies to wholesalers in countries suspected of being popular sources for traders. In the current *Bayer* case[60] the Commission took action against the company on the grounds that it had forbidden wholesalers in France and Spain to export Adalat to other EU countries, mainly to the UK. It was required to desist and to assure wholesalers that it would not oppose them supplying traders.

Another strategy for international firms is to seek common prices throughout the Union. The prices in question do not have to be identical; rather they should be within a band whose boundaries are sufficiently close to discourage the trade on purely commercial grounds. A number of firms claim to have followed this policy with success (Section 4.9.2). However, it should be noted that prices may be closely similar at launch but then diverge, as nations allow or do not allow for inflation, and devaluations take place. Traders are quick to exploit such divergences: for example, imports of finished medicines from Italy to the Netherlands rose sharply when the Italian lira was devalued against the Dutch guilder in 1992. In principle companies might also reduce their prices to a level sufficient to deter traders. It is significant that when prices in Germany were lowered by the advent of reference pricing, parallel imports were significantly reduced. In practice firms have not usually followed this route, except in the case of bulk purchasers such as hospitals.

From the standpoint of the EU parallel imports of medicines result in a dilemma. On the one hand, they have the potential to remove the fragmentation of the European market through price differences; were the trade to take a substantial proportion of the whole, prices would have to converge. On the other hand, they have the potential to inflict serious damage on the innovative sector of the industry. As already noted (Section 3.2.2), the trade was legalized by decisions of the European Court of Justice which in effect gave precedence to Article 30 of the Treaty of Rome over that part of Article 36 which allows restrictions on imports in order to protect

[59] See op. cit. note 57.

[60] Case T-41/96.

intellectual property. The Commission has accordingly taken legal action on occasion to remove barriers to the trade.

There are, however, signs that the emphasis is changing. In the *Bayer* case the Commission imposed a fine of ECU 3,000,000 on the company. On appeal the Court of First Instance of the European Court of Justice granted a stay of execution until the Court proper heard the full case. The President indicated that the company's argument that the price differences in question were beyond its control merited consideration. In the case between Merck and SmithKline Beecham versus the parallel importers Europharm and Primecrown,[61] the latter had relied on the decision in a much earlier case[62] that once a medicine had been launched in one Member State the maker could not stop the medicine being imported into another Member State even if the latter did not have normal patent protection. The Court's Advocate-General has given an opinion in favour of the companies and indicated that the earlier decision should be reversed. If upheld by the Court, this would seriously limit the use of Spain – where prices are low and patent protection was formerly seriously inadequate – Italy, Greece and Finland as sources of parallel imports.[63]

4.2.3. Cross-border marketing

Marketing is extremely important in the pharmaceutical industry, but the methods used depend on the products in question.

Most prescription-only medicines are sold under brand-names and promoted to physicians by specialist sales staff and by advertising through the medical press. The former account for 75% or more of such expenditure. Although products may be sold internationally, the methods used to do so must allow for differences in medical traditions and attitudes towards medicines in different countries. In every country the sales force must, of course, be composed of locals. Sales and promotion are therefore organized largely on national rather than European lines. Branded generics – the norm outside the Netherlands and the UK – are in a similar position, although marketing expenditure is usually lower. Self-medication products are normally branded; they are promoted directly to consumers through the public media.

In all member countries national regulations have a substantial impact on marketing. Such controls affect not only what may be sold and under what circumstances, but also brand-names, the contents of advertisements, and the information to be given to patients. They often differ markedly from one member country to another. The 'rational use of medicines' Directives were intended to harmonize such regulation. As yet they have had a limited effect, mainly because their enforcement has been left to the individual countries. Thus a medicine may be available without prescription in one country but not in another; an advertisement may be acceptable here and not there. There may be restrictions on the use of brand-names.

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[61] Case C-267/95 *Merck & Co.* v *Primecrown* (unreported).

[62] Case 187/80 *Merck and Co.* v *Stephar BV*, in which it was held that since Merck had freely marketed a medicine in Italy where it was unpatentable, it could not prevent it being exported to the Netherlands where it was protected. By marketing in Italy it had exhausted its rights (this and related cases are discussed in Ranson, P. *Parallel imports and the law*, Richmond-on-Thames, PJB Publications, 1988, pp. 65-67).

[63] There has been great anxiety within the industry about imports from Spain, where prices are among the lowest in Europe (Table 4.22) and where until 1992 only process patents were available with the onus of proof of infringement on the plaintiff. Since then Spain has adhered to the European Patent Convention but the large majority of the products attractive to traders had been patented before then. For this reason Article 47 of the Treaty of Accession forbade parallel imports from Spain for a further three years.

Such differences represent a barrier to cross-border marketing. They are of particular concern to the self-medication sector, which is becoming more international in orientation, and which anticipates considerable opportunities for growth in the future. Hitherto there have been few Europe-wide brands and still fewer such companies active in all Member States.[64] For the research-oriented companies these matters are less vital. They have no choice but to maintain large local sales forces in all countries in which they are active and they are accustomed to operating on a multinational basis. For them the critical factor is the speed with which marketing authorization is granted and other considerations are secondary.

An issue of some interest is distance selling.[65] The mail-order distribution of medicines is widespread in the USA where it has about 10% of the market and has contributed to the growth of pharmacy discounts. As yet it has hardly developed within the EU. Indeed, it is illegal in Belgium, France, Italy, Portugal and Spain. Elsewhere it is permitted but only in the Netherlands – where, uniquely, prescription-only drugs may be delivered in this way – has an appreciable market coming into being. Its development depends on incentives for the parties involved. Patients are in favour of mail-order delivery on the grounds of convenience. Manufacturers see it as a means to build direct links with patients and compile databases. Naturally, retail pharmacists are opposed.

Cross-border distance selling is no more than a possibility at present, although price differences between member countries might make it worthwhile were the legal problems to be overcome. Significantly, the only example known to the present investigators was driven by this factor.

4.2.4. Distribution

Medicines are sold by manufacturers to wholesalers who in turn sell to retail pharmacies. The number of wholesalers is relatively small but the number of pharmacies is very large.

A full-line wholesaler is expected to carry a complete range of medicines – usually several thousand products – to deliver them to pharmacists rapidly and reliably and, increasingly to offer services such as training, advice and credit. Such firms hold the large majority of the wholesale market in pharmaceuticals. All member countries of the Union control licensed wholesalers and require them to adhere to specified minimum standards. They also regulate their margins, which are everywhere some proportion of the manufacturers' selling price. When selling on to retailers, discounts are normal and the effective mark-up of the wholesaler is therefore substantially smaller than the permitted maximum (Table 4.6).[66]

Wholesalers as a group have been affected by the 'rational use of medicines' Directives and in particular by the Wholesaling Directive (92/25/EEC). The provisions of this measure have been discussed earlier. Major wholesaling firms report that its provisions corresponded closely to their own existing practices; adjustment costs may be a more serious problem for their smaller competitors, especially in southern Europe where the industry is less

[64] Based on information from the AESGP and the PAGB; it has been estimated that there were no more than six pan-European self-medication products in 1987 and ten in 1995, although 70% of all such medicines are more than ten years old and 50% more than 20 years old.

[65] This section is based on papers presented at the conference 'Mail Order Pharmaceuticals' held in London (17-18 January 1996). Member States are permitted to ban distance sales under Directives 89/552/EEC and 92/28/EEC.

[66] MacArthur, D. *Pharmaceutical distribution in Europe*, London, Financial Times Business Information, 1993, p. 21; information from the GIRP and Gehe AG.

concentrated. The Labelling Directive (92/27/EEC) would obviously be to the advantage of the sector if and when pan-European packs of medicines appear.

Wholesaling is still relatively fragmented. During the past decade there has been a trend towards concentration, first at the national and now at the European level. As Table 4.6 shows, in several major markets this has already gone far, while a single company accounting for 20% of the European market has recently emerged. Several independent factors have encouraged this trend. Pharmaceutical wholesaling, like many other kinds of wholesaling, is characterized by narrow profit margins – typically no more than 1-2%. Fierce competition, especially from short-line wholesalers who carry only a limited range of popular products, has been a feature of the sector. Companies have responded by merging and by vertical integration into other aspects of the supply chain.

A further consideration has been the trend towards mergers among the research-based pharmaceutical companies. Wholesalers have seen the possibility that they might be placed at a disadvantage *vis-à-vis* the latter were they not to merge themselves. For their part manufacturers have also felt that the emergence of very large wholesalers might change the balance of power in the opposite direction. So far these hopes and fears have not been realized. Wholesalers do not generally receive discounts from manufacturers, nor have manufacturers cut wholesalers' margins. A potential and unresolved source of anxiety for manufacturers is the possibility that pan-European wholesalers might supply a large part of the Union market from low-price countries, so greatly increasing the scale of parallel trade.

The Wholesaling Directive (92/25/EEC) has undoubtedly made it easier for wholesalers to operate in several different member countries of the Union. However, it is clear that the trend towards concentration predates the Directive. Interviews suggest that the opportunities offered by the development of the single market were as important as the specific measure itself.

4.3. Scale and scope effects

The pharmaceutical industry contains many different kinds of company, ranging from large international firms to small local ones (see Appendix B). The measures taken by the Union to bring about a single market for medicines would be expected to reduce the need for the dominant research-oriented firms to operate on a multinational basis. It would also offer smaller firms the opportunity to enlarge their field of activities. In either case, it would be expected that where economies of scale exist they would be realized. Competition would increase and the less efficient firms would be eliminated.

Thus it would be predicted that:

(a) firms would take advantage of opportunities to realize economies of scale;
(b) the number of facilities operated by multinational companies would fall, and their size would increase;
(c) where barriers to entry are high, the number of firms would probably fall; where they are low, they would probably remain stable or increase.

4.3.1. Where do scale and scope effects exist in the pharmaceutical industry?

Economies of scale are found in the capital-intensive stages of production.[67] The relationships between cost and capacity in the chemical industry apply to the synthesis of active materials. However, the magnitude of these effects in the pharmaceutical sector is less than in, say, the heavy chemicals sector. Volumes are relatively small and general-purpose rather than dedicated plant is often used. Moreover, the costs of production are a smaller proportion of the whole than is usually the case in manufacturing (Section 4.1.2). Formulation and packaging may be highly automated, when the same considerations apply; however, they are more usually comparatively labour-intensive. Economies of scope exist where common intermediates are used to make different medicines and where common services may be used. They are limited by the need for extreme purity in the final products.

Table 4.6. Distribution of medicines in the EU in 1994

	Number of full-line wholesalers	% market held by top 3 firms	Wholesalers' selling price (manufacturer's selling price = 100)[1]	
			Maximum	Actual
B	37	31	112.3	109.0
D	17	93	109.7	106.7
DK	3	93	114.0	107.8
E	83	30	112.0	106.7
F	31	76	113.9	108.4
I	165	22	110.7	107.5
NL	6	80	116.5	112.9
UK	14	70	112.5	105.4

[1] 1991.

Source: MacArthur, D. *Pharmaceutical distribution in Europe*, London, Financial Times Business Information, 1993, p. 21; information from the GIRP and Gehe AG.

The nature and extent of economies of scale in research and development is less clear-cut. Academic work in the USA[68] suggests that large firms were significantly more successful in terms of cost per new active substance to enter the market than medium- or small-sized companies, while sales per new medicine increased sharply with size of company. It was concluded that there are considerable economies of scale, especially at the discovery and pre-clinical development phases. There are also economies of scope at the discovery stage, in that the approaches used may lead to several essentially different products. Industrial opinion is less certain about economies of scale in R&D. In their view, a high threshold size is necessary for effective innovation but beyond that there are few such economies. Where R&D is concerned, mergers save money not by raising productivity but by eliminating overlapping projects. Indeed, there is some anxiety about diseconomies of scale in giant organizations.

[67] The major pharmaceutical companies are markedly capital-intensive, generating about two units of sales from each unit of fixed assets.

[68] DiMasi, J. A., Grabowski, H. G. and Vernon, J. *International journal of the economics of business*, No 2, 1995, pp. 201-19. It should be noted that the products studied were first tested in humans in 1970-82.

Where marketing and sales are concerned there are both economies of scale and of scope. A sales force can promote a number of medicines simultaneously; a large one can be more readily divided into specialized groups to deal with specialized markets. The same is true of distribution. The existence of economies of scope is the rationale behind the separation of manufacturing, wholesaling and retailing in the pharmaceutical sector.

4.3.2. The burdens of multinational operation

The multinational system of operation predates the Second World War. German, Swiss and American pharmaceutical companies began to create networks of local subsidiaries in European countries from the turn of the century onwards. Until the 1950s, however, most of these affiliates were purely marketing organizations. Local manufacturing became widespread in the aftermath of the war, mainly in response to restrictions on imports imposed by governments anxious to economize on foreign exchange and to encourage a local pharmaceutical sector. For many research-oriented firms, local production was then in effect a pre-condition of operation in a country. Subsequently, many countries within and without the Union provided incentives to encourage foreign firms to enlarge their local operations.[69]

The result was a considerable multiplication of plants and research laboratories. In 1984, before the SMP started, there were 200 instances of foreign firms having production facilities in member countries of the Union. American companies accounted for 45% of this total; at that time production within Europe made up 95% of what they sold there. Some firms owned as many as six plants.[70] A large number of them worked at well below capacity; in 1987 it was estimated that somewhere between one-half and two-thirds were redundant. Economies of scale could not be fully realized. Admittedly, most of these plants undertook no more than formulation and packaging in which such economies are less important than in the production of active materials, but it was nevertheless estimated that industry costs were increased by between 1.6 and 2.8%.[71] American and Swiss firms were the most affected.

At that time there was general agreement that the key to improved efficiency and reduced costs lay in concentrating manufacturing. Most companies considered that one or perhaps two European plants were all that they needed. However, existing official incentives based on price and profit controls made this course of action unattractive. Such incentives were a major consideration in decisions about investment in manufacturing. Moreover, international companies were uneasy about the general consequences of closing plants; national governments, it was thought, would view such action highly unfavourably.[72] However, given the doubtful legality of many of these incentives under the Treaty of Rome, it was hoped that the then forthcoming Transparency Directive would 'smoke out' attempts to discriminate between companies on the basis of their local activities.

The situation in the case of research and development was rather different. Then as now the majority of subsidiary centres were used for development work and for clinical research. The development of existing products to perfect them for local markets is often best done in the

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[69] Burstall, M. L., Dunning, J. H. and Lake, A. *Multinational enterprises, governments and technology – The pharmaceutical industry*, Paris, OECD, 1981.

[70] REMIT Consultants. *American pharmaceutical companies: R&D and manufacturing investment in Europe*, 1995.

[71] Burstall, M. L. and Reuben, B. G., op. cit. p. 21, note 20.

[72] Burstall, M. L. and Wallerstein, K. R. B. *American pharmaceutical companies in Britain and Europe*, London, Economists Advisory Group, 1988, pp. 44-73 and 108-11.

country in question, while clinical research is necessarily carried out where there are appropriate patients and centres of excellence. Thus, some degree of decentralization is unavoidable. Discovery research has always been concentrated in a company's country of origin; nevertheless, a number of large firms have set up centres for such research elsewhere. The dominant factor has been the wish to exploit the particular strengths of the national science base and the stock of high-quality scientists. Local incentives have played a lesser part (Section 4.4.1). The scope for rationalization via concentration is therefore more limited than in the cases of manufacturing.

Sales forces must remain local if the individual characteristics of the national market are to be fully exploited. Again, therefore, the room for economies through pan-European operation is limited.

4.3.3. The developments of the past decade: the position of the major companies

For the larger firms, then, economies of scale exist; they are mainly to be found in production and the potential for realizing them by strategies of concentration is substantial. To what extent have they been realized?

The numbers of companies with plants within the EU but outside their own country of origin in 1984 and in 1994 are shown in Table 4.7. The measure used is approximate but revealing. The numbers have not significantly changed. A detailed study of US companies operating within the Union confirmed this conclusion. In 1993-94, 13 such firms owned 50 chemical and 92 formulation plants within the EU. Between 1984 and 1994 they had closed 13 of them. Most took a cautious view of plant closures; where possible, plants were sold on rather than shut down. Other strategies were favoured instead. The production of a single product might be concentrated in a single plant which served the Union and even the world market. Piecemeal improvements were sought and found, as the rise in productivity discussed in Section 4.7 demonstrates.

From the company standpoint there are both positive and negative reasons for this behaviour. The positive reason is that national incentives for investment remain an important consideration. The study of American companies mentioned above showed that they ranked closely behind stability of government policy towards the industry and historical factors as a determinant of investment policy. Ireland is still an attractive centre for making active materials because of the subsidies and tax concessions it offers. The price and profit concessions discussed in Section 3.2.2 remain in place and have not been challenged in the courts as discriminatory. It may be argued that they are of declining importance and that, as so often in other sectors, investment decisions would be unchanged in their absence. This is not the view of the companies.

Table 4.7. Number of companies having production facilities within the EU but outside their country of origin

	F	D	UK	CH	USA	Other	All
1984							
B	3	1	1		5	1	11
D	2		3	3	11	3	22
E	5	6	5	3	13	6	38
F		6	6	3	15	5	35
GR	2	2	3	2	5	0	14
I	3	5	5	3	16	4	36
NL		1			1	2	4
P	2	2		2	5		11
UK	3	4		3	16	3	29
EU	20	27	23	19	87	24	200
1994							
B	2	1		1	6	2	12
D	4		3	3	8	3	21
E	5	8	4	3	13	7	40
F		6	6	3	15	2	32
GR	2	3	2	3	5	3	18
I	3	8	5	3	12	5	36
IRL							
NL		2		2	1	2	7
P	3	2		2	6	3	16
UK	2	3		3	12	5	25
EU	21	33	20	23	78	32	207

Source: Based on an analysis of company descriptions in the commercial literature, supplemented by company reports. It should be pointed out that a company may have several plants in a single country. The reader is warned that the two data sets are not strictly comparable, given that a number of mergers have taken place between the dates in question; this has been allowed for as far as possible.

The negative reasons are connected with employment. At a time when unemployment is high within the Union, governments are not keen to see it increase. Employment in the industry is a small part of the whole but it is of a superior nature. Moreover, because the majority of medicines are supplied by public health care systems, pharmaceutical companies are particularly exposed to official hostility. National labour policies are also a consideration. In practice it is easier to rationalize facilities in some member countries than in others. More plants and laboratories have been shut by American companies in the UK – otherwise an attractive location – than in other countries and the more flexible labour policies followed by the UK government played some part.

The recent wave of mergers appears likely to lead to more extensive rationalization. A number of very large companies, including Bayer, Glaxo and Pharmacia-Upjohn, have announced their intention to reduce the number of their plants very considerably.

4.3.4. The developments of the past decade: the size of companies

Evidence of changes in the total number and size of firms is fraught with difficulties. Eurostat data (Table 4.8) suggests that the number of companies remained roughly constant rather than decreased over the period 1978-92, while the number of employees per firm rose except in the UK. A way to gauge changes in the size distribution of companies is to use the median of first moment distribution, which measures the size at which half the employment of the industry comes from larger firms and half from smaller ones.[73] Table 4.9 suggests that this measure has shown no consistent trends in the decade 1981-91. It rose in France, Germany and Italy, particularly after 1986, but it fell in the UK.

Thus, there is only limited evidence that the distribution of company sizes has shifted in favour of the larger firm. However, data of this kind refer to all companies active in the pharmaceutical sector. Evidence presented elsewhere suggests that markets have become more concentrated in terms of sales – again, except in the UK – but not in terms of products. The number of research-based firms operating in the Union has fallen since the early 1980s as the smaller companies in this category have merged or been taken over; however, their share of the market has not.[74] How may these conflicting findings be reconciled?

A tentative explanation would be that within the EU a two-tier industry has developed. The number of research-based companies has fallen because the threshold investment needed for innovation has risen; new firms have not appeared because the barrier to entry which this represents is too high. A large number of small firms survive in the generic and self-medication sectors where the R&D effort needed is limited, most active materials can be bought in and the minimum viable size is relatively small. As interviews confirm, barriers to entry are low, the number of firms high and potential growth may attract new participants.

4.3.5. The impact of EU measures

Thus it is clear that so far progress towards the creation of a single market in pharmaceuticals has been accompanied by only limited progress towards the realization of economies of scale and the emergence of an integrated pharmaceutical industry.

The rationalization of facilities has been limited by the continued ability of Member States to use controls over pharmaceutical expenditure to reward local investment by foreign companies and by the political difficulties of action in this direction. Here the inability of the EU to engineer agreement on alternative approaches has been an important factor. Economies of scale have been less completely realized than would otherwise have been the case.

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[73] This measure is discussed in the Economists Advisory Group's report for the European Commission, *The extent of realization of economies of scale due to the internal market programme.*

[74] In 1984 there were 55 research-based firms operating directly within the EU; the number today is 34. The minimum sales required to support a serious product innovation programme has risen from ECU 150 million to at least ECU 1,000 million and in all probability to ECU 1,500-2,000 million.

Table 4.8. Number of companies and average number of employees, 1978-92[1]

	Number of companies				Employees per company			
	1978	1982	1990	1992	1978	1982	1990	1992
B	56	46	43		178	219	271	n.a.
D	268	262	265	267	311	331	376	398
DK	17	17	24	25	376	443	444	471
F	262	261	263	272	235	245	292	296
I	255	258	247	249	244	248	279	283
UK	136	137	153	164	533	491	490	480
EU	994	981	995		298	305	344	n.a.

[1] Companies with 20 or more employees only.
Source: Eurostat.

Table 4.9. Median of first moment distribution for the pharmaceutical industry, 1981-91

	1981	1986	1991	% change 1981-86	% change 1986-91
B	511	581	n.a.	14	n.a.
D	n.a.	1658	1840	n.a.	11
F	447	533	659	19	24
I	606	608	746	0.3	23
UK	1,995	3,260	1,995	63	-40

Source: This measure is discussed in the Economists Advisory Group's report for the European Commission, *The extent of realization of economies of scale due to the internal market programme* (to be published as *The Single Market Review*, V: *Impact on competition and scale effects*, Vol. 4: *Economies of scale*, Office for Official Publications of the EC and Kogan Page.Earthscan).

More positively, however, the new systems of marketing authorization[75] and the 'rational use of medicines' Directives[76] have made it easier in principle for firms specializing in generic and self-medication products to expand their operations into other member countries. The emergence of relatively large pan-European firms in this last sector, free, since pricing is free, from official pressures, would be an interesting development.

4.4. Foreign direct investment

Foreign investment in the pharmaceutical industry of the EU has been a feature of the sector for many years. The majority of the EU market is held by companies operating outside their country of origin but relying in the main on local production to supply local markets. The

[75] Regulation (EEC) No 2309/93.

[76] Directives 92/25 – 28/EEC.

reasons have already been explored in Section 4.3. In a genuine single market the following changes would be expected:

(a) companies would concentrate their facilities in those member countries where they would be most effective;
(b) inward investment would similarly be concentrated among the chosen host countries; elsewhere disinvestment would take place;
(c) competition would increase and firms would respond through mergers and acquisitions to maintain and improve their positions.

4.4.1. Patterns of internal investment

The pharmaceutical industry has been dominated since the 1960s by a relatively small number of large research-oriented companies that operate on a global basis. Their frame of reference is the world. They have placed facilities where it was inherently attractive to do so, where there were external incentives or where they had no choice.[77]

Where have international companies placed their investment in the past? Some light is thrown on this question by a recent study of American companies operating in the EU (Table 4.10).[78] As already noted, US firms supply European markets mainly from their European subsidiaries. This showed that France, the UK, Germany, Ireland and Italy in that order were the favoured countries. As far as production is concerned, Ireland has attracted considerable inward investment, very largely in connection with the synthesis of active materials. Elsewhere, investment is clearly linked to the size of the local market, to official pressures and incentives, to costs and, naturally enough, to past investment. R&D is concentrated in the UK and France, with a significant amount being carried out in Germany and Italy.

Current thinking among US firms is that new green-field facilities are unlikely. Both selective investment and disinvestment are probable. Section 4.3 has already shown that the latter is already in progress, if slowly. The steps taken will depend on the position of the individual firm. Nevertheless, there is a broad and relatively stable[79] consensus on the relative attractions of the various member countries of the Union. From the standpoint of production Greece and Portugal have little to offer in any respect; the Netherlands and the Scandinavian countries are too small and too expensive. Spain enjoys low costs but Germany high ones. Ireland retains its advantages, thanks to government policies.

