# EUROPEAN PHARMACEUTICAL POLICIES

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# PREFACE

The following publication is a summary of key policies toward pharmaceuticals in three European countries, Britain, France and West Germany, in 1989. Four key policy areas are covered: pricing and reimbursement, registration, research and development and patents.

Some reference is made to pharmaceutical policies in other European countries where this is thought to be particularly relevant or illuminating.

The paper does not pretend to be comprehensive, for reasons both of length and availability of information. It provides an overview of key policies and may be regarded as a primer for non-experts.

Policies, particularly those relating to the European Community, are in a state of flux. This document does not therefore attempt to give an up-to-the-minute picture of policy development but rather the general background. It is intended as a guide to policy-makers in this important and complex area.

CONTENTS

# 1. PRICING AND REIMBURSEMENT

## Introduction

State funding of pharmaceuticals is an important factor in European countries, ranging from around 50 percent of total funding (Belgium, Denmark, Greece and Ireland), through to around 65 percent (France, Italy, Netherlands, Portugal) with the UK accounting for the highest state funding, 76 percent of the national bill for drugs. In most European countries the state is by far the largest buyer of pharmaceuticals. This high level of state funding is of course related to the major involvement of the state in European healthcare systems, and 80 percent of pharmaceutical expenditure in the EEC is on prescription products.

The high level of state funding of pharmaceuticals means that pricing and reimbursement by government are intimately linked in all European countries. Governments which pay over 50 percent of the national drug bill set prices and reimbursement levels or control profits with a view to achieving their own political objectives. This often means balancing what they can afford to pay with what in some countries at least see to be the need to maintain a productive local pharmaceutical industry.

Generally speaking, there are four different pricing systems for new products:

1. cost-plus - the price is based, product-by-product, on the costs of production, e.g. in Greece, and (until recently) Italy;

2. internal reference - the price is based on the price level of comparable products already on the market with an added premium for the research content of innovative products with therapeutic advantages, e.g. in France and (from 1989) Italy;

3. international comparison - the price is based, product-by-product, on that pertaining in other countries, e.g. Spain; and

4. profit control - the manufacturer is allowed freedom to price individual products while his overall profitability is controlled, e.g. Britain.

Only in Denmark, and West Germany, is the manufacturer relatively free to set prices without Government interference. Total expenditure is still limited by pressure on doctors to economise, and management of reimbursement.

An industry's ability to fund research and development (R & D) expenditure depends to a large extent on the prices it can get for its products. But low prices are not the only factor. Countries with low prices often have high volumes of sales, which ameliorates the situation to some extent. [See table 1.2].

Price to the patient is of course important. That is why countries with low prescription charges often have high consumption. Consumption is also influenced by prescribing practices, which vary greatly from country to country. According to the Dutch "Pharma Facts 1987" the number of GP/specialist consultations after which no prescription was written varies from 45 percent in the Netherlands, 28 percent in the UK, 21 percent in Spain, 7 percent in Belgium, to 4 percent in Italy. (No data is available for Germany). The reasons for these prescribing differences are various and include pricing, reimbursement and doctor's remuneration, as well as cultural differences that are more difficult to quantify.

Pricing is one influence on generic penetration, which differs greatly throughout Europe. Generally speaking, it is highest where prices are high, constituting 20 percent (by value of the prescription market) in Denmark, 9 percent in Britain, 8 percent in Germany and the Netherlands, but reducing to 1 to 2 percent in France, Italy and Spain. In Belgium it is more-or-less nonexistent. Generic substitution has not yet been legalised in any EEC country.

# PRICING AND REIMBURSEMENT: UNITED KINGDOM

## The healthcare system

Britain has a centrally tax-funded National Health Service, wholly controlled by the national government. Britain now spends a little over six per cent of GDP on healthcare, one of the lowest proportions in Europe.

With the exception of a few minor charges, the NHS is free at the point of use to the consumer. Resources tend to be rationed by queue instead of price, and there are long waiting lists for many operations and other medical services.

## Drug policies

Most drugs are paid for by the government through the National Health Service (NHS). The NHS is by far the UK pharmaceutical industry's largest purchaser. In 1985 the NHS absorbed 45% of the industry's gross output, 33% was absorbed by exports, 10% by household medicines, and 10% other, (including inter-company trading, costs of services rendered, veterinary products, etc.).

The patient pays a contribution of £2.60 towards the cost of the drug unless he or she is exempt from this charge or has purchased a 'season ticket', (a four-month or one-year pre-payment certificate). In fact about 75% of UK prescriptions are exempt. Exempt groups include all pensioners, all those under 18, young people under 19 in full-time education and pregnant women. The average cost of an NHS prescription was estimated in 1988 to be £5.55.

The cost of medicines in England to the DHSS in 1986/7 was given as £1,787 million, only £145 million (8%) of which was recouped through prescription charges.

In fact the cost of some drugs is below the £2.60 prescription charge. In 1987 the pharmacists body, the National Pharmaceutical Association, issued a list of commonly prescribed medicines which could be bought over-the-counter at less than the £2.60 prescription charge. It said that 32% of the 80 million prescriptions paid for in 1987 were for products which cost less than the prescription charge.

Almost 80 per cent of NHS medicines (by value) are distributed via the family practitioner services (FPS), the vast majority being dispensed by community pharmacists.

Under the Pharmaceutical Price Regulation Scheme (PPRS) the government allows innovative pharmaceutical companies to set their own prices for individual drugs, subject to some negotiation, but limits the overall profitability.

The scheme does not apply to generic manufacturers or producers of OTC products. Profitability is defined in terms of a return on capital on sales made to the NHS. The allowable return on capital has gradually been increased from 15-17 percent in 1984, through 16-18 percent in 1986 up to 17-21 percent in 1987. R & D costs and limited sales promotional expenses are considered prior to overall profit calculations, but capital investment is funded from profits.

The PPRS also enables the government to control the amount companies can spend on promotional activities, by imposing limits related to company turnover. UK promotion costs as a percentage of prescription medicine outlays currently stand at around 9 percent, down from about 14 percent in 1975.

In February 1985 the government introduced a negative list. This removed many brand name drugs for some illnesses from reimbursement and restricted GPs choice in these areas to a small number of generic products. The therapeutic areas involved were vitamins, antacids, laxatives, cough medicines, analgesics, hypnotics and tranquillizers. The target saving of £75 million in England and Wales for the negative list's first year was achieved.

The 1989 Government White Paper on the National Health Service has proposed flexible limits on GPs' prescribing of drugs through 'indicative drug budgets' along with practice budgets for larger practices to increase the accountability of GPs. Regional formularies will also be encouraged, although ostensibly only on an advisory basis.

The declared intention of the indicative drug budgets is to put a downward pressure on the rise of spending on medicines. Local family practitioner committees will have powers to curb 'excessive prescribing.' These new measures, if implemented, would encourage generic prescribing (see below) and where possible cheaper therapeutic alternatives, as well as patiwnt screening by G.P.s. These reforms are being vigorously resisted by the medical profession.

The annual inflation rate for pharmaceutical expenditure in the NHS is about 10 percent and rising. Of this figure, about 2 percent is accounted for by a volume increase, about 6 percent is due to a change in the product mix (i.e, newer, more expensive products replacing older, cheaper ones), and about 2 percent is due to price increases on existing products.

## Policies on generics

Since 1983 the number of FPS prescriptions dispensed in generic form has risen significantly. Generics received a boost from the introduction of the negative list in 1985, which prohibited reimbursement for brand-name products in certain therapeutic areas.

The policy of the Department of Health has been to encourage economic prescribing (which generally means generic prescribing) but to reject the principle of generic substitution, (which involves substituting a generic product for a brand-name product). The policy of indicative drug budgets is also likely to lead to increased generic prescribing.

Government encouragement of economic prescribing has already increased the level of generic prescribing and dispensing from 16 percent of scripts written in 1980 to 30 percent of scripts written in 1988. This trend will be hastened by the introduction of indicative drug budgets.

# PRICING AND REIMBURSEMENT: FRANCE

## The healthcare system

France spends a little over 9 percent of its GDP on healthcare. Most patients are expected to pay for services at the time of use, but can later reclaim some 70 percent of the cost from the national health insurance scheme, part of the social security system. This is financed by contributions of 5.9 per cent of wages for employees and 12.6 per cent for employers. For the 2.8 million people classified as poor, treatment is free, as is treatment for 30 defined 'serious' illnesses, such as cancer.

The overall budget of the social security system is under the control of the Minister of Social Affairs.

The 30 percent of the cost which the national insurance scheme does not cover is topped up, wholly or partly, by the 'Mutuelles,' private non-profit schemes. Their terms and coverage vary, but usually cost about another 2.5 percent of salary. Ordinary private insurance is also available.

