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ON THE OUTLINES OF AN INDUSTRIAL POLICY FOR THE PHARMACEUTICAL SECTOR IN THE EUROPEAN COMMUNITY

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Introduction

The aim of the present Communication is to lay down the outlines of an industrial policy for the pharmaceutical sector. This industry is a substantial asset for growth and employment in the European Union. However, in the context of stiffening world-wide competition and of continuous increases in the cost of research and development in this sector, there are signs that the competitiveness of the Community industry is yielding in comparison with its main competitors. Its ability to finance the research and development of new therapeutically innovative medicines, which is a condition for its long term competitiveness, in particular seems to be relatively weak.

Although it is essential to ensure that the European pharmaceutical industry retains its competitiveness, the ways and means of this action must however be considered by taking into account the specificity of this industry. Medicinal products play an essential role in the field of public health. Moreover, pharmaceutical spending represents an important share of social security budgets, whose financing is a subject of concern in most Member States at the very moment that these are required to contain public deficits in order to prepare for economic and monetary union. The Community policy in favour of the pharmaceutical industry must take notice of this twofold context of public health and social security, which - in conformity with the principle of subsidiarity - is ascribable to Member States in the first place.

By the year 2000, restructuring and amalgamation will have radically changed the face of the European pharmaceutical industry. The industrial policy for this sector should strive to accompany these changes, in order to foster the emergence of firms able to stay in the vanguard of tomorrow's global industry. Following the way paved by the Commission *White Paper : Growth, Competitiveness, Employment*, the Community and Member States must together ensure that the conditions necessary for the competitiveness of the EC pharmaceutical industry are in place.

Chapter 1

Growth, competitiveness, employment in the pharmaceutical sector

The European pharmaceutical industry is a substantial asset for the European economy. However, it would seem that it is not well enough prepared to brace itself against stiffening international competition and with the relentless rise of the cost of pharmaceutical research, and that its competitiveness could prove insufficient in regard to its main competitors. The first signs of structural difficulties in this industry have indeed appeared recently

A) The pharmaceutical industry: an important asset for the European economy

The pharmaceutical industry is among Europe's best-performing high-technology sectors. It generates over 1% of EC gross national domestic product and has grown at an annual rate in excess of 6% between 1982 and 1992. Its production was worth ECU 68 billion in 1992, with an average value added of 40%, and it has a very high labour productivity rate.

As a result of significant R&D efforts in the past, the EC pharmaceutical trade surplus (nearly ECU 4.9 billion in 1992, and growing steadily) has for many years helped to improve the Community trade balance. The position is slightly less favourable for active substances, which generate more added value, than for finished or semi-finished products. The site of research and production of active substances are often linked. Overall, however, EC pharmaceutical trade is in surplus with all third countries except EFTA countries, and to a lesser extent, with the United States.

The pharmaceutical industry generates many jobs upstream, such as basic and speciality chemicals, starch and sugar production, medicinal plants, packaging, special glass manufacturing and computer technology.

B) Growing research and development costs

Pharmaceutical research is long and costly. It takes 10 to 12 years to develop a newly-synthesised active substance into a marketable medicine which can be used in current medical practice. The average cost of researching and developing an entirely new medicinal product, several dozen of which are launched each year on the world market, is estimated at ECU 200 million.

Because such an investment can be financed only if the company is able to generate the necessary cash flow during the period of patent protection, it is essential to launch the medicinal product on the markets of large industrialised countries as quickly as possible. The survival of large pharmaceutical companies depends on the profitability of a small number of products (sometimes on that of just one successful product), and also on the regular renewal of portfolios of patents on new medicinal products.

Yet total investment in research and development has quintupled in the past fifteen years. Development costs in particular have soared. This rapid growth in costs is generally attributed to progress in molecular biology and especially in knowledge of the pathogenesis of diseases, to technical improvements in tools for therapy or prevention, and to increasingly stringent technical requirements designed to ensure the quality, safety and efficacy of medicinal products. On average, out of every 10,000 substances synthesised by the pharmaceutical industry, only one or two will become marketable medicines.

C) Stiffening world-wide competition

The industry's globalization demands that companies expand their activities, first within Europe, by consolidating their positions, then world-wide. Community firms account for 2/3 of the market in the EC, 1/3 in the USA and 10% in Japan. The US pharmaceutical industry has similar market shares in the EC and Japan. The Japanese pharmaceutical industry has 80% of its own market, and although it has so far won only 1% of the market in the US and Europe, is likely to increase its penetration with new medicinal products researched and developed in Japan and purchased under licence by American and European companies.

For innovative firms it is important to benefit from a substantial home market to generate the cash flow needed to finance their research and development costs. Overall, the EC pharmaceutical market is the world's largest: it accounts for about ECU 63.5 billion in 1992, i.e. about a third of the total. But until all the measures adopted recently by the European Community are translated into reality, this market will remain relatively fragmented by its many national partitions. The financial resources required to pursue research and development efforts will only be available for European pharmaceutical companies if these are allowed an effective access to third countries' markets.

D) The vulnerability of the European pharmaceutical industry

European pharmaceutical companies are still relatively well-placed in the world ranking: in 1992, 8 EC firms appear among the 20 leading pharmaceutical groups.

The huge risks involved make individual companies very vulnerable, not least because 90% of R&D spending is financed by the industry itself. It is therefore the long-term capacity to generate the resources needed to bring new products to the market - a capacity which depends on the success of those already on the market - that determines the ability to compete of the principal multinational companies. This capacity can be measured by the return on investment, which includes net profit and cash flow, as calculated in world-wide consolidated accounts. Indeed pharmaceutical companies resort only occasionally to borrowing to cover R&D costs; in most cases R&D is financed through the allocation of a share of profits to investments required for research programmes.

On average, European companies generally obtain results vastly inferior to those of American companies: for many years, budgets allocated to R&D investments by EC companies have accounted for only half of the budgets available to American companies. Thus, the operational profit of the 8 top Community pharmaceutical groups, British groups not included, is around 13%. Only 2 British companies have come close to the ratios achieved by American and Swiss companies (around 28%), which explains the rise of some of the former in world rankings.

Additionally, European companies are, in general, of a smaller size than US companies, which therefore have from the very start greater resources for their R&D spending.

The concept of major global drugs encompasses medicinal products which are present on 6 of the 7 biggest markets in the world, and is therefore a good indicator of innovation. Today the United States hold 43% of these major global drugs, Europe 31% and Japan 11%. Furthermore, the capacity of EC firms to innovate appears to be declining, and they are under-represented in some new fields.

Twenty years ago, half of all new medicines were developed in the Community. Today, this share has fallen to about one-third. Over the same period, the USA has continued to discover about a quarter of all new active substances, whilst Japan has increased its share from 10% to 22%. Among the medicinal products launched in Europe since 1987, 37 originated in the United States, 28 in Europe. It is hard to escape the conclusion that the United States, rather than Europe, is now the main base for pharmaceutical research and development and for therapeutic innovation.