Research and development is normally concentrated in a company's country of origin. Where investment elsewhere is concerned, the most important factors are the general quality of research in a country, its track record in relevant research and its supply of suitable personnel. Countries which score highly in these dimensions have strong innovative companies and are fundamentally attractive to foreign firms. Within the Union, the UK is the best placed, followed by France and Germany. Belgium, Denmark and the Netherlands show elements of

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[77] Burstall M. L., Dunning J. H. and Lake, A. *Multinational governments, governments and technology - The pharmaceutical industry*, Paris, OECD, 1981.

[78] REMIT Consultants. *American pharmaceutical companies: R&D and manufacturing investment in Europe*, London, 1995, pp. 55-59.

[79] As is shown by a comparison of the assessments made in this report with those in Burstall, M. L. and Wallerstein, K. R. B. *American pharmaceutical companies in Britain and Europe*, London, Economists Advisory Group, 1988.

strength but are limited mainly by their relatively small size. Italy, Spain and still more Greece and Portugal are comparatively weak.

Table 4.10. Activities of US pharmaceutical companies in Europe, 1994

	ECUm			Production centres		R&D laboratories		Total assets in million ECU	Employees
	Sales in EU	Imports	Exports	Chemical	Other	Labs	Expenditure in million ECU		
B	529	71	207	3	6	4	192	917	8,284
D	2031	74	97	8	12	9	134	1,888	12,520
DK	57	13	0	0	1	0	4	32	261
E	767	36	3	5	14	5	30	525	5,717
F	3,257	79	451	10	18	12	412	2,950	19,604
GR	160	13	15	0	1	0	2	71	844
I	1,735	88	29	6	16	5	82	1,330	10,648
IRL	102	5	74	8	5	2	11	1,828	2,529
NL	363	13	224	0	1	1	29	854	1,633
P	312	2	1	1	5	1	4	145	2,205
UK	1,133	8	284	9	13	12	531	92,372	20,294
EU	10,446	402	1,385	50	92	51	1,431	1212	84,539

Source: REMIT Consultants, *American pharmaceutical companies: R&D and manufacturing investment in Europe*, London, 1995, especially pp. 55-59 and Table 3.1; the data are based on a sample of 13 firms.

In both areas France and the UK are the most attractive. Both are well-qualified in terms of existing investment, science base and achievements in pharmaceutical research. Both offer inducements for inward investment; in both, the government values the industry. These judgements are widely shared among other large pharmaceutical companies. However, it should be remembered that future investment may not take place in Europe at all. It might be directed at the upper strata of developing countries – seen very generally as the growth markets of the future – at Japan or at the USA. If, as seems likely, the basis of pharmaceutical innovation were to move towards biotechnology, the already commanding position of the USA would be further strengthened.

4.4.2. Mergers and acquisitions

In recent years mergers and acquisitions have become increasingly important as a means of foreign direct investment.

The AMDATA database provides an approximate way to quantify such activity.[80] Table 4.11 summarizes transactions in the period 1989-94. Looking first at domestic activity it seems that the French industry has undergone the largest internal rationalization, but there has also

[80] It should be noted that the database is compiled from reports in the local financial press and that the values of transactions are often not reported, especially in those countries where many firms are privately owned.

been a trend in this direction in Germany, Italy and the UK. As far as cross-border activity is concerned, Italy has seen the largest number of acquisitions by companies based elsewhere in the Union, but France and the UK lead in terms of value. In the case of investment from outside the Union in EU firms one single transaction – the merger of the US company SmithKline with the UK company Beecham – dominates the picture,[81] although the high level of transactions involving French and especially German targets is notable. It is also highly significant that both in terms of number and value merger and acquisition activity has been much greater in the pharmaceutical sector than its size would suggest.[82]

Table 4.11. Mergers and acquisitions in the EU pharmaceutical sector, 1989-94

	Number of mergers and acquisitions						Total 1989-94		Mean value each ECUm
	1989	1990	1991	1992	1993	1994	Number	Value ECUm	
Domestic activity									
D	2	3	12	6	4	2	29	n.a.	n.a.
F	6	5	6	9	3	7	36	2,139	59.4
I	3	2	1	1		2	9	565	62.8
UK	3	7	2	8	5	9	34	475	14
Other	4	4	1	4	1	1	16	n.a.	n.a.
Total	18	21	22	28	13	21	123	n.a.	n.a.
Cross-border activity within the EU									
Target nationality									
D	2	2	0	4	2	3	13	n.a.	n.a.
F	2	3	5	2	2	3	17	1,096	64.5
I	4	4	1	1	6	2	18	n.a.	n.a.
UK	3	0	1	1	3	1	9	1,135	126.1
Other	4	8	3	3	5	4	27	n.a.	n.a.
Total	15	17	10	11	18	13	84	n.a.	n.a.
Extra-EU activity									
Target nationality									
D	4	5	4	9	1	6	29	225	7.8
F	3	4	3	3	2	7	22	565	25.7
I	1	1	3	4	6	2	17	220	13
UK	3	2	2	6	0	0	17	8,306	488.6
Other	5	5	2	5	2	5	20	n.a.	n.a.
Total	16	17	14	27	11	20	105	n.a.	n.a.

Source: Note 78.

[81] It is a moot point which firm absorbed the other.

[82] Taking the Union as a whole, the pharmaceutical sector accounted in 1990 for 2.48% of industrial value-added and 1.63% of employment but between 1989 and 1994 for 2,43% of the number and 9.36% by value of industrial mergers and acquisitions.

It is clear not only that many mergers and acquisitions have recently taken place but also that they involve small and medium-sized as well as large firms. Apart from the single instance already mentioned, the mean value per transaction is generally below – often much below – ECU 60 million, which is well under the level required to support genuine innovation. This is especially true in the case of Italy and to a lesser extent France. It appears that the small, often family-controlled firm with a national or even local orientation so characteristic of these countries is increasingly at risk.

4.4.3. The impact of the single market

Thus, a restructuring of the pharmaceutical industry is in progress.

In the research-based sector it appears that a limited number of very large companies are emerging. The central feature of this process is that it is not confined in any way to the EU: rather, it is world-wide. Thus within the Union, BASF has acquired Boots, Rhône-Poulenc Rorer has acquired Fisons and Glaxo merged with Wellcome. However, among US firms, Rorer took over Revlon before being absorbed by Rhône-Poulenc; Merrell-Dow merged with Marion before being acquired by Hoechst; Bristol-Myers merged with Squibb; Syntex was bought by Roche. Elsewhere Upjohn has merged with Pharmacia and CIBA proposes to do so with Sandoz. Only the major Japanese companies, weak outside but strong inside Japan, have remained aloof.

The principal driving force has been the wish to reduce costs, in part by eliminating overlapping functions, in part by realizing the economies of scale previously identified. At a time when downward pressures on pharmaceutical expenditure are felt everywhere in the developed world, while the costs of developing new medicines continue to rise, this is seen as a matter of urgency. In addition there are firm-specific reasons. Thus, improved access to the US market was an important consideration in Hoechst's acquisition of Marion Merrell Dow, while Roche bought Syntex – as it had bought Genentech – in order to benefit from the commercial potential of its biotechnology work.

The single market has been a factor of only minor significance to these companies. Globalization rather than regionalization has been the characteristic of the process. There has been no trend in the timing of mergers and acquisitions. If the SMP was critical, significant restructuring at the beginning of the period would be expected followed by a tailing off. Alternatively, such activity might increase as the full impact of the programme was felt. This has not happened, either among the major research-based firms or among pharmaceutical companies as a whole. Instead the trend follows the broad macro-economic cycle.

The impact on small and medium-sized companies is more difficult to assess. Here, too, some degree of concentration may be taking place. Many such firms are active in the generic and self-medication sectors which have hitherto been national rather than pan-European in nature. The scale effects discussed in Section 4.3 are less important than for the research-based companies: active materials are bought in, while R&D is limited. Marketing is less important for generic houses and takes a different form in self-medication. Nevertheless, to the extent that the EU's measures have encouraged these sectors, foreign direct investment may have been encouraged as national firms seek to expand their activities in other countries.

4.5. Sourcing patterns and upstream-downstream linkages

By removing barriers to trade the SMP should facilitate specialization of function within the Union.

4.5.1. The place of the pharmaceutical industry in the economy

The input-output tables for the UK, which has a particularly large and successful pharmaceutical sector, illustrate the position of the industry within a national economy.[83]

The distribution of pharmaceutical output is simple. In the period 1978-90 between 80% and 90% went straight to final demand. Intermediate demand was modest: almost one-half represented transfers within the pharmaceutical sector itself and animal feed and services accounted for most of the rest. There is every reason to suppose that this is typical: the sector has little impact on industries further downstream. Supplies of goods and services to the industry show a more complex pattern. Raw materials and intermediates – mainly pharmaceuticals, chemicals (especially organic chemicals) and packaging materials – made up 45-55% of inputs and services the balance. The latter have shown a tendency to increase in relative weight since 1978.

How important is the pharmaceutical sector to other parts of the economy? In purely economic terms, not very. Even allowing for indirect demand, in 1990 it absorbed only 2.4% by value of the UK output of organic chemicals, 2.7% of other chemicals, 2.3% of packaging, and less than 1% of all services.[84] This is what might be expected; although the industry presents a high profile it makes a relatively modest contribution to national income even in the UK. Thus, no other part of the economy is greatly dependent on the pharmaceutical sector. However, this generalization requires a major qualification. The industry requires unusually large numbers of specialized personnel, especially for research and development. As a major employer of scientists, its needs have a significant impact both on the scientific community and on higher education.[85]

4.5.2. Evidence of specialization

Raw materials

It is not easy to pronounce with confidence on the ways in which pharmaceutical companies obtain the materials they need to make their products. As Section 4.1.2 made clear, much turns on the nature of the production process. Nor is it easy to assess the impact of the SMP in this area. There are no comprehensive data concerning the trade in pharmaceutical intermediates.

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[83] Central Statistical Office. *Input-output tables for the United Kingdom 1990*, London, HMSO, 1995 and earlier issues. In qualitative terms the position of the sector has remained unchanged since 1978.

[84] Authors' calculations from ibid., Tables 4 and 5.

[85] Pharmaceutical research spending was 5.9% of all research spending in France in 1992; the corresponding figure for other member countries of the EU were Germany: 5.4%, Italy: 6.5%, Spain: 6.1% and the UK: 11.2%. As a proportion of R&D employment, that in the pharmaceutical sector was France: 3.9%, Germany: 3.2%, Italy: 4.7%, Spain: 3.3% and the UK: 8.1%.

A rough measure suggests that imports of such materials have risen as a proportion of production since 1988-90 in France, Germany, Italy and the UK, but remained constant in Spain, Japan or the USA.[86] This may suggest that the production of particular substances is becoming more concentrated. However, the changes are not large and there are obvious alternative explanations. There is no evidence that the Union is becoming more self-contained in this respect.

Qualitative information throws further light on this issue. The research-based companies interviewed reported that most of their traditional (i.e. non-biotechnological active materials), were made by themselves from relatively simple starting materials. There appears to be more outsourcing where medicines based on biotechnology are concerned. In part this is due to a lack of appropriate facilities; in part to the limited availability of natural materials of an adequate standard. For all starting materials quality assurance is of critical importance in the decision to use outside sources or not. That said, companies' needs are extremely diverse and generalization about patterns of supply is impossible.

Since the quantities involved in production are often small, it is quite practicable to carry out particular operations at geographically separate locations. In this way specialized facilities may be used intensively. The SMP has made it significantly easier to do so. One company described how they sent raw materials from one member country to a plant in another, re-importing the modified product after specialized treatment there. Formerly, bonds had to be posted on these materials; working capital was tied up, larger than necessary stocks had to be maintained and extensive documentation was required. The removal of such barriers had been markedly beneficial. In this case production costs had been reduced by as much as 2.5%.

The situation in the generic sector is rather different. Most companies of this type buy in active materials and do no more than convert them into dosage forms. The majority of such materials are commodities; the technology of their production is well understood and products of a satisfactory standard are widely available both from within the Union – 75% of what is used there is made there – and from Eastern Europe and India. Downward pressures on prices are strong and countries with low labour costs have a definite advantage. Given that the use of generic medicines is increasing, there is a possibility that the manufacture of out-of-patent active ingredients will move away from Europe.[87]

Research and development

To what extent have companies moved their plants and laboratories to other more attractive locations within the European Union?

The factors that make a country attractive or unattractive for particular purposes have already been discussed in Section 4.4.1, where it was shown that they are the result of long-term national developments. However, for a particular multinational company the decision to concentrate facilities is more complex. The existing pattern of investment must be considered,

[86] The measure used is pharmaceuticals (SITC54) - medicaments (SITC542), which has been found to be a reliable indication of the direction and magnitude of the trade in pharmaceutical intermediates. On this basis imports as a proportion of production rose from 7 to 8% between 1985 and 1993 in France, from 9 to 10% in Germany, from 10 to 15% in Italy, and from 5 to 8% in the UK.

[87] Information from interviews with the British and European Generic Manufacturers' Associations and with individual generic companies. Differences in manufacturing standards between European countries were mentioned by some respondents.

as must be the ease or otherwise with which existing facilities may be rationalized. For a small or medium-sized firm the emotional and practical difficulties associated with a move away from its place of origin may be overwhelming. For these reasons mergers and acquisitions play a dominant part in the redistribution of facilities.

That said, however, the SMP has had a positive effect on certain activities. The abolition of many restrictions on the movement of persons has encouraged the development of a European pool of highly skilled personnel. More directly, the measures taken have made it easier to use centres of excellence for clinical research, knowing that the data generated will have been compiled to common standards acceptable throughout the EU.

4.6. Concentration and competition

The creation of a single market for medicines would be expected to increase competition as barriers to entering the national markets fall. The various players would respond by counter-measures to protect their position. It might be expected that price competition would increase, followed by market concentration through mergers and through the elimination of marginal producers.

4.6.1. Concentration

Has concentration taken place?

Measures of concentration in the pharmaceutical sector as a whole within individual Member States are presented in Tables 4.12 and 4.13.

Table 4.12. Concentration in terms of market share by company

% pharmacy market held by top N firms

N	B	F	D	GR	I	NL	P	E	UK
1984									
1	6	4	3	4	4	6	4	4	5
10	32	22	22	29	28	35	30	26	31
25	54	44	39	54	48	64	56	46	60
50	76	64	58	73	67	83	78	66	87
75	89	77	70	84	79	91	92	80	97
1994									
1	5	5	4	5	4	9	5	4	7
10	32	29	23	36	32	43	28	28	38
25	60	51	43	62	53	68	53	50	59
50	84	71	61	82	74	89	79	72	80
75	94	82	72	92	85	97	92	86	91

Source: IMS.

As far as sales by individual companies are concerned, it is clear that concentration in the pharmaceutical sector has increased in the majority of countries. This has been a relatively slow process which has been in progress since the 1970s. The market is still relatively fragmented: in each of the five major markets of the Union, no one company has more than

7% of sales.[88] Typically, the top ten by sales have 25-30% of the retail market, the top 25 have 40-50% and the top 50 have 60-70%. Concentration is highest in the UK and lowest in Germany. Taking the Union as a whole, no firm held as much as 5% of the market in either year.

Table 4.13. Concentration in terms of market share by product

	% pharmacy market held by top N products								
N	B	F	D	GR	I	NL	P	E	UK
1984									
15	19	13	10	18	16	19	14	12	24
50	35	28	21	35	29	37	31	25	43
100	48	40	31	48	39	52	46	35	58
No holding 50%		161	265		170			208	67
1994									
15	13	12	7	17	13	20	13	25	22
50	29	28	17	37	25	35	30	25	38
100	43	41	26	51	37	46	44	38	50
No holding 50%	131	146	356	95	194	122	129	169	100

Source: IMS.

The top ten firms are almost always large research-based enterprises; only in Germany had a specialist in generics appeared in this category by 1994. There is considerable stability in the membership of this class: in every country at least half the companies that appeared in 1984 appeared again ten years later.[89] Firms specializing in self-medication products are always considerably smaller. In Germany, the Netherlands and Spain there has been a trend towards concentration through mergers and acquisitions; by contrast France and Italy have seen the reverse as new players have entered a hitherto under-developed market.[90]

Concentration in terms of medicines gives rather different results. The best-selling medicine in any country normally has less than 5% of the market by value. The top 15 have 10-20% of the market, the top 50 have 25-35% and the top 100 have 40-50% by value. In the major markets concentration by product is greatest in the UK and least in Germany. However, the development of such concentration varies by country. Both in Germany and the UK it fell between 1984 and 1994: the data suggest that this is due to the entry of generic products on a large scale.[91] Elsewhere, concentration remained broadly constant.

Although the overall level of market concentration is low, within a particular therapeutic area it may be high, with three or four medicines accounting for 80% or more of sales. Such

[88] These estimates are from IMS. They are on an enterprise rather than ultimate owner basis; thus two of the top ten appearing for the UK in both years belong to the same company.

[89] At least four out of ten appear under the same name in both years; allowing for mergers the number is higher.

[90] The global share held by the top ten companies was 27% in 1982 , 32% in 1990 and 31% in 1994; for the top 20, the corresponding figures were 44, 53 and 54%; and for the top 50, 68, 80 and 85%.

[91] In the UK generics were 5% by value of all medicines in 1984 and 14% by 1994; in Germany the corresponding figures were 4 and 16%; and in the Netherlands 9 and 15%. In France, Italy and Spain they were below 5% in both years.

oligopolies are usually transient and change as new products – and new versions of old but still useful ones – are introduced. It is significant that out-of-patent products account for a rising proportion of prescriptions in France, Germany and the UK.

The role of the single market

Concentration in the pharmaceutical industry is a world-wide phenomenon. It has been in progress for a decade or more. The driving forces have been rising costs coupled with downward pressures on expenditure; these factors have been present in all developed and many developing countries during the past decade. The research-based companies have been particularly affected. They have responded in part by merging with similar companies in order to realize economies of scale, reduce overlapping functions and activities and attain the critical mass necessary to reduce their risks to an acceptable level. They have also diversified into the generic and self-medication areas, most commonly by buying specialist firms.[92] More generally, throughout the industry, a colder economic climate leads to marginal companies dropping out. Thus, a trend towards concentration is understandable.

What of the European Union? Both costs and pressures are largely beyond its control. Mergers are subject to regulation under certain conditions but have been little affected so far. So far they have been below the critical size or have not involved overlapping products. As noted elsewhere, the Glaxo-Wellcome merger was permitted on condition that a product under development was licensed out to prevent its being abandoned. The SMP specifically has had little effect.

4.6.2. Competition

The nature of competition in pharmaceuticals

In terms of value the pharmaceutical market in every member country of the Union is composed largely of medicines available only on prescription. A large majority are branded products. Self-medication represents perhaps 15% of the total, though nearer 40% in volume.[93]

Virtually all medicines start their commercial life as prescription-only products, protected by patents, sold under brand-names and, within the EU, largely paid for by public health care systems. In such cases the prescribing physician is the prime customer. In the past doctors outside hospitals[94] were largely insulated from economic considerations – as were and are their patients – and made their decisions purely on medical grounds. Medicines were therefore promoted in terms of their therapeutic advantages and cost was a secondary consideration. This is not to say that it was of negligible importance. Higher prices were only acceptable where the therapeutic advantage was clear-cut. To a considerable extent these generalizations still hold.

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[92] For example, all the major UK generic firms are owned by foreign multinational companies.

[93] Information from the AESGP. Taking the major EU markets, self-medication products rose from 10 to 12% of total consumption by value in Germany between 1987 and 1994, from 6 to 15% in Italy, from 6 to 10% in Spain and from 10 to 14% in the UK; only in France did they fall from 20 to 17%.

[94] Hospitals have always been more cost-conscious (Section 4.2.2).

Once a successful product comes out of patent, generic copies appear. In order to overcome the goodwill attached to the originator, they are offered at relatively low prices. Price competition is often fierce and originators may be forced to cut their prices so as to retain a substantial share of their former market. Self-medication products are promoted directly to consumers through the public media. Since the latter pay the full cost, price sensitivity is relatively high. As with other consumer products, though, brand-names play a major role in establishing and maintaining the reputation of a product, and this moderates price competition in most member countries.

Has competition increased?

Here it is necessary to distinguish between different types of medicine.

In the field of in-patent prescription products competition ultimately turns on the ability to innovate. The barriers to entry are high. Relatively few companies are able to carry out this function and new entrants to their ranks are rare. Mergers are now reducing their number. The number of genuinely new products entering the Union market has been stable for the past decade. Price competition in this sector remains limited (Section 4.9.1).

Within the Union competition in the out-of-patent prescription market turns critically on cost structures and also, in practice, on the actions of public health care systems. In member countries where prices are controlled, they are often too low for generic products to be commercially attractive; generics have only flourished where prices as a whole are relatively free and relatively high. Their use has been encouraged by official action, in particular through pressures on physicians to control their spending on medicines. Competition between originators and generic producers has undoubtedly increased, as witnessed by the rising proportion of the market taken by generic products in those countries where the environment is favourable.

Competition between self-medication products and prescription medicines depends primarily on the extent to which competition is allowed, i.e. the range of drugs which may be sold without a prescription. It also turns in part on whether or not self-medication products may be reimbursed if prescribed under the public health care system and, if so, the level of co-payment required. Thus, in Italy the self-medication market grew suddenly when in 1993-94 a large range of non-prescription medicines were removed from reimbursement. The trend in most member countries of the Union is to a more liberal attitude towards self-medication, and self-medication products are slowly rising as a proportion of all pharmacy sales.

The impact of the EU legislation

The measures taken by the EU have had an appreciable impact on competition between in-patent original medicines, generics and self-medication products.

The introduction of Supplementary Protection Certificates for pharmaceutical products has undoubtedly helped the research-oriented companies and handicapped the generic sector. All parties are agreed on this point. Effective patent lives have been prolonged, though it is not yet possible to indicate by how much. The generic houses were also concerned about marketing exclusivity; here their complaint is that the period of protection varies from country to country, so constituting a barrier to trade.

The Classification Directive (92/26/EEC) requires Member States to classify medicines as prescription-only or non-prescription and lays down the criteria involved. This should enlarge the potential market for self-medication products. However, as previously noted, decisions rest with national governments, whose attitudes vary considerably. The Advertising Directive (92/28/EEC) similarly leaves the detailed regulation of advertisements for non-prescription medicines to individual countries, whose practices differ.

The decentralized system for granting marketing authorization should be of assistance to all companies, but especially to those specializing in generic and self-medication products. It promises to be simpler, cheaper and quicker than existing procedures. For small firms with limited resources that would represent a substantial gain and one that is of particular significance for companies interested in expanding beyond national horizons. Once again, problems in the administration of the procedure have appeared due to differences at the national level (Section 4.2.1).

4.7. Productivity and competitive strength

The SMP should ultimately result in the elimination of surplus capacity. Productivity should rise and the competitive position of the EU-based industry be enhanced.

4.7.1. Costs, profits and productivity

Value added and labour costs

The evolution of value added, of labour inputs and of capital investment during the past decade is presented in Table 4.14.

As a proportion of turnover, value added varies considerably between Member States. It is unusually high in Denmark, Ireland and the UK; except in France, Italy, and the Netherlands, it is significantly higher than for other sectors of the manufacturing industry.[95] These differences have been present for many years, dating back to the mid-1970s, if not earlier. It is also significant that value added has consistently been a much higher proportion of turnover in the USA and in Japan than in any member country of the EU.

Why should such differences exist? One reason is that national pharmaceutical industries differ. Thus, value added is high in Ireland where the sector is almost exclusively concerned with the production of active materials which are then exported to affiliates elsewhere. Conversely, it is low in countries such as Greece where all active materials and indeed a high proportion of finished medicines are imported. Moreover, since value added is the difference between what is bought in and what is sold, market prices have a considerable impact. In the USA free pricing prevails and average price levels are high both by European standards and relative to prices in general. In Japan, though prices are controlled and are falling, they remain very high.[96] At the other end of the spectrum prices are low in France and Italy and value added is correspondingly

[95] Throughout this period value added for manufacturing as a whole was in the range 30-35% of turnover in all major member countries, with the exception of Greece where it was nearer 20%. The chemical sector was similar.

[96] Comparisons of prices are difficult for reasons explained in Chapter 4.9.2, but there is no doubt that US and still more Japanese prices are much higher than those within the EU. Various comparisons between Italy, other EU countries, the USA and Japan in 1994 (Farmindustria. *Indicatori Farmaceutici 1995*, pp. 97-102) suggest that if the EU average is 100, that in the USA is about 200 and that in Japan perhaps 3-400. In 1994 the general price level within the USA was about 90% of that in the EU and that in Japan about 50% higher.

below the Union average (Section 4.9.2). It is also possible that economies of scale may have been more fully realized in large unified markets such as the USA.