The Mutuelles are becoming increasingly popular as the burden of cost passes further onto patients. Whereas they only covered 51 percent of the population in 1970 that proportion had increased to 69 percent by 1980. They are supervised by the state and provide additional benefits such reimbursement of the "ticket" or co-payment for drugs.

Reimbursement by the state and the Mutuelles means that patients have to pay very little, or more usually nothing, for their drugs. Furthermore, there are no limits on the number of doctors a patient may see, or the number of drug prescriptions he may request. This tends to increase drug consumption which is high in France.

Because prices of drugs are low in France the industry has been forced to compensate by increasing sales volumes. Some 18-19% of industry expenditure is devoted to marketing and advertising, which is markedly higher than in many other countries.

It should be noted that a major reform of the French healthcare system is now under discussion.

## Drug policies

Drugs are reimbursed by the state at one of three levels - 100 percent, 70 percent and 40 percent - related to the severity of the disease. Life-saving therapies used to treat 30 specific diseases qualify for 100 percent reimbursement, most other drugs qualify for 70 per cent reimbursement, and drugs which treat minor disorders are 40 percent reimbursed.

Pricing approval is necessary before a drug can be reimbursed at any of these levels. This approval must be obtained from the DPhM, the French Medicines Directorate, after marketing authorisation has been obtained from the Authorising Committee for Marketing Medicines.

The DPhM passes the pricing approval request to the Transparency Commission which reviews the product against one or more reference products and decides whether it offers a therapeutic advantage. The Commission's assessment is based on research effort, improved efficacy, novelty of therapeutic indications, generic form, dosage, suitability of the formulation, length of treatment and expected level of patient part-payment.

An innovative product will be allowed a higher price in order to cover R & D expenditure. However, if a product is judged not to have any therapeutic advantage then it will be added to the reimbursement list only if it is cheaper than its therapeutic equivalents.

In theory products may be launched before the DPhm gives its approval, but in practice sales are so low without reimbursement that this is not worthwhile. The DPhM approval usually takes some 1-2 years.

Price controls were removed from OTC and hospital products in 1985, although not from drugs sold to hospitals. Drugs are increasingly sold by the manufacturer direct to the hospitals, bypassing the wholesalers. This has resulting in falling prices, as competition has intensified.

Manufacturers may seek price increases, specifying their reasons and sending supporting documentation to DPhM, but such applications are rarely granted. Existing products are subject to across-the-board increases but these are also rare. There were no price increases allowed between 1984 and July 1986 when a general rise of 2 percent was given, followed by 1 percent in April 1988. However, companies are sometimes allowed to reprice products within their portfolios, raising the price of successful products and reducing other prices.

Drug prices in France are comparatively lower than most other European countries, although there have been some price rises recently. According to SNIP, the French National Pharmaceutical Union, low drug prices have curbed domestic pharmaceutical research and will hamper the industry's ability to compete in the single European market.

## Policies on generics

Unlike the government, which sees itself has having some responsibility to encourage the French drug industry as well as a need to control cost, the Mutuelles are only concerned with cost. Thus the greater importance of the Mutuelles may result in more generic prescribing. The association of the Mutuelles, Mutualite Francais, has published lists of 50 brand leaders for which one or more cheaper copies exist. However, primarily due to low French drug prices the market for generics is very small.

## Policy evolution

Policy change is unlikely in the short term. In October 1988, Health Minister Claude Evin said that liberalization of drug prices was "excluded in the short or medium term." He told the industry: "your figures and account books are not those of a needy industry."

SNIP, the industry association, is optimistic about policy changes in the medium to longer term. It says that the government (and the main opposition) agree that measures have to be taken to revitalise the French pharmaceutical industry.

SNIP says that a consensus has emerged between the industry and the government that prices will rise but that volumes of sales will have to fall. This may be achieved by reductions in marketing expenditure, by measures to make doctors prescribe more economically, and by freeing the drug price from the social security price.

## PRICING AND REIMBURSEMENT: WEST GERMANY

### The healthcare system

Germany spends a little over eight percent of its GDP on healthcare. Employers and employees divide equally the compulsory health insurance costs of 12 to 14 per cent of salary, with the government topping up the balance. These monies are directed to more than 1,000 sickness funds (Krankenkassen).

About 92% of Germans are enrolled in this national health insurance system. Those earning more than $30,000 a year can opt out and arrange their own private insurance. In practice, less than 10% of the population does opt out.

### Drug policies

Germany has traditionally had higher prices for drugs than other European countries. Drug prices have been determined by the manufacturer without government controls. In 1982 there was a voluntary agreement between manufacturers and the Krankenkassen to restrict price increases. In 1983 a negative list of drugs for which there would be no reimbursement was introduced. Neither of these measures succeeded in reducing the increases in Krankenkasssen expenditure, and the government decided to reform the healthcare system.

The German Healthcare Reform Act came into force on January 1, 1989. The new legislation is being introduced in three phases, the first of which is now in effect and consists of the following main elements:

1. The Labor Ministry establishes limits on how much the Government reimburses the insurance system for off patented drugs. These "reference prices" are maximum allowable reimbursement prices and have lead to a downward spiralling of prices for certain compounds.

2. A doctor's prescription budgets will be monitored. If his prescribing costs are above the regional average he will meet with a review board.

Phase 2 of the reforms, if it is implemented as planned in the early 1990s, will introduce a reference price for products which are chemically related and are pharmacologically and therapeutically comparable. Phase 3 would introduce a reference price for products which are not necessarily chemically related, but which are pharmacologically and therapeutically comparable.

The reform plan was strongly opposed by the German pharmaceutical industry and the US pharmaceutical industry, which succeeeded in amending the original proposals which were even more unfavorable to the innovative pharmaceutical industry.

## Policies on generics

The recent healthcare reform will have the general effect of encouraging generics. The pressure on doctor's prescription budgets will encourage generic substitution, although there are still legal restraints on the introduction of generics, which will slow such a trend.

But the imposition of reference prices will narrow the difference between branded and generic products, reducing the incentive for doctors to prescribe generically, unless the generic companies reduce their prices further. Already there is evidence of a peer pressure problem, with doctors being unwilling to prescribe products for which a reference price has not been set.

## PRICING AND REIMBURSEMENT: OTHER COUNTRIES

In Italy, reimbursement pricing is an integral part of the process of obtaining a marketing authorisation. In Belgium, Greece, Portugal and Spain, as in France, a new product is only allowed to be reimbursed by the government when a price and reimbursement price has been agreed between the manufacturer and the government.

Current spending by patients towards drug costs in Italy is around 20 percent, and 1989 government proposals envisage this rising to 40 percent, with only a restricted list of essential drugs remaining fully reimbursable. Drug prices in Italy are held low.

Spanish pharmaceutical prices are among the lowest in Europe and imports only account for 2 percent of the market. This results from the Spanish government's policy of awarding prices which are equal to or lower than the lowest price for the same or similar product in the rest of Europe; the only exception being products which have originated from domestic research.

The Spanish policy may be summarised as one of taking advantage of innovative research in other parts of the world without contributing anything to its costs.

Domestic pricing arrangements in Switzerland are much less important for the Swiss pharmaceutical industry because of the limited size of the domestic market and the much greater importance of world markets. (Ciba-Geigy, Roche and Sandoz obtain 95 percent of their turnover from outside Switzerland). Price changes are permitted once every two years. The Swiss Association for the Chemical Industry (the SGCI), reports that steady volume growth has enabled companies to offset the very limited price rises permitted. Profitability has worsened, with price trends failing to keep pace with inflation. Only intensive efforts in export markets and steady rationalization have enabled Swiss firms to continue to achieve good results.

One effect of adverse policy changes in Europe for the European pharmaceutical industry is to encourage European companies to focus on other markets. For example, the three major Swiss companies, Ciba-Geigy, Hoffman-LaRoche and Sandoz, are concentrating much more on expanding their US operations, which account in each case for about a third of their business. In 1985, the introduction of a limited list of medicines by the British government cut Hoffmann-LaRoche's UK business by about 60%.

The development of a unified European market after 1992 will have significant effects on pharmaceutical pricing. The removal of all barriers to cross-barrier trade in pharmaceuticals within the EEC leaves more room for parallel importers to exploit the significant price differences between markets. A study by Shearson Lehman Hutton Securities has predicted that this could result in the "exportation" of price controls from low priced countries to the rest of the EEC. The effect could be a total market shrinkage of 5-10 percent in sales value.

In summary it is clear that the French pricing system is more intrusive than the British. A bureaucratic organisation decides the price of each drug, a process which adds a further one or two years to the time it takes to get a drug on the market.