The picture is most worrying in respect of biotechnology: 65% of patents are American, 15% European and 13% Japanese. Where in the USA around 1000 small and medium size enterprises are active in the pharmaceutical field, there are only 30 such companies in Europe, and they only started to emerge in recent years. Among the 50 new medicinal products appearing each year on the world market, 10 to 15 are derived from biotechnological methods. This proportion will gradually increase over the next years. Rapid technological progress, especially in genetics and molecular biology, have opened up new areas of still untreated illness to medical intervention, thanks notably to genetic therapy. World pharmaceutical consumption is predicted to rise on present trends by 36% or more by the year 2000. Most of this growth will be fuelled by the uptake of new products derived from biotechnology.

E) Employment in the pharmaceutical sector

The pharmaceutical industry employs almost half a million people directly within the EC. It needs many highly skilled staff, and employs 62,000 people in research. Despite the recession, the pharmaceutical industry has been expanding its workforce between 1981 and 1992, by an average of 2.4% per year. Since the beginning of 1993, however, this trend has gone into reverse. For the first time in 20 years the total employment in the pharmaceutical industry did not increase in 1993, but rather decreased by 1.4%. Furthermore even more important reductions of the workforce have already been announced and will take place through the coming years. Thus, within three years (1993-1995), nearly 27,000 jobs could be lost in the European pharmaceutical industry. A substantial part of the lay-off stems from the closing of research or manufacturing sites, or delocalizations.

Equally worrying is the importance of disinvestment. Several companies have definitely abandoned plans to develop or to establish new research or manufacturing units. One must therefore take into account the fact that, over the next years, the European pharmaceutical industry will not be able to create 5,000 to 10,000 new jobs a year, as in each of the last years.

F) New approaches and the restructuring of the pharmaceutical industry

Besides the dominant multinational firms, there are many medium-sized companies whose activities are not world-wide but are nonetheless international. They exploit both the products of their own research and other companies' products under licence. A large number of small local companies, some working in promising specialised fields, complete the fabric of the pharmaceutical industry.

In Japan, and even more so in the USA, much innovation, particularly in the biotechnology and genetic engineering fields, stems from the dynamism of small and medium-sized enterprises which are more or less independent of large pharmaceutical groups. In Europe, by contrast, SMEs generally concentrate on traditional production, contrary to the situation observed in Japan and especially in the US. This ultimately exposes the vulnerability of the fabric of European industry since the totality of innovative potential is not fully exploited. Yet these companies have a human resource and experience which they should be able to exploit more satisfactorily. Given a better access to research at both national and European level, the flexibility of these SMEs could be an important advantage in niche innovation.

It is also important to take into account some new trends and particularly the development of products for self-medication. The turnover for self-medication varies greatly from one country to another (representing between 8% and 17% of the market in 1992 according to AESGP/IMS). This segment of the market has experienced an average growth rate of 9.9% since 1987, and the demand for these products is likely to increase in future years. This has been confirmed by the fact that many large pharmaceutical companies are now developing their products for this segment of the market, in order to respond in certain cases, to the change in behaviour of patients. The Community has recently adopted directives on the rational use of medicinal products which supply a common regulatory framework for these medicines which are advertised to the public in accordance with the conditions set out in Community legislation (directive 92/28/EEC).

In some countries, collaboration between firms, e.g. through co-marketing ventures and investment by major multinationals in local research and development and/or manufacturing units, has helped to hatch a local research industry later able to position itself on world markets. Technical collaboration between world class research companies and local undertakings closer to the culture of their markets often results in marketing agreements, or in more elaborate joint venture research programmes, which provide development opportunities in a growth industry from which these countries would be excluded without the contribution of know-how essential to a successful start-up.

The European pharmaceutical industry's structure was not, of course, radically changed by the advent of the single market in 1993. Indeed, several measures which were adopted in view of the completion of the internal market still have to come into effect in this sector. Nonetheless, significant changes could occur by the year 2000, and it is up to industrialists to prepare for them. Community initiatives will facilitate the restructuring and rationalisations which should allow the EC pharmaceutical industry to become more competitive.

Firstly, and independently of any specific initiative by the Community, the structure within which pharmaceutical companies are used to working has been profoundly shaken by the soaring cost of pharmaceutical research and development, the emergence of new technologies

such as biotechnology, the international trend towards greater concentration of capital and the means of production.

The fragmentation of national markets had led to a dispersion of production sites, and is a considerable source of waste. Some European companies have yet to take full account in their business strategies of the potential offered by the Community's new regulatory framework.

Although a great number of enterprises are active in the pharmaceutical industry, large multinational firms are each pre-eminent in one or more of the many market segments constituted by diverse therapeutic indications. Consequently, the trend for large companies to link up or merge is likely to gather pace and to sweep up European firms ever more frequently.

Chapter 2
The context : public health and social security

Thus, the Community has to maintain and to reinforce the competitiveness of the European pharmaceutical industry. However Community initiatives in this field must take into account the specificity of this industry - on the one hand because pharmaceutical products play a key role in the context of public health; -on the other hand because the manner in which the consumption of these products is financed has a direct impact on the social security budgets of the Member States. The Community pharmaceutical policy must be inserted in this twofold context: public health and social security, although there could be no question of challenging the Members States' competence in this field.

A) Medicinal products and public health policy

In the field of public health, Article 129 of the Maastricht Treaty provides that "the Community shall contribute towards ensuring a high level of human health protection by encouraging co-operation between the Member States and, if necessary, lending support to their action". This implies that the Community should improve the collection and exchange of data in the field of public health, strengthen networks and joint projects and promote the exchange of experience and expertise. The Commission has identified already certain priority fields which will be the subject of pluriannual Community action programmes.

As proposed by the Commission in its Communication of 24 November 1993 (COM(93)559), the Community strategy in the field of public health will aim essentially at fostering the ability of each European citizen to protect and to promote its own health by supplying him with the necessary information in this respect. This strategy requires the development of new forms of preventive medicine as well as other forms of prevention linked with hygiene and life-styles. It also implies a strengthening of the pharmaceutical industry's ability to supply therapeutic and diagnostic means at the best cost. Only if it is effective and competitive will the EC industry be able to significantly contribute to the struggle against the many diseases not yet mastered by medical progress, be it diseases which are very common in developed countries or in the third world, or indeed so-called rare diseases.

Progress in medicine and therapeutics has helped greatly to reduce mortality, prolong life and eliminate major diseases. The most spectacular successes have been the prevention of many scourges (including childhood diseases), through vaccination (rabies, typhoid, tuberculosis, diphtheria, tetanus, whooping cough, poliomyelitis and cholera) and anti-infectious treatments, such as antibiotics. Moreover, new and important progress has been made in the treatment of cardio-vascular diseases and cancer.

Still, there are many diseases which cannot yet be treated satisfactorily. We have only partial answers to some, and new ones appear, or are identified, as knowledge progresses. We still lack effective treatments and cures in the important field of chronic degenerative diseases, which impose the heaviest burden on public health spending. Wide fields of investigation are still opening up to researchers in the fields of immunobiology, tropical diseases, AIDS and

gene therapy. These fields are particularly exposed and vulnerable, because success, or even a return on investment, is rarely assured.