Taking costs as what is bought in *plus* labour costs, it may be seen that within the EU the latter generally form between 20 and 30% of the total. In Ireland they are much less, for the reasons already explained, while in Germany they are rather higher, reflecting the generally high costs of labour there. Interestingly, labour forms much the same proportion of costs in the USA and Japan as among the major EU producers. This suggests that the cost structures are much the same in all three areas, with labour forming a rather greater part of the whole than is general in manufacturing industry.

Gross operating rates (value added *less* labour costs) are exceptionally high in the USA and Japan and generally much lower in Europe, with the partial exceptions of Denmark, Ireland and the UK. Even so they are substantially higher than in manufacturing industry in general.[97]

Sources of productivity

Measured in constant terms, value added by the pharmaceutical sector rose rapidly between 1984 and 1994 and has continued to do so (Table 4.15). Why? The number of employees increased modestly up to 1992 and has since fallen. Labour productivity has risen; the rate of increase was above average in France and the UK and below it in Germany and Italy. It was much above that in both the chemical sector and in manufacturing industry as a whole. Interestingly, productivity growth in the American pharmaceutical sector was significantly lower, though starting from a very much higher base. That in Japan was even higher than in the European Union.

Table 4.14. Inputs to the EU pharmaceutical industry, 1983-93

	As % of turnover											
	Value added			Labour costs			Gross operating rate			Gross investments		
	1983	1988	1993	1983	1988	1993	1983	1988	1993	1983	1988	1992
B	37.1	42.6	39.8	21.2	21.2	22.5	15.9	21.4	17.3	6.2	7.4	9
D	42	41.2	40.2	28.2	28.2	29.1	13.8	13	11.1	4.4	4.3	5.7
DK	44.5	56	61	22.4	25.7	23.9	22.1	30.2	37.1	8	9.1	12.2
F	28.9	28.8	28.3	21.1	18.1	18.2	7.8	10.7	10.1	2.3	2.8	3.3
I	36.2	33.8	31.4	22.1	19.9	25.9	14	13.9	5.5	4.2	4.4	5.2
IRL	70.3	59.7	58.3	7.8	9.6	6.3	62.5	50.1	52	4.2	8.1	
NL		32.8	22.9		21.3	16.9	7	11.6	6	4.4	8.4	6.3
UK	49.5	53.4	49.6	20.8	19.3	19.4	28.6	34.2	30.2	7.4	8.8	9.7
EU		39.1	38.1		20.3	21.2	16.6	17.8	16.9	4.4	5	
USA	68.8	71.7	71.7	16	13.5	11.6	52.7	58.2	60.1		4.7	5.7
Japan		69.6	68.5		10	9.8		59.6	59		3.9	5.4

Source: Eurostat.

[97] Gross operating rates for manufacturing industry as a whole are in the range 8-12% depending on the country.

The productivity of capital is much more difficult to estimate. Measurements of the stock of capital are affected by accounting conventions; much of the period under review was one of inflation; and pharmaceutical technology has changed considerably during that time. Investment has increased as a proportion of turnover everywhere. On the whole – France is a major exception – countries which have invested heavily on capital items have enjoyed exceptionally fast growth in labour productivity. Capital has bolstered labour and to some extent replaced it. However, much of the growth must have been due to a better use of resources.

This is borne out by interviews. Companies have managed to increase turnover greatly, and value added, while in most cases holding profit margins steady. Costs have not increased disproportionately. This has been achieved by detailed improvements and especially better planning and organization rather than any single factor. Major firms in particular have eliminated borderline activities that are better done by others and realized economies of scale wherever possible. This has enabled them to offset the downward pressures on pharmaceutical spending that are now widespread. Thus, the apparent stability of cost structures shown in Table 4.14 is the product of a dynamic rather than a static equilibrium.

Table 4.15. Employment and productivity, 1983-93 *(1983 =100)*

	Value added in 1990 price			Employees			Labour productivity[1]		
	1983	1988	1994	1983	1988	1993	1983	1988	1993
B	100	140.1	179.6	100	101.3	118.7	100	138.3	151.3
D	100	117.7	137.8	100	107.5	116.5	100	109.5	118.3
DK	100	156.8	239.5	100	123.5	155.9	100	127.0	153.6
F	100	155.9	211.3	100	107.8	122.5	100	144.6	172.5
I	100	144.7	143.8	100	106.6	111.1	100	135.7	129.4
IRL	100	n.a.	n.a.	100	140.4	204.4	n.a.	n.a.	n.a.
NL	100	92.5	83.0	100	105.7	98.7	100	87.5	84.1
UK	100	152.8	206.8	100	106.8	116.0	100	143.1	178.3
EU	100	136.4	171.9	100	106.5	114.4	100	128.1	154.3
USA[2]	100	118.5	156.6	100	103.6	118.1	100	114.4	132.6
Japan	100	163.9	181.5	100	99.9	103.7	100	165.6	175.0

[1] Value added in 1990 prices/head.
[2] 1982, 1987 and 1992.
Source: Eurostat.

The impact of the single market

The productivity of the pharmaceutical sector might be affected by the SMP in several ways.

In so far as national markets are opened up, less efficient producers with high costs and low productivity would be forced to improve or be eliminated. It has been seen (Section 4.2.1) that there is some evidence that the EU market is somewhat less partitioned than formerly. However, the major research-based firms that dominate the prescription market had already penetrated all member countries through the multinational system of operation. The generic and self-medication sectors may have had more to gain. Most such companies have hitherto been national in their orientation. The steps taken to ease marketing authorization and the

'rational use of medicines' Directives (92/25-28/EEC) have probably assisted them to sell their products more widely.

Productivity may be increased by other means. Economies of scale can be realized by the concentration of facilities. Again, it has been seen earlier that progress in this direction is being made but with caution. Member countries are anxious about unemployment and national governments retain powers to reward and to punish firms supplying public health care systems. As internal barriers vanish a greater development of specialist suppliers is highly likely, but as yet this is in an early stage of development. Once again, the main beneficiaries may be the generic and self-medication sector in that they are not hampered by pre-existing production facilities.

The actions of the Union are on balance likely to have had a positive effect on productivity by making it somewhat easier to control and reduce costs. They are unlikely to reduce the downward pressures that are the other element in the dynamic equilibrium described above. The SMP has had only a limited influence in this area and moves to give the EU greater powers have so far been rejected.

4.7.2. Competitive strength

Shares in major markets

The simplest measure of competitive strength is market share. Some relevant data are presented in Table 4.16. They refer to shares of the EU, US and Japanese markets, which currently account for about 75% of world consumption by value.[98]

It is apparent that the distribution of competitive strength is remarkably stable. Change has been limited during the period 1982-93: the share of the Union market held by firms based there has fallen but only slightly. The share of the UK has risen, while that of Italy has fallen. The share of Swiss and American companies has remained broadly constant, while that of Japanese – and more recently Swedish – firms has risen, the former from a very low base. EU companies have penetrated the US market to an increased extent; this is very largely the achievement of German and particularly British firms. They have held their own in Japan, where the market is still mainly in the hands of local firms. The latter have had little direct impact outside Japan, in contrast to Swiss and US enterprises which are active everywhere.

Strength in innovation

We have already seen that product innovation is a key factor in competition in the prescription medicines sector. Data indicating strengths and weaknesses in innovative capacity are presented in Table 4.17.[99]

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[98] Authors' calculations from the *World Drug Market Manual*, various issues, and from IMS information contained in SNIP. *L'industrie pharmaceutique, ses réalités*, 1990-95.

[99] Ibid., based on information from the Centre for Medicines Research and from Barral, P. E., *20 ans de résultat de la recherche pharmaceutique dans le monde (1975-94)*, unpublished.

Table 4.16. Pharmaceutical market shares by value in the EU, the USA and Japan, 1982-93, by nationality of ownership

	F	D	I	E	UK	EU	CH	USA	Japan
EU									
1982	16.7	22.3	9.4	2.6	9.4	65.6	10.1	23.5	0.1
1987	14.7	23.9	10.2	2.7	9.8	65.8	8.7	22.8	0.1
1991	14.1	23.4	9	2.9	11.8	64.2	8.8	19.9	0.6
1993	14.7	22.9	6.5	2.5	15.1	61.4	8.5	21.1	0.9
USA									
1982	0.3	3.9	0.2	0	5.1	10.1	9.2	80	0
1987	0	4	0.3	0	9.8	14.4	8.2	74.8	0
1991	1.2	4.6	0.1	0	14.6	20.6	8	70.2	0.3
1993	1.5	4.7	0	0	15.1	21.9	7.7	69.2	0.3
Japan									
1982	0.6	4.8	0	0	1.9	7.8	2.8	12.2	77.1
1987	0.1	3.8	0	0	1.3	5.4	3.4	10.3	80.7
1991	0.2	4.8	0	0	2.9	8.1	0.3	5.9	82.1
1993	0.3	3.9	0	0	2.6	7.3	3.3	6.4	82.3

Source: Authors' calculations from the *World Drug Market Manual*, various issues and from IMS information contained in SNIP. *L'industrie pharmaceutique: ses réalités*, 1990-95.

It is necessary to take into consideration not merely the number of new active substances introduced by companies of a particular nationality but also the extent to which they are used and the therapeutic improvement that they represent. Most new medicines (76%) are based on active materials which are modifications of those already known; most (69%) are at best only minor improvements in terms of treatment. Only 10% are both novel and highly efficacious. The countries in question accounted in 1975-94 for more than 90% of all products developed and all those sold globally. US firms are clearly *hors concours*: between 1975 and 1994 they discovered approximately 25% of all NASs and exactly one half of those which were globalized. Swiss firms also show great strength. At the other extreme, Japanese companies have produced a large number of new products, most of which were not sold outside Japan.

The position of the Union as a whole is equivocal. EU firms are second only to those of the USA; in recent years, however, they have owed this position almost entirely to German and British companies. The innovative achievements of firms based in other member countries is substantially lower. A further decline in European strength may follow to the extent that biotechnology becomes the basis for innovation. The USA enjoys an advantage in basic scientific resources and in availability of venture capital. Within the Union the UK leads in number and effectiveness of biotechnology companies, closely followed by France. Belgium, Germany, the Netherlands and Scandinavia also have elements of strength. Nevertheless, it is significant that European pharmaceutical companies invest heavily in American biotechnology firms, whereas the converse is not the case.

Table 4.17. Measures of innovative capacity

	NAS introduced		NAS globalized		Products in world top 50 in 1992
	1975-89	1990-94	1975-89	1990-94	
B	10	1	2	0	0
D	114	15	11	0	6
DK	6	4	0	0	0
E	20	5	0	0	0
F	67	9	5	0	0
I	76	10	1	0	0
NL	7	2	0	0	0
UK	41	17	20	2	11
EU	341	63	39	2	17
S	33	5	8	0	1
CH	63	17	12	3	5
USA	213	49	66	2	24
Japan	160	56	11	1	3
Total	810	190	136	8	50

Source: Ibid., based on information from the Centre for Medicines Research and from Barral, P. E., *20 ans de résultat de la recherche pharmaceutique dans le monde (1975–94)*, unpublished.

Financial strength

The world pharmaceutical market is dominated by large research-oriented firms, many of whom have significant interests in the generic and self-medication sectors. Size is an advantage in both innovation and production. Accordingly, much of the competitive strength of a country is incorporated in its major companies, which alone are able to provide the resources and take the risks associated with global activity.

The sales needed to support a free-standing company of this type is currently at least ECU 1,000 million. In 1994 there were 48 such companies, of which 16 were based in the EU, 14 in Japan, 13 in the USA and three elsewhere. If, as current thinking implies, the threshold is put at sales of ECU 2,000 million, these figures become seven, five, ten and five. Greece, Ireland, Portugal and Spain have never had firms even approaching the lower limit. Italy no longer has enterprises of this size; the largest local firm was acquired by the Swedish firm Pharmacia. France, Germany and the UK are home to international companies of the largest size, but those in Belgium and the Netherlands are perhaps less strongly placed.

A further point deserves attention. As has been seen already, profit margins differ considerably among developed countries. Companies whose sales are mainly in countries where they are high enjoy an advantage over others. British firms are especially well placed, since a high proportion of their sales are in the USA and Japan; those based in France are in

the opposite position since their major markets are in France itself, in Italy and in Spain.[100] Germany is in an intermediate position.

The impact of the single market

The current distribution of strengths and weaknesses is largely the result of complex long-term factors. Indeed, it has changed surprisingly little since the mid-1970s.[101] The UK has improved its position; Italy, the Netherlands and, less certainly, France have declined in importance; Germany has held its place. The USA remains the dominant player; Japan has failed to make the headway formerly expected.

In 1994 the Commission issued a Communication outlining an industrial policy for the pharmaceutical industry.[102] Expressing anxiety about the rising costs of innovation, stiffening global competition and the increasing vulnerability of the EU industry, it urged the need for a better-integrated pan-European market for medicines characterized by greater competition. It reviewed the steps which it had already taken – whose impact is considered in other parts of this report – and made further suggestions, directed towards the creation of a more favourable environment for biotechnology, the integration of R&D efforts, and encouraging price competition via generics, parallel trade and the modification of national cost control measures. This Communication was received coolly by the European Parliament who considered that the vulnerability of the industry had been exaggerated and that the policies suggested were unduly favourable to it.[103]

No further action by the EU has as yet resulted. It is far from clear that the measures already taken will necessarily increase the competitive strength of the innovative European companies. Improved methods of granting marketing authorization and enhanced protection of intellectual property benefit all firms and not just those based within the Union. Steps which enable companies to reduce the number of their European plants must be to the short-term advantage of those – mainly Swiss and American – who have the most to gain. Increased price competition from low-cost suppliers would hit hardest those firms most heavily dependent on sales within the low-price member countries of the EU.

4.8. Effects on employment

A single market for pharmaceuticals would mean increased competition and the chance to realize economies of scale. It would be expected that employment would grow more slowly than output or value added and might actually fall. Given that considerable excess capacity has existed for many years it would seem probable that the effect would be felt most in production.

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[100] Taking the combined market European Union + USA + Japan, 58% of sales by British companies were in the USA or Japan compared to only 12% of those of French firms.

[101] See, for example, Burstall, M. L., Lake, A. and Dunning, J. H. *Multinational entreprises, governments and technology - The pharmaceutical industry*, Paris, OECD, 1981, and Burstall, M. L. and Senior, I. S. T. *The Community's pharmaceutical industry - Evolution of concentration, competition and competitivity*, European Commission, Luxembourg, Office for Official Publications of the EC, 1985.

[102] Communication from the Commission to the Council and the European Parliament on the outlines of an industrial policy for the pharmaceutical sector in the European Community, COM(93) 718 final.

[103] European Parliament. Draft Report, DOC EN\PR\284\284060, 21.11.1994.

4.8.1. Patterns of employment

Trends in overall employment in the pharmaceutical sector between 1983 and 1994 are shown in Table 4.18.[104]

The industry employs fewer workers in relation to its turnover and still fewer in relation to the value it adds than manufacturing industry as a whole. A relatively high proportion are non-manual; a relatively high proportion are university graduates or otherwise qualified. Rates of pay are above the average for manufacturing industry; the sector is a desirable employer. Taking the EU industry as a whole, some 45-50% are currently involved in production and about 15% each in R&D and in marketing and selling. These proportions vary considerably: thus, in large research-oriented firms fewer are employed in production and more in R&D, while in smaller companies the reverse is true.[105]

Table 4.18. Employment in the pharmaceutical sector, 1983–94

	1983	1988	1990	1991	1992	1993	1994
B	10,145	10,278	11,638	11,871	12,162	12,045	
D	86,907	93,455	99,505	102,869	106,208	101,322	96,053
DK	7,673	9,851	10,661	10,056	11,775	11,958	
E	32,135	33,232	35,193	36,374	30,958	29,345	29,076
F	64,764	69,732	76,688	77,958	80,426	79,303	78,812
GR	5,824	5,571	6,470	6,312	6,261	6,211	6,190
I	62,351	66,500	68,910	70,888	70,179	69,251	63,380
IRL	3,836	5,392	6,469	6,912	7,518	7,850	
NL		12,636	12,690	12,663	12,574	12,094	
P	7,765	7,876	8,852	9,007	8,406	7,611	
UK	66,592	71,140	74,916	77,474	78,710	77,279	73,912
EU	359,718	385,663	411,992	422,384	425,177	414,269	396,679
USA	153,011	162,600	171,470	164,440	169,661	172,724	169,439
Japan	99,322	98,560	98,826	99,048	100,107	102,914	

Source: Eurostat.

Between 1983 and 1992 employment in the sector rose by 17%. Growth was above the European average in Denmark and Ireland and below it in Italy and the Netherlands. Nowhere did it increase as rapidly as value added; as already noted, the period was characterized by rapidly increasing productivity in all member countries. However, a maximum was reached in 1992 and in most member countries employment fell in 1993 and 1994; it is probable that this decline has continued since then. Employment in R&D rose by about 50% between 1983 and 1993 (Table 4.19) but has since fallen.[106]

[104] For the sake of comparability the data for NACE 257 is used, although certain kinds of employment are omitted. The figures given by EFPIA are 20-25% higher. The trends in employment, however, are very similar.

[105] A large British R&D company employs about 25% of its labour force in production and about 20% in R&D.

[106] Authors' calculations based on Eurostat, and on Farmindustria, *Indicatori Farmaceutici*, various years. It should be noted that the basis for inclusion as R&D personnel may differ between countries.

4.8.2. The impact of the single market

The period up to 1992 is one characterized by rising productivity and slowly rising employment. The period since has seen continued increases in both production and productivity but falling employment. Why is this so?

The role of the EU in the first period is discussed in Section 4.7.1 above, where it was concluded that the Union may have made adjustment to a more hostile environment easier. Companies maintained their margins in the main by internal improvements to their operations, which, of course, often included the loss of jobs. The distinguishing feature of the later period has been the wave of mergers and acquisitions between major research-based firms. Such mergers were not unknown in the 1980s but those in recent years have been both larger and more frequent. They have inevitably been accompanied by substantial losses in employment as facilities are concentrated, overlapping projects abandoned and sales forces rationalized. Furthermore, even those firms which have not been involved have frequently announced sweeping rationalizations.[107] They have taken place both within the EU, where it has been estimated that they amount to some 30,000 posts, and in the USA.

Table 4.19. Employment in pharmaceutical R&D, 1983–94

	1983	1988	1990	1991	1992	1993	1994
B	1,220	1,300	1,660	1,660	1,880	1,900	2,000
D	11,200	12,600	15,000	16,290	15,300	15,400	15,300
F	7,500	9,250	10,200	11,000	11,600	12,000	12,000
I	6,250	6,730	6,910	6,370	7,630	6,750	6,570
NL	2,650	2,650	2,130	2,300	2,600	2,820	2,300
Other	3,250	3,850	4,200	4,250	4,800	6,000	6,250
UK	11,500	15,800	15,490	19,090	19,000	20,740	20,740
EU	43,570	52,180	55,590	60,960	62,810	65,610	65,160
USA	39,300	51,400	54,260	56,750			
Japan	17,800	22,590	24,340	32,500	34,400	34,540	30,304

Source: Eurostat and authors' calculations based on Eurostat, and on Farmindustria, *Indicatori Farmaceutici*, various years. It should be noted that the basis for inclusion as R&D personnel may differ between countries.

Some indications of the scale of employment losses are summarized in Table 4.20. From the standpoint of this study the main point is that the initiative for these measures lay with the companies involved. The EU as such played no direct part except in so far as the mergers were subject to general EU law. As suggested elsewhere, the actions of the Union are not responsible for the mergers themselves; equally, they have done little either way to influence the decisions taken.

[107] EFPIA; *Scrip*, various issues. Thus Lilly and Pfizer announced cuts of 4,000 posts to take place in 1994-96, and Merck of 2,800; several EU-based companies took similar action, though on a smaller scale.

Table 4.20. Losses in employment through recent mergers

Merger/acquisition	Date	Expected losses	Nature and location
Rhône-Poulenc/Rorer	1990	2,000	400 in France
AHP/Cyanamid	1994	2,300	300 in USA
Roche/Syntex	1994	5,000	Mainly in Switzerland, USA
Hoechst/MMD	1994	8,000	1,400 in Germany
BASF/Boots	1995	250	UK, USA
Rhône-Poulenc/Fisons	1995	2,900	470 in UK
Glaxo/Wellcome	1995	9,000	Mainly in UK
Ciba/Sandoz	1996	10,300	

Source: EFPIA; *Scrip*, various issues.

4.9. Evolution of final prices

The prices of medicines vary widely between member countries of the EU. Earlier sections of this report have suggested some of the reasons. National per capita incomes and price levels vary. National preferences and national regulation of the sale of medicines have segmented the Union market to a considerable extent. The creation of a genuine single market for medicines should bring about a convergence of prices as barriers to trade are removed and competition is increased.

However, before considering the extent to which this has happened, it is first necessary to examine both the institutional and economic constraints on pharmaceutical pricing.

4.9.1. Price controls and price setting

As already noted the manufacture and distribution of medicines are normally separate activities. Manufacturers sell to specialized wholesalers who in turn sell to specialized retailers. Value added tax may or may not be charged. Final prices to consumers are therefore determined by a variety of factors which are, at least in theory, independent.

Price controls

Table 4.21 summarizes the controls used in member countries of the EU over the prices of medicines at various points in the distribution chain. In a majority of countries, manufacturers' prices of products that are reimbursed under public health care systems are fixed at launch according to various criteria. The UK permits free pricing but regulates global profits on sales to the National Health Service; Denmark, Germany and the Netherlands allow free pricing but fix reimbursement levels. In every country except Denmark price rises subsequent to introduction require official permission. In most, not all, Member States the prices of medicines that are not reimbursed or are intended for self-medication are not controlled.

Distributors' margins are also shown. They are controlled in all member countries. Those of wholesalers are maxima; as has been seen in Section 4.2.4, discounts to retailers are common and actual margins are substantially lower than those permitted. Retailers are in a different

position. In most nations of the Union *de facto* retail price maintenance is in force. Wholesaling is a highly competitive business; retailing is much less so. Retailers have other advantages. They everywhere have a monopoly of dispensing prescription medicines which is extended to self-medication products in a majority of member countries. The numbers of retail pharmacies are often regulated – their density varies greatly – and chains under common ownership forbidden.[108]

Supply, demand and the pricing of medicines

In all member countries of the Union a large majority of sales by value are of medicines prescribed under the public health care system (Table B.1 in Appendix B). The patient pays only a part – often a small part – of the cost. Various studies have shown that the price elasticity of their demand is low, typically -0.1 to -0.2 and always well below -1.0.[109] Downward pressures on prices come from health care systems, not patients. With self-medication products, the user pays the entire bill. Prices are lower in general. Price sensitivity is higher, though it is not the only factor influencing demand, since branded products enjoy a large advantage over non-branded ones.

Where prices are free, the general principle is to charge what the traffic will bear, taking into consideration the technical advantages of the medicine, local purchasing power, and the prices of competitive products. A genuinely innovative drug typically commands a two- to three-fold premium over its competitors; such premiums are generally acceptable even in countries where prices are controlled. Attempts by the makers of older medicines to hold market share by cutting their prices are rare. 'Me-too' products are price-takers; they are usually introduced at or somewhat below the price of the original 'breakthrough' drug. Once launched, the nominal price of a medicine usually remains constant and therefore falls in real terms, as increases to compensate for inflation are denied or prove inadequate.[110]

When patent protection expires, a successful product can expect generic equivalents to enter the market. They must do so at substantially lower prices in order to overcome the goodwill accumulated by the originator. Significantly, generic medicines have only taken a substantial share of the market where prices were high and their use has been actively encouraged.

[108] It may be noted that permitted distributors' margins and VAT rates are generally higher for self-medication products than for prescription-only medicines.

[109] Ryan, Mandy, *Estimating the effects of prescription charges on the use of NHS drugs in England*, University of Aberdeen, 1989, estimated an elasticity of -0.1 rising eventually to -0.2. Lavers, R. J. (*Applied economics*, No 21, 1989, pp. 1043-52) found a similar figure. Data from Australia and the USA are in the same range.

[110] Based on an unpublished study by REMIT Consultants of price evolution in major innovative medicines introduced between 1976 and 1993.

Elsewhere, the necessary price differentials may not be commercially attractive.[111] Price competition between prescription and self-medication versions of the same products is conditioned by the indications for which the latter may be sold and the co-payments charged for the former. Thus in the UK, where a high flat-rate prescription charge is made, most self-medication drugs are at a distinct advantage. In France, where co-payments are a proportion of the retail price – which is in any case relatively low – this is not so.

[111] Thus, they have 10-20% of the market by value in Denmark, Germany, the Netherlands and the UK but only 1-5% in Belgium, France, Italy and Spain.