## 2. REGISTRATION

### Introduction

European countries all have different registration systems and none automatically recognises any other, with the exception of Luxembourg, which does not have evaluation facilities of its own. The difficulty in getting a new drug speedily approved by all EC countries is a central problem in European drug policy.

In 1972 the BENELUX authorities (Belgium, The Netherlands and Luxembourg) established a department for the registration of medicines. In 1978 the choice between the national procedure and the BENELUX procedure was abolished, but the resulting surge in applications led to long delays. However, the Department was dismantled in 1982 partly for economic reasons and partly because of anticipation of progress within the EEC.

The EEC established a multistate procedure in an attempt to speed approvals and move toward a pan-European system. The Committee for Proprietary Medicinal Products (CPMP) was established in order to help the process. The central idea was that once a product has received a full assessment in one member state, it should be possible for other member states to carry through a more limited assessment. A company would apply for authorisation to one of the member states, including with the application three good expert reports summarising the pharmaceutical, pharmaco-toxicological and clinical parts of the dossier.

In considering the application, this first country would undertake a full review and would prepare an assessment report commenting on the first dossier. After authorisation in the first country, a firm would then be able to apply, using the same dossier, for an extension of the authorisation to two or more of the other member states, which would then undertake their assessments on a simplified basis, taking no longer than 120 days. Objections to granting authorisation would only arise in exceptional cases, which would be referred to the CPMP for an opinion, delivered within 60 days.

The CPMP was established with the aim of offering companies accelerated access to an EEC-wide market. (The choice of addressing applications to the regulatory agencies in the individual states remained). The procedure has not been a success.

National registration organisations have been reluctant to give up their authority or even let it be diluted. To date, every application has been referred to the CPMP because one or more of the national authorities has formulated objections.

Once the CPMP has given a favorable opinion, countries still take a long time to grant approval. [See table 2.1]. Its decisions are not binding.

Reforms to the system have made it rather more popular with companies who think that countries with big backlogs may give priority to multistate applications. There were some 80 applications in 1988.

In 1987 the Community established a mechanism wherby the CPMP considers applications for bew biotechnology products prior to their evaluation and grat of a marketing authorisation by a member state. The 1987 EEC legislation introduced a "concertation" proceedure with the intention of reducing differences between the decisions being taken at member state level. The main objective of current EC policy effort is to make CPMP decisions binding on the member states.

REGISTRATION: UNITED KINGDOM

The current statutory framework for drug registration was created by the 1968 Medicines Act. (Before that time the process was voluntary. A Committee on Safety of Drugs, which had no legal powers, operated with the voluntary agreement of the Association of he British Pharmaceutical Industry (ABPI) and Proprietary Association of Great Britain.)

The major features of the current framework are:

(a) A Medicines Commission, which advises Ministers on the execution of the Act and on medicinal products generally. This Commission consists of some 20 members, most of whom have some relevant experience as doctors, veterinary surgeons, pharmacists, etc..

(b) Expert committees, created by Ministers on the advice of the Medicines Commission. These include:

(i) The Committee on Safety of Medicines (CSM) which advises the licensing authority on questions of the safety, quality and efficacy of medicines for human use. This body collects, evaluates and advises on reports of adverse reactions to drugs, and scrutinises before clinical trial and marketing, as well as after marketing.

(ii) The Committee on the Review of Medicines (CRM), established in 1975, which reviews the safety, quality and efficacy of existing products on the British market.

(iii) The British Pharmacopoeia Commission, which prepares future editions of the British Pharmacopoeia containing all the published standards for medicines.

(c) A licensing system which regulates clinical trials, marketing, importation, manufacture and distribution of medicinal products. The Medicines Division of the DHSS acts as the licensing authority, with the CSM advising it on new drugs and the CRM on existing products.

(d) Restrictions on the advertising and promotion of medicinal products.

Companies are obliged to hold a Clinical Trial Certificate before a product can be imported, sold or supplied for a clinical trial. (Studies in volunteers do not require a CTC). The data requirements for obtaining a CTC involve submission of full reports on chemistry and pharmacy, pharmacology, pharmocokinetics, toxicology, and any previous experience in man, as well as details of the proposed trial.

The UK was probably the most demanding country in which to obtain clinical trial approvals, and the increasing delays resulted in mounting criticisms from industry and from departments of clinical pharmocology that the procedure was too rigorous and caused many companies to conduct clinical trials outside the United Kingdom. Lis and Walker (1988) demonstrated that the time between application and approval for a clinical trial certificate increased from less than 3 months under the voluntary system in the 1960s to more than 8 months in the late 1970s.

In response, the Clinical Trial Exemption Scheme (CTX) was introduced in March 1981. Under CTX a company is required only to supply summaries of the necessary data. The licensing authority has 35 days in which to consider the submission and inform the company if it objects to the proposed trial. The authority may request a 28-day extension of this period.

The consequences of the changes have been dramatic. In 1980 (the last full year before the changes were implemented), only 87 CTCs were granted. But in the first 12 months of operation of the CTX scheme 258 applications were made, of which 233 were approved, 8 refused and the rest were under consideration. During the same period 15 applications for CTCs were received. Although the vast majority of companies now use the CTX scheme, some companies still apply for CTCs either if their CTX application is rejected, or if they wish the benefit of a review by the CSM at an early stage in the development of a product.

Griffin and Speirs (1983) demonstrated that the number of NCEs submitted for clinical evaluation increased two-fold in the first year of operation of the CTX scheme compared with the average of the previous three years, and that the scheme operated at no increased hazard to the patients participating in the clinical studies.

However, despite this sharp improvement in the clinical trial procedure, there are still substantial problems with the product license approval part of the system. Lis and Walker (1988) have demonstrated that the delay in the time take to grant a product licence has increased substantially, from 3-6 months in the 1960s to more than 15 months in the early 1980s. By 1987 the delay had lengthened to almost 2 years.

Of the 88 percent of applications received by the Department of Health that require no referral to the CSM (Committee for the Safety of Medicines) 46 percent take longer than 120 days and 29 percent longer than 210 days. The problems is not confined to NCEs. All applications are taking longer than the recommended time for review.

There are a variety reasons for the lengthening of approval times, including increased number and complexity of applications. The Evans-Cunliffe Report, Study of control of Medicines, found that lengthening of approval times was related to outside events, such as withdrawal of medicines, and that fear of making incorrect decisions was an important factor in the delays. The report recommended increased staffing, better pay, and increased use of information technology within the approval process. These measures would raise costs by some 10 percent, which could be met by increasing the registration fees. (Fees and levies on company turnover currently cover some 60 percent of the department's costs. Fees are tax deductible for the companies).

According to Dr J.P. Griffin, Director of the ABPI and former Professional Head of Medicines Division, Department of Health, it is difficult to asses whether the objectives of regulation, namely evaluation of safety, efficacy and quality of new medicinal substances have been achieved, since the regulatory authorities do not regularly undertake self-analysis. Medicines regulations have undoubtedly safeguarded the public, but whether this has been achieved through industry striving to achieve prescribed standards or through regulatory scrutiny is a matter for debate. Dr Griffin points out that in the last few years the regulatory delay in the UK for the bulk of both major and minor applications for marketing has put the UK Licensing Authority in breach of the EC directives.

## REGISTRATION: FRANCE

France is the only country which generally meets the EEC guidelines for an approval procedure which comes to a decision within 210 days. However, subsequent delays in getting the necessary pricing approval can draw out the whole procedure for 1-2 years. (In theory products may be sold without this pricing approval sales of non-reimbursed drugs are so low that in practice it is not worth launching products without it).

The first modern French drug law was enacted in 1946 and provided for a ministerial authorisation for commercialisation, called a "visa". A committee of scientists and interested professionals advised the government on the granting of the visa. In 1959 the system was amended to add a technical analysis of the drug by "experts." The manufacturer chose several experts from lists provided by the Ministry of Public Health. One expert evaluated manufacturing and compounding data, experts in toxicology and clinicians investigated the safety of the drug in man, and clinical experts evaluated the therapeutic interest or value of the medicine.

The expert acts as an intermediary between the manufacturer and the government. He is a sort of third partner in the drug evaluation and approval process, with responsibilities and ethical and scientific authority accepted by both the government and the pharmaceutical industry.

The system was modified again in 1976 when new requirements for clinical data and clinical trials were introduced. The experts were now mandated to actually carry out the clinical trials required by law as well as obtaining data in other ways. The total data, together with the expert's evaluation and opinion, form the basis for marketing approval.

In 1978, Minister of Health Simone Veil created a 'Commission d'autorisation de mise sure le marche,' (CAMM) charged with the task of evaluating preclinical and clinical safety and efficacy in order to advise on whether to issue an 'autorisation de mise sur le marche,' (AMM). CAMM's support staff are drawn from the Office of Pharmacy and Medications of the Ministry of Health. The membership of CAMM is drawn from academic physicians, pharmacists and medical practitioners. A representative of the Syndicat National de l'Industrie Pharmaceutique (SNIP) can attend and speak at CAMM meetings as an observer.