A whole series of diseases (about 5,000 have been identified) are described as "orphan", because they are too rare, or because developing a treatment for them would be too costly for a private company to venture investing the time and money needed to research, fulfil marketing authorisation requirements for, and produce such a treatment. Whilst state support may be obtained fairly easily for research in fields which the general public recognises as important, e.g. cancer and AIDS, cystic fibrosis and multiple sclerosis, this is not the case for most other such diseases.

B) Social security and pharmaceutical spending

In a difficult economic context and in the transition phase towards Economic and Monetary Union, keeping health care cost under control is of increasing concern for all Member States. A reduction in the share of health care spending which is collectively financed (between 70% and 90% according to the Member States) could result in important inequalities based on revenue in terms of access to health care and medical care, in a context where European citizens remain, as regards the financial risk involved with disease, deeply attached to the principle of solidarity, which is at the very heart of their social system.

The overall increase in health spending is attributable partly to impressive scientific and technical progress particularly in the pharmaceutical field but also to population ageing and to the extension of social security cover. OECD figures show that Europe spent ECU 330 billion on public health in 1990. The enormous health care expectations of European citizens (and hence their pharmaceutical consumption) stem from their deep-rooted belief in social solidarity and hope for continuous improvements in the quality of life.

The share of pharmaceutical expenditure in total social security spending ranges from nearly 10% to more than 20% in the Member States (in 1990, according to OECD). As a share of health insurance spending, it averages only about 16%, and this share is in relative decline, compared with rising expenditure on hospital care.

The medicinal product is still the therapeutic tool of choice which in some circumstances achieves a better cost/benefit ratio than other treatments. It can allow savings to be made in other health sectors, and helps to improve medical care. Although in most industrialised countries pharmaceutical consumption accounts for about 1% of gross domestic product, consumption volumes and medicinal product prices still differ widely from one EC Member State to the next. Differences in prescribing practices and pharmaceutical consumption patterns do not always correlate well with the levels of health protection achieved.

In most Member States, the entire population benefits from a publicly financed health care cover, as far as pharmaceuticals are concerned. This is also reflected in the reimbursement rate which, in the Community, exceeds half even two thirds, of expenses on pharmaceuticals.

The part of pharmaceutical spending which is not covered by social protection systems is born either by private insurance, or by patients themselves. The cover ratio is generally higher for products which are only available on medical prescription and therefore for innovative products.

The Community has undertaken to promote a high level of social protection and to ensure a high level of health protection. In its Recommendation 92/442/EEC of 27 July 1992 on the convergence of social policy objectives, the Council recommends that each Member State should offer, under the conditions that it has laid down, the benefit of its human health protection system to persons lawfully residing on its territory, whatever the level of their income.

Member States remain responsible, of course, for the organisation and the financing of their social protection systems and are only committed in respect of the social protection objectives to be reached.

C) Cost containment and the needs of the health policy

Since public or social insurance funds bear a considerable part of the costs related to the consumption of pharmaceutical products, health authorities have an obvious and legitimate interest in containing the spending in this area. Moreover, they have an interest in ensuring that they get good value for the money spent.

Most Member States have taken measures to contain spending on medicinal products. These vary from country to country and include direct or indirect controls on prices or profits, restrictions on the categories of products reimbursed, and percentage limits on the proportion of spending reimbursed by the health and social security systems.

On the other hand, Member States have an interest in maintaining an advanced industry capable of continuous development and of supplying products which correspond to the needs of the health care sector. It is therefore important that the cost containment measures do not hamper industry's capability to meet these demands. Moreover, national cost containment measures should not provide an opportunity for arbitrary discrimination or restrictions of competition within the internal market.

The divergence of national pharmaceutical pricing and reimbursement systems as well as cultural differences tend to make the European market for pharmaceutical products more fragmented than is the case in the USA and Japan. Although price control and reimbursement systems fall within the competence of Member States, these should take into account the potential effects of such measures on the functioning of the internal market. The Commission will see to it that any price control system is operated in such a way that the price setting mechanism is fully transparent and that all forms of discrimination are prevented.

Chapter 3

Growth, competitiveness, employment in the sector

Several Community actions will soon ensure a quick access to the entire Community market, will create a more favourable environment for R&D and therapeutic innovation, and will facilitate access to third countries market for European companies. The pharmaceutical market remains however fragmented, notably as a result of social security and health policies. This has sometimes contributed to the lack of transparency of the EC pharmaceutical market.

A) Consolidating the internal market in the pharmaceutical sector

The main measures needed for the completion of the single market in the pharmaceutical sector have now been adopted. They will gradually come into effect over the coming months.

1. Access to the market - European Medicines Evaluation Agency

Since 1992, criteria and procedures for authorizing the marketing of human and veterinary medicines, and for the inspection of good manufacturing practices, are fully harmonized for all industrially produced medicinal products.

In June and July 1993 the EC Council of Ministers adopted Regulation (EEC) 2309/93 and three Directives (93/39/EEC, 93/40/EEC and 93/41/EEC) laying down the future marketing authorization system for medicinal products for human and veterinary use and establishing the European Agency for the Evaluation of Medicinal Products. Thus, from 1995, firms wishing to gain rapid access to the single market will be able to choose between two procedures:

- a centralized procedure, leading to a single authorization for the whole of the European Community, reserved for certain new medicinal products and mandatory for those derived from biotechnology;
- a decentralized procedure, designed for most medicinal products, based on mutual recognition of national marketing authorizations (with disputes to be settled by binding Community arbitration).

The European Agency for the Evaluation of Medicinal Products, which will help to operate the system, will be an administrative and technical secretariat with substantial scientific support provided by the competent authorities of the Member States. Once a product has undergone one of these authorization procedures, the Commission will turn the Agency's opinion on it into a binding decision.

The future marketing authorization system should give firms access to the large internal market they need to recoup their research and development costs. Sharing the workload between the European Agency and existing national ones should reduce the time taken to authorize a product from several years to 300 days, and halt runaway increases in registration fees. The greater transparency of the European Agency's evaluations and scientific opinions should help to restore consumer confidence, which is sometimes shaken by marked differences of views between national authorities. Public health will be better protected by pooling all the

expertise available from various national authorities and by strengthening pharmacovigilance. Telematic networks should in particular facilitate notably the exchange of information between national authorities.

2. *Transparency of national price control measures*

Price control and reimbursement systems operated by some Member States contribute to the fragmentation of the EC pharmaceutical market. It would not be acceptable that national decisions relating to price fixing or admission for reimbursement are influenced by the origin of products and discriminate products imported from other Member States vis-à-vis domestic products. Some Member States have even used their price control or reimbursement system to favour inward investment (typically, the price of medicinal products is not approved or reimbursement is not granted, unless the manufacturer undertakes to invest on the national territory). Such practices are, of course, contrary to Article 30 of the EC Treaty, and are challenged by the Commission each time they are brought to its attention.

Council Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems undoubtedly improved the transparency of national measures relating to the pricing and the reimbursement of medicinal products. This Directive lays down the transparency rules that Member States must conform to in this field, by establishing that national measures shall be based on objective and verifiable criteria and that all individual decisions shall be duly motivated. However, despite the fact that all Member States have taken the necessary steps to formally implement this Directive, the current situation remains unsatisfactory at times. Further progress should be accomplished over the next years in the framework of an improved co-operation between Member States, in particular within the Committee instituted by the Directive. This Committee constitutes an important forum for discussion and exchange of information in this field.