Table 4.21. Controls over prices of medicines within the EU in 1994

	Manufacturers' prices controlled?		Other controls over public expenditure on medicines				Prices of prescription medicines at each stage (manufacturer's price = 100)			Characteristics of retailing medicines		
	Reimbursed	Self-medication	Profit controls	Positive list	Negative list	Reference prices	Wholesaler	Retailer	Consumer incl. VAT	Pharmacies have monopoly of all sales?	*De facto* price maintenance	Pharmacy chains forbidden
B	Yes	Yes	No	Yes	Yes	No	115	167	177	Yes	Yes	No
D	No	No	No	No	Yes	Yes	116	157	181	Minor exceptions	Yes	Yes
DK	No	No	No	Yes	No	Yes	107	144	180	Yes	No	No
E	Yes	No	No	No	Yes	No	114	162	167	Yes	Yes	Yes
F	Yes	No	No	Yes	No	No	111	152	155	Yes	No	Yes
GR	Yes	No	No	Yes	No	No	108	160	200			
I	Yes	No	No	Yes	No	No	111	149	163	Yes	Yes	Yes
IRL	No	No	No	No	No	No	115	176	176	No	No	No
NL	No	No	No	No	No	Yes	120	162	172	No	Yes	No
P	Yes	Yes	No	Yes	Yes	No	111	139	146	Yes	Yes	Yes
UK	No	No	Yes	No	Yes	No	107	140	140	No	Yes	No

NB: It may be noted that permitted distributors' margins and VAT rates are generally higher for self-medication products than for prescription-only medicines.
Source: National sources.

4.9.2. Have prices converged?

This question is more difficult to answer than might at first appear. A very large number of individual medicines are on sale in any member country at any time. Not all are common to all countries. A basket of products sold everywhere must therefore be constructed. This can never be totally representative; moreover, it can rapidly become misleading as new drugs are introduced and old ones fall out of use, and as prices and exchange rates change.

Comparisons of the retail prices of a common basket of products during 1988-93 are presented in Table 4.22.[112] They show that throughout this period prices in Denmark, Germany, Ireland, the Netherlands and the UK were consistently above the unweighted EU mean and those in France, Italy, Portugal and Spain were below that average. However, prices in Germany fell significantly, probably as a result of reference pricing and the steps taken to encourage generics products. Those in Spain and Italy rose, though in the case of Italy the impact of devaluation is evident. However, as measured by the standard deviation, there was no evidence of convergence. A study of differences in manufacturers' prices confirmed this conclusion,[113] though the rank order of countries changed somewhat.

Table 4.22. Relative retail prices of medicines within the EU, 1988-93

(EU = 100)

	1988	1989	1990	1991	1992	1993
B	88.6	91.0	92.6	100.5	107. 7	116.3
D	128.4	123.5	116.6	110.5	105.0	105.4
DK	128.1	131.1	136.7	143.4	134.6	133.5
E	71.6	70.8	76.6	83.7	89.4	93.5
F	71.5	69.0	66.9	63.8	60.2	63.4
GR	73.8	80.0	80.0	85.5	80.8	84.7
I	79.1	83.1	89.4	96.1	102.8	95.5
IRL	133.2	129.5	129.8	132.2	129.8	130.5
L	97.1	95.6	93.5	94.5	93.6	97.1
NL	131.9	127.7	129.9	134.1	139.0	148.4
P	67.5	61.7	57.9	57.7	60.9	67.0
UK	115.9	123.1	125.6	124.6	126.4	122.7

Source: See note 110.

[112] Figures from the German pharmacists association ABDA; the sample of products is that used by Sermeus, G. and Andriaenssens, G., *Drug prices and drug legislation in Europe*, Brussels, BEUC, 1988. For a sharp criticism by the Dutch industry association Nefarma of the methodology used, see *Scrip*, No 1997, 7.2.1995, p. 4. The methodology of price comparisons is reviewed by Van Andel, F. G., *How do UK drug prices compare to other European countries?*, 1994.

[113] Retailers' permitted margins have changed little since 1980 (MEFA, *Tal og Data*, various issues).

This basket is biased towards older medicines and contained many products that were already out of patent and therefore subject to generic competition. However, the numerous comparative studies carried out during the past decade have given qualitatively similar results, though the quantitative differences between Member States depend markedly on the products considered. During the past few years many companies have stated that they now aim for a common price or prices within a fairly narrow band and have reported that they are quite often successful (see the case studies of Zeneca and Merck). As already noted in Section 4.2.2, an important consideration in this policy is anxiety about parallel trade.

Table 4.23 indicates the launch prices for a number of medicines that represented significant therapeutic advances and might be seen as price-setters for their classes of product. Denmark, Germany and the UK permitted launch prices to be set by the company involved throughout the period while France did not. These data suggest that where launch prices are free, they are higher in Germany and Denmark than the UK, but also that they are generally higher in all three countries than in France. Companies were sometimes successful in obtaining a narrow price band and sometimes not. Other studies suggest that it is difficult to generalize about trends towards pan-European pricing. There are recent examples in both directions.[114] What is beyond doubt is that prices diverge as exchange rates vary and public authorities allow or disallow price increases to compensate for inflation. The companies and industry organizations interviewed identified this as a long-term problem.

Table 4.23. Launch prices of major products

(ECU per day for typical daily dose)

	F	D	UK	DK
Cimetidine	1.61	1.89	1	1.89
Captopril	0.92	0.86	0.77	1.24
Acyclovir	9.35	8.82	9	8.75
Buspirone	1.37	2.47	1.8	2.21
Fluvoxamine	1.2	2.17	1.77	2.1
Simvastatin	0.62	1.21	0.93	1.47
Omeprazole	2.19	2.91	1.82	4.12
Alteplase		3415	1344	
Ondansetron		44.4	24.5	40.4

Source: National sources.

The position of self-medication products is more straightforward. Their prices are comparatively low and parallel trade is therefore unimportant. There are few pan-European brands. Prices are free and differ between member countries, without this having become a major issue to either industry or consumers.

[114] A study of five drugs introduced since 1986 into all member countries of the Union showed that on an exchange rate basis the standard deviations were 11, 12, 13, 23 and 47% of the means of the launch prices. The standard deviations in most estimates of comparative prices are much larger, but these reflect factors after launch.

4.9.3. The role of the European Union

Thus, evidence of converging prices is ambiguous. It appears that progress in this direction has been limited and that it has been due to the initiative of individual companies and the responses of public bodies. What has been the impact of the SMP?

The effects of the Transparency Directive (89/105/EEC) have been modest and attempts to extend it have been rebuffed by the Member States, in whose hands powers to control public expenditure on medicines firmly remain. The only limits on their powers are the articles of the Treaty of Rome and the decisions of the European Court of Justice which exclude policies that discriminate against imported products or in favour of local firms. However, the parallel trade in medicines, which owes its existence to the Court of Justice and the Commission, is a significant factor in decisions by international companies to seek common launch prices for new medicines. That the trade has developed only slowly and is so far an annoyance rather than a serious threat is irrelevant: it has always been its potential that has caused anxiety.

4.10. Contribution to sustainable development

Sustainable development has been defined as the use of ecological habitats – ecosystems with diverse flora and fauna, geological and physiographic features and natural beauties – in ways that satisfy the needs of current generations without compromising the ability of future generations to meet their own requirements.[115]

In the context of the pharmaceutical industry this means:

(a) the control of potentially dangerous processes;
(b) the efficient use of resources such as raw materials, water and energy;
(c) reductions in waste streams, such as discharges to the atmosphere, to water courses or to the soil;
(d) disposal of unused medicines and of packaging.

4.10.1. Production of medicines

Where sustainable development is concerned, the pharmaceutical sector differs from much of the chemical industry. In the heavy chemicals industry, volumes are large, prices low and the commercial lifetime of products long. Production costs are typically a large proportion of income and manufacturers have a powerful economic incentive to optimize processes by efficient use of inputs, recovery and re-use of solvents and energy and minimization of waste. In the pharmaceutical industry, volumes are low, prices are high and the lifetime of products is relatively short. Production costs are a more modest proportion of income (Section 4.1.2). Thus the economic need to optimize is reduced.[116] Rather, the force driving sustainable development is the powerful physiological effects of medicines and the need to prevent their inadvertently reaching the environment.

Like other parts of the chemical industry the pharmaceutical sector is subject to environmental regulation. Such controls are a national responsibility. However, the Union has laid down

[115] Kirkwood, R. C. and Longley, A. J. (ed.). *Clean technology and the environment*, London, Blackie Academic and Professional, 1995.

[116] Johnson, P.A. *Agricultural and pharmaceutical chemicals*, in ibid. Annual production volumes range from aspirin (25,000 tonnes in the EU, the USA and Japan) through ampicillin (1,750 tonnes) to methotrexate (0.15 tonnes).

basic requirements in its legislation, notably in the so-called 'framework' Directives 65/65/EEC and 75/319/EEC and Directive 91/356/EEC concerning the principles and guidelines of good manufacturing practice. Horizontal legislation concerning the handling of genetically modified micro-organisms (Directives 90/219/EEC and 90/220/EEC) and packaging waste (Directive 94/62/EC) is also relevant to the operations of the pharmaceutical sector. Interviews show that national requirements have so far determined company attitudes to the environmental impact of production. In addition, international firms wish to be seen as good corporate citizens. Significantly, there has been no relocation of production to countries with low environmental standards.

4.10.2. Disposal of medicines and packaging waste

This is still under national control. The Packaging Waste Directive (94/62/EC) is still being phased in. The role of the Union has therefore been modest. It has required Member States to take various kinds of environmental impact into consideration and has set minimum standards. For the reasons already explained, differences between them have not so far emerged as a major issue for the pharmaceutical sector or for others.

4.11. An overview: how effective have the measures of the European Union been?

Chapter 3 and the preceding parts of this chapter have examined the individual measures taken to bring about a single European market in pharmaceuticals and assessed the impact of these measures. This section examines the single market programme as a whole and addresses how effective it has been and what barriers remain. In answering these questions it is necessary to emphasize that much of the legislation has been in place for only a comparatively short time and adjustment is still in progress. It must also be remembered that the industry itself has been undergoing changes which are global in scope and which are largely unconnected with the EU legislative process.

The ways in which national governments regulate the pharmaceutical industry have been identified. Taken as a whole they have the potential to fragment the European pharmaceutical market, reduce competition and inhibit intra-EU trade. They might do so in the following ways:

(a) by hindering admission to national markets on technical or economic grounds;
(b) by imposing conditions on how products may be marketed;
(c) by discriminating against supply through trade and in favour of local supplies;
(d) by partitioning the market through price differences;
(e) by partitioning the market through differences in the protection of intellectual property.

This is not to say that they would be totally effective; rather, that they would have an inhibiting effect and make the operation of a single market more difficult, more expensive and less effective.

4.11.1. What has been done to remove barriers to trade and how effective has it been?

Barriers to admission to national markets

The Union's actions have undoubtedly harmonized the technical evidence required for admission. The procedures for evaluating applications have only been in place for some 18 months but the initial experience has been encouraging. If they prove to work as intended, they

will make it considerably quicker for companies to obtain admission to the markets of member countries.

Controls over admission to reimbursement and agreement on prices may also constitute barriers to trade. In practice international companies rarely refuse to enter national markets, even if the prices offered are low, but the delays involved may be considerable. The Transparency Directive (89/105/EEC) has had only a modest effect here.

Controls over marketing and distribution

National differences in the classification of medicines as prescription-only or self-medication products, rules about what may be advertised and how, and about what information must be given to patients are barriers to trade. The Directives (92/26/EEC and 92/28/EEC) affecting these areas leave much to national governments, whose practices continue to vary. Permitted pack sizes have not yet been harmonized and add to production costs.

The Wholesaling Directive (92/25/EEC) has made it easier for wholesalers to operate in several countries and has facilitated the concentration of the sector which was already taking place. Retail distribution remains a matter for individual member countries.

Discrimination against trade

In the past Member States have rewarded local investment through their pricing and reimbursement policies. This has promoted the unnecessary multiplication of production and research facilities and so raised costs. The Transparency Directive (89/105/EEC) was expected to expose such policies, which, depending on their nature, may be against the Treaty of Rome. In practice this has not happened. Governments retain full control over their policies and the onus of proof that their policies are discriminatory rests with companies affected.

Partitioning the market through price differences

The majority of medicines are reimbursed through public health care systems. Governments control expenditure on this account and prices are regulated in most Member States. This inhibits trade. Although this formed no part of the SMP, a parallel trade in medicines was legalized by decisions of the European Court of Justice and has been enforced by the Commission.

Partitioning the market through differences in the protection of intellectual property

The extent of patent protection has differed between member countries. The Union has provided increased patent lives and marketing exclusivity for medicines. However, discretion was given to Member States to determine the effective period of such extra protection.

4.11.2. To what extent has the market been unified?

The evidence presented in Section 4.2 suggests that the SMP measures have had a positive if modest effect in aiding the unification of the pharmaceutical market. Trade has become a rather larger proportion of consumption, especially in those countries where it was hitherto small; national companies have lost some ground; and local production by foreign firms has been somewhat reduced.

However, the market is still far from completely unified. This is especially true of the generic and self-medication sectors, where many of the firms are small and hitherto oriented to their domestic markets. There are signs, however, that at least some of them are encouraged by the actions of the Union to expand into other member countries. In contrast, research-oriented firms have operated on a multinational basis for many years and the benefits to them are more marginal.

Parallel trade has so far failed to develop on a scale which would bring closer prices within the EU.

4.11.3. Who has benefited and how?

The distribution of gains and losses from the SMP may be summarized as follows:

(a) All manufacturers active in more than one member country stand to gain from more rapid processes for marketing authorization.
(b) International research-based firms gain from the extension of patent life. They feel threatened by parallel trade.
(c) Generic companies are handicapped by the extension of patent protection. They are not much affected by parallel trade, since their prices are generally low.
(d) Firms active in the self-medication field are not generally affected by price controls which do not apply to them in most member countries. They would gain from the Classification and Advertising Directives if standards were common and preferably liberal.
(e) Wholesalers have benefited from the actions of the Union but retailers are unaffected.
(f) Consumers may gain from increased choice and competition, especially in the self-medication field. They should benefit in the prescription area in that they may have more rapid access to new medicines.

4.11.4. What further action is necessary?

In the light of what has been said above, there would seem to be a case for extending the Directives concerning the classification and advertising of medicines so as to reduce and if possible eliminate the differences that still remain between member countries. These differences may not be major barriers to trade – it is difficult to estimate their impact in quantitative terms – but they undoubtedly reduce choice and competition. There remain some differences in the protection of intellectual property: here the main impact is on competition between original and generic copies.

Issues related to prices and price controls present greater difficulties. Logically, prices should converge in a free and unified market to the point at which parallel trade would no longer be worthwhile. The problem arises in that prices are not free. National governments have their own priorities and prices and pricing systems therefore differ. National authorities have made it clear that in this area they intend to retain their right to do as they see fit. The Union as such then faces a dilemma. To encourage parallel trade might bring about a more unified market but might at the same time drive down prices to levels which could inflict serious damage on the European pharmaceutical industry.

It is far from clear that a solution exists to this problem. Certainly, it is seen as the area where the impact of the SMP has been least felt. Member countries have different per capita incomes. Would free prices be fair to, say, Greece or Portugal? In the past pan-European prices coupled

with rebates have been suggested as the solution. However, France and to a lesser extent Italy enjoy incomes close to or above the Union mean and relatively low prices for medicines. They would only accept freer prices were they to be convinced that they would gain from such a change. So far this has not proved possible.

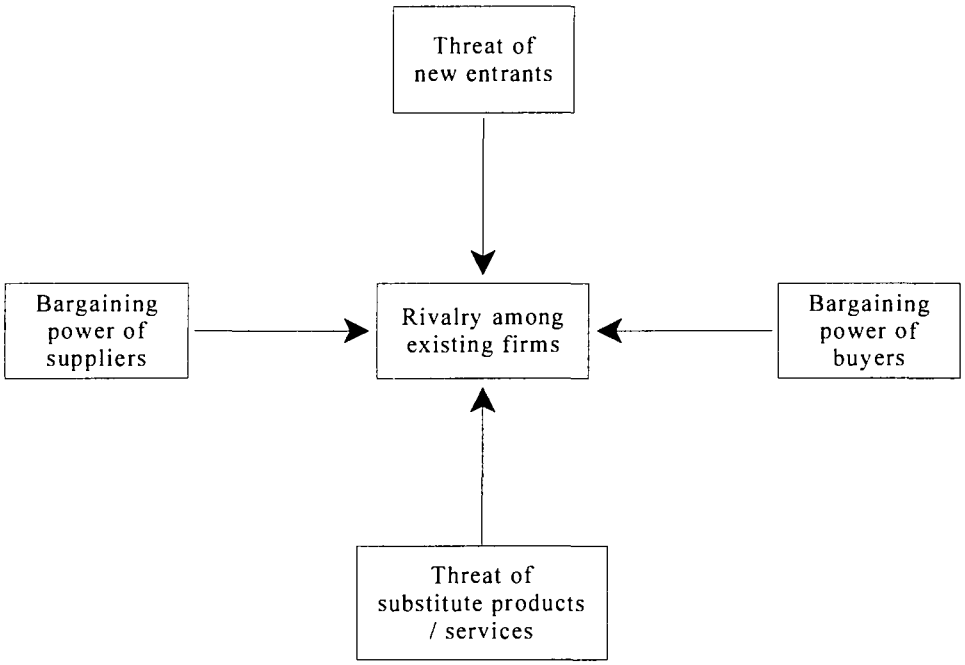
5. Business strategy

5.1. Implications of the SMP on factors determining corporate strategy

In this section, we will consider the relationship between the SMP and those factors which determine corporate strategy for pharmaceutical companies.

Porter[117] identifies five forces that shape the competitive environment in which firms operate. In any given industry, the relative intensity of these forces drives down profits to their competitive floor rate. This is measured as the returns to capital invested and will never be below the prevailing interest rate or investors will go elsewhere and firms will exit the industry. The five forces driving industry competition are identified by Porter below.

Figure 5.1. Porter's five forces



In order to assess how and to what extent the competitive environment has been changed by the SMP, we use this basic model as a starting point.

5.1.1. Threat of new entrants

The dominant characteristic of pharmaceutical innovation during the past decade has been a rapid increase in its cost, both in relative and absolute terms. Research-based companies have become critically dependent on block-buster products. Entry to the research-based sector,

[117] Porter, M. *The competitive advantage of nations*, Macmillan, 1990, p. 35.

never easy, has become prohibitively difficult. As already noted, this is a world-wide development and cannot be attributed to the SMP.

On the other hand, the rise of the biotechnology sector, often as suppliers or partners to the major research-based pharmaceutical companies, has also contributed to a change in the competitive environment. More significantly, the emergence of more generics companies poses a specific threat to research-based firms when their products cease to be protected by patent. One of the most relevant single market measures from the standpoint of the pharmaceutical industry has been the extension of patent protection through supplementary protection certificates (SPCs). These are partly a response to the erosion of effective patent life which pharmaceutical companies have experienced in recent years and partly a response to the extension of patent life which the US and Japanese governments have granted to their pharmaceutical industries.

Most extra-EU suppliers have ensured access to the EU markets. The major Swiss and US pharmaceutical firms have been established in the EU for half a century or more, and are effectively considered to be 'insiders' by most of the EU-based purchasers. Japanese companies have been more cautious. They have yet to make major moves into the EU market, preferring to form strategic alliances with EU companies. This is changing: thus, Yamanouchi and Takeda now have substantial direct investments in the EU. The creation of a single market for medicines may encourage Japanese companies to enter the Union in greater force, knowing that they are protected to some extent from arbitrary discrimination from Member States.

5.1.2. Bargaining power of buyers and suppliers

Scholars such as Chaudhry et al.[118] have argued that the bargaining powers of buyers are stronger within the Union than Porter supposed and the threat of substitute products in the form of generics and parallel imports greater. Suppliers have never had much bargaining power, and although concentration is increasing it is still low overall and the SMP has not markedly affected this. However, the extra patent protection now available does help research-based firms. By the same token it handicaps the generic and self-medication sectors, reducing the threat of substitute products and therefore limiting the bargaining power of buyers.

Nevertheless, overall the bargaining power of buyers has increased. For public health care systems seeking economies, expenditure on medicines is an obvious target, and they have taken action accordingly. The active encouragement of generics by these buyers increases their bargaining power considerably. Within the Union parallel trade is another source of downward pressure on prices. A general tendency in official circles to give the interests of consumers increased priority over those of producers is evident. It is also possible that large wholesalers such as Gehe, a pan-European distribution capability and associated generic operations, could be in a position to demand price concessions from the research-based manufacturers, but they have not yet done so.

[118] Chaudhry, P. 'An exploratory analysis of the effects of the European Community integration on the pharmaceutical industry', PhD thesis, Madison, University of Wisconsin, 1992. This reports field research among 13 European pharmaceutical firms conducted in 1990 and is referred to as the 1990 survey. Elements of this thesis were subsequently published in Chaudhry, P., Dacin, P. and Peter, J. 'The pharmaceutical industry and European integration', *European Management Journal*, Vol. XII, No 4, December 1994, pp. 442-53.

5.1.3. Threat of substitute products/services

Despite the provisions of SPCs which extend the patented life of new products, the threat of generic substitutes has increased dramatically over the period of the SMP. This is primarily a result of the pressure being exerted on pharmaceutical prices by national administrations, rather than a result of the SMP itself. However, the new systems of marketing authorization, labelling and packaging and the classification of medicines will have a particular effect on the generic and self-medication sectors whose activities have hitherto been oriented towards national markets. These companies, unlike the research-based ones (typically multinational enterprises (MNEs)), previously had much greater difficulty in accessing markets other than their domestic ones.

5.1.4. Rivalry among existing firms

Competition in the research-based sector depends on developing new and superior medicines. Firms in this category focus on particular therapeutic sub-markets rather than geographically bounded areas. By doing so they can realize economies of scale and scope and overcome the problems of the high cost of innovative research.

In the face of these costs, some research-based companies have sought to form strategic alliances with other firms that offer a complementary range of products, or to diversify by entering the generic and self-medication markets. Here the SMP has had little direct effect, although rivalry is intensifying in the key therapy areas, as larger, merged MNEs challenge each other for shares of each sub-market.

Other types of firms in the pharmaceutical sector, such as generic and non-prescription manufacturers and wholesalers, have been more affected. For them, easy access to geographically-defined markets remains critical and the steps taken by the Union are of significant help. For example, the Wholesaling Directive (92/25/EEC) harmonizes standards and encourages pan-European operation where hitherto it has been lacking.

The establishment of the European Medicines Evaluation Agency will cut the costs of gaining regulatory approval in all Member States. Once approval is given, either on a centralized basis or through mutual recognition, manufacturers will be able to supply anywhere in the Union. These procedures should benefit the research-based industry by cutting the costs of gaining Union-wide regulatory approval, maximizing effective patent life and facilitating agreement on admission to national markets with the USA and Japan.

As yet, though, there is little evidence of a true European market of homogeneous products and consumers. National traditions of medicine remain, classifications are different and national governments are still the major purchasers and pursue active and varying policies of expenditure control (Section 4.9).

5.2. Nature of the strategic response

5.2.1. Introduction

Section 5.1, together with a review of the recent literature,[119] suggests that integration should influence the business strategies of the pharmaceutical industry in the EU in several major areas, specifically: procedures for obtaining market authorizations, dependence of firms on domestic markets, the role of parallel trade, pricing of pharmaceutical products, expenditures on research and development, rationalization of manufacturing facilities, opportunities for market consolidation through mergers and acquisitions, and the continuance of multi-domestic selling of pharmaceutical products.

In this section these specific issues are explored. For each of them, the propositions and results of the 1990 survey reported in Chaudhry et al.[120] are compared with research undertaken in the context of the present study during 1995.[121] This allows us to make a longitudinal assessment of corporate responses to the SMP. In broad terms, we can relate these corporate responses to the generic strategies outlined by Porter [1990], i.e. product differentiation, cost leadership and focus.

Generally speaking, ethical manufacturers are pursuing a policy of differentiation through their R&D programmes. The new therapeutic products that emerge will give them a competitive advantage for the duration of the patent and beyond. Indeed, differentiation can still be pursued by pharmaceutical firms even for products that have gone off-patent by aggressive marketing and promotion activities. The bargaining power of buyers is reduced by the 'uniqueness' – either perceived or patented – of the product, and for the same reason, rivalry among existing firms and the threat of substitutes is ameliorated.