For each drug considered for an AMM there are at least four reports presented to the CAMM plenary meeting. These reports are prepared by independent reviewers or 'rapporteurs' chosen by the administrative staff. These rapporteurs may be "experts" for other drugs in the same field but must not have worked on that particular drug for the applicant company. In 1980 Dr. Legrain,

Chairman of the CAMM, stated that they reviewed 400 applications yearly of which 40 were for new drugs and 10 for NCEs. The approval process is usually carried out within the four month period required by law.

Independent observers have praised the French registration process. Weintraub, (1982), called it "flexible, pragmatic, rapid and independent," and contrasted it with adversarial, legalistic systems operating in countries such as the USA. According to Weintraub, the involvement of industry representatives decreases paranoia, as well as acting as a conduit for education, helping to inform companies of recurrent problems and changing policies.

## REGISTRATION: WEST GERMANY

West Germany, although having the highest prices for pharmaceuticals in Europe, also takes among the longest times of any European country to give a marketing authorisation, primarily due to the inability of the regulatory agency, the BGA, to handle the volume of applications.

Before 1961 the manufacture of drugs was entirely unregulated in Germany. In that year the first Drug Law was passed:

* Proprietary Medicinal Preparations became subject to registration with the Federal Health Office (Bundesgesundheits amt, BGA).

* Manufacture of drugs required permission from the local health authorities.

* Industrial manufacture and commercialisation came under the supervision of the local health authorities.

Nevertheless, registration was still only a formal procedure. The BGA had no authority over the review of a drug's development and documentation and the assessment of its quality, safety and efficacy.

After the EEC passed "Directive 65/65/EEC a revision of the German regulatory system was necessary and a new Drug Law was passed in 1976, (and subsequently amended in 1983 and 1986). The main features of the new law were:

* Preventive control of drugs in terms of quality, safety and efficacy, need for approval by BGA prior to commercialisation;

* Review of "old drugs" (those already on the market) and registration by 1989 on the basis of the new law;

* Protection of man during clinical trials;

* Risk monitoring of approved drugs;

* Supervision of development, clinical trials, manufacture, quality control, import and marketing of pharmaceutical preparations.

Responsibility for these tasks is split between the federal authorities the BGA and the Paul Erlich Institut, both under the supervision of the Ministry of Youth, Family, Women and Health (BMJFFG) and the different German state health authorities.

Unlike that of the U.S. and U.K., the German system does not involve close contact between the company and the government

during the development of a drug. The product has to be developed pharmaceutically, preclinically and clinically according to relevant directives, then a submission is made containing the complete information gathered during the development process.

Clinical trials are not entirely unsupervised, however. There are stringent rules contained in the Drug Law and in federal guidelines. Before a clinical trial can start, the results of the pharmacological and toxicological evaluation must be available for deposition with the BGA. This documentation is not reviewed by the agency but is held for possible use as evidence in the event of severe adverse drug reactions during the trial. In such an event, if the suspicion exists that the person/company responsible for the clinical trial has not adhered to their obligations set out in the law and the guidelines, then the material may be passed to the state attorney for investigation and possible prosecution.

More than 6,000 different pharmaceutical preparations (including different strengths/different galenic forms of the same active) have been approved between 1980 and 1987. Around 600 have been rejected by the BGA and a similar number have been withdrawn by the applicant during the same period.

The BGA is required to complete the entire approval process within 4 months, 7 in "exceptional" cases. The review is done within the BGA by its own pharmaceutical, pharmacological, toxicological and clinical experts. In the case of NCEs an expert commission has to be heard prior to approval. These experts are appointed by the ministry from those put forward by the professional associations of pharmacists, physicians, dentists and the pharmaceutical industry.

In fact, the BGA has not in recent years met the legal requirement to come to a decision within 4 to 7 months. A group of major German companies have recently taken the BGA to court over the lengthy approval delays. BGA officials told the court that applications can now take up to six years to process. There is now a back-up of over 9,000 drug applications at the BGA.

The log-jam has a number of causes, including the number of "old drugs" which have to be approved before the 1990 deadline, and a flood of approval applications for generics before a 1986 revision incorporating EEC directive 87/21/EEC into law.

A legal revision of the 1989 drug law seems likely to ameliorate the situation to some extent. The revision makes it easier for the BGA to use outside experts to ease its caseload and the notification of any significant changes (to indications, for example) is to be restricted to prescription drugs. Drugs on the market before 1978 will simply have to be notified in future instead of requiring new marketing approvals. However, the approval period will become only a guideline and legal actions will no longer be possible.

## REGISTRATION: OTHER COUNTRIES

Switzerland was one of the first countries to enact a system of drug regulation, establishing in 1900 the Interkantonale Kontrollstelle fur Heilmittel (IKS). The IKS is authorised to assess new therapeutic agents prior to marketing and to notify local government units responsible for healthcare of its conclusions regarding composition, advertising and price, as well as its decision regarding approval or denial of authorization for sale. The Swiss system of drug approval is noted for its simplicity and absence of detailed specifications and requirements. Burrell (1980) has commented upon the remarkable feature of the high level of co-operation between the IKS and the industry.

Sweden, Norway and Denmark regulate drugs more strictly than most other countries. Sweden keeps the number of approved drugs on the market small through strict approval requirements. It has an approved list of only about 2500 to 3000 drugs. Some drugs are licensed only for use in hospitals, others with highly specified use receive licenses for distribution only to a very limited number of people.

The Swedish Department of Drugs is organised within the National Board of Health and Welfare but acts largely as a separate body. The Department is almost wholly financed by fees paid by the pharmaceutical industry. In recent years the Department has made efforts to shorten the processing times of applications for registration, but at the same time the number of applications has increased. Delays are still a problem. According to Roland Olson, Director of the Swedish Pharmaceutical Industry Association, the Swedish domestic market is stagnant, which means the industry must concentrate more on exports.

Norway, Denmark, Iceland have similar drug approval systems. A drug's "relative need" is assessed before it is given approval in Norway. In 1976 Norway had about 1800 pharmaceutical products. Iceland has a similar low number of medicines on the market, with Denmark and Finland having around twice that number.

## 3. RESEARCH AND DEVELOPMENT

### Introduction

Research costs have risen sharply over the past decades. The most recent research (Wiggins, 1987) suggests the cost of developing a new drug has risen to $125 million.

These cost increases are to a large extent a function of lengthening development times. The development time for an NCE is now over 12 years, in contrast to the early 1960s when only 3 years or less were required. Walker and Parrish (1989) estimate that by the year 2000 the average development time for an NCE from date of first synthesis to marketing will approach 15 years in the UK. The complexity of the drugs which are left to conquer is also an important factor in cost increases. Of course many research projects are rejected or abandoned long before they reach fruition. The success ratio is small. But this process of trial and error is crucial to the successful development of complex new drugs.

The pharmaceutical industry is unique among innovative industries in that it finances most of its own R & D from cash flow. In Italy the industry finances 90% of its R & D costs, while in France, Germany and the UK close to 100% of R & D costs are self-financed.

The time taken by new drugs to recoup their R & D expenditure is lengthening. In Britain even the top 10% (by sales revenue) of marketed NCEs take longer than their effective patent life to recoup their R & D investment from UK sales, and the majority do not even achieve this after 21 years. In fact, as Hansen has reported, few drugs generate sufficient sales in a single national market to repay the average development cost. Companies have to rely on sales in multiple national markets.

## RESEARCH AND DEVELOPMENT: UNITED KINGDOM

### The British pharmaceutical industry

The British pharmaceutical industry is the third largest manufacturing sector contributor to the UK balance of trade. The industry consists of some 300 companies directly employing some 87,000 people. 75 percent of these companies have less than 100 employees while 11 major companies employ more than 1,500 people each, accounting for more than 54 percent of employment and 68 percent of capital expenditure.

The British industry has developed internationally at a particularly fast rate since 1970 and now only 25 percent of sales are to the home market. It has maintained a high level of corporate profitability, though on average lower than that of the US.

### Pharmaceutical R & D

The UK has a good reputation as a centre for innovation. It attracts about 8% of worldwide industry R & D expenditure, although it accounts for only 2-3% of world sales. In the past two decades the UK pharmaceutical industry significantly increased the overall amount spent on R & D both in absolute terms and as a percentage of the overall spend in the UK.

Lumley, Prentis and Walker (1987) studied research and development spending trends in Britain between 1982 and 1984. They found that total R & D expenditure showed an increase in real terms of almost 32%. Over a 20 year period (1965-84) the UK pharmaceutical industry has significantly increased the overall amount spent on R & D, both in absolute terms and also as a percentage of the overall spend in the UK.