3. *Wholesale distribution, classification and advertising of medicines*

The Community has no intention to intervene directly in the fixing of intermediaries' margins, the structure of distribution channels, or the exercise of the pharmacists' professional monopoly, so long as these comply with the E.C. Treaty. However, two Council directives, which have just come into force, will help to approximate and rationalize distribution practices and some of the rules governing the supply of medicinal products to the public.

Firstly, Council Directive 92/25/EEC on the wholesale distribution of medicinal products for human use will facilitate and stimulate intra-Community trade whilst ensuring the integrity of the transactions involved. In particular, it lays down rules for the recall from the market of defective products, and principles of good distribution practice which should make it easier to detect counterfeit medicinal products.

Secondly, Council Directive 92/26/EEC on classification for the supply of medicinal products for human use harmonises classification criteria for medicinal products which may be obtained only on medical prescription. EC citizens travelling within the Community still encounter marked differences in rules governing their access to medicinal products, and the costly visit to a prescribing doctor required in one Member State may appear unjustified if no such visit is required in the next.

After intensive consultations with European organizations representing the industry, consumers, and health professionals, the Community has taken a series of measures to improve information for the proper use of medicinal products, both to protect patients and to limit the cost of consumption by preventing waste. On the one hand, Council Directive 92/27/EEC, on the labelling of medicinal products for human use and on package leaflets, aims to ensure that patient information is as legible, comprehensive and comprehensible as possible. On the other hand, Council Directive 92/28/EEC on the advertising of medicinal products, lays down rules governing the advertising of these products to the general public, including television and cross-frontier advertising, and requirements to be met by promotional activities directed at prescribing doctors and other health professionals.

All the relevant EC rules, as laid down in several regulations and directives, standard format for authorization applications, good clinical practice guidelines, guide to good manufacturing practice, etc, were brought together in an informal compilation entitled "The Rules Governing Medicinal Products for Human Use in the European Community" (published in several volumes by the EC Official Publications Office). The Commission will soon start working on a complete recast of the EC pharmaceutical legislation with a view to making it more transparent and accessible to all interested parties.

B) A better protection for therapeutic innovation and intellectual property

The research-based pharmaceutical industry has an obvious interest in the quality of protection afforded by industrial property rights to new medicinal products in the Community and in third countries.

In theory, patents granted under the Munich Convention, to which all EC Member States are party, afford 20 years' protection, which runs from the date the patent application is filed. In practice, by the time a medicinal product has been developed and a marketing authorisation obtained, only 8-10 years' protection remain.

To remedy this anomaly, the Council adopted Regulation (EEC) 1768/92, creating a supplementary protection certificate for medicinal products to provide up to 15 years' protection from the date of the first marketing authorisation in the Community. This gave the European industry better protection, similar to that obtained in the USA in 1984 and Japan in 1986.

The European industry has long been drawing the attention of the authorities to the need for providing better legal protection for biotechnological inventions.

As early as 1986, the Community adopted specific provisions (Directive 87/21/EEC) stipulating that a minimum period must elapse between the grant of the first marketing authorisation for a new medicinal product (requiring comprehensive trials to prove quality, safety and efficacy) and the filing of a second (abridged) application for the authorisation of a generic copy of this product. This special clause, providing 10 years protection without prejudice to patent rights, was confirmed by the Council at the time of adoption of the future marketing authorisation for human and veterinary medicinal products.

In 1992, the Commission has submitted to the Council a proposal for a directive on the legal protection of biotechnological inventions, the revised version of which takes account of certain ethical questions raised by the Parliament. The Council adopted a common position on this

text on 7 February 1994, which suggest that the text will be definitely adopted by Parliament and Council sometime in 1994.

However necessary, the protection of therapeutic innovation alone will not suffice to establish an adequate environment for biotechnological R&D.

C) A stable and safe environment for biotechnology

In its *White Paper - Growth, Competitivity, Employment* the Commission stressed the importance of the biotechnological challenge for the Community. It identified the key factors that may jeopardise the expansion of applications in those sectors based upon biotechnology. It also indicated the necessary steps needed to promote the competitiveness of the biotechnological industry on the one hand, and to ensure the correct application of biotechnology on the other hand.

Among unfavourable factors, the first one to note is the shortfall in R&D funding in the Community, which lags behind similar expenditures in competing countries, and the fact that this shortfall has not been compensated by privately financed research and development on biotechnology in the Community. It is obvious that public concerns regarding diffusion of biotechnology are in general more pronounced in the Community than in the USA.

Investment in biotechnology should increase, focusing on the most vigorous biotechnology R&D domains, and co-operation between the Community and Member States should improve in order to avoid duplication. Moreover, it will be necessary to bring greater attention to ethical questions associated with certain applications of biotechnology and to enhance public understanding about it. In view of this, the Commission set up a Group of Advisers on Ethical Implications of Biotechnology.

In general, the Community should be open to review its regulatory framework applicable to biotechnology in the light of advances in scientific knowledge, in order to ensure that regulatory oversight is based on potential risks and to bring Community regulations closer in line with international trends. With a view to facilitating the diffusion of these new technologies whilst maintaining a high level of protection of health and the environment, it is important to pool the existing expertise of the Member States in order to accelerate the implementation of legislation, to make it more effective and as necessary, to adapt it. The Commission regularly reviews the legislation relating to advances in biotechnology. It is in this context that it is currently studying the means of adapting and simplifying Directives 90/219/EEC and 90/220/EEC concerning respectively, the contained use of genetically modified micro-organisms, and the deliberate release into the environment of genetically modified organisms.

This applies in particular in the pharmaceutical sector, which is one of the first fields of application of biotechnology. The localisation of fundamental research, of laboratory experimentation and of testing very often decides the localisation of production.

In 1986, the Council adopted, on the Commission's proposal, a series of Directives for high technology medicinal products, and in particular those derived from biotechnology. Since July 1987, when Council Directive 87/22/EEC introduced a procedure for EC-wide "concertation" prior to any national decision on one of these products, every marketing authorisation application has been examined jointly by all the Member States. The Committee for Proprietary Medicinal Products has evaluated about 50 innovative medicinal products,

including human insulin, synthetic growth hormone, erythropoietin, coagulation factor VIII, hepatitis B vaccine, interferons, anti-AIDS products, etc. The Committee for Veterinary Medicinal Products has evaluated a dozen new biotechnology veterinary vaccines.

To help companies to determine the profiles of their clinical trials, the Commission, after consulting the above two committees and their working parties on pharmaceutical biotechnology and veterinary immunology, published a series of manufacturing and quality control guidelines for these new products. Under the future marketing authorisation system, these medicinal products will automatically be eligible for centralised authorisation, valid throughout the Community. For those (rare) medicinal products which contain genetically modified organisms, the Council has decided, as the Commission wished, to introduce a single evaluation procedure, to be performed by the European Agency for the Evaluation of Medicinal Products, in liaison with the bodies set up by the Community or the Member States.