In contrast, generic manufacturers and wholesalers seek competitive advantage through overall cost leadership. Governments are anxious to squeeze prices, but at the same time they are responsible for the health of their citizens and accountable to an electorate which expects as a right access to modern medicines. They cannot therefore force down prices below the level at which the second most efficient producer of any given drug must exit the industry or they will create a monopoly. At that point, the company with overall cost leadership is still in a position to make above-average returns on its investments. Ratiopharm of Germany has been an extremely successful manufacturer, but like most generic pharmaceutical firms it does not depend entirely on low cost, since the branding is still important in the eyes of its customers.

Focus is the third generic strategy identified by Porter. He identifies a number of ways in which a company can focus its activities, including buyer group, geographic market or product segment. Focusing on buyer groups is of little value to ethical R&D firms as the public health care system constitutes a monopsony, but for some generic firms there may be a value in targeting certain wholesale or hospital purchasers. With respect to geographic markets, some non-prescription or generic manufacturers do find a such a focus useful. Of much greater

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[119] For example, see Burstall, Dunning and Lake. op. cit. note 73; Burstall. op. cit. note 20; Chaudhry. op. cit. note 121; Chaudhry, Dacin and Peter. op. cit. note 118; *The outlines of an industrial policy for the pharmaceutical sector in the European Community*, COM(93) 718 final, 1993; REMIT Consultants. op. cit. note 39.

[120] See note 118.

[121] 'The impact of European integration on the pharmaceutical industry: a longitudinal analysis', based on field research undertaken by Chaudhry, P. in 1995 designed to complement that referred to in note 118.

relevance for the research-based companies is the strategic decision to focus their R&D on particular therapeutic categories – in Porter's term, product segmentation.

In previous research for the UN,[122] EAG modelled the 'impacts' through which the single market would be felt. Competition between firms was expected to intensify, but with the emphasis increasingly on product differentiation rather than lower cost, if over-capacity could be rationalized. Smaller firms were expected to be most vulnerable to this increased competition. This analysis seems well grounded in its application, firstly, to the research-based pharmaceutical industry, where the ability to market products on a regional, if not global, scale has become a significant competitive factor. The extension of patent protection under the SMP would be important to this process. However, as Member State governments seek to control pharmaceutical spending, there is now also a growing emphasis within the industry on strategies of cost reduction. Increasingly, a medicine must not only be safe, efficacious and of good quality but it must also be priced to be cost-effective.

Secondly, for smaller companies, focus is particularly important if the SMP is to be exploited as an opportunity, rather than seen as a threat. This is evident as either a geographic focus or (more commonly) a product focus. Biotechnology and OTC manufacturers are progressively focusing on product niches.

Thus, within the broad definition of the pharmaceutical sector, companies are increasingly being forced to seek competitive advantage, either through product differentiation derived from R&D based innovation or non-prescription focus, or through low-cost generic manufacturing. Few multinational companies are able successfully to combine these two activities, although they are clearly to some extent inter-dependent.

The growth in the market for non-prescription medicines has also led several major research-based companies to exploit their product portfolios more widely in this way, or to acquire non-prescription based firms. The costs of entry to this sector by competitors producing similar products are also lower than in the prescription sector.

While real growth in the Union's pharmaceutical market[123] overall has slowed down dramatically (from 22% in the period 1985-88 to less than 5% in 1991-94), and has been behind the rates of growth in the USA and Japan, the non-prescription sector offers strategic opportunities.

The growing demand for advanced medicines from Eastern European countries has also been a fillip for the EU pharmaceutical industry, which enjoys a substantial and growing trade surplus on this account. Union firms are best placed strategically to respond to this new marketing opportunity for a range of historical, geographical and political reasons. The Cooperation Agreements with the most developed states of Eastern Europe and the pre-accession strategies outlined by the Commission facilitate such commercial exchanges, but although they substantially liberalize trade across former cold war borders, they cannot really be considered part of the single market.

[122] A multi-sector survey of 51 MNEs conducted by EAG for the UN Centre on Transnational Corporations in 1990-91. This was reported, together with other research on the impact of the single market programme, in 1994.

[123] See Appendix B, Table B.1.

5.2.2. Research evidence

The changes in corporate strategy that have resulted from the SMP have been assessed in a longitudinal fashion, by comparing the findings of two surveys of pharmaceutical company managers conducted in 1990 and 1995.[124]

In both 1990 and 1995, the survey interviews began with a *grand tour* type of question to determine what issues the participant saw as the most prominent regarding the impact of regional integration on the pharmaceutical industry. Thus, the first interview question was general: 'What have been the major implications of regional integration for the pharmaceutical industry within the European Union?', to provide the pharmaceutical manager the chance to disclose initially what he or she considered to be the critical issues confronting the firm or industry. The results of this inquiry are revealed in Table 5.1.

Table 5.1. Major implications of regional integration for the EU pharmaceutical industry

Issue (1990)	%	Issue (1995)	%
Continuance of regulated price variation	16.6	Centralized product registration	24.1
Centralized product registration	13	Continuance of regulated price variation	17.3
Stricter guidelines for the promotion of drugs	13	Diverse health care systems	17.3
Diverse health care systems	11.1	Increased parallel trade	13.8
Continuance of multi-domestic selling	11.1	Horizontal and vertical integration of firms	6.9
Distinct medical cultures	9.3	Continued fragmentation of regional markets	6.9
Patent term restoration	5.5	Consolidation of wholesalers	3.4
Increased parallel trade	5.5	Decreasing barriers to entry	3.4
Consolidation of wholesalers	3.7	Patent term restoration	3.4
Higher research and development costs	3.7	Other	3.5
Increased competition	3.7		
Potential for the non-prescription market	1.9		
Growth in mergers and acquisitions	1.9		
Total	100	Total	100

Source: See notes 121 and 122.

Overall, the pharmaceutical managers in both surveys (1990 and 1995)[125] exhibited a reactive response to the changing pharmaceutical marketplace, that is a consequence of continually adapting to regulatory controls. Indeed, several of the most frequent responses to this question contained negative attitudes towards the effects of regional integration on this industry. National regulations were still seen as having a major influence, especially through the public health care systems. The market was not integrated. The European Commission had few powers to bring this about, desirable as it was.

Marketing authorization

The results of the 1990 survey suggested that the majority of respondents expected a change in marketing authorizations resulting in more opportunities for the pharmaceutical industry. Some of the benefits of the harmonization of product registration mentioned included the increased speed of product registration, which should positively affect patent protection;

[124] See notes 121 and 122.

[125] See notes 121 and 122.

elimination of repetitive work by the firm; the provision of both a centralized system and mutual recognition; and the unification of EU registration, which would create a dialogue with the US and Japanese registration systems. However, several managers expressed uncertainty about how the new regulatory system would function in the future.

In 1995, the same themes emerged from the interviews. In general, all but one of the pharmaceutical firms responded with a favourable attitude towards the centralized product registration system. However, some firms were very concerned about the decentralized procedure, i.e. mutual recognition. Problems of the mutual acceptability of expert reports and general delays were mentioned. Some managers were also anxious about the existence of the lowest-common-denominator effect in the EMEA due to the diverse medical cultures (i.e. Latin-European, German, and Anglo-Saxon) represented within the Agency.

Overall, there was some uncertainty about how well the new systems would work since the EMEA had just begun operating at the time of the interviews. However, the firms were primarily optimistic about this new regulatory agency in the EU.

Dependence on domestic markets

In the 1990 survey the majority of the respondents anticipated greater threats from European integration to a firm currently selling to only one country within the EU. Managers emphasized the problems associated with the small firms, including the lack of adequate research and development expenditures to create innovative products and the exorbitant costs associated with pan-European expansion from scratch.

In contrast, the 1995 survey revealed that the majority of the managers viewed several opportunities for this type of firm in the current EU marketplace. They stressed opportunities for this type of firm to use niche strategies in the market, to gain pan-EU market access through the EMEA, and the chance to use their national health authority as the *rapporteur* country in the product registration process. However, several firms viewed this type of local drug firm as a likely take-over target for multinational firms.

Pan-European presence

The opposite response was expected from pharmaceutical managers when discussing the effects of market integration on a pharmaceutical firm selling to several countries within the EU. It was believed that their market positioning would allow these firms to benefit significantly from the removal of barriers to trade. Several opportunities for this type of pharmaceutical firm would include the ability to launch pan-European products as a result of a unified product registration system that would increase marketing economies of scale; an established network of operations that would competitively position these firms, especially since they had already incurred the cost of regional expansion; and the removal of governmental barriers to entry.

Participants in the 1990 survey frequently responded to this issue as an 'opportunity'. Managers mentioned improved market access by means of pan-EU product launches, better economies of scale in manufacturing, and the removal of governmental barriers to entry. The majority of pharmaceutical firms still had favourable responses in 1995. Several managers talked about the rationalization of production facilities and the positive impact of the EMEA. However, others raised negative issues that include: the growth of parallel trade, the

continuance of diverse price regimes, and the consolidation of generic firms. Overall, the attitudes were positive when answering the question about how a 'hypothetical' pharmaceutical firm with a Union-wide presence had been affected by regional integration. This is an interesting finding, especially when compared to the rather negative responses to the *grand tour* question at the beginning of the interview.

Parallel imports

Respondents in 1995 reported that parallel imports in the EU are growing, but identified few strategies to combat parallel trade. Thus, several managers claimed that legal authorization of the parallel imports left them with few – if any – ways to reduce the volume of parallel trade of their products. There is great anxiety about Spain as a source.

The market strategies that were discussed in the interviews include: trying to launch the product at a uniform price or within a narrow price band; monitoring the volume of parallel trade through IMS statistics; differentiating the product by drug delivery (e.g. tablets versus ampoules); attempting to postpone the entrance of drugs from Spain; and negotiating with national health authorities to allow the firm to 'modulate' (raise) the price of other drugs in order to compensate for lost revenues resulting from the parallel trade of a different drug.

Regulated prices

Price diversity of pharmaceutical products within the EU is a direct result of national government regulation.

In the 1995 survey, the diverse regulated price regimes in the EU were perceived as a significant paradox regarding the effect of regional integration. On the one hand, the EU is promoting the free flow of pharmaceutical products – even through parallel trade – and EU-wide market access by means of the EMEA. On the other hand, the pharmaceutical market-place is decisively fragmented by nationally regulated price regimes and distinct national health care systems and reimbursement policies. Managers expressed a high level of frustration regarding this issue, especially since no apparent solution to this dilemma was projected for the future.

Several managers felt that the Transparency Directive (89/105/EEC) had little, if any, effect on their price negotiations with national authorities. Indeed, several managers reported that maintaining a local presence in a national market still assists the company with obtaining a better regulated price. To rationalize activities was then to run the risk of antagonizing the local government with possibly serious consequences.

Innovation

Industry leaders projected that, in a unified EU, the best attribute for competitiveness in the pharmaceutical industry would be the level of innovation of the firm. Indeed, pharmaceutical firms must introduce prescription drugs on a regional, if not global, scale to recover the initial research and development expenses and increase overall profitability.

In the 1990 and 1995 surveys, many of the pharmaceutical managers discerned innovation as the mission objective of their industry, regardless of whether the EU regional economic

integration would develop in the future. Thus, the issue of economic integration was seen as irrelevant to maintaining the new product pipeline.

A significant trend has been the rise of strategic alliances. Data from MERIT (University of Maastricht) indicate that alliances involving an EU partner in the biotechnology sector doubled from 1980-86 to 1987-93.

Manufacturing facilities

The results of the 1990 survey indicated that the majority of managers were planning to rationalize their production facilities as a result of market integration, and most perceived this, in general, as an opportunity for the pharmaceutical industry.

By 1995, all but one firm had started to rationalize manufacturing facilities. The common theme regarding plant consolidation was reducing the number of firms into centres of excellence, i.e. selecting central locations for the production of drugs to achieve optimal logistics and substantial cost-savings for the entire EU marketplace. This might involve concentration of all products in a few plants or the concentration of all production of a single medicine in one plant.

American firms have generally been quicker to take action on this than their EU counterparts. However, early indications from EAG research[126] were that the SMP was having little impact on the intra-EU location of facilities.

Mergers and acquisitions

In the 1990 survey the majority of respondents expected future consolidation in the industry through mergers and acquisitions of small and medium-sized companies realigning themselves to prepare for the EU marketplace. The managers felt very strongly about increased mergers and acquisitions at the national level, but did not perceive the EU market integration as the catalyst for industry consolidation among the large multinational pharmaceutical firms.

The results of the 1995 survey indicate that global trends, not regional integration, have promoted the recent mega-mergers in the industry. Managers see the need to attain critical mass in R&D and corresponding sales, the importance of the synergies possible from a larger firm, and the attractions of diversification into the generic and self-medication fields as driving forces. Regional integration was at most a secondary consideration, although the increased bargaining power of buyers across the EU has accelerated the process of industry concentration.

Multi-domestic selling

All managers agreed that a multi-domestic selling strategy, not an EU-wide selling approach, would be used by their companies for several years, if not decades. National – sometimes even local – cultures and health care systems are too different for selling to be organized otherwise. However, were managed-care systems to develop, companies rather than individual physicians would become the customers and methods would change. European integration had so far had no effect on sales techniques.

[126] See note 118.

Promotion

In the 1995 survey, opinion was sought as to whether the Advertising Directive (92/28/EEC) had changed the promotion tactics of EU pharmaceutical firms. Overall, participants agreed that the Directive had provided the industry with stricter guidelines on promotion. Moreover, the participants viewed this Directive as an opportunity, not a threat, for the pharmaceutical industry. Several managers claimed that this Directive gave the industry more credibility, since unethical promotional practices were now curtailed by the new regulation.

5.2.3. Strategic analysis

In the 1995 survey, each participant was asked: 'Can you think of any strategic issues related to regional integration that have affected the pharmaceutical industry?' Those mentioned include:

(a) monitoring the potential for vertical and horizontal integration of the wholesale distribution in the Union;
(b) estimating changes in supply-side competition, such as the encouragement of the generic industry and pharmacists' reimbursement strategies;
(c) forecasting the negative impact of demand-side controls (such as price-cutting trends, reducing medical doctor drug budgets, and promoting health care economics);
(d) seeking research and development synergies with other firms;
(e) developing new price tactics, such as regional price-bands;
(f) rationalizing production facilities;
(g) changing the organizational structure of the firm, e.g. from a decentralized to a centralized approach;
(h) minimizing the impact of Spain on parallel trade;
(i) developing more co-marketing and co-licensing agreements;
(j) creating one pan-European trade name;
(k) monitoring the growth of the non-prescription market.

The most frequently cited response to this question was monitoring the potential for EU-wide wholesale distribution in the single market. Two major themes about alliances among the wholesalers were the changing balance of power between manufacturer and wholesaler and the potential for increased parallel trade by means of future pan-European wholesale operations. Extensive vertical and horizontal integration in the distribution chain were foreseen.

Expenditure controls by health care systems were much discussed. They are general in developed countries, though the strategies followed vary considerably. Increasingly, though, nations are aware of what is done elsewhere. Thus, France is moving towards supply-side measures, such as encouraging the use of generics, as well as price controls. The USA is imposing price cuts and freezes on medicines supplied under Medicare or Medicaid. Demand-side measures like generic substitution and drug budgets for out-of-hospital doctors were also mentioned.

Managers were also concerned about successfully implementing price strategies in the single market. As previously discussed, the diverse regulated price regimes of the EU were considered to be the most significant obstacle that precludes the industry from reaping the benefits of regional integration. Several of the firms mentioned the price strategy of launching new products within price bands. Others expressed their desire for European Monetary Union

to prevent price fluctuations resulting from exchange rate volatility within the Union. The difficulties of Europe-wide prices were acknowledged: pressures existed to make them low rather than high. Member States were increasingly using inter-Union averaging to set prices.

Several managers recapitulated their firm's desire to further rationalize production facilities. A single European market would facilitate this. Capacity would be specialized; for example, a single plant for injectables, one for liquids and one for capsules. This would reduce costs and inhibit parallel trade. However, there was still anxiety about the political repercussions of rationalization. Prices might well suffer. The Transparency Directive (89/105/EEC) has done little to break the link between price and local investment in some member countries.

The potential for the non-prescription market aroused interest. There was an increasing trend to remove medicines in non-critical areas from reimbursement. General practitioner budgets in the UK encouraged doctors to advise patients to use self-medication. A wider range of drugs is being made available for this purpose. In France and Italy products of borderline significance were being removed from reimbursement. Other member countries have still to catch up.

5.2.4. The future

The managers were asked: 'In response to regional integration, what types of strategies do you think a firm such as yours should be adopting in the next decade?' They were also asked: 'Of the strategies that you have just mentioned, which is most important?' The answers to the second question were:

(a) persuading government decision-makers to develop a uniform industrial policy for this sector, especially in the area of regulated prices;
(b) moving towards a pan-European selling approach;
(c) monitoring pan-European distribution networks;
(d) focusing on the company's R&D by investing more so as to maintain a 'critical mass';
(e) rationalizing production facilities; and
(f) vertically integrating the firm into disease management areas.

Other responses were:

(a) developing pan-European clinical trials for their drug dossiers;
(b) horizontally integrating the firm with another large company in order to survive;
(c) developing strategies for the Triad (i.e. the United States, the European Union, and Japan) instead of regional markets;
(d) focusing on core products;
(e) investing in biotechnology and purchasing these types of firms;
(f) promoting the convergence of medical philosophies in the EU; and
(g) changing the Biotechnology Directive to resolve certain issues.

It might well be concluded that estimating the impact of regional integration on this industry will take at least another five years. In several interviews, the managers emphasized that the industry was still in an uncertain strategic environment. For example, it was difficult to predict the opportunities (or threats) of the EMEA since this Agency had just commenced its operations. Therefore, the pharmaceutical managers felt that analysing the influence of regional integration on their industry and business strategies was premature at this time.

The *Financial Times* recently published a letter from the chief executives of the UK's three biggest pharmaceutical manufacturers which supports the conclusions of the interview programme.[127] The letter, which was almost unprecedented in being co-signed by three such prominent members of any industry, called on Member States to 'work with the Commission to remove the untenable combination of government price controls and the free movement of goods'. The SMP was 'seriously distorted' by parallel traders, leading the chief executives to conclude: 'As matters stand, the pharmaceutical sector does not enjoy the benefits of a free and fair single market.'

The letter also cites in support the statement by Peter Sutherland, former Commissioner and head of GATT, who described the pharmaceutical sector as the most spectacular failure of the single market. While the industry executives obviously have a vested interest, it is not easy to dismiss Sutherland's observation in the same way. Clearly, further collaborative work by firms, Member States and the Commission is needed before the benefits of the single market will really be felt.

[127] *Financial Times*, 25.1.1996.

APPENDIX A

List of organizations interviewed and sample interview guide

ABPI (Association of the British Pharmaceutical Industry) – United Kingdom

AESGP (European Proprietary Medicines Manufacturers' Association) – Belgium

AGIM (Association générale de l'industrie du médicament) – Belgium

Amgros – Denmark

APIFARMA – Portugal

Approved Prescription Services – United Kingdom

BAH (Bundesfachverband der Arzneimittel-Hersteller e.V.) – Germany

BFAH (Bundesverband Forschender Arzneimittel–Hersteller e.V.) – Germany

BG (Bundesministerium für Gesundheit) – Germany

BGMA (British Generics Manufacturers Association) – United Kingdom

Boots Healthcare International – United Kingdom

BPI (Bundesverband der Pharmazeutischen Industrie e.V.) – Germany

Centrapharm – Netherlands

Dupont – United Kingdom

EFPIA (European Federation of Pharmaceutical Industries' Associations) – Belgium

EGA (European Generic Medicines Association) – Belgium

Eli Lilly – United Kingdom

EMEA (European Medicines Evaluation Agency) – United Kingdom

Gehe – Germany

Generics – United Kingdom

GIRP (Groupement de la Répartition Pharmaceutique Européenne) – Germany

IPHA (Irish Pharmaceutical Healthcare Association) – Ireland

INTERPHARMA – Switzerland

Laboratorios ALMIRALL SA – Spain

MEFA (Association of the Danish Pharmaceutical Industry) – Denmark

Merck – USA

Ministère de la Santé publique – France

NEFARMA (Nederlandse Vereniging van de Innoverende Farmaceutische Industrie) – Netherlands

PAGB (Proprietary Association of Great Britain) – United Kingdom

Pharmaceutical Economics Committee – France

Pharmachemie – Netherlands

Proprietary Association of Great Britain – United Kingdom

SFEE (Federation of Pharmaceutical Companies of Greece) – Greece

SNIP (Syndicat national de l'industrie pharmaceutique) – France

United Kingdom Medicines Control Agency – United Kingdom

Upjohn – United Kingdom

Warner-Lambert – United Kingdom

Wellcome – United Kingdom

Wyeth – United Kingdom

Zeneca – United Kingdom

A.1. Sample interview guide – specialist non-prescription pharmaceutical firms

We have been asked by the European Commission, Directorate-General XV, to investigate the impact on the pharmaceutical sector of the various measures taken by the EU to bring about a single European market.

In part our studies are concerned with the broad picture and the effects on all companies and all countries. We have also been asked to provide case studies of the impact on individual pharmaceutical companies of different kinds and sizes. As a firm specializing in the non-prescription medicine market we are most grateful for your cooperation. Where it is possible, we would greatly appreciate any quantitative data that you might be able to provide. Naturally, we would not disclose anything that you would wish to remain confidential.

Our focus is on the effects of Union legislation, but, at the same time, we are very aware that it is but one factor affecting the changes now taking place in the pharmaceutical industry. We

would therefore welcome the opportunity to explore with you how the activities of the Union fit into the broader picture.

1 THE BACKGROUND

1.1 It is often said that the self-medication market is now growing at unusual speed. Do you agree? If so

- In which Union countries? In which non-Union countries?
- In which therapeutic areas?
- Why?

1.2 Which therapeutic areas are suitable for self-medication? In particular

- Are any especially attractive in commercial terms?
- Are any potentially attractive but not yet fully exploited?

2 YOUR COMPANY

Could you briefly describe to us your company's current operations?

2.1 Activities and sales

- What were your non-prescription sales in 1994? How many products did you sell? Which – if any – products are particularly important to you?
- Which are your major markets within the EU? And elsewhere? Have you significant sales outside Europe?
- Are most of your sales for self-medication as opposed to non-prescription products that are nevertheless prescribed?
- How have your sales developed since 1990? In geographical terms how have your markets changed during the past five years?
- What prescription-only sales do you have? In which therapeutic areas? How important are they compared to your non-prescription sales?

2.2 Manufacturing

- What manufacturing operations do you carry out (manufacture of active materials, formulation, packaging)? Where are your plants? Which is the most important?
- What use do you make of contract manufacturers for any of these activities? Where are they located?
- Do you import any of the (a) active materials (b) dosage forms? If so, from where?
- How has this situation changed since 1990?

2.3 Research and development

- Could you describe to us how you develop new non-prescription products? In particular
  - How do you decide which sort of product to target?
  - What kinds of R&D do you find necessary?
  - Where do you carry it out? Do you make any use of contract research organizations?

2.4 Marketing

- Are most of your products branded? Do you sell any as generics?
- Which media do you employ to promote your branded products? Does this vary between member countries of the Union?

2.5 Employment

- How many people do you employ within the EU? In broad terms where are they located?
- Again in broad terms what do they do, e.g. proportions in manufacturing, marketing etc.?
- How have these figures changed during the past ten years?

2.6 Costs

- Very roughly, how are your costs broken down between manufacturing, product/process development, marketing/selling, other?

3 THE IMPACT OF UNION LEGISLATION

The legislation designed to bring about a single market has been in part specific to the pharmaceutical sector and in part applicable to all kinds of industry and services. Taking the former first, could we discuss

3.1 Admission of new medicines to the European market

- Could you describe to us the process of obtaining marketing authorization for a non-prescription product? What evidence must you submit? How long does this take to prepare? What does it cost?
- In 1993-94 how long did it take on average for your non-prescription products to obtain authorization in (a) Denmark (b) Germany (c) the Netherlands (d) the UK? How much did it cost in each of these countries?

- In your experience do the various member countries of the EU have different requirements? If so, which countries and in what ways?

- Did you use the mutual recognition process in force from 1986 to 1994? In particular

  - If so, did you find that approval times and costs were reduced?

  - If you did not use them, what were your reasons?

- New systems of approval are now in place.

  - Have you made any use of the decentralized system? If not, what do you see as their potential advantages/disadvantages for your company?

- In your experience, has admission to the market of non-prescription medicines become easier or more difficult during the past five years? If so, what is the main reason?

3.2 Pricing

- In most Union countries the prices of self-medication products are not officially controlled. How do you go about setting prices, i.e. what factors do you take into account?