Prentis, Walker, Heard and Tucker (1988) found that the average R & D expenditure per NCE marketed in the UK has risen sharply without any commensurate increase in UK sales. This has contributed to the decline in the industry's return on capital, which has fallen from 27.2 percent in 1967 to 14.6 percent in 1983. The decline has not been sharper primarily because UK companies now market their products internationally to a far greater extent.

Prentis, Lis and Walker (1988) investigated measures of pharmaceutical innovation in Britain. They took the number of NCEs first administered to man as the most useful index of innovation, and found that the number administered to man by the seven UK-owned research-based companies showed an upward trend over the 22-year period 1964-1985. There was an increase in the number of NCEs investigated each year in man from an average of 12 per year up to 1980 to over 20 per year between 1981 and 1985. (In contrast, the number of NCEs investigated in the USA, West Germany and Switzerland all fell. See below).

The Clinical Trial Exemption Scheme (CTX) which enables pharmaceutical companies to secure exemption from the need to hold a Clinical Trial Certificate and proceed to rapid clinical trial for chemicals of interest as prospective medicinal products, has undoubtedly boosted research and development activity in Britain. It has been a major advance in permitting studies of promising compounds at an early stage so that manufacturers can decide whether to continue with further expensive studies or to discontinue work on the compound. The scheme effectively encourages clinical trials to be held in Britain rather than elsewhere.

According to Jonathan Gregson writing in the "Sunday Telegraph", the strengths of British research in pharmaceuticals are "the stable funding of projects, the close links between academic and industrial research, and a reluctance to stifle original thought through excessive regimentation."

## RESEARCH AND DEVELOPMENT: FRANCE

### The French pharmaceutical industry

The French pharmaceutical industry is composed of some 300 companies, with 1986 sales of 6.3 billion francs (about $1 billion). Foreign companies occupy between 50% and 60% of the French market, including products manufactured under license. Domestic subsidiaries of foreign groups control more than 40% of the domestic market. 60 percent of the industry's sales are to the home market.

In contrast to the British and West German industries, the French market has no core of large pharmaceutical companies: state-owned Rhone-Poulenc holds only 9% of the domestic market; Sanofi, an Elf-Acquitaine subsidiary, 6.5%; and Roussel-Uclaf, a subsidiary of West Germany's Hoechst, 4.5%. Only 2 French firms - Rhone-Poulenc and Sanofi - appear in the top 50 pharmaceutical companies worldwide, and the largest of these, Rhone-Poulenc only ranks 18th.

Whereas the industry used to be among the world leaders, in recent years its performance has lagged behind its British, German, Swiss and American competitors. It failed to establish itself at an early stage in profitable foreign markets. Profitability levels are at only 2-4 percent of sales and French companies have found it increasingly difficult to compete in multinational investment.

### Pharmaceutical R & D

The majority of French companies lack the resources to invest sufficiently in R & D and to move into an increasingly competitive world market. The nannual research budget of some major US pharmaceutical companies is greater than that of the whole French pharmaceutical industry's combined. On average, for every franc invested in research by a French pharmaceutical company, West German companies invest one Deutschmark (three times as much) and US companies a dollar (six times as much).

According to the Organization for Economic Co-operation and Development, "the French pharmaceutical industry is made up of a lot of small laboratories without sufficient resources for research or international marketing." Most analysts, as well as SNIP, blame government price controls as the primary reason for the lack of research. Price controls allowed pharmaceutical prices to rise only 37% in the 1970s, while France's cost of living index doubled.

In 1985 spending in France on research and development in the pharmaceutical industry was 889 million ECUs. According to Eurostaf Dafsa Associates, the decreasing productivity of research in France has led to a decline in the number of new drugs brought to the market. According to French SNIP research France only counts for 6% of new drug discoveries.

## RESEARCH AND DEVELOPMENT: WEST GERMANY

### The German pharmaceutical industry

Germany is currently the third-largest drug producer, after the United States and Japan, and is the world's leading exporter of pharmaceuticals. The West German pharmaceutical market is worth around $10 billion, about 20% of which is controlled by American companies. One third of total sales are to the home market.

Pricing freedom in its domestic market has helped the industry considerably, but not as much as pricing freedom in the US has benefited the U.S. industry. The German industry relies too much on old products which coming under increasing therapeutic scrutiny. The 1988 Health Reform Act could pose a severe threat to the profitability of the German market.

### Pharmaceutical R & D

The West German pharmaceutical industry spent 4 billion marks ($2.2 billion) on research and development in 1988, up from the 3.7 billion marks ($2 billion) spent in 1987.

According to Mattison the number of NCEs investigated for the first time is on a downward trend, declining from 37 in 1971 to 20 in 1978. According to French SNIP research West Germany accounts for 9% of new drug discoveries.

The German government's new drug reimbursement program will severely hit research and development, according to the German pharmaceutical industry. According to Mr. Otto May, head of the health policy department of Boehringer Ingelheim AG, the introduction of reference prices will accelerate a trend toward shifting research to the United States and Japan.

## RESEARCH AND DEVELOPMENT: OTHER COUNTRIES

Studies of the number of NCEs investigated in Switzerland and the USA show a downward trend over the past decades. Mattison, Trimble and Lasagna (in press) examined new drug development in the USA between 1963 and 1984 and found that filings by US-owned companies declined from an average figure of 68 in 1964-1966 to a low of 28 per year during 1976-1978. This figure increased to 35 per year for the period 1980-1982. The authors suggest that the decline was due to scientific and regulatory pressure exerted in the mid 1970s.

NCE investigations by the three major pharmaceutical companies in Switzerland (which account for 90 percent of the pharmaceutical research in that country), show a similar decline. According to Mattison et al. (1984), the rate of administration to man declined from 86 in 1960 to less than 30 each year between 1972 and 1980.

The Swiss pharmaceutical industry has remarkable international spread, high profitability, and higher penetration of the US market than any other foreign pharmaceutical industry. However, its research productivity has not been good in recent years despite high R & D spending.

Italian pharmaceutical industry R & D productivity has been remarkably low, mainly due to unfavorable domestic policies. Some 70 percent of sales are to the home market, where strict product price controls keep prices down, and where before 1978 there was no proper patent protection. The industry is not internationally competitive.

## RESEARCH AND DEVELOPMENT: CONCLUSION

Britain clearly is ahead in Europe in success of R & D. Britain has the most productive research in the world. Ten of the world's fifty top selling drugs originated in Britain, including the world's best-selling drug, Glaxo's Zantac. Furthermore, Britain's big pharmaceutical companies - Glaxo, Beecham, ICI, Wellcome and Fisons - have a promising bunch of new drugs coming through the R & D process.

This healthy British situation may be contrasted with that in France, where the industry spends almost as much on R & D but does not have one drug in the top fifty. The West German and Swiss industries spend even more on R & D but have not had as much success as Britain.

Government spending on R & D does not seem to be a particularly important factor. Differences in spending on civil research between countries are not great, and although Britain spends slightly less than the average this does not seem to have affected her good record in pharmaceutical innovation.

There does seem to be an inverse relationship between product price control and international competitiveness. All those industries with product price control systems have shown serious weakness in international competitiveness. The exception is the Swiss industry, which despite controls in its small domestic market, made early strides in profitable markets without product price control.

## 4. PATENTS

### Introduction

Under EEC law all EEC countries are required to have product patents, (namely patents which cover the actual substance itself, rather than having only process patents, which only cover the method of manufacture). However, some countries have yet to introduce such patents. The major European countries have had the stronger product patents for at least 20 years, with the exception of Italy, which only introduced them in 1979, and Spain and Portugal, which still have only process patents. After joining the EEC they were given until 1992 to introduce product patent protection. The situation in Greece is unclear.

Following the 1977 European Patent Convention all 13 contracting countries, (all countries then in the EEC except for Denmark and Ireland, plus Austria, Sweden, Switzerland and Liechtenstein), raised their patent term where necessary to 20 years from date of filing of the patent application. Despite not signing, Denmark and Finland followed suit.

The European pharmaceutical industry and concerned observers are fully cognisant of the 5 years increased patent protection recently granted to medicines in the USA, by the 1984 Drug Price Competition and Patent-Term Restoration Act, and similar increased patent protection in Japan. Such increased protection clearly gives a significant competitive advantage to companies with a majority of their sales in those markets. (However, it should be noted that the 1984 Drug Price Competition and Patent Term Restoration Act did also facilitate the entry of generic products into the market).

Effective Patent Life has been gradually declining in Europe, with the effect that the effectiveness of patents as a stimulus to pharmaceutical research has sharply diminished in recent years.