The pharmaceutical industry has many years' experience of handling, under stringent safety conditions, the pathological micro-organisms which are used to manufacture vaccines for the diseases that they cause. New biotechnological techniques may offer greater safety, and everyone wants the first effective vaccines for AIDS and other unbeaten diseases to be developed as quickly as possible. Another promising line of research for the coming years is genetic therapy to combat serious hereditary diseases, such as cystic fibrosis.

D) Programmes better suited to pharmaceutical R&D

One of the major hindrances to the efficiency of research is its fragmentation among universities and institutes (which tend to organise their work along national lines). This makes it difficult for companies to exploit their results. This scattering and lack of co-ordination of scientific research potential is prejudicial to scientific progress. The remedy is to encourage multi- and inter-disciplinary research and industry/university interaction, in particular by exchanging researchers, as a means of diffusing scientific knowledge.

In the pharmaceutical field, it is often difficult to dissociate pre-normative research from research and development. The Community's draft proposal for a Council decision concerning the fourth framework programme of EC activities in the field of research, technological development and demonstration (1994-1998) seeks to tackle this specific problem by promoting integration and co-operation in R&D efforts.

Furthermore, to allow a better structured pharmaceutical research within the Fourth framework programme (1994-1998), a series of pilot projects was launched in 1992-93 (*Life Science specific programme)*, the aim of which was to evolve research priorities in fields such as the development of *in vitro* evaluation models, the study of methodological bases for the surveillance of adverse effects of medicinal products (pharmacovigilance), the exploration of new therapeutic approaches, and the setting up of EC-wide networks for clinical trials.

The success of these pilot projects, and the example of what is happening in the USA, have inspired plans for more intensive Community action to develop the scientific and technical bases needed to evaluate new medicinal products.

The domain of research on "biomedicine and health" also aims to promote work on preventive medicines (e.g. vaccines) and rare diseases (*orphan drugs*), research into which may not be commercially viable. It will take into account the needs of the functioning of the internal market and of the setting up of the European Agency for the Evaluation of Medicinal

Products. Besides direct scientific support, training schemes could be established to upgrade the general scientific and technical skills of Agency staff and national experts evaluating medicinal products on the Agency's behalf.

E) Towards a more competitive pharmaceutical market

The pharmaceutical market is not a normal market. Companies channel competitive efforts into therapeutic innovation and continued improvements to existing products. Competition between companies focuses on therapeutic innovation. Promotion activities with health professionals play a key role. Enterprises are therefore often less concerned about competing on prices, and rather concentrate on their costs, finances and sales volumes.

Moreover, some Member States operate a price control system for reimbursed medicinal products, indeed even for non-reimbursed medicines. The Commission is prepared to address with the Member States the impact of direct price control on competition and the management of health expenditure. In the case of medicinal products which are available without prescription, and which are not eligible for reimbursement by social security, it seems that, in some Member States, the market is often competitive enough to ensure an affordable price level.

In the case of reimbursed medicinal products, it could be interesting to consider other cost containment measures. Such methods would be based on competition between undertakings for those therapeutic categories where several treatments are available.

From this point of view, the launching of new truly innovative medicinal products, which bring about a significant therapeutic breakthrough, to the extent that they almost represent a new therapeutic category on their own, raises a serious problem which the Danish authorities have recently brought to the attention of the Council and the Commission. This concern is obviously shared by other Member States. The point is that Member States should not be forced to accept excessive pricing of medicinal products which are not subject to competition, whilst ensuring that the pharmaceutical industry maintains its financial capacity necessary to support its R&D activities. The Commission is examining this problem in close co-operation with the competent authorities of the Members States, notably within the Committee instituted by Directive 89/105/EEC.

It is, of course, for each Member State to appreciate, in the light of the specificity of its own system, which measures are most likely to increase competition without jeopardising the financial balance of social security budgets. This problem could be the subject of co-operation between Member States and, indeed, of discussions at Community level.

F) A more transparent pharmaceutical market

If there is little competition in the pharmaceutical market, it is probably because there is also little transparency. Social security institutions, health professionals and consumers do not benefit from sufficient information, both therapeutic and socio-economic, on the various medicinal products which are available. The pharmaceutical industry has now grasped the need to open a dialogue not only with health professionals and patients, but also with politicians and the general public with a view to contributing to reforms in process.

For its own part, the Community already took several initiatives towards more transparency on the pharmaceutical market.

Firstly, the adoption of the new Community procedures in respect of the marketing authorisation of medicinal products, co-ordinated by the European Agency for the evaluation of medicinal products, will in due course reduce the great diversity which can still be observed with regard to various characteristics of medicinal products: different information about therapeutic indications, posology, side effects, presentation and package size specific to each market, differences in legal status, etc.

Secondly, several Council Directives have recently been implemented by Member States. Directive 92/27/EEC concerning the labelling and the leaflet of medicinal products substantially reinforces the relevant requirements concerning information conveyed to users and patients. Directive 92/28/EEC strictly regulates advertising of medicinal products to the general public, promotion with health professionals (medical representatives, doctors' participation in conferences and meetings organised by the pharmaceutical industry for promotional purpose, distribution of free samples), and further prohibits all incentives to prescribe or to dispense medicinal products. These two Directives make it compulsory to mention, in all communication about the medicinal product, the common designation (generic name) of the product. Directive 92/26/EEC lays down common criteria for the classification of medicinal products (products available on prescription only, and products available without prescription).

Much has still to be done, especially at national level, as regards the information for public authorities, health professionals and consumers about the cost of the various treatments which are available. The Commission, for its part, is endeavouring to develop in close co-operation with Member States a European data bank on medicinal products (ECPHIN - European Community Pharmaceutical Products Information Network), which is to include, besides information of a therapeutic nature, useful socio-economic information such as: price of the medicinal products, cost of the treatment, eligibility for reimbursement, prescription only or non-prescription). The dissemination of this information, which should ultimately be available for all health professionals and citizens throughout the Community, will be greatly facilitated by the development of telematic networks, notably by allowing interactive access to ECPHIN.

In this context it is worth indicating that the Commission is currently considering the modalities of using telematic networks for the exchange of information between Member States, the Commission and the future European Agency for the evaluation of medicinal products, in the fields of monitoring side-effects to medicinal products (pharmacovigilance), scientific co-operation and evaluation of medicinal products.

Lastly, the same medicinal product is often sold throughout the Community under different package sizes (number of units per pack). This complicates wholesale distribution and price comparisons, and is likely to constitute a hindrance for the free movement of products. Normalisation is probably the best way of tackling this problem.

G) Better use of medicinal products

Greater transparency of the pharmaceutical market should benefit social security bodies, health insurance funds, doctors, pharmacists, consumers. It could lead to a more rational use of medicinal products and, ultimately, contribute to cost containment. Generally, awareness of the price of medicinal products whether by the health professional or the patient is insufficient. The decision to prescribe one product or another is often neglects socio-economic aspects.