- Do you aim for a pan-European price for a particular medicine? If so, are you usually successful?

- Have you suffered at all from parallel imports of your products?

- In most Union countries non-prescription medicines may qualify for reimbursement if they are prescribed. In such cases, their prices are often controlled.

  - The prices of prescription-only products vary widely between member countries of the Union. Is this true to the same extent of non-prescription products?

  - The so-called Transparency Directive came into force in 1989. In your experience, has it reduced the time taken to agree a price? Made the process of price determination more transparent to you?

- It is often said that in some European countries prices are linked to local investment.

  - Has this been your experience? If so, where?

  - What form have the inducements taken?

3.3 Intellectual property

The European Commission has taken steps to restore patent protection or its equivalent for medicines.

- How have these actions affected your non-prescription activities?

3.4 Other measures

The Union has recently introduced a package of measures designed to promote the rational use of medicines. They concern

- the classification of medicines;
- advertising medicines;
- labelling and patient information;
- wholesale distribution.

How have these measures affected your European operations? In particular have they

- Increased or decreased your costs in any of your markets? Why?
- Made it is easier for you to introduce and market your medicines in other member countries? In what ways?

How might they do so in the future?

3.5 Horizontal measures

These are measures which apply to all kinds of economic activity. Could you tell us which have had or might have an effect on your company? We would be especially interested in those which affect your ability to sell throughout Europe.

- Some are measures of obvious relevance to the industry
  - product liability, in particular the development defence;
  - trade marks, especially the creation of a central European trade mark organization in Alicante;
  - removal of frontier controls and associated paperwork?

  Are there any remaining non-tariff barriers to the free movement of goods. Have you experienced any such restrictions? If so, what form do they take?
- Some are measures of potential significance
  - taxation, especially the transfer of funds between countries;
  - competition policy, especially involving policies affecting mergers.

4 CHANGES IN THE STRUCTURE OF THE INDUSTRY

The world pharmaceutical industry is undergoing a process of change, which affects its position in Europe and elsewhere.

- There is a strong movement towards mergers and rationalization in the research-based sector of the pharmaceutical industry.
  - Is this taking place in the non-prescription market?
  - What do you see as the advantages and disadvantages of specialized firms such as yourselves when compared with large research-based company in the non-prescription sector?
- In your opinion, have the various measures taken by the EU to bring about a single market in medicines affected the changes now taking place in the industry?
- In your opinion have they changed the relative positions of the research-based and non-prescription sectors within the Union?

5 THE FUTURE

- Where do you see the growth markets for non-prescription products?
- What factors do you expect to bring these markets into being? If you were a government interested in stimulating the non-prescription sector, what would you do?
- How would you supply these markets? Do you anticipate any changes in what you do now?

APPENDIX B

The pharmaceutical sector of the EU

The discovery, production and marketing of medicines is necessarily different from other forms of industry. This chapter describes the salient features of the pharmaceutical sector and its current position within the EU.

B.1. The pharmaceutical market of the Union

The pharmaceutical market is highly fragmented. The demand for medicines is a demand for specific remedies to treat specific conditions. There are no universal remedies. Human responses vary considerably, and for every illness a choice of medicines is desirable. In all member countries of the Union more than 1,000 physiologically active ingredients are in use, incorporated in a larger number of products and even more individual dosage forms. No single product holds more than a few per cent of any national market by either volume or value, and most hold considerably less.

In 1994 total sales of medicines within the Union and at manufacturers' prices were ECU 51,850 million or about 24% of the world total (Table B.1). Such consumption typically represented 7-14% of national health care expenditure and 0.5-1.5% of GDP. Expenditure is determined in part by national population and income, but traditions of medical practice and attitudes to the place of medicines within them are also important. Other things being equal, member countries in southern Europe consume more than those in northern Europe. Medicines prescribed by physicians working outside hospitals everywhere account for the majority of spending. Those prescribed in hospitals form 10-20% and those bought for self-medication 10-15%. This last category is slowly increasing in importance.[128]

The types of medicine used within the Member States are broadly similar. Products for conditions of the circulatory and digestive systems are everywhere the most important categories by both value and volume, followed by those for the central nervous system, for infections and for the respiratory tract.[129] National differences exist, but in the case of serious diseases they are of degree rather than kind. The same classes of medicine, often the same products are used. To this extent a potentially pan-European market in medicines exists. Nevertheless, there are much larger variations where remedies for minor conditions are concerned.

Between 1982 and 1991, consumption in terms of real value increased substantially in all member countries and in all but Ireland more rapidly than GDP.[130] Since 1991, such growth

[128] European Federation of Pharmaceutical Industries' Association (EFPIA), *EFPIA in Figures 1995;* national sources; author's estimates.

[129] Farmindustria. *Indicatori Farmaceutici 1995*, Tab. 115; Institut Belge de l'Economie et de la Santé. 'Le marché du médicament en Belgique en 1993' summarized in *Scrip*, No 1981, 6.12.1994, p. 3.

[130] Taking 1981-91 public spending, the elasticities of health care expenditure with respect to GDP were Belgium 1.81, Denmark 0.62, France 1.31, Germany 0.72, Greece 1.81, Ireland 0.24, Italy 1.84, Netherlands 0.93, Portugal 0.54, Spain 1.60 and the UK 1.08. The corresponding elasticities for pharmaceutical expenditure with respect to GDP were Belgium 1.95, Denmark 0.63, France 1.69, Germany 1.19, Greece 2.92, Ireland 1.00, Italy 2.63, Netherlands 2.10, Portugal 0.33, Spain 1.42 and the UK 2.09 (sales through retail pharmacies only) (OECD, Health Database, 1995).

has moderated and in places been reversed. Prescription medicines everywhere form part of the service offered by public health care systems, but self-medication is never included. In 1994, approximately 69% of the Union medicines bill was paid for from public funds, although the proportion varied widely between countries.

B.2. The operations of the industry

The principal operations of the industry may be summarized as follows.

B.2.1. Innovation

The development of new medicines plays a key role in competition within the sector, which is unusually research-intensive. The process is difficult, expensive and prolonged, and failure is the norm.[131] Only large companies – those with annual sales of ECU 1,000 million or more – are by themselves able to develop genuinely new products, although smaller firms often devise novel modifications, mixtures, production routes and methods of administration.

B.2.2. Production

For most medicines the scale of production is small, but the methods necessary are specialized and demanding.[132] Active ingredients are made by extraction from plant and animal sources, by biotechnological processes such as fermentation or by chemical synthesis. They are usually made by batch processes using multipurpose equipment. Depending on circumstance, the starting materials and intermediates may be made on the spot or bought in. The products are made up into bulk drugs which are then converted into dosage forms, such as tablets, capsules and injectables. The several stages may be separated geographically and often are.

B.2.3. Marketing

The pharmaceutical sector is not only research-intensive but also marketing-intensive. Novel medicines normally start life as in-patent products sold under brand-names and available only on prescription. They are promoted directly to physicians by medical sales people and by advertising in the medical press. In no Member State of the Union may they be advertised to the general public. When a successful product comes out of patent, it is often copied by others and sold at a substantial discount. Depending on national regulations, such generic products may be marketed to doctors under brand-names or under their chemical international non-proprietary (INN) names.[133] Only products specifically permitted for self-medication may be advertised to the final user.

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[131] Figures of one in 2,300, one in 4,300 and one in 6,200 were found by DiMasi for Japanese, European and US firms (DiMasi, J.A. 'Risks, regulation and rewards in new drug developments in the United States', *Regulatory toxicology and pharmacology*,Vol 19, No 2, 1994). Most of attrition takes place at the discovery stage, and only a few candidates go into the development phase, where up to 75% of the costs are incurred. Industry sources suggest that about one-third of the products which reach the market are commercially successful.

[132] Reuben, B. G. and Wittcoff, H. A. *Pharmaceutical chemicals in perspective*, New York, Wiley Interscience, 1990, pp. 97-110.

[133] Generic products form about 8% by value of EU consumption, though a much larger proportion by volume. The main markets are Denmark, Germany, the Netherlands and the UK.

B.2.4. Distribution

Because the pharmaceutical market is highly fragmented, manufacturers do not usually distribute their products themselves. Instead, they sell to specialized wholesalers who in turn sell to retail pharmacists. The mark-ups charged at each stage are a significant proportion of manufacturers' prices. However, manufacturers often supply hospitals directly, and much of the trade in self-medication products also by-passes the wholesaler.

B.3. The structure of the industry

The pharmaceutical industry of the Union comprises companies of widely differing sizes and activities (Table B.2).

The dominant firms within the Union are the large research-based companies which dominate world markets as a whole. In 1994, they numbered 48, of which 14 were based in the USA, 15 in the Union, five in EFTA countries, and 14 in Japan. Together they held 65% of the world market by value, accounted for more than 80% of pharmaceutical R&D spending and were ultimately responsible for the large majority of genuinely new medicines to be commercialized. Many are also prominent in the generic and self-medication fields. Apart from the Japanese firms, they are normally organized on a multinational basis: they not only sell medicines but make them and conduct research in a number of different countries.

Smaller companies are more diverse in nature. A considerable number are the local affiliates of the major firms just described. Others are independent enterprises. A few are surviving research-oriented companies of medium size. Some specialize in generic products; they include two substantial firms with increasingly pan-European activities. Others concentrate on self-medication or niche products. Many are oriented towards national or even local markets but this is by no means universal: especially in the self-medication field, some small firms sell their medicines throughout Europe.

B.4. Income, costs and profits

The pharmaceutical industry is significantly more profitable than other parts of manufacturing industry.

Taking all types of company together, goods and services bought in make up between 50 and 60% of turnover, of which about one-half are raw materials and intermediates. This proportion is substantially higher for generic companies. Labour costs are a further 20-25% of turnover and the gross operating rates are unusually high in the UK and even higher in the USA. Conversely, they are low in Italy. These figures are above the norm for manufacturing industry.

In terms of function, and again taking the industry as a whole, production is 30-40% of turnover, R&D 10-15% and sales and marketing 15-20%. Research is proportionately more important in large innovative firms, production in the generic sector and marketing in self-medication.

Table B.1. Sales of medicines for human use at manufacturers' prices in EU Member States in 1994

	Million ECU	By type of product in %			Per head in ECU	As % of health care[2]	As % of GDP[3]	% paid from public funds	Real growth 1985-94 in %[4]		
		Prescribed		Not prescribed[1]					1985-88	1988-91	1991-94
		Out of hospital	Hospital								
B	1,840	64	20	16	183	11.8	0.96	61	9.8	25.6	10
DK	570	63	17	20	110	6.9	0.46	48	25.7	16.4	10.4
F	12,920	74	13	13	223	11.4	1.15	66	29.2	13.9	13.5
D	14,900	70	18	12	183	11	0.96	69	12.3	17.2	-0.3
GR	1,000	70	15	15	96	25	1.53	75	13.1	28.4	54.9
IRL	270	77	14	9	74	9	0.61	59	7.5	18.4	11.3
I	7,440	77	13	10	130	10.2	0.87	61	19.8	16.3	-14.5
NL	1,690	74	16	10	110	6.7	0.61	87	21.4	27.5	25
P	1,110	82	10	8	112	22.4	1.68	42	24.2	38.2	6.8
E	3,960	74	14	13	101	14.2	0.98	77	63.5	-4.3	3.6
UK	6,040	69	17	14	104	10.2	0.7	84	20.5	9.2	20
EU	51,740	74	15	11	149	11.3	0.93	69	22.2	14.5	4.8
USA	67,600	60	15	25	259	8.5	1.19		25.5	32.7	19.2
Japan	43,990	<----------90---------->		10	352	15.6	1.14		5.5	25.2	20.3
World	212,320	n.a.									

[1] Sales for self-medication only.
[2] 1993.
[3] At market prices.
[4] Deflated using the GDP deflator and 1994 exchange rates.
Source: European Federation of Pharmaceutical Industries' Association (EFPIA), *EFPIA in Figures 1995*; national sources; authors' estimates.

B.5. Patterns of supply within and without the Union

In 1993 pharmaceutical production within the Union, including active materials and bulk drugs as well as finished products, amounted to ECU 67,820 million or about 35% of world output (Table B.3).[134] Of the Union total, France accounted for 24%, Germany for 23%, the UK for 18%, Italy for 15% and Spain for 7%.

Table B.2. Structure of the pharmaceutical industries of EU Member States in 1994

		Number in categories of global sales ECU 1,000 million			
	No of firms	Above 4	2-4	1-2	Above 1
B	157	0	0	1	1
D	1,200	1	3	2	6
DK	23	0	0	1	1
E	240	0	0	0	0
F	334	0	1	2	3
GR	59	0	0	0	0
I	295	0	0	0	0
IRL	70	0	0	0	0
NL	61	0	0	1	1
P	114	0	0	0	0
UK	109	2	1	0	3
EU	2,662	3	4	7	15
CH	110	3	0	0	3
S	65	0	2	0	2
USA	775	6	4	4	14
Japan	1,556	1	4	9	14
World	n.a.	13	14	20	48

Source: National sources; Farmindustria. *Indicatori Farmaceutici 1995*; PJB Publications, Scrips's League Tables, 1995.

[134] Production figures from EFPIA, op. cit., note 1; trade figures refer to SITC 54. The division of supply is based on a conflation of trade figures and known market shares of companies of particular origin.

Patterns of supply within the Union are more complex than might at first appear. The medicines sold within a nation may be imported; they may be made locally by the affiliates of a foreign company; or they may be the product of a locally-owned firm. Taking the Union as a whole, trade was the least important source, amounting to 20% of the consumption of finished medicines, of which 14% came from within the Union. The balance came from Switzerland, Sweden and the USA in that order. Medicines made locally by foreign firms were 39% of total consumption. US firms accounted for nearly one-half of this total, Union firms – predominantly those from Germany and the UK – for a further third, and Swiss companies for most of the balance. Finally medicines made by locally owned companies and sold in their country of origin formed 41% of consumption.

The Union is a major supplier of medicines to the rest of the world. As Table B.3 shows, it enjoys a large positive balance of payments surplus, due mainly to France, Germany and the UK. The working of the multinational system makes trade alone a doubtful measure of competitive strength, but global sales indicate that Union companies have considerable competitive strength.

Table B.3. Production and supply of pharmaceuticals within the EU in 1993

	Production ECUm	Employees	Intra-union trade ECUm[1]		Extra-union trade ECUm[1]		Supplies of finished medicines %		
			Exports	Imports	Exports	Imports	Imports	Local manufacture	
								Local firms	Foreign firms
B	2,590	18,780	1,712	1,689	1,466	823	52	16	32
D	15,940	122,490	3,281	2,415	5,611	2,542	14	53	33
DK	1,515	14,250	343	420	1,267	289	56		
E	4,870	39,980	468	1,054	511	740	16	29	55
F	16,290	101,000	2,837	2,490	3,253	1,902	13	45	42
GR	710	8,000	52	470	34	218	39		
I	10,148	68,600	1,332	2,040	1,774	1,974	14	34	52
IRL	1,240	7,500	821	428	808	89	88		
NL	1,680	13,300	2,045	1,352	560	1,456	76	16	6
P	800	10,000	53	348	47	141	23	15	62
UK	12,340	80,900	2,813	2,247	3,595	1,497	27	37	36
EU	68,130	484,720	15,064	15,646	19,620	10,961	20		

[1] SITC 54.
Source: See note 1.

APPENDIX C

Case studies

C.1. Zeneca case study

C.1.1. Position in the market

Zeneca is a pharmaceutical, agrochemical and speciality chemical company. Pharmaceuticals accounted for 44% of its total sales in 1994 and 79% of its trading profit. In that year its pharmaceutical sales were UK£ 1,958 million, making it the 18th largest company in the world. In terms of therapeutic area, cardiovascular agents made up 50% of its sales, anti-cancer agents 28% and products acting on the central nervous system 14%. Its major market, the USA, accounted for ECU 404-412 million. European sales for 1994 totalled ECU 517-559 million with a maximum of ECU 135-143 million in France and ECU 118-126 million in both Germany and Italy. Sales in Japan accounted for ECU 286-294 million.

C.1.2. Manufacturing

In Zeneca's view the choice of location is a trade-off between the need to source international markets and local investment opportunities and tax costs. Thus, the USA and Japan are major markets for the company, and this has had an influence. So has history: 50% of its assets are in the UK, and it has large plants in Germany and France. Except for the USA and Japan, it supplies markets outside the Union from the UK. Within the Union, Macclesfield is the only source of Zoladex, but Tenormin and Zestril are supplied by both Macclesfield and Rheims.

Manufacture of active ingredients is carried out in the UK – at Macclesfield and Avon, near Bristol – at Planckstadt, near Heidelberg (D), at Rheims (F) and in Puerto Rico. In the USA and Japan, synthesis begins with commercially available intermediates rather than raw chemicals. As needed, materials move from one plant to another for purification and further treatment. Formulation is done mainly in Macclesfield, Rheims and Planckstadt and at less important sites in Italy, Spain and Belgium.

In spite of its focused asset base Zeneca has considerable manufacturing capacity. There are economies of scale where capital expenditure is high as in the manufacture of active materials and bulk drugs. Packaging is less of an opportunity as it is more labour-intensive. At present manufacturing, including raw materials, overheads and so on, represents about 25% of the cost base and employs about 25% of the work-force directly. It is difficult to say whether these costs are falling as a proportion of the whole. The products of the 1980s were tablets involving relatively straightforward chemical processes. The compounds of the 1990s are more complex. Manufacturing processes and costs are determined by what is made.

The guidelines for Good Manufacturing Practice have had an effect on countries with lower standards, which do not include the UK or Germany. Overall, the impact has not been very great; movement of goods across frontiers is rather easier, and having a single point for testing allows for a more sensible approach to supply. It is still handicapped by the need to prepare separate packages for each member country, so adding to logistical and stock control problems at the factory level with the associated costs.

Zeneca has not had to rationalize its manufacturing operations to the same extent as many other companies, because it was relatively highly focused to begin with. It has tended to sell off redundant plants rather than simply shut them down. It sold off self-medication operations in the USA and antiseptics in the UK.

C.1.3. Research and development

Zeneca spends 15% of its pharmaceutical sales value on R&D. This is about the average amount, the range being 12 to 18%. More than two-thirds is disbursed in the development phases; this proportion is on the increase, because regulatory bodies are now asking for health economic as well as clinical data. At any given point in time, an average of about 35 new products are under development; of these, about one-third would be – if successful – significant step changes in therapy.

The discovery process begins with the identification of therapeutic areas. Zeneca has identified six to seven such areas, two of which are the prime responsibility of the US centres. Programmes are then designed to lead to opportunities rather than products. Once a promising candidate has been identified it will have to pass five major decision points: (1) should development go ahead? (2) should it go into phase I clinical trials (40% pass)? (3) should it go into phase II trials (70% pass)? (4) should it go into phase III trials (50% pass)? (5) should it go forward to registration (66% pass)? So only one in 12 actually makes it to the market. The whole process costs UK£ 80-100 million per successful product – UK£ 400 million allowing for failures – and takes eight years.

Discovery research is concentrated in the UK, partly for historical reasons and also because there is access to good science and good scientists, and in the USA, where the company inherited a small discovery capability that was further developed because of the high quality of American science. There is a small group in France which is really a satellite of the UK group. Most non-clinical development is done in the UK and the USA. Clinical research is done in a number of countries – although the UK and the USA are still the most important – since an adequate patient base is needed; patients are often a scarce resource because protocols are tightly defined. The determining factor in the choice of countries for clinical research is the quality of medical science and the ability of centres to comply with Good Clinical Practice. Standards in most of Western Europe are high, and now that the harmonization process is under way, further convergence is taking place.

Zeneca has 6-700 staff in discovery research and 2,000 in development research. There have been few changes in the location of R&D in recent years. Capabilities in Japan have been built up, because the Japanese market differs markedly from that of Europe or North America. To be effective a critical mass is necessary; this corresponds to an annual budget of UK£ 3-400 million. There are small but genuine economies of scale in discovery research, especially where new generic technologies are concerned. In development, a large income reduces the impact of failure, which is the norm in pharmaceutical innovation. However, there are diseconomies of scale: a doubling of size would lead to increased bureaucracy and would stifle the original thinking which produces ideas.

Zeneca considers that companies are learning to get more out of investment in R&D. Processes are getting faster, even though serendipity is not. Ten years ago, each product was handled differently. Now, most projects go through the 'standard template' for product

development. All companies working in the same area have access to the same science and scientists. The winners are those who are quickest and most effective.

C.1.4. Marketing

Zeneca considers that there are six major world markets: the USA, Japan, Germany, France, Italy and Spain. The biggest single market for Zeneca products is currently the USA, followed by Europe. While good progress has been made in Japan during the past decade, further growth there is a high priority. In geographic terms, the growth markets of the future are seen as being Asia and the Pacific Rim, where demand is high. However, Europe, the USA and Japan still have growth potential in some therapeutic areas. In terms of therapy, growth is expected in cancer treatment, anti-infection agents and those for age-related disorders. There are great marketing opportunities for the transfer of medicines from prescription to non-prescription status.

Marketing operations in Europe demand different groups concentrating on different customers, e.g. physicians, hospital doctors and managers, wholesalers and so on. The key selling point is the efficacy of the product; this is what drives sales. More peripheral points are local practice and culture: inhalers are thus favoured in the UK, while other countries prefer oral preparations. Such differences must be taken into consideration in the marketing strategy; there are no really global brands sold in the same way in every country.

Zeneca does not think that free pricing is going to come about in Europe. Pressures on prices may mean that companies will have to concentrate on volume. In the past, really innovative products were sold at a premium price and were followed by 'me-toos', but there are signs that this is not necessarily the case now. The SB antidepressant paroxetine is a case in point; it was introduced at 20% below the price of the market leader, and this gained it extra volume. The Sandoz cholesterol-lowering product fluvastatin is another example.

The pharmaceutical industry as a whole is undergoing a process of restructuring in three ways: through mergers and acquisitions between leading research-based companies, by the acquisition of traditional small- and medium-sized European firms by major international companies and by the emergence of science-driven biotechnology firms, especially in the USA. This results in the consolidation and downsizing of both R&D and manufacturing.

Zeneca considers that as a result Europe might lose more innovative capacity than the USA or Japan. Europe suffers in particular from over-regulation of pharmaceutical spending in the pursuit of short-term cost-containment, a weakening of the effective protection of intellectual property and, less certainly, lower research productivity.

C.1.5. Actions of the Union: admission to the market

There are still problems in obtaining marketing authorization in Europe. Although data requirements have been harmonized since the mid-1980s, biological scientists often reach different conclusions about thresholds or the risk/benefit balance. Even a small difference can then create a stumbling block. The attraction of the USA is that a single step gives you access to a huge market.

The time taken to gain approval varies greatly in Europe; it can vary from six to 34 months, Portugal being the worst offender. The UK and France are fastest, followed by Ireland,

Denmark and the Netherlands. Technical approval can be obtained in the UK and France in eight months, but in France reimbursement also requires approval which can amount to a barrier to trade. Approval times started to fall after 1990 as countries followed the UK in instituting medicines agencies separate from Health Ministries. The main exception has been Italy, where times have been lengthened when the agency was overhauled, new staff were appointed and the procedures completely restructured.

The FDA requirements are incredibly high and seem always to be changing. This is particularly the case in manufacturing. To satisfy the FDA, plants must comply with regulations at the time of application as if they were already producing. This has an impact on investment decisions. Plants always work to FDA standards. However, the FDA is now faster in granting marketing authorization since it went over to user fees. Now the industry pays a fee, but the FDA is committed to delivering on time, and approval times have fallen from 18-24 months to around nine months. They are still 18-24 months in Japan, but the whole dossier has to be different there.

Zeneca has used the multistate procedure twice – once for a minor product, the second time for a new medicine aimed at the Italian market where approval was held up because of national problems. It did not make more use of it, since there was no saving in time. It has used the decentralized procedure in 'sweep-up' mode, lodging an application in a few member countries of the Union and sweeping up the rest by mutual recognition. It tends to begin with the UK, where approval is rapid. Zeneca did not use the concertation procedure, because it had not the appropriate biotechnology-based products to register. For similar reasons, it has not yet used the centralized procedure which replaced it.

The advantages of the new EU systems versus the national systems are uniformity, potential speed, simplicity and resource saving. However, they mean that Member States will have equal power to cause delays by raising objections: everyone has an equal voice at the CPMP. If the system of appeals up to the Council of Ministers were to be triggered, the cost in time would be considerable. Three measures that would improve the new systems are:

(a) to reduce fees for the centralized procedure to attract more business;
(b) to increase payments to Member States for work done or to claw back national fees in cases of failure to agree to mutual recognition;
(c) to streamline the stages critical in converting draft decisions into binding ones.