EEC Council Directive 87/21/EEC may have some effect in preventing patent term erosion. The directive grants marketing exclusivity which prohibits generics from using the original data on a product for a minimum of 10 years. The idea was to give some degree of protection so that information submitted in support of a marketing authorisation by the innovative company cannot be used to support the application of a second company for ten years.

Generic companies can only obtain a derogation from the ban by negotiation with the innovative company.

If permission is not given the company must wait until 10 years after the date of first authorisation within the EEC before being able to present a simplified dossier concentrating on the quality of the copy and if necessary the bioavailability.

So far, only Germany has incorporated the directive into national law, but the UK, France, Italy, Belgium and the Netherlands have informed the Commission of their intention to do so. Due to their late entry into the EEC, special provisions apply to Portugal, Spain and Greece which have until 1992 to implement this directive.

The introduction of patent restoration certificates or complementary certificates of protection is currently under discussion within European Community institutions but has yet to be finalised.

## PATENTS: UNITED KINGDOM

The 1977 Patent Act provided for a 20-year life from date of registration for all UK patents, bringing the country into line with the rest of the European community. (Previously, British patents had lasted 16 years).

However, patents granted on applications filed between 1967 and 1978, so-called 'new' existing patents, were open to licence of right (LOR) provisions for the last four years of their term. In that last four years any company could as of right obtain a licence to manufacture the product in return for a royalty payment to the patent holder.

The Copyright, Trademarks and Patents Act, which received royal assent in late 1988, ended the licence of right provision for those drugs whose patents expire during the four years from 1993. Thus products which would have become available for copying from November 1989 now have a further four years of protection. (It has been calculated that some 150 large-selling pharmaceuticals with total annual sales of £170 million are involved. The best known is Glaxo's Zantac). However, those licences already granted on products patented between 1967 and 1978 have not been revoked by the legislation.

The Centre for Medicines Research has assembled data on EPL for 75.5% of the 669 NCEs marketed in the UK between 1960 and 1986. The EPL, excluding the four year patent-term extension granted with the licence of right (LOR) provisions fell from 13 years in 1960 to less than six years in 1986. Even when allowance is made for the four year LOR extension, the average EPL of NCEs entering the market in 1985 and 1986 was only seven years.

## PATENTS: FRANCE

SNIP, the French national pharmaceutical union, collected aggregated data from 34 groups of laboratories who returned a questionnaire on novel products commercialised between 1977 and 1987. The SNIP study is based on patent data for 143 NCEs (55%) out of a total of 261 NCEs marketed over the period of the study. The mean effective patent life in 1985 was just over 8 years, having declined slightly since 1978.

SNIP has pressed strongly for patent term restoration, launching various initiatives, including one to increase effective patent life by 10 years by introducing a "complementary protection certificate." It has been active in pressing for a solution on a European Community level.

PATENTS: WEST GERMANY

Data on the EPL of new medicines approved and marketed between 1960 and 1978 have been gathered by the Medizinisch Pharmazeutische Studiengesellschaft (MPS) and for the period 1979-1986 by Suchy.

In interpreting this data Lis and Walker have calculated that there has been a downward trend in EPL for NCEs marketed or approved until 1981, falling from 16 years in 1961 to a mean of seven years in 1981. EPL rose again for unexplained reasons to nine years by 1985, but in 1986 the yearly mean effective patent life fell again to a mean of about 4 years for the seven NCEs marketed in that year. This fall is at least partially related to the increasing delays in the drug approval system after 1986.

## PATENTS: OTHER COUNTRIES

The Danish Medicine Importers Association (MEDIF) carried out an investigation among their 40 members representing all the major research-based pharmaceutical companies. The study examined the effective patent life of 142 NCEs marketed in Denmark from 1957 to the end of 1987. The results demonstrated that EPL declined from around 15 years in 1960 to eight years or less in 1985, although there was an upsurge in the 1980s peaking at 12 years in 1982.

Both Japan and the US have recently undertaken patent restoration measures. EPL in the USA had declined from 15 years in the early 1960s to around eight years in 1980. In 1981 it started an upward trend, even before the 1984 Competition and Patent term restoration legislation added another 5 years protection.

## 5. TABLES

Table 1.1: **INDICES OF LEVEL OF PRICES OF MEDICINAL PRODUCTS**

| Prices | FRG | DK | NL | IRL | UK | BE | FR | GR | IT | ESP | PO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| EC Stats. 1983, (EC average = 100) | 169 | 159 | 149 | 118 | 103 | 106 | 78 | 75 | 59 | | |
| EAG, 1983. (UK = 100) | 140 | 140 | 130 | | 100 | 66 | 57 | | 66 | 50 | |
| BEUC 1987 (EC Average = 100) | 153 | | 140 | 142 | 123 | 80 | 69 | | 72 | 61 | 65 |

Table 1.2: **INDICES OF PER CAPITA CONSUMPTION**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Per capita consumption (US$) EAG 1983 | 93 | 51 | 33 | 37 | 48 | 69 | 78 | 36 | 59 | 37 | 35 |
| Per capita consumption EAG 1984 (ECU) | 125 | 74 | 46 | 46 | 62 | 90 | 102 | 45 | 78 | 48 | 35 |
| As % GDP (1984) | .89 | .50 | .38 | .67 | .59 | .81 | .81 | .95 | .91 | .81 | 1.0 |
| As % of health care costs (1983) | 11.0 | 7.0 | 4.1 | 8.8 | 9.6 | 8.6 | 8.8 | 20.2 | 12.4 | 12.1 | 18.9 |
| Relative volume per capita (UK = 100) | 122 | 77 | 51 | 65 | 100 | 140 | 216 | 99 | 221 | n/a | n/a |

Source: "European regulations," & "Agenda for health", ABPI.

EAG = Economist's Advisory Group.

BEUC = Bureau Europeen des Unions de Consommateurs; (Consortium of consumer organisations in the EEC.

Table 1.3: RELATIVE PRICE OF REIMBURSABLE DRUGS AS A FUNCTION OF THEIR AGE- 1987, (France = 100).

| Age of Product | Spain | Greece | France | Italy | Belg. | UK | Holl. | FRG |
|---|---|---|---|---|---|---|---|---|
| Less than 10 years | 92.1 | 91.0 | 100 | 116.1 | 115.2 | 119.7 | 161.8 | 169.4 |
| From 10 to 20 years | 83.1 | 88.3 | 100 | 105.5 | 122.1 | 136.3 | 198.8 | 209.1 |
| More than 20 years | 79.6 | 83.6 | 100 | 102.4 | 123.9 | 154.4 | 216.8 | 229.9 |
| All products | 84.4 | 87.8 | 100 | 107.3 | 120.9 | 136.7 | 194.4 | 204.7 |

Source: SNIP, 1989.

Table 1.4: OUTLINE OF NATIONAL REIMBURSEMENT SYSTEMS FOR PHARMACEUTICALS IN EC COUNTRIES

| | Member State | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Be | Dk | Fr | FRG | Gre | Ire | Ita | Nl | P | Sp | UK |
| **Nature of controls** | | | | | | | | | | | |
| price/profits control | x | x | x | | x | x | x | | x | x | x |
| official price approval required before any mktg | x | | | | | | x | | x | x | |
| prior price approval for reimbursement | x | x | x | | x | | x | | x | x | |
| positive reimb--ursement list | x | | x | | x | | x | | x | x | |
| some types of products excluded but all others allowed | | | | x | | x | | x | | | x |
| **Patents contribution** | | | | | | | | | | | |
| fixed fee per item | | | | x | | | | x | | | x |
| fixed fee plus variable element | | | | | | | x | | | | |
| percentage of controlled public price | x | x | x | | x | | | | x | x | |
| no charge | | | | | | | x | | | | |

Source: "Blueprint for Europe," ABPI

Table 1.5: **COMPARATIVE HEALTH DATA**

| Country | Health spending as % of GDP (1984) | | Life expectancy | | Infant Mortality (1983) |
|---|---|---|---|---|---|
| | Public Spending | Total Spending | Males | Females | Per 1000 live births |
| Britain | 5.3 | 5.9 | 71.4 | 77.2 | 10.2 |
| France | 6.5 | 9.1 | 70.4 | 78.5 | 8.9 |
| Italy | 6.1 | 7.2 | 69.7 | 75.9 | 12.2 |
| Sweden | 8.6 | 9.4 | 73.0 | 79.1 | 7.0 |
| F.R.G. | 6.4 | 8.1 | 70.2 | 76.8 | 10.2 |
| U.S. | 4.4 | 10.7 | 70.5 | 78.2 | 10.9 |

Source: Barr, Glennerster and Le Grand, 1988.