Efforts to improve transparency will favour multi-source competition (between different uppliers of the same product containing the same active substance). Such efforts have been made by some Member States in two ways: promotion of parallel imports and of the use of generic medicines. Parallel imports proliferate wherever prices differ substantially between national markets. The Court of Justice has on many occasions ruled that parallel imports are legal, irrespective of the factors that determine price differences. Various actions from pharmaceutical enterprises, such as resorting to different brand names for different markets, as well as State measures can substantially detract from parallel imports. Competition rules (Articles 85 and 86 EC) and provisions relating to the free movement of goods (Articles 30 and 36 EC) allow the Commission to tackle these problems.

Obviously, generic competition only arises when intellectual property protection conferred by the patent and, as the case may be, by the supplementary protection certificate, is exhausted.. Whenever doctors and pharmacists are better informed about the cost of the various treatments which are available, they can select the treatment offering the required therapeutic benefit which is less expensive for society. Thus, prescribing doctors, if better informed about the cost/efficacy ratio of medicinal products will tend to prescribe generically. Pharmacists will tend to deliver the product offering the best value, if the prescription allows it.

Such measures should be supported by a significant effort in terms of health education of the population. Member States have developed numerous health campaigns, general or specific, in this field. If needed, these campaigns could be intensified or co-ordinated at Community level.

H) A better access to third country markets

In all industrialised countries, the pharmaceutical industry is amongst the most stringently regulated and controlled. This also explains that access to third country markets is not easy. The Community, as the world's leading producer and exporter of medicinal products, has taken several international trade initiatives in order to favour exports.

Within GATT, the Community has advocated the "zero-zero" option, i.e. the total abolition of customs duties on pharmaceutical trade; hence, as a net exporter of medicinal products, the Community will benefit from the conclusion of the Uruguay Round, where this option was upheld. The part of the Agreement relating to TRIPS (Trade-Related Intellectual Property Rights) was also supported by the Community, which regularly leads bilateral initiatives to combat the counterfeiting of medicinal products in certain third countries.

The Community's success in harmonising pharmaceutical regulations has enabled it to take the initiative of progressively harmonising regulatory requirements with the USA and Japan. At the first International Conference on Harmonisation (ICH1) held in Brussels in November 1991, a trilateral programme of harmonisation, spread over 5 years, was adopted. Further progress was made at the second conference (ICH2) in Orlando, in November 1993. Eventually this work should eliminate unnecessary duplication of tests on human beings and on animals, which should also help to reduce global research costs. A third conference (ICH3), is foreseen in Yokohama, in November 1995. It is already the subject of intense scientific consultations between the Commission, supported by experts from the Member States and from the European industry, the US Food and Drug Administration and the Japanese Ministry of Health and Welfare.

The Community marketing authorisation, after evaluation of the medicinal product by the European Agency, will furthermore supply European firms with a prestigious label which should allow them easier access to other important external markets, notably the USA and Japan.

The EC harmonisation process has had a significant impact on our EFTA neighbours, through the agreement on the European Economic Area. Regular scientific consultations have enabled an easy adoption of the pharmaceutical *acquis communautaire*. East and Central European countries should one day be able to do likewise, and have already begun to adopt EC-approved good manufacturing practices. The Community is soon to join the European Pharmacopoeia Convention, which provides an ideal framework for co-operation with all these countries.

The Community also actively promotes bilateral contacts in order to reduce unjustified barriers to trade to pharmaceutical exchanges with its principal trade partners.

Conclusion

The European pharmaceutical industry needs a better integrated EC-wide market with more open competition to enable it to regain its competitiveness and remain a world player.

The legitimate concern to limit public expenditure must not be allowed to jeopardise the future of pharmaceutical research in Europe. Public health and social security have nothing to gain from a weakening of the European pharmaceutical industry, because a substantial share of pharmaceutical spending will continue to have to be reimbursed in any event, even if innovative activity is pursued in the United States and Japan in the future.

The Commission, for its part, intends to intensify the dialogue already initiated in the pharmaceutical field with the Member States along the following lines:

- Consolidate and update the body of EC pharmaceutical legislation in a clear, codified form which makes it easy for companies and health professionals to consult, and see that Community legislation is fully and correctly transposed by the Member States;
- Introduce the future marketing authorisation system rapidly, in particular by helping to establish the European Agency for the Evaluation of Medicinal Products, in close consultation with national authorities and interested firms.
- Enforce, and indeed improve, the intellectual property protection granted to genuine innovation in therapies, in order to ensure similar protection to that available in the main competitive markets.
- Create an environment more favourable to biotechnology by the adjustment of the regulatory framework to the needs of research and current international developments.
- Promote the integration and co-ordination of research and development efforts in the pharmaceutical industry - this is moreover one of the priority objectives of the fourth framework programme for research and development in the Community (1994-1998).
- Monitor the impact on the functioning of the internal market of national pharmaceutical pricing and reimbursement measures in order to avoid any discrimination and to ensure transparency, and to assess the need to adapt Directive 89/105/EEC in the light of experience.
- Enhance competition in the pharmaceutical market, by rendering it more transparent and allowing generic medicines to stimulate competition on price.
- Provide health professionals and consumers with the necessary information so as to promote the rational use of medicinal products, notably through the harmonisation of labelling and patient leaflets, and the setting up of an computerised data bank on medicinal products, access to which should eventually be opened to the general public (ECPHIN).
- Pursue and intensify harmonisation work, across the Community and world-wide (ICH), to reduce the cost of research and development in the pharmaceutical sector and facilitate the access to external markets of medicinal products manufactured in the Community.

Annexes

I - The rules governing medicinal products in the European Community

II - Main economic indicators

III - Investment in research and development

IV - Trade balance of the Community in the pharmaceutical sector

V - Geographical origin of new medicinal products

VI - Employment in the Community pharmaceutical industry

VII - Price control, reimbursement and co-payment in the Member States

VIII - Average prices for pharmaceuticals in the Member States

IX - Self-medication share of the pharmaceutical market

X - Composition of price of medicinal products

Annex I

The rules governing medicinal products in the European Community

Volume I: *The rules governing medicinal products for human use in the European Community (Catalogue N°: CO-71-91-631-EN-C)*

Volume II: *Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community (Catalogue N°: CB-55-89-293-EN-C)*

Volume III: *Guidelines on the quality, safety and efficacy of medicinal products for human use (Catalogue N°: CB-55-89-843-EN-C)*

Addendum N° 1*, July 1990 (Catalogue N°: CB-59-90-936-EN-C)*

Addendum N° 2*, May 1992 (Catalogue N°: CO-75-92-558-EN-C)*

Volume IV: *Good Manufacturing Practice for medicinal products (Catalogue N°: C0-71-91-760-EN-C)*

Volume V: *Veterinary Medicinal Products (Catalogue N°: C0-77-92-384-EN-C)*

N.B. These texts, and the official journals cited, are on sale at the:
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2 rue Mercier L-2985 LUXEMBOURG
Tel (352) 49 92 81 Fax (352) 49 00 03

Annex II
Main economic indicators (in current prices)