All will turn, however, on the new systems being faster than the existing ones. European differences are still there, and if a wrangle occurs, everything is tied up. Convoys move at the speed of the slowest ship, and Zeneca would be reluctant to sacrifice the speed of the UK.

C.1.6. Actions of the Union: prices and reimbursement

There are considerable problems in pricing given the diversity of situations arising from national policies.

When pricing a new medicine in a country where prices are free, Zeneca takes into consideration the product's strengths and weaknesses, the nature of the competition that it faces, and the probable price sensitivity of demand. It commissions research in these areas. It aims to launch such a product throughout the Union at prices within a band of about 20%, although it is not always successful. Once the medicine is launched, however, the band is

distorted by inflation, exchange rate fluctuations and official actions. There was a degree of convergence in prices before 1992 in that those in the high-price countries were falling while those in low-price countries remained constant. Price erosion has been the main problem of the 1990s.

The Transparency Directive has proved a disappointment. It has had little effect on reducing the time taken to agree a price in those countries where prices are controlled, although there is a greater awareness of the need for improvement. France is still slow, although Spain now does better. The Directive has done little to make the process of decision notably more transparent. *Ad hoc* measures to restrain public spending on medicines abound and have seriously distorting effects. Rewards in terms of priority in reimbursement/pricing still survive in varying degrees as in the *Plan de Fomento* in Spain. They must be taken into account. Price averaging in Italy proved unsatisfactory: the PPP exchange rates used were unfair, and the scheme did not permit price increases, as had been expected. Zeneca has also had problems with reference pricing in Germany.

Parallel trade is an increasing problem for Zeneca. Levels of parallel imports into the UK have risen significantly during the past year. The decline of the Italian lira against other currencies has made Zeneca's products very cheap in Italy and has stimulated the trade to the point where it has seized a considerable part of its German and Dutch markets. There are safety hazards with parallel imports; Zeneca found that a seriously misleading label had been attached to imports of Zoladex into the UK. There is little that can be done about parallel trade unless prices increase in the supplying countries.

C.1.7. Actions of the Union: intellectual property

All Union countries have now acceded to the European Patent Convention. In practice, though, implementation and enforcement still differ; member countries in northern Europe stick more closely to the law. Zeneca itself has not had serious problems in Greece, Portugal or Spain; its old products are out of patent and thc new ones are not yet big enough to attract generics.

The extent of patent life is sometimes a factor in deciding whether or not to go ahead with product development. If the area is one where everyone else is working, filing for patent may well take place one or two years into development, thus giving at best 11 years of protection once the drug is on the market. The Supplementary Protection Certificate (SPC) is helpful, because it can give the inventor 15 years from the date of marketing. Zeneca thinks that this Regulation and the Waxman-Hatch Act in the USA are essential to its business, even though declines in sales often occur before a patent expires. However, the SPC term starts when the product is launched in a single member country, whatever the size of its market. Zeneca would prefer it to be linked to launch in a basket of countries to eliminate the part played by luck. It should cover the entity itself and obvious equivalents and trivial variations.

Marketing exclusivity has not proved very useful to Zeneca. The provisions of the Directive vary from country to country. Even though generic companies are forbidden to use one's data, they sometimes can piece together enough to apply the day after the patent expires. The Roche-Bolar clause allows American generic firms to start work while the patent is still in force, provided that it is intended 'solely' for regulatory approval. EU generic companies would like a similar clause in Europe. Zeneca would be opposed.

Trade marks are valuable because they last indefinitely, although in these cost-conscious days their value does decline after patent expiry. Zeneca views the European approach with favour, as it means going to a single place for protection. It would like to use the same trade mark in all member countries, but this is not always possible: other companies may have registered it already. The provision that the same brand-name must be used everywhere if an application is made through the centralized procedure is an unexpected and unwelcome interpretation.

C.1.8. Actions of the Union: other pharma-specific measures

The Labelling Directive is pretty clear, but each state has translated it in terms of its own and has done so differently. Every time a labelling change is made, 11 different packs have to be produced. If there are time windows for approval, these can take anything from one month to two years. Some of the markets are very small, which adds to the cost.

C.1.9. Actions of the Union: horizontal measures

An important issue for Zeneca is compliance with competition law. Zeneca's policy is always to comply with all the laws of every country in which it operates, including competition law, and it provides training for all relevant members of staff.

Issues related to competition law with which the pharmaceutical industry in general has recently been concerned include:

(a) The continued supply of products to wholesalers and other customers (highlighted in the Bayer parallel import case which concerned refusal to supply in circumstances where the party concerned was not in a dominant position but an agreement between the supplier and the potential customer was imputed for the purposes of Article 85(1) of the EC Treaty).
(b) The measure of dominance. The test for the relevant market is substitutability/ interchangeability, but it is not always clear what can be deemed a substitute for any given product for these purposes.
(c) Merger control, which needs to be included in consideration of projected acquisitions, divestments, joint ventures, etc.

C.1.10. Actions of the Union: an overall view

Zeneca considers that the Union has had relatively little effect on its operations and strategy. The market is still fragmented. Where the Union has acted, it has left much to member nations whose responses have differed widely. However, the steps taken to safeguard intellectual property are a positive move. The new systems of marketing authorization may also be so, but it is too soon to know whether or not they will work as intended. There is an underlying fear that the Union will merely add a further layer of regulation rather than simplify operations.

C.2. Gehe case study – pharmaceutical wholesaling in the EU

C.2.1. Company background

Gehe AG was founded in Dresden in 1835 by Franz Ludwig Gehe. Initially concerned with pharmaceutical trading and retailing, it began to manufacture medicines in 1865. It became a

public company in 1903 and by 1943 had seven branches, mostly in the eastern part of Germany. After the Second World War, the headquarters and large parts of the company were seized by the GDR, and it was refounded in Munich from where it built up an extensive business in Germany through both organic growth and acquisitions and mergers. In 1981, it underwent a major reorganization and its headquarters were transferred to Stuttgart.

From the mid-1980s a vigorous policy of internationalization was followed. A number of other companies were merged or acquired, including Gaerner, operating in Germany, Austria, Switzerland and the Netherlands; Brown and C&H Distributors (USA), OCP (France) and AAH (UK). After the reunification of Germany, Gehe founded a number of new branches in the former East Germany and also in Poland, the Czech Republic and Russia. During the same period, Gehe moved back into manufacturing by acquiring the generic company Azuchemie GmbH and the Jena-based Jenapharm. By 1995, it accounted for some 20% of EU pharmaceutical wholesaling with particular strength in Germany (20%), France (42%) and the UK (30%).

Gehe AG is now a holding company active in the following areas:

(a) pharmaceutical wholesaling, comprising the Gehe group, with 18 branches in Germany, Russia and the Czech Republic, and the OCP group, with 66 branches in France, Belgium, Italy, Luxembourg, Poland, Portugal and Spain;
(b) pharmaceutical production, comprising Azupharma, Gerlingen, Jenapharm, Allphamed, Goettingen, Aliud Pharma, Laichingen and Laboratoires Biostilex;
(c) home care services, comprising French and German subsidiaries offering a range of services, such as home nursing care, rehabilitation, medical appliances, etc.;
(d) mail order distribution of office equipment, comprising subsidiaries in most EU countries and in Switzerland, Canada and the USA.

C.2.2. Company performance

In 1994, turnover in the pharmaceutical wholesaling business was DM 14,196 million (ECU 7,375 million), of which one-third was realized by the Gehe group and the balance by the OCP group. Total employment was 8,694. Gross profits were DM 196 million (ECU 102 million), corresponding to an overall margin of 1.38%; the Gehe group was the more profitable with a margin of 1.95%, compared to 1.1% for OCP. The economic climate for pharmaceutical wholesaling was relatively unfavourable due to measures taken to restrain public spending on medicines in France and Germany.

The other activities of the company were much less important. Pharmaceutical production in 1994 amounted to DM 449 million (ECU 233 million). Azupharma is now the third largest generics firm in Germany, while Jenapharm is the largest producer of oral contraceptives. Mail order office equipment turnover was DM 656 million (ECU 341 million). Home care services were not integrated into Gehe until 1995, and no financial data are available for 1994. Thus, the overall breakdown of Gehe's sales was as follows: pharmaceutical wholesaling 93%, pharmaceutical manufacturing 3% and office equipment 4%. However, profit margins were higher in these latter areas, and office equipment in particular is less exposed to political risks and pressures.

C.2.3. Pharmaceutical wholesaling

Gehe considers that a wholesaler who, like themselves, operates on a pan-European basis must carry a very wide range of medicines, including even very exotic and rarely prescribed items. Retail pharmacists must be able to supply patients with what they need or lose custom and goodwill; for their part, wholesalers must be able to supply retailers with anything that they need. Furthermore, the necessary products must be supplied frequently – often up to five times a day – rapidly and reliably. In practice, they are also expected to provide a variety of services to retailers. In most Member States, retail pharmacists are independent businesses, and chains under common ownership are forbidden. Close relationships between wholesaler and retailer are therefore common.

An effective wholesaler must therefore:

(a) maintain a large and varied stock of medicines covering all manufacturers;
(b) take orders rapidly and efficiently, usually by on-line operation;
(c) put together orders within two hours or less;
(d) deliver the order as soon as it is ready;
(e) maintain a comprehensive accounting and billing system;
(f) correct mistakes and recall suspect product batches;
(g) provide marketing aid and advice to retailers.

Gehe carries out all these functions in-house except for deliveries which are sub-contracted.

C.2.4. Actions of the Union and their impact

Pricing

Wholesalers are paid a fixed margin which is a proportion of the manufacturers' prices. Gehe noted that in all member countries of the Union these are controlled by law, as are those of retailers. The methods used to do so vary, as do the margins themselves. In Germany, they are regressive, i.e. they are larger for those products where the manufacturer's price is low and smaller where it is high. Gehe explained that manufacturers do not offer discounts for quantity to wholesalers, although they may offer benefits in kind or in the form of other services. However, this is generally on a small scale. In contrast, discounts by wholesalers to retailers are common and are an important form of competition. Currently, a typical wholesaler's margin in Germany might be about 13% of the manufacturer's selling price and discounts 5-6%.

The regulation of distributors' margins remains a matter for the individual Member States of the Union, and the SMP has had no effect here.

Parallel trade

Gehe has been obliged by the German Supreme Court to take part in the parallel trade in medicines, which account, however, for less than one half of one per cent of its business. It sees the trade as a demonstration that a genuine single European market for medicines does not exist.

Within Germany the market for parallel traded products is limited. Gehe mentioned several reasons. Pharmacists dislike the irregular deliveries that are common with parallel traders. They have a financial incentive to dispense the product obtained through the normal channels, since

their margin is a proportion of the sale price; they have been compelled by law to dispense cheaper imported drugs since 1988, but have been given no incentive to seek them out. Gehe noted that in the Netherlands and the UK, official incentives to deal in them were in place. Finally, reference prices and other measures taken under the Heath Care Reform Acts of 1988 and 1992 had reduced prices in Germany and often made parallel trading no longer worthwhile. Generics are now frequently prescribed and are often cheaper than parallel imports.

Generics

Generic medicines are growing in importance in a number of Member States of the Union, including Germany. It seems likely that the generic market will continue to increase as a result of the rising emphasis on containing public health care expenditure. Thus, in Germany, reference pricing now covers about 60% by value of the market with the potential of covering 75-80%.[135] The market penetration of generics is already 40% in terms of volume and 30% in terms of value. As a generic manufacturer Gehe is participating in this trend in association with the international company Bristol-Meyers-Squibb.

An important issue of policy is the right of the pharmacist to substitute a cheaper generic form of a medicine for the branded form prescribed. National policies regarding generic substitution still differ widely, though. For example, in the UK substitution is forbidden; in Germany it is permitted with the agreement of the physician; in Spain it is allowed except for certain specified cases. These national regulations have not been harmonized as yet.

Rational use of medicines

Gehe is affected by the Classification, Labelling and Advertising Directives in that they influence the technical equipment used and the operations involved. It is concerned about the continuing lack of harmonization in the classification of medicines, especially in view of the category 'pharmacy-only' self-medication products. It suggests that Directive 92/26/EEC should be modified to take this into account. Gehe would like to see wholesalers brought into discussions of the normalization of pack sizes and product codes, since they are the part of the pharmaceutical industry that is most directly concerned. It favours the rapid introduction of uniform packs with multilingual labels and leaflets; until they are available, pan-European wholesale distribution is not possible.

The Wholesaling Directive (92/25/EEC) has had an obvious direct impact; however, Gehe reports that it already met or exceeded the specified standards and practices, and no substantial extra expenditure was needed in order for it to conform.

Horizontal measures

Product liability is an issue for 'manufacturers' of products; wholesalers who engage in parallel trade become manufacturers if they change packages and information leaflets. This is not Gehe's practice, so the Union's rules do not affect their wholesaling business. Similarly, the new arrangements for trade marks are not at issue, since they do not have their own brands.

[135] It should be noted that this estimate includes sales of the original products for which generic forms now exist.

Public procurement is not a matter of great importance to Gehe. In Germany, as in most other Member States, hospitals buy most of their drugs directly from the manufacturer. Wholesalers merely fill the gaps, supplying in cases of emergencies or rarely prescribed medicines.

C.2.5. The process of concentration

To what extent has the SMP influenced the trend toward concentration exemplified by Gehe?

Between 1988 and 1994 Gehe's sales expanded from DM 2,878 million (ECU 1,415 million) to DM 15,201 million (ECU 7,896 million). Much of this expansion involved mergers and acquisitions, notably that of OPC whose sales were twice its own. As has already been seen, it has remained primarily a pharmaceutical wholesaler throughout. What were the reasons behind this policy? One reason was the realization that a single European market was in the process of development and that this presented both problems and opportunities. Given that this would take some considerable time, Gehe decided on a pro-active policy of expansion in what was still a relatively fragmented sector. As one company executive put it: 'If the internal market does not come to us, we have to make the first move.' As its company slogan 'We want to be the best' suggests, Gehe considers itself to be at the forefront of modern pharmaceutical wholesaling and to be – and always to have been – a strong competitor to its rivals both in technical and commercial terms.

Another consideration has been the changing structure of the pharmaceutical sector and in particular the relationships between manufacturers and wholesalers. Concentration among the research-based pharmaceutical companies might lead to long-term changes in the balance of power between manufacturers and wholesalers. Given that prices are under increasing pressure, the former might respond by attempting to improve their margins at the expense of the latter. The Glaxo strategy of employing wholesalers as mere distribution agents for its own products was mentioned. As yet similar arrangements have not developed, not least due to the modest success of the Glaxo scheme. However, they remain a possibility and a potential threat, given the relatively narrow margins in wholesaling.

Gehe has responded by building up its own strength in wholesaling so as to attain the critical mass required to safeguard itself against such pressures. It has followed policies of vertical integration, upstream into generic manufacturing and downstream into retailing, as evidenced by its bid for the 1,000-strong pharmacy chain Lloyds. It has also diversified into office equipment and home care services.

C.2.6. An overview

Gehe takes a generally positive view of the measures taken under the SMP, although they have so far had a modest impact on its operations. On the one hand, this conclusion reflects the fact that many of the issues with which it is most concerned remain the responsibility of Member States, or, where the Union has intervened, much still needs to be done to achieve genuine harmonization. On the other hand, Gehe considers that its standards were already high and that its practices already conformed with those laid down by the relevant Directives.

Company strategy has been influenced by the knowledge that a single market was to come into existence, although other factors have played a part.

C.3. Merck case study

C.3.1. Position in the market

Merck is the world's second largest pharmaceutical company. In 1994 its sales were US$ 14,970 million (ECU 12,616 million), of which human pharmaceuticals accounted for 66%, animal health products for 7% and health management for 27%. In terms of therapeutic area, cardiovasculars made up 57% of pharmaceutical sales, anti-ulcerants 17%, antibiotics 9%, vaccines/biologicals and ophthalmologicals 5% each and other products 7%. In geographical terms, their main market for pharmaceuticals has always been the USA, with 58-60% of the total in 1992-94; Western Europe currently accounts for 24%, Asia-Pacific for 15% and the rest of the world for the balance. France, Germany and Italy each account for about 20% of the European total, the UK for 8-9%, Spain for 7%, the Netherlands and Switzerland for 4-5%, and Belgium and Portugal for 2-3%. Total employment in Europe is 8,500-9,000 or about 23% of the world total; this figure fell by some 10% between 1985 and 1995 but is now rising again.

Merck sees both the US and EU markets as mature although still growing. Japan is an attractive market. Prospects elsewhere in the Asia-Pacific rim and in Eastern Europe are promising, but adequate protection for intellectual property would be a pre-condition. Sales by therapeutic class follow essentially similar patterns in all developed countries, although some allowance must be made for cultural differences.

C.3.2. Manufacturing

Merck has 31 manufacturing plants throughout the world.

In Europe they make active ingredients at Ballydine, Ireland; Ponders End, England; and Le Puy, France. The first two are the most important. Formulation is carried out at Cramlington, England; Haarlem, Netherlands; Pavia and Milan, Italy; Alcala de Henares, Spain; Quelez, Portugal; and Riom and Clementel, France. Of these plants, Cramlington is used for major high volume medicines, while Haarlem is used for shorter runs of minor products and packages specialized medicines for the rest of the world. Of the French formulation facilities, one is for ophthalmologicals and the other serves only the French market. In Italy, one plant makes antibiotics and the other supplies Italy alone. The Spanish and Portuguese plants were built before those countries joined the EU and serve only their own markets.

Merck considers that as a result of national policies in the past, it has more plants in Europe than it needs, but it has approached rationalization cautiously. During the past few years, it has disposed of only two facilities, both of which were small and had old technology. Bad Aibling in Germany was sold on, and Hoddesdon in the UK was closed. It does not plan any further disposals. A major consideration is the political repercussions. Thus, Merck has an understanding with the French authorities that in return for reasonable prices, they will maintain local employment levels. Conversely, rationalization is easier in member countries with flexible labour policies – a point which emerged in interviews with other American companies.

Merck's preferred alternative to plant closures is to consolidate facilities logistically if not physically. Manufacturing throughout the world is now controlled centrally by Merck Manufacturing Division instead of local subsidiaries. There is a central management site at Hoofdorp in the Netherlands which coordinates activities. Where possible, the production of individual intermediates and finished medicines is concentrated in a single site. This optimizes

plant utilization and aids Good Manufacturing Practice. In any case, economies of scale in production in no way compare with those in heavy organic chemicals. If sales are on a plateau, they are limited to economies in infrastructure, such as shared information systems and environmental facilities, plus, as already noted, the possibility of dedicated plant.

Local tax concessions play a part in decisions about manufacturing investment. Merck's largest and most modern European active material plant is in Ireland, and local tax concessions had played some part in bringing this about. Significantly, another major plant is in Puerto Rico where similar factors apply. However, other factors were also important. Ireland was seen as having an effective educational system, to be English-speaking and to provide relatively cheap labour. As yet, the SMP has not had much direct effect on the company's manufacturing policies.

C.3.3. Research and development

In 1994, Merck spent US$ 1,650 million (ECU 1,400 million) or 17% of its sales income from pharmaceuticals on research and development, compared with 11% in 1978. It has been outstandingly successful in developing new medicines since 1985. Currently, three of its products have global sales exceeding US$ 1,000 million (ECU 840 million), a further three have sales of between US$ 500 and 1,000 million, and seven have sales of between US$ 100 and 500 million.

Merck's view is that non-clinical work must be centralized. Everyone reports to the head of research in New Jersey. The principal research centres are in the USA. There are also major laboratories in England, dealing with diseases of the nervous system; Italy, concentrating on non-AIDS antivirals; Spain, which screens natural products; Japan, investigating cancer and infectious diseases; and Canada, studying asthma, allergies and inflammatory conditions. Clinical research is done where the necessary expertise is to be found. It is controlled from the USA, and the 'hard core studies' are done there.

Merck's research strategy is fundamentally science-based. Research-driven projects are more important than market-driven ones, although they are reluctant to put effort into minor disease areas. Merck does not have a stake in any particular therapeutic area; thus, it had no background in bone biology before developing the osteoporosis product Fosamax. Ideas for new products come from top managers and by maintaining contacts and joint ventures with a large number of people and institutions. Suitable organization can facilitate new ideas, but cannot bring them about. Many European companies are less successful in this quest.

In Merck's eyes, the only economies of scale in research arise through the elimination of duplicate projects. It feels that its success is due to the quality of leadership, the quality of the research personnel and the choice of projects. The location of research depends to some extent on local costs and local infrastructures as well as the science base. Local incentives are usually offered for entire businesses rather than for research, although France is keen to attract research investment. The increasing importance of biotechnology has favoured the USA as a location, due in part to political problems in some European countries.

In general terms, Merck sees markets in the developed world as becoming more difficult. Generic substitution – and perhaps therapeutic substitution – will make it more difficult to recover investment in innovation. Moreover, the time gap between the first innovative drug in a field and the followers is shrinking. It is increasingly important to be the first or second into the

market; under present conditions, to be third or later is to fail. This is a major consideration for Merck; it was first with Fosamax.

Merck does not consider that the SMP has yet had much impact on its R&D operations and strategy.

C.3.4. Marketing

Unlike research and manufacturing, marketing is decentralized. Local managers handle sales, advertising and allied activities. The European market is fragmented. Indications for medicines differ from one country to another, as do languages and medical cultures.

C.3.5. Actions of the Union: admission to the market

To a large extent, Merck has continued to apply for registration through national authorities, at least for important products.

They used the multistate procedure with Zocor and with Sinemet CR. In the first case, they used the procedure in 'sweep-up' mode (see C.1.5 Zeneca case study) to obtain authorization in Germany and Spain, having successfully filed nationally elsewhere. Sinemet CR was not based on a new active material and so met with few problems at the CPMP level; however, there were significant delays between the CPMP opinion and national approval in Belgium and Spain. The concertation procedure was used for Recombivax HB and Trusopt. The latter was a completely new product; France and Spain were the *co-rapporteurs*. The system worked well; thus, the questions from the evaluators were submitted *en bloc*, saving time and effort. The overall process took 13 months, which was seen as satisfactory. Once again, however, several member countries were slow to respond to the CPMP opinion.

Merck's approach to the new centralized procedure is cautious, though not unfavourable. If the timetables laid down are respected, there would be a saving in time compared to national registration, though not in money. Up to the beginning of 1996, they had not yet made use of it, preferring to see how it worked for other companies. At the time of interview, they were anxious about the choice of *rapporteur* country and the mechanics of the system. Accordingly, they intended to file nationally for the time being. They noted that unlike the FDA, the EMEA did not yet have a system of continuous consultation by which the company developing a new product would be guided as to what evidence would be required. They had found this helpful.[136]

In general, the EU and the US now require the same data for approval. Some member countries of the EU may require extra information; Germany is thus especially concerned about BSE and insists on guarantees that nothing is derived from contaminated sources.

C.3.6. Actions of the Union: pricing and reimbursement

Merck considers that the Transparency Directive has indeed made the processes of price determination more transparent. In their experience, however, it has not reduced the time taken to agree a price where this is an issue. Moreover, they think that the systems used are not necessarily fairer. A local manufacturing presence still comes up in price negotiations – in France, Italy, Spain and the UK for example, though not in Germany. This limits rationalization.

[136] The EMEA has since indicated that it intends to move in this direction, though in a less formal way than the FDA.

However, the Directive was of assistance when the price of a Merck product was unilaterally reduced in France; Merck complained and was compensated.

When introducing a new product, Merck aims for a standard price. They consider that they have been generally successful except in Italy, where the price-averaging system results automatically in a relatively low price. In Merck's opinion, prices are converging to some extent; increased prices in one country are often used as a reference by another. However, currency fluctuations may upset such policies: Merck's product Proscar was introduced into most EU countries at US$ 1-40 (ECU 1.09) per tablet in May 1992 only for the devaluations of September 1992 to produce an instant diversity of prices. Merck has been affected by parallel trade, but so far to a limited extent.

C.3.7. Actions of the Union: intellectual property

The supplementary protection certificate scheme has worked quite well in Merck's view. Two Merck products have benefited. The absence of a Bolar-Roche clause is essential for adequate protection. However, there are still differences between member countries as to the scope and applicability of such protection. Moreover, protection starts from first marketing anywhere in the Union: this handicaps companies in member countries where approval is slow, as in Germany. Marketing exclusivity is less useful; it suffers in that different member nations offer different periods of exclusivity.

The new trade mark regulations present Merck with potential problems in relation to the centralized procedure for obtaining marketing authorization. A firm may only file a single trade mark. A trade mark suitable for use in all member countries is difficult to find. Moreover, if a firm wishes to register a product in its own name and that of a co-licensee or distributor, the applications must be made in sequence and not in parallel. This wastes time and could delay the launch.