Table 1.6: **PAYMENT FOR PHARMACEUTICALS BY INSURANCE AND STATE FUNDING**

(National insurance scheme and state spending as a percentage of total spending on medicines)

| Country | Percentage |
|---|---|
| Austria | 50.4 |
| Belgium | 52 |
| Denmark | 53.4 |
| Finland | 61.8 |
| France | 65.2 |
| Germany | 56.4 |
| Greece | n/a |
| Ireland | 48 |
| Italy | 64 |
| Netherlands | 63.5 |
| Norway | 60 |
| Portugal | 67.2 |
| Spain | 66.9 |
| Sweden | 62 |
| Switzerland | 52 |
| United Kingdom | 75.6 |

Source: **EFPIA in figures.**

Table 1.7: DIRECT PAYMENTS FOR DRUGS BY PATIENTS

| Country | Medicines | Doctor's fees | Hospitals |
|---|---|---|---|
| Belgium | some | approx 25% | Yes, but fully reimbursed |
| Denmark | 25%, 50% or full cost | none | none |
| Britain | £2.60 but 75% exempt | none | none |
| France | some 30%; 60% or full cost | approx. 30% | approx. 25% |
| Ireland | for some patients costs upto £28 per month | sometimes | sometimes, at fixed prices in private wards |
| Italy | most, £1 or more | none | none |
| Netherlands | £1 | fixed charge | only for chronic sick |
| Spain | usually 40% with exemptions for pensioners | none | none |
| Sweden | approx £6 with | approx £5 the | approx £5 per day |
| Switzerland | 10% of costs or 50% if medicine not on recommended list | £20 in hospital & 10% of ambulatory care | Yes, in private hospitals |
| West Germany | approx £0.6 per prescription | none | approx £2 per day |

Source: Office of Health Economics, 1988.

Table 1.8: PHARMACEUTICAL SHARE OF HEALTH CARE COSTS, 1982-1984

| | % of consumption ex-manufacturer (1) | retail (2) | % of social securit health insuran (3) |
|---|---|---|---|
| LOW SHARE OF CONSUMPTION | | | |
| USA | 5 | 7 | 6* |
| Canada | 5 | | |
| Netherlands | 4 | 8 | 14 |
| Denmark | 5 | 9 | |
| Sweden | 7 | 10? | |
| Switzerland | 8 | 15 | 20 |
| Ireland | 8 | 12 | |
| UK | 10 | 14 | 10 |
| MEDIUM SHARE OF CONSUMPTION | | | |
| France | 11 | 18 | 14 |
| Germany | 11 | 18 | 15 |
| Belgium | 13 | 19 | 14 |
| HIGH SHARE OF CONSUMPTION | | | |
| Italy | 14 | 20 | 15 |
| Spain | 17 | 22 | 18 |
| Japan | 20 | 30 | 28 |

* Medicaid only.

Source: Redwood, The pharmaceutical industry.

(1) = share of national health care consumption; pharmaceuticals at manufacturers prices;

(2) = the same, with pharmaceuticals at retail prices;

(3) = pharmaceuticals as a % of social security health insurance costs.

Table 2.1: TIME TAKEN TO REACH A DECISION ON DRUG APPROVAL THROUGH THE CPMP MULTISTATE PROCEDURE

| Country | Median time (in months) needed to reach a decision |
|---|---|
| Belgium | 11 |
| Denmark | 10 |
| France | 13 |
| Germany | 13 |
| Greece | 17 |
| Ireland | 12 |
| Italy | 26* |
| Luxembourg | 6 |
| Netherlands | 12 |
| United Kingdom | 11 |

* Figures in the table are median terms to the nearest whole month. Italy has to be excluded as atypical since it had not to June 1987 made a decision on 32% of applications forwarded to it under the CPMP procedure under directives 75/319/EEC and 83/570/EEC. Having excluded Italy, the medians are approximately normally distributed.

Source: A brief guide to the European directives concerning medicines, ABPI, 1988.

Table 3.1: **PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT SPENDING, 1985**

| | |
|---|---|
| FRG | 1142 |
| Switzerland | 1088 |
| UK | 934 |
| France | 889 |
| Italy | 410 |
| Sweden | 255 |
| Netherlands | 114 |
| Belgium | 91 |
| Denmark | 66 |
| Spain | 52 |
| Finland | 35 |

TOTAL 5,076 Million Ecus. (1 ECU = $0.984 in 1986).

Source: **EFPIA, 1986.**

Table 3.2: **RESEARCH AND DEVELOPMENT EXPENDITURE IN SEVEN COUNTRIES (1985)**

| Country | R&D spending as % of output | Method of calculation |
|---|---|---|
| UK | 13.8 | Domestic pharmaceutical R&D spending/gross output |
| USA | 12.9 | Worldwide pharmaceutical R&D spending of PMA member firms/Worldwide pharmaceutical sales of PMA member companies |
| Japan | 7.0 | Domestic pharmaceutical R&D spending/Domestic pharmaceutical sales |
| France | 12.3 | Total R&D spending by French pharmaceutical companies/ Pharmaceutical industry turnover |
| West Germany | 15.9 | Domestic pharmaceutical R&D spending/Domestic pharmaceutical sales |
| Italy | 10.5 | Italian pharmaceutical R&D spending/Pharmaceutical turnover |
| Switzerland | 15.0* | Domestic pharmaceutical industry spending/Gross output |

* 1982 data; information for 1985 not available

Source: Lumley & Walker, 1989. See table 3.6 for definition of output.

Table 3.3: WORLD TRADE IN PHARMACEUTICALS, 1986.

| Country | Exports £m | Imports £m | Trade balance £m |
|---|---|---|---|
| Switzerland | 1,616 | 484 | 1,131 |
| West Germany | 2,241 | 1,270 | 971 |
| UK | 1,621 | 786 | 835 |
| USA | 2,191 | 1,421 | 770 |
| France | 1,369 | 731 | 638 |
| Denmark | 420 | 220 | 200 |
| Belgium | 608 | 491 | 117 |
| Sweden | 390 | 295 | 95 |
| Ireland | 177 | 153 | 24 |
| Netherlands | 564 | 559 | 4 |
| Spain | 219 | 260 | -40 |
| Portugal | 40 | 112 | -73 |
| Norway | 45 | 127 | -82 |
| Greece | 25 | 108 | -83 |
| Austria | 240 | 325 | -85 |
| Finland | 49 | 134 | -85 |
| Italy | 706 | 911 | -205 |
| Japan | 350 | 1,175 | -826 |

Note: Figures are based on SITC 54 and have been converted from US$ to Sterling by an exchange rate of £1=US$1.467.

Source: UN Commodity Trade Statistics.

Table 3.4: GOVERNMENT SPENDING ON CIVIL RESEARCH AND DEVELOPMENT IN 1981 AND 1983

| | 1981 % of GDP | $ millions | 1983 % of GDP | $ millions |
|---|---|---|---|---|
| France | 0.812 | 4,371 | 0.943 | 5,786 |
| Germany | 1.050 | 6,698 | 1.035 | 7,275 |
| Italy | 0.612 | 2,783 | 0.666 | 3,295 |
| Japan | 0.522 | 5,213 | 0.515 | 5,559 |
| Britain | 0.642 | 3,000 | 0.677 | 3,745 |
| USA | 0.589 | 17,134 | 0.422 | 13,832 |
| Average | 0.705 | | 0.710 | |

Note: Japanese figures are for 1980 and 1981 respectively.

Source: Annual Review of Government funded R&D, 1984 & 1985.

Table 3.5: DEPENDENCE OF PHARMACEUTICAL INDUSTRY ON HOME MARKET

| Country | Percentage |
|---|---|
| Switzerland | 10 |
| United Kingdom | 25 |
| West Germany | 33 |
| USA | 50 |
| France | 60 |
| Italy | 70 |

Source: Macarthur, Pricing and reimbursement of pharmaceuticals, 1989.

Table 3.6: **PROFITABILITY OF NATIONAL PHARMACEUTICAL INDUSTRIES***

Profit (before depreciation and interest), % of gross output

Manufacture of pharmaceutical products, average 1980-81

| Country | Percentage |
|---|---|
| UK | 29.2 |
| Denmark | 18.4 |
| Italy | 14.9 |
| Germany | 14.8 |
| France | 8.5 |

Source: Redwood, 1987.

* Profitability is calculated by deducting personnel costs from value added, leaving profit before depreciation, interest, exceptional provisions and tax. This residue, as a proportion of gross output, gives an approximate measure of profitability. Value added is defined as gross output less the cost of bought-in goods and services. Gross output is the sale of goods (+/- stock changes) and of services).