MILLION ECU	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992
APPARENT CON,SUMPTION	27 311	30 018	33 250	34 922	36 572	39 496	45 492	50 747	55 065	60 943	63 711
PRODUCTION	30 122	32 997	36 679	38766	40 357	43 289	49 460	54 889	59 103	65 324	68 601
EXTRA-EC EXPORTS	4 334	4 799	5 508	6 193	6 246	6 302	6 817	7 621	7 974	9 124	10 559
TRADE BALANCE	2 811	2 979	3 428	3 843	3 785	3 793	3 968	4 143	4 038	4 381	4 889

Member States	Total expenditure on health (as % of GNP)	Medicines ependiture (% health expenditures)	Medicines (% GDP)	Reimbursed medicines (% total)
Belgium	6.3	16.8	1.12	66
Denmark	6.1	11.1	0.66	61
Germany	13.1	15.9	1.40	63
Greece	6.6	31.0	1.90	70
Spain	5.3	14.3	0.76	61
France	8.2	17.1	1.40	64
Ireland	6.6	07.7	0.50	75
Italy	5.2	17.9	0.93	69
Luxembourg				
Netherlands	9.9	07.7	0.76	68
Portugal	3.7	30.7	0.67	62
United Kingdom	6.7	11.6	0.80	78

Annex III

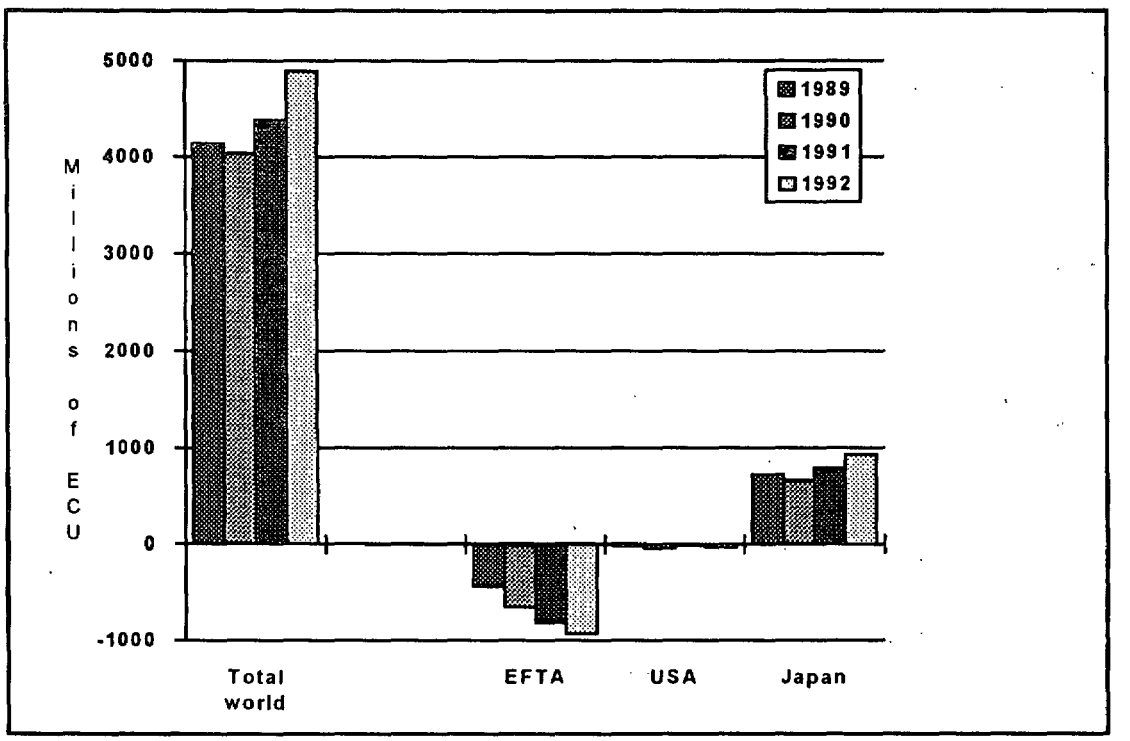
Investment in research and development as a percentage of production (per Member State)

	PRODUCTION MILLIONS ECU	R&D SPENDING MILLIONS ECU	R&D SPENDING % PRODUCTION
EC	**62185**	**6584**	**10.6**
Belgium	1718	206	11.2
Denmark	1086	173	15.9
Spain	5560	191	3.4
France	13343	1578	11.8
Greece	456	-	-
Ireland	792	-	-
Italy	11111	1008	9.1
Netherlands	1568	221	14.1
Portugal	686	-	-
Germany	15085	1471	9.8
UK	10780	1786	16.6

Source : EFPIA 1991

Annex IV

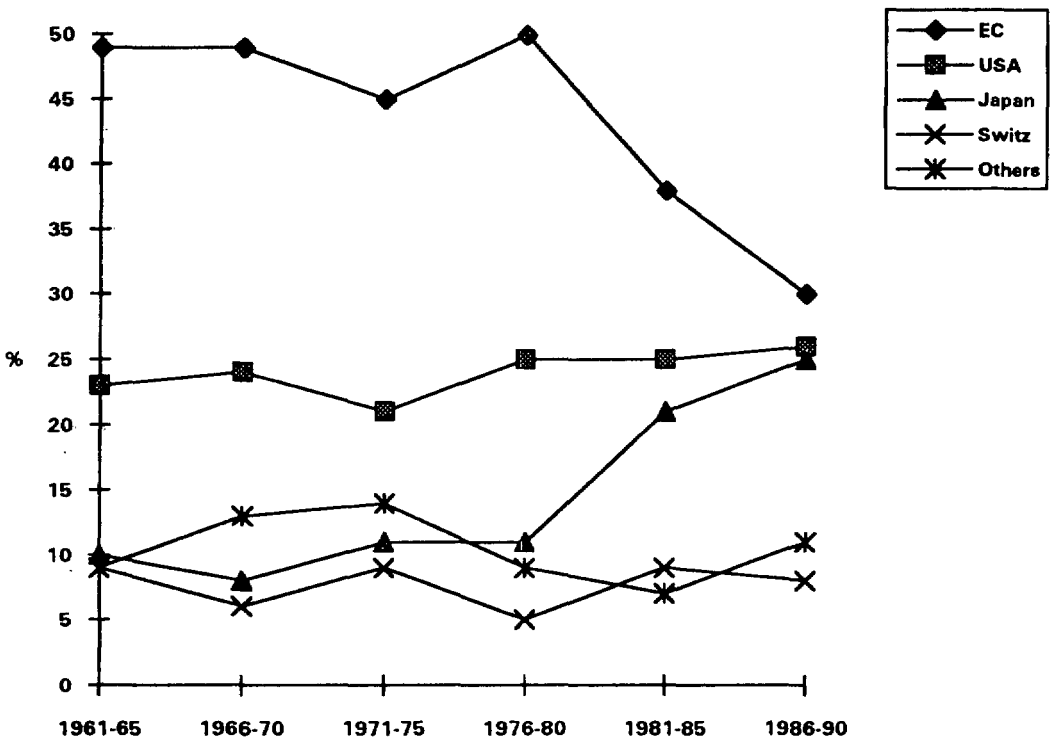
Trade balance of the Community for pharmaceuticals