The rejection of the proposed Biotechnology Patent Directive was not a major blow. It did no more than set minimum standards that most developed countries already exceeded.

C.3.8. Actions of the Union: other pharma-specific measures

Merck considers that there is a role for direct contact between the pharmaceutical industry and patients. It favours consumer awareness programmes focusing on disease areas, compliance and self-regulation. It has developed such programmes in the USA and would like greater freedom to do so in Europe. This is not possible under the Advertising Directive. They also felt that promotional codes were not uniformly enforced in some member countries.

Labelling and patient information is less elaborate in the EU than in the USA. As yet, there are no uniform labels within Europe. Merck supplies the same information to all, but the countries come to different decisions. It feels that it is too early to comment on the Labelling Directive.

C.3.9. Actions of the Union: horizontal measures

In this area, Merck's main concern is the tax treatment of transfer pricing. They complain that national authorities take the bulk active ingredient price as the arms-length transfer price even when it is that charged by pirate manufacturers or results from compulsory licensing. The

transfer prices used within the Union are neither uniform nor transparent. Merck feels that the Union harmonization measures have done little to solve this problem.

C.3.10. Actions of the Union: an overview

A frequent response within Merck to enquiries about the effect of the SMP was to deny that a single market yet exists. There are so many cultural differences within the Union that Merck does not see a rapid unification. These differences are not only in regulation, but also in popular attitudes and in medical education.

To some extent these responses reflect the fact that Merck is a multinational company to which Europe is an important but not predominant market. Moreover, it is a mature market, and growth is more likely elsewhere. Nevertheless, Merck is in favour of what the Union is trying to achieve. There was general agreement that the SMP, for all the problems, had made Europe a better place for both research and production. Merck sees much of the SMP as being in the early stages of application. The establishment of a genuine single market would be a slow process. In the mean time, they would take advantage of the benefits of fragmentation, such as obstacles to parallel trade or tax concessions in Ireland, while trying to benefit from reforms, such as extended patent protection and easier movement of goods between member countries.

When asked about further measures to bring about a single market in pharmaceuticals, the following suggestions were forthcoming:

(a) a single European currency;
(b) convergence between European health care systems;
(c) a greater consensus about treatment policies such as immunization, in which Merck has a strong interest;
(d) freer pricing, in particular the separation of pricing from reimbursement.

C.4. Amgros case study

C.4.1. Background

This case study was conducted with the cooperation of the Amgros management. Amgros was founded by some public hospital owners in Denmark, in 1990.

Amgros is a wholesale company, but more specifically it is a purchasing company providing its owners with pharmaceuticals and other medical products. Amgros only delivers to its owners, i.e. Danish public hospitals.

The suppliers to Amgros are Danish producers, foreign producers through subsidiaries and representative offices in Denmark and parallel importers. Amgros does not import products directly.

Hospital pharmacies order pharmaceutical products from Amgros, which then orders the goods from various suppliers on the basis of one-year contracts. The producers deliver the pharmaceuticals directly to the hospitals.

Since 1990, more public hospital owners in Denmark have joined Amgros, increasing its purchasing power considerably. Amgros' market share today amounts to approximately 60%

of sales to hospitals in Denmark. The logic of the company is simple: through its considerable purchasing power, Amgros is able to exploit economies of scale, i.e. bargaining power, to the benefit of its owners. The employment in Amgros is modest: only five people are employed full time.

About 80% of annual turnover is from products bought by tenders. These are issued once a year in accordance with EU rules. In 1995, Amgros tendered out about 1,050 products or approximately 155 substances. Amgros demands fixed prices for the whole year, which means purchasing at the lowest prices compared to other suppliers. The balance is from supplementary contracts for other pharmaceutical products.

Amgros charges a 2% profit, but even with this commission the prices are typically the lowest available to hospitals, with average savings to hospitals of 20%.

Amgros' performance is measured as the commission plus achieved savings minus administrative costs. Achieved savings is defined as the savings to the owners of Amgros. The idea of Amgros has proved very profitable. The result has risen from DKR 1.7 million in 1991 to a forecast DKR 78 million in 1995. Rather remarkably, turnover is stable, and it has shown falls partly due to the considerable savings obtained and partly to the cost containment efforts in the publicly managed hospitals. In 1994, the turnover amounted to DKR 330 million or approximately ECU 45 million.

C.4.2. The single market for pharmaceuticals

No doubt the single market of the EU has led to increased competition in the markets for pharmaceuticals and other medical products.

The tender procedures followed by Amgros are in accordance with the general EU rules. However, the same mechanisms would have been applied without the EU rules.

According to the management of Amgros, the single market and the different specific initiatives within pharmaceuticals have had an impact on the activities of Amgros.

The most important mechanism in the pharmaceutical purchasing of Amgros has been parallel import. The implementation of the free movement of goods as one of the horizontal and general measures of the single market has been the most important vehicle for the more general tendency for cost containment within the public hospitals in most of the European countries.

Amgros has established many contacts with other institutions, organizations, wholesalers, etc. in Europe, the United States and even Japan, enabling the company to keep abreast of price levels all over the Western world. Prices are always compared on the basis of volume times unit price.

If potential suppliers in Denmark are unwilling to deliver at prices that can be found elsewhere in the world, Amgros may ask a parallel importer to import the pharmaceutical products in question. This mechanism has proven very efficient if not in a direct way. Only approximately 60 product varieties have been purchased through Danish parallel importers over the years. The indirect pressure on producers and importers in Denmark from parallel import has made these much more open to price reductions. Hence, the incentive for Amgros

to ask for parallel imports has been nullified. Importantly, this case seems to illustrate that the impact of parallel imports cannot be measured purely as the volume of products thus traded or the turnover of parallel trade.

Formal barriers to parallel trade still exist. An approval from the National Board of Health is needed before parallel import can take place. Also, the Danish registration number has to be marked on the imported product and patient information in Danish must be included with the product.

C.4.3. Impact of Union legislation

Concerning the vertical measures in the SMP, Amgros has had the following experiences:

(a) Price reductions: prices have undoubtedly fallen during the last five to eight years. The management of Amgros holds the opinion that prices would also have been significantly reduced if the single market legislation had not been implemented. Cost containment has had a major impact on the price level in itself and particularly due to the formation of Amgros. Large variations in the price of different pharmaceutical products still exist for the same substances, leaving room for more price reductions.
(b) Labelling and patient information: for Amgros, the legislation has been of no relevance.
(c) Classification and approval of pharmaceuticals: Amgros does not have any experience within this field, since it is the responsibility of the producers of medicines.
(d) Product liability: no experience, since, again, it is the responsibility of the producers.

Concerning the horizontal measures, Amgros has the following experiences:

(a) Trade marks: no significant impact – even if it has been seen that in this very professional environment trade marks turn out to be appreciated.
(b) Public procurement: the procedures and mechanisms are very straightforward and fair. If the rules had not been set on paper, Amgros would have used similar mechanisms in their efforts to exploit their economies of scale in purchasing.
(c) Competition policy: Amgros has no experience with the enforcement of EU competition policy among its suppliers.

C.4.4. Future development

Different national public reimbursement systems have no impact on price levels as far as Amgros is concerned. However, the different systems give the producers the opportunity to differentiate their supply of pharmaceuticals including the price. For the management of Amgros, it is almost impossible to imagine harmonization of the national reimbursement systems.

Amgros foresees that tough competition will continue. Unit prices are, on average, still expected to fall. All kinds of reactions to this relatively new trend of falling prices within the pharmaceutical industry will mean considerable strategic activities in the industry.

(a) Producers: producers will strive to minimize production costs and will have to pass on a share of the profits earned from distribution to the end-user. Economies of scale and scope will prove to be essential for profitability. It is noteworthy that the exploitation of economies of scale tends to concentrate the purchases and limit the number of suppliers,

whereas the exploitation of economies of scope may allow Amgros to take advantage of many different suppliers.[137] The producers seem to have a very strong capital base for making forward vertical integration.

(b) Wholesalers: wholesalers must also grow bigger or become more internationalized in order to sustain their positions. The Amgros case is an example of the risk of wholesalers being by-passed.

(c) Pharmacies: pharmacies and other retail shops must join by forming retail chains or cooperating to strengthen their positions *vis-à-vis* wholesalers and producers.

This activity has already been put into action by companies in many countries. Vertical integration is perhaps the most important way for producers to benefit from the profit found in distribution channels, internationalization perhaps the most important for big wholesalers. National monopolies and oligopolies in the form of retail chains seem to be the most important tool for national pharmacies and retail shops selling pharmaceutical products.

C.5. Generic pharmaceutical companies

This case study differs from the others in this report. A number of generic firms were interviewed, but they are all relatively small. Moreover, as the European Generic Manufacturers Association commented, there is no such thing as a standard generic company. For this reason we present an overall view of the sector, pooling information gathered from interviews and elsewhere, indicating common themes and identifying differences of opinion as appropriate.

C.5.1. Generic medicines and the generic market

What is a generic medicine?

There is a considerable variation of opinion here. Some take a broad view and include all medicines that are out of patent; others take a narrow view and include only products that are sold under their INN name. The most common definition – and that followed here – is that a generic medicine is one that is a copy of an existing product, and sold by a firm other than the originator at a price substantially below that of the original product. It may be sold under a brand-name, which may be no more than a tag to identify the maker, such as *Diazepam-Ratiopharm,* or under its INN name alone.

The generic market and industry

According to this definition, generics make up about 10% of the Union market by value; this proportion is growing. They are a larger proportion of consumption in Denmark (20%), Germany (20%), the Netherlands (15%) and the UK (14%). They constitute less than 5% in France, Italy and Spain. Much turns on prevailing price levels: where these are low, generics are commercially unattractive. The governments of some Member States encourage their use – this has been true of Germany and the UK for many years – and this is becoming more common. Thus, the current French system of contracts between government and pharmaceutical firms has among its objectives the creation of a substantial generic sector in France.

[137] This is due to a fully computerized ordering system between suppliers, Amgros and hospital pharmacies.

Most generic firms are relatively small – sales rarely exceed ECU 100 million and are usually considerably lower – and, until recently, focused on their own national markets. Less than ten have foreign subsidiaries. There is now increasing interest in operating in Europe and elsewhere. France, in particular, is expected to emerge as a significant market in the near future. There is a trend towards mergers in the sector, while a number of leading firms have been bought by major research-based firms. For example, Berk merged with Approved Prescription Services, and the combined company was then taken over by Rhône-Poulenc. This is a global trend: thus Rhône-Poulenc had already acquired the American firm Rorer. The driving force is downward pressure on pharmaceutical spending by health care systems; research-based companies are diversifying into generics and self-medication products as a defensive measure.

C.5.2. The operations of generic companies

Manufacturing

Generic companies typically make a large range of medicines; one company with a turnover of ECU 80 million offered 200 products. They do not make active ingredients. They buy them in from within the Union – especially Italy and Spain, who are major suppliers for North American firms – from Eastern Europe and elsewhere: India, China, South Africa and Argentina were mentioned. This is a commodity business, and price competition is keen. Formulation and packaging are largely done inside the Union; some firms did it all themselves, while others made considerable use of sub-contractors. In the latter case, quality is important. There is some feeling that manufacturing standards vary between member countries. A Dutch company considered that they were high in Belgium, the Netherlands, Sweden and the UK but lower in Germany. This is a major issue for firms exporting to the USA.

Research and development

Since a generic medicine is a copy of an original product, generic firms are mainly concerned with development work intended to enable them to enter the market as soon as patent protection expires. This is universally seen as critically important: the first to arrive has a lasting advantage. They may also develop new formulations or delivery systems.

Marketing

Marketing methods depend on national regulations and on national health care systems and forms of medical practice. They are sold under INN names alone in the Netherlands and the UK; branded generics have been unsuccessful there. Accordingly, they do not have to be promoted to doctors. In Germany, they are by custom sold under brand-names, and a sales force is necessary.

Prices are always lower than those of the originals; the differential is generally large in Denmark and the UK, rather smaller in Germany and smaller still in the Netherlands. In part, these variations are due to differences in national reimbursement systems.

There is some feeling that a national company knows its own market best and that the advantages of operating multinationally are exaggerated. However, the companies interviewed now all sell in several countries.

Cost structures

The generic business is less profitable than the research-based sector. Margins average 7-10% on sales. Manufacturing is the main cost, bought-in materials alone being 60-70% of the total and R&D 4-5%, though for companies interested in the American market FDA requirements make this as high as 8-10%.

C.5.3. The impact of Union actions on the generic sector

Admission to markets

There was general agreement that admission to markets via national systems may take as long as for a genuinely new medicine. Provisions for abbreviated applications work well in some countries but not in others. Germany was singled out as a problem country. There is some feeling that local companies are treated more favourably by national authorities.

Generic companies had made use of the multistate procedure between 1986 and 1994. There was no consensus on whether or not it was superior to national registration; given that companies have hitherto been mainly concerned with their own national markets, this was understandable. The current system of mutual recognition is viewed with caution. In principle it is excellent, provided that dossier requirements and interpretations are truly identical; at present, there are still frequent differences between national authorities. However, the mutual recognition process looks complex, and the appeals system is disquieting. The critical factor will be the difference it makes to the speed of approval.

Prices and pricing

The Transparency Directive has had no effect at all. National governments remain in control. The proposed extension to the Directive proposed a greater use of generics, but it was abandoned. Systems for agreeing prices are complex and often opaque. Two companies noted that local firms obtained better prices; however, the links between foreign direct investment and prices seen in the research-based sector were not important. Parallel trade in generics is not an issue as yet; where prices are low, generics are little used.

The Rational Use of Medicines Directives

Their effect has been greatest in the UK where original pack dispensing was not compulsory and traditionally pills had been sold in bottles of 1,000. No patient information leaflets had to be provided. The new regulations would increase costs: thus a pack of 28 diazepam tablets would cost ECU 0.07, but a blister pack would bring this up to ECU 0.16. There would also be additional costs in distribution. However, the costs of re-equipment would force many of the small independent companies out of business, and this would increase margins in Britain where they have been low. If pack sizes were standardized throughout Europe, there would be significant economies of scale: production runs would be longer and down-times reduced.

Elsewhere the effects of these Directives have been modest.

Intellectual property

There is unanimous agreement that the actions of the Union have been negative for generic companies.

The system of Supplementary Protection Certificates introduced in 1993 provides up to five years of further protection to patent holders and obviously handicaps generic firms. Moreover, it prevents them from beginning product development, preparation of a dossier and submission of an application for marketing authorization until the relevant patents have expired. Unlike the analogous Waxman-Hatch Act in the USA, it makes no provision for such work to start before that time. Thus, it has to be carried out later, and entry to the market may be delayed for several years. In addition, the necessary transitional dates vary between member countries.

Related problems arise from other national and Union provisions. National laws usually allow 'experimental work' to be done during the lifetime of a patent, but define this work as being strictly non-commercial. Such interpretations have been upheld by the courts. Some member countries, however, allow the data necessary for an application to be imported, but others do not. The Marketing Exclusivity Directive also precludes work beginning before a set period after the first authorization of a product within the Union. A majority of member countries fixed the period at ten years, but some at only six.

Such measures not only handicap the generic sector within the Union, but amount to potential barriers to trade. Generic firms also claim that they are placed at a disadvantage to their competitors outside the Union. The Spanish and Italian companies making active ingredients are seen as especially at risk: US and Canadian companies are major customers of theirs, and if Europe could not supply them, they would look elsewhere. Some firms reported that development work was being moved outside the Union in order to overcome these problems.

Horizontal measures

These measures attracted few comments. There is some feeling that there are still problems with the free movement of goods.

General comments

Several companies considered that the Commission was biased in favour of the research-based sector, which attracted some hostility. The treatment of intellectual property was seen as an example. It was suggested that large firms had too much say in setting standards and that this handicapped the smaller companies.

C.5.4. The future

The market for generics will continue to grow, especially in France, Italy and Spain, where it has been relatively unimportant until now. In those countries, however, much will depend on government action to encourage generics. Pressures towards a greater use of generics within Europe are inexorable. Firms will continue to expand into extra-EU markets, including North America and the developing world. Economies of scale will become increasingly important. There is also interest in producing in Eastern Europe and Asia, where labour costs are lower.

Mergers and acquisitions will also continue. Independent generic firms need a steadily rising critical mass in order to survive. To an increasing extent they will develop new variants on existing products and form strategic alliances with major companies. The boundaries between the research-based and generic sectors will become blurred. One company foresaw the two combining at the therapeutic level to offer treatment packages of which some items would come from the innovative firm and others from generic firms.

APPENDIX D

Community legislation, etc.

D.1. Regulations

Council Regulation (EEC) No 4064/89 of 21 December 1989 on the control of concentrations between undertakings (OJ L 395, 30.12.1989, p. 1).

Commission Regulation (EEC) No 2367/90 of 25 July 1990 on the notifications, time limits and hearings provided for in Council Regulation (EEC) No 4064/89 on the control of concentrations between undertakings (OJ L 219, 14.8.1990, p. 5).

Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products (OJ L 182, 2.7.1992, p. 1).

Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (OJ L 214, 24.8.1993, p. 1).

Council Regulation (EEC) No 40/94 of 20 December 1993 on the Community trade mark (OJ L 11, 14.1.1994, p. 1).

Commission Regulation (EC) No 3384/94 of 21 December 1994 on the notifications, time limits and hearings provided for in Council Regulation (EEC) No 4064/89 on the control of concentrations between undertakings (OJ L 377, 31.12.1994, p. 1).

D.2. Directives

65/65/EEC: Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 22, 9.2.1965, p. 369)

66/454/EEC: Council Directive of 28 July 1966 amending Article 22 of the Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 144, 5.8.1966, p. 658)

68/360/EEC: Council Directive of 15 October 1968 on the abolition of restrictions on movement and residence within the Community for workers of Member States and their families (OJ L 257, 19.10.1968, p. 13)

75/318/EEC: Council Directive of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ L 147, 9.6.1975, p. 1)

75/319/EEC: Second Council Directive of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13)

78/25/EEC: Council Directive of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products (OJ L 11, 14.1.1978, p. 18)

81/464/EEC: Council Directive of 24 June 1981 amending Council Directive 78/25/EEC on the approximation of the rules of the Member States relating to the colouring matters which may be added to medicinal products (OJ L 183, 4.7.1981, p. 33)

83/189/EEC: Council Directive of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations (OJ L 109, 26.4.1983, p. 8)

83/570/EEC: Council Directive of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 332, 28.11.1983, p. 1)

84/450/EEC: Council Directive of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising (OJ L 250, 19.9.1984, p. 17)

85/374/EEC: Council Directive of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (OJ L 210, 7.8.1985, p. 29)

86/609/EEC: Council Directive of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (OJ L 358, 18.12.1986, p. 1)

87/18/EEC: Council Directive of 18 December 1986 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 15, 17.1.1987, p. 29)

87/19/EEC: First Council Directive of 22 December 1986 amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ L 15, 17.1.1987, p. 31)

87/21/EEC: Council Directive of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 15, 17.1.1987, p. 36)

87/22/EEC: Council Directive of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (OJ L 15, 17.1.1987, p. 38) [repealed by Directive 93/41/EEC]

88/182/EEC: Council Directive of 22 March 1988 amending Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations (OJ L 81, 26.3.1988, p. 75)

88/320/EEC: Council Directive of 9 June 1988 on the inspection and verification of Good Laboratory Practice (GLP) (OJ L 145, 11.6.1988, p. 35)

88/361/EEC:Council Directive of 24 June 1988 for the implementation of Article 67 of the Treaty (OJ L 178, 8.7.1988, p. 5)

88/379/EEC: Council Directive of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations (OJ L 187, 16.7.1988, p. 14)

89/104/EEC: First Council Directive of 21 December 1988 to approximate the laws of the Member States relating to trade marks (OJ L 40, 11.2.1989, p. 1)

89/105/EEC: Council Directive of 21 December 1988 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 (OJ L 40, 11.2.1989, p. 8)

89/341/EEC: Council Directive of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ L 142, 25.5.1989, p. 11)

89/342/EEC: Council Directive of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens (OJ L 142, 25.5.1989, p. 14)

89/343/EEC: Council Directive of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals (OJ L 142, 25.5.1989, p. 16)

89/381/EEC: Council Directive of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma (OJ L 181, 28.6.1989, p. 44)

89/552/EEC: Council Directive of 3 October 1989 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the pursuit of television broadcasting activities (OJ L 298, 17.10.1989, p. 23)

90/18/EEC: Commission Directive of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of good laboratory practice (GLP)

90/219/EEC: Council Directive of 23 April 1990 on the contained use of genetically modified micro-organisms (OJ L 117, 8.5.1990, p. 1)

90/220/EEC: Council Directive of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (OJ L 117, 8.5.1990, p. 15)

90/435/EEC: Council Directive of 23 July 1990 on the common system of taxation applicable in the case of parent companies and subsidiaries of different Member States (OJ L 225, 20.8.1990, p. 6)

90/679/EEC: Council Directive of 26 November 1990 on the protection of workers from risks related to exposure to biological agents at work (OJ L 374, 31.12.1990, p. 1)

91/356/EEC: Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ L 193, 17.1.1991, p. 30)

91/507/EEC: Commission Directive of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (OJ L 270, 26.9.1991, p. 32)

92/25/EEC: Council Directive of 31 March 1992 on the wholesale distribution of medicinal products for human use (OJ L 113, 30.4.1992, p. 1)

92/26/EEC: Council Directive of 31 March 1992 concerning the classification for the supply of medicinal products for human use (OJ L 113, 30.4.1992, p. 5)
92/27/EEC: Council Directive of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets (OJ L 113, 30.4.1992, p. 8)
92/28/EEC: Council Directive of 31 March 1992 on the advertising of medicinal products for human use (OJ L 113, 30.4.1992, p. 13)
92/73/EEC: Council Directive of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products (OJ L 297, 13.10.1992, p. 8)
93/36/EEC: Council Directive of 14 June 1993 coordinating procedures for the award of public supply contracts (OJ L 199, 9.8.1993, p. 1)
93/39/EEC: Council Directive of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products (OJ L 214, 24.8.1993, p. 22)
93/41/EEC: Council Directive of 14 June 1993 repealing Directives 87/22/EEC on the approximation of national measures in respect of medicinal products relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (OJ L 214, 24.8.1993, p. 40)
94/10/EC: Directive of the European Parliament and the Council of 23 March 1994 materially amending for the second time Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations (OJ L 100, 19.4.1994, p. 30)
94/15/EC: Commission Directive of 15 April 1994 adapting to technical progress for the first time Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (OJ L 103, 22.4.1994, p. 20)
94/51/EC: Commission Directive of 7 November 1994 adapting to technical progress Council Directive 90/219/EEC on the contained use of genetically modified micro-organisms (OJ L 297, 18.11.1994, p. 29)
94/62/EC: European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste (OJ L 365, 31.12.1994, p. 10)

D.3. Other

89/569/EEC: Council Decision of 28 July 1989 on the acceptance by the European Economic Community of an OECD decision/recommendation on compliance with principles of good laboratory practice (OJ L 315, 28.10.1989, p. 1)
90/230/EEC: Commission Decision of 3 May 1990 amending the lists of standardization institutions set out in the Annex to the Council Directive 83/189/EEC (OJ L 128, 18.5.1990, p. 15)
91/448/EEC: Commission Decision of 29 July 1991 concerning the guidelines for classification referred to in Article 4 of Directive 90/219/EEC (OJ L 239, 28.8.1991, p. 23)
91/596/EEC: Commission Decision of 4 November 1991 concerning the summary notification information format referred to in Article 9 of Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (OJ L 322, 23.11.1991, p. 1)
92/146/EEC: Commission Decision of 11 February 1992 concerning the summary notification information format referred to in Article 12 of Council Directive 90/220/EEC (OJ L 60, 5.3.1992, p. 19)
Commission Decision of 16 January 1996 amending Directive 91/448/EEC concerning guidelines referred to in Article 4 of Council Directive 90/219/EEC on the contained use of genetically modified micro-organisms (OJ L 31, 9.2.1996, p. 25)
COM(85) 310 final: Completing the internal market (White Paper from the Commission to the European Council)
COM(88) 496 final: Proposal for a Council Directive on the legal protection of biotechnological inventions
COM(92) 589 final: Amended proposal for a Council Directive on the legal protection of biotechnological inventions
COM(93) 718 final: Commission communication to the Council and the European Parliament on the outlines of an industrial policy for the pharmaceutical sector in the European Community
COM(95) 661 final: Proposal for a European Parliament and Council Directive on the legal protection of biotechnological inventions

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