Table 3.7: **THE STRUCTURE OF THE PHARMACEUTICAL INDUSTRY IN SIX NATIONS**

| Country | No. of companies | No. of large** companies | % of ownership (related to sales) | | | |
|---|---|---|---|---|---|---|
| | | | Own | European | USA | Other |
| West Germany* | 530 | 38 | 57 | 24 | 18 | 1 |
| France | 320 | 40 | 57 | 20 | 22 | 1 |
| Italy | 345 | 30 | 47 | 47 | 6 | 0 |
| Switzerland | 250 | 4 | 100 | 0 | 0 | 0 |
| UK | 212 | 24 | 46 | 21 | 33 | 0 |
| USA | 950 | 57 | 70 | 30 | - | 0 |

* denotes figures for percentage ownership relate to all companies.
** the definition of a 'large' company is not consistent between the different countries.

Source: Office of Health Economics, 1985.

Table 3.8: SHARE OF NATIONAL PHARMACEUTICAL MARKETS ATTRIBUTABLE TO COMPANIES OF EACH OF SIX NATIONS, 1983

| | Companies | | | | | | |
|---|---|---|---|---|---|---|---|
| Market | Local | US | German | UK | French | Italian | Swiss |
| France | 53 | 20 | 11 | 5 | 53 | <1 | 7 |
| FRG | 56 | 18 | 56 | 4 | 3 | 1 | 11 |
| Italy | 46 | 17 | 15 | 7 | 3 | 46 | 10 |
| USA | 82 | 82 | 4 | 5 | - | <1 | 8 |
| UK | 36 | 38 | 9 | 36 | 3 | <1 | 8 |
| Switzerland | 50 | 16 | 13 | 6 | 5 | - | 50 |

Source: Office of Health Economics.

Table 4.1: NUMBER OF YEARS OF PATENT PROTECTION REMAINING AT THE TIME OF MARKET INTRODUCTION.

| Country | Years (in 1983) | Years (in 1985) |
|---|---|---|
| West Germany | 6.4 (1981) | 9 |
| France | 13 | 8.5 |
| United Kingdom | 8.7 (1982 | 6 |
| Italy | 8-10 | |
| Switzerland | 11 | |

Source: Office of Health Economics & Centre for Medicines Research.

Table 5.1 ROUGH COMPARISON OF THREE NATIONAL INDUSTRIES

| | Policy area | | | | Profitability |
|---|---|---|---|---|---|
| Country | Registration | EPL | R&D | Pricing | |
| UK | Middling | Low | Good | High | Good |
| France | Fast | Middling | Middling | Low | Poor |
| West Germany | Slow | Low | Good | High | Middling |

Source: Author's estimates

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| | Companies | | | | | |
|---|---|---|---|---|---|---|
| Market | Local | US | German | UK | French | Italian | Swiss |
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Source: Author's estimates

## 6. LITERATURE

Pricing/reimbursement:


Adriaenssens G. and G. Semeus, Drug Prices and drug reimbursement in Europe. Case study: The Spanish and Portugese Drug Systems. BEUC, 1987.

Brenna, Th., C. Lecomte, C. Lucioni and S. Sandier, Comparaison des prix des produits pharmaceutiques dans les pays de la CEE. Problemes metholodiques et propositions. CREDOC/Istituto per la Ricerca di Economica di Sanitaria, Paris/Milan, 1981.

Burstall, M.L. and B.G. Reuben The cost of non-Europe in the pharmaceutical industry, Economists Advisory Group, London 1988.

Burstall M.L. and I. Senior, The Community's pharmaceutical industry - evolution of concentration, competition and competitiveness, Economist's Advisory Group, London 1985.

Cooper M.H., European pharmaceutical prices, Croom Helm, London 1975.

Dajda R and D. Owen, Price sensitivity analysis in the UK pharmaceutical market, 1986.

EUROSTAT, The structure of prices in the EEC in 1985. Series D, Luxemburg, 1988.

Loreti P. and M. Racco, Pricing and forecasting in the pharmaceutical industry - a matter of growing concern, Ephmra/Esomar seminar, Copenhagen, March 1987.

Luce, T.R.H., 'Thirty years of pharmaceutical price regulation:developments in the NHS Price Regulation Scheme since 1957,' in Costs and benefits of pharmaceutical research, ed. George Teeling Smith, Office of Health Economics, London 1987.

Macarthur, Donald Pricing and reimbursement of pharmaceuticals in the European Community - Transparency and beyond, PJB Publications Ltd., London, 1989.

Ranson, P. Parallel imports and the law, PJB Publications, London, 1988.

Reekie, W.D., Price comparisons of identical products in Japan, the United States and Europe, Office of Health Economics, 1981.

Reekie, W.D., and D.E. Allen, "Drug prices in the UK, USA, Europe and Australia," Australian Economic Papers, June 1984.

SNIP, Les prix des specialites pharmaceutiques remboursables dans la communaute europeenne, Paris, 1989.

Registration:

Andrews, P.A., G.M. Thompson, and C. Ward, 'A regulatory view of the medicines act in the United Kingdom,' Journal of Clinical Pharmacology, 24:6-18, 1984.

Backhaus, Jurgen, 'Competition, Innovation and Regulation in the Pharmaceutical Industry,' Managerial and Decision Economics, Vol. 4, No. 2, 1983.

Burrell, C., "Drug assessment in uproar," in Risk and regulation in medicine, A.W. Harcus, London, 1980.

De Mourot, Giles, 'The industry and the international regulatory environment,' EFTA Bulletin, 22/1-17, June/Aug 1981.

Griffin, J.P., (ed.) Medicines: regulation, research and risk, Queen's University of Belfast, 1989.

Hartley, Keith and Alan Maynard, The costs and benefits of regulating new product development in the UK pharmaceutical industry, Office of Health Economics, London, March 1982.

Hartley, Keith, R.J. Lavers and A.K. Maynard, "Regulation and development times in the U.K. pharmaceutical industry," Scottish Journal of Political Economy, Vol. 33, November 1986.

Lee, Philip R. and Jessica Herzstein, 'International Drug Regulation,' Annual Review of Public Health, 1986.

Richard, Barbara W., and Louis Lasagna, 'Drug Regulation in the United States and the United Kingdom: The Depo-Provera Story,' Annals of Internal Medicine, Vol 106; no. 6, June 1987.

Schmitt-Rau, Karlheinz, 'The drug regulatory affairs system in the Federal Republic of Germany', Journal of Clinical Pharmacology, 28: 1064-1070, 1988.

Teff, Harvey, "Drug approval in England and the United States," American Journal of Comparative Law, Vol. 33, Fall, 1985.

Weintraub, Michael, 'The French Drug Approval Process,' Clinical Pharmacology, May-June 1982.

Research and development:

Baily M., 'Research and development costs and returns' Journal of Political Economy, January/February, 1982.

Burstall, Michael and John Dunning, 'International investment in innovation,' in Pharmaceuticals among the sunrise industries, St. Martin's Press, New York, 1985.

Clymer H. 'The changing costs and risks of pharmaceutical innovation,' in Cooper J.D. ed, Economics of drug innovation American University.

Gregson, Jouncing, "Britain's booming pharmaceuticals," Sunday Telegraph, April 23, 1989.

Lumley, C.E., R.A. Prentis and S.R. Walker, 'Trends in R&D expenditure by the UK pharmaceutical industry, 1982-1984, Pharm. Med 1987; 2.

Mattison N., E. Thomas, A.G. Trimble, and W.M. Wardell, "The development of self-originated new drugs by Swiss pharmaceutical companies (1960-1980). Regulatory Toxicology & Pharmacology, 1984.

Mattison N., A.G. Trimble and L. Lasagna, "New drug development in the U.S. (1963-1984)", Clinical Pharmacology and Therapeutics, (in press).

Parrish J.A., C.E. Lumley and S.R. Walker, Survey of research and development spending by pharmaceutical companies in the UK between 1982 and 1987, Centre for Medicines Research, 1987.

Prentis, Roger A., Stuart R. Walker, David D. Heard and A. Martin Tucker, 'Pharmaceutical Innovation and R&D Investment in the UK,' Managerial and Decision Economics Vol. 9, 197-203 (1988).

Reis Arndt, E. 'A quarter of a century of pharmaceutical research/New drug entities 1961-1985, Drugs made in Germany - International views 30, 1987.

Speirs, C.J. R.M. Saunders and J.P. Griffin, "The UK Clinical Trial Exemption Scheme - its effects on investment in research," Pharmacy International, 1985.

Walker, Stuart R. and J.A. Parrish, Innovation and new drug development, Centre for Medicines Research, 1989.

Walker, S.R., R.A. Prentis and M.K. Ravenscroft, "Pharmaceutical innovation in the UK (1960-1983), Pharmacy International, June 1986.

Wells, Nicholas, Crisis in research, Office of Health Economics, London, 1986.

Wells, Nicholas, Innovative Chemical