Source: Eurostat

Annex V

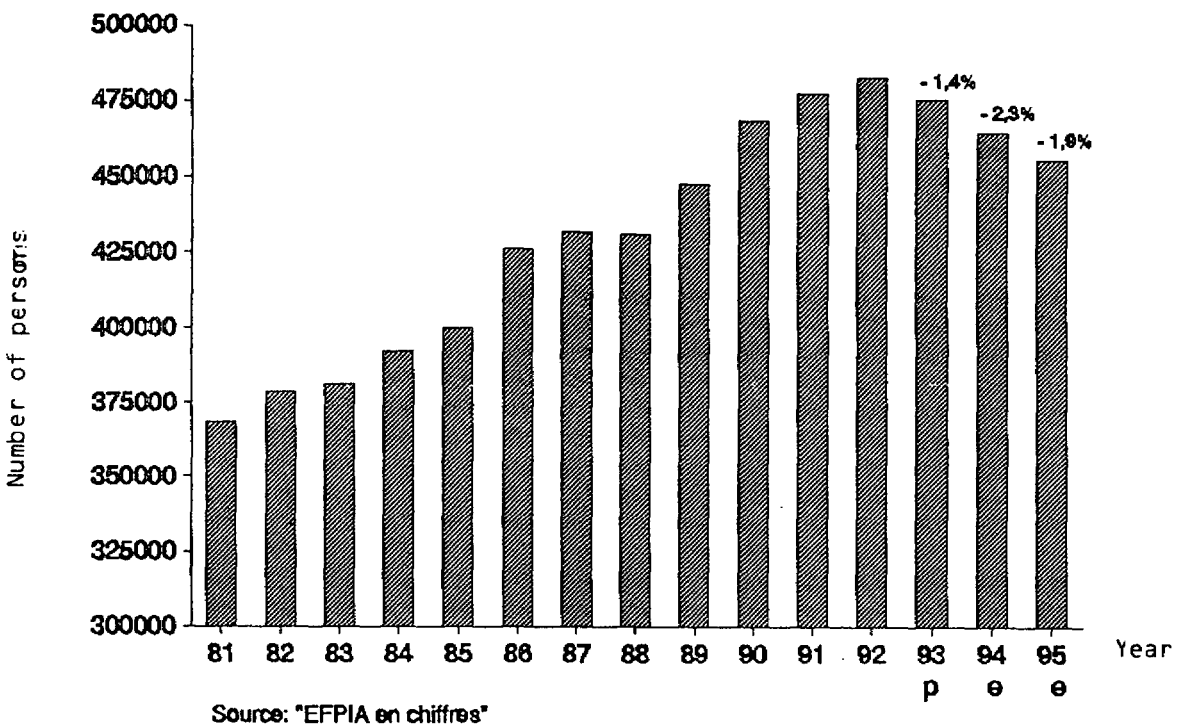
Geographical origin of new medicines (1961-1990)



Source: Reis Arndt, Neue pharmazeutische Wirkstoffe 1961-1990) Pharm. Ind. N 56, Nr 1 1993

Annex VI

Employment in the Community pharmaceutical industry (1981-1995)



Source: "EFPIA en chiffres"

Annex VII

Price control, reimbursement and co-payment in the Member States

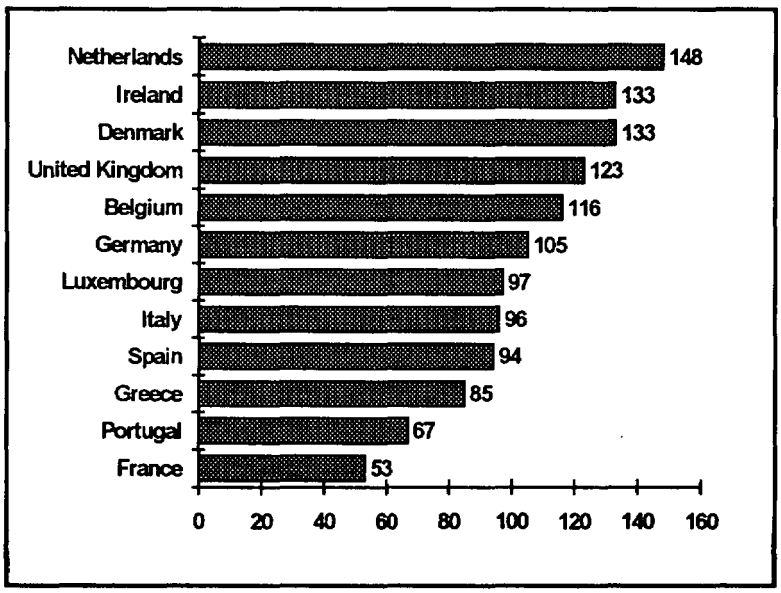
Member State	Pricings	Reimbursement	Co-payment (1)
Belgium	Price control	Positive list	25 - 50 - 60 - 80 %
Denmark	Price freedom	Reference price	(2)
Germany	Price freedom	Reference price	(2)
Greece	Price control	Positive list	10 or 25 %
Spain	Price control	Positive list + negative list	10 or 40 %
France	Price control	Positive list	35 or 65 %
Ireland	Price freedom + agreement with industry	Positive list	(3)
Italy	Price monitoring +reference to average EC price	Positive list	50 % or Lit 5000
Luxembourg	Price may not exceed price in the country of origin	Negative list	20 %
Netherlands	Price freedom	Reference prices	(2)
Portugal	Price control	Positive list	30 - 60 %
UK	Price freedom + profit control	Selected list	£ 3.75 per item

Co-payment : (1) In alll countries, derogations are provided for social or therapeutic purpose.
(2) In reference price systems, the part of the price which exceeds the reference price is tantamount to a co-payment..
(3) No co-payment for the lower income group (approximately 37% of the population), other patients pay a maximum of £ 90 per calendar quarter for their prescribed medecines with any excess expenditure over that amount being refunded to the patient by the health service.

Source : Report on the measures taken by the Member States for the impàlementation of Directive 89/105/EEC

Annex VIII

Average prices in the Member States (EC = 100)



Source : ABDA (Situation 1.1.93)

Annex IX

Self-medication share of the pharmaceutical market

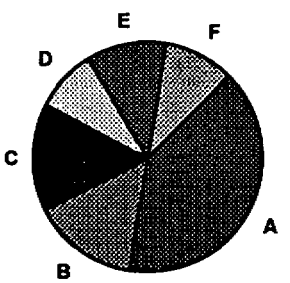
Total market share (%)
at public price level

	1988	1989	1990	1991	1992
Belgium	18	18	19	18	17
Germany	16	16	17	16	15
Spain	11	11	12	11	11
France	19	20	20	18	17
Italy	9	9	9	8	8
Netherlands	9	10	10	11	10
United Kingdom	13	14	13	13	12

Source : AESGP/IMS (1993)

Annex X

Composition of price of medicinal product in the Member States (share of the manufacturer)



A - Manufacturing	40 %
B - R&D and licences	15 %
C - Medical information and advertising	15 %
D - Distribution	9 %
E - Administration	11 %
F - Benefit and risk covering	10 %

Source : PharmaInformation

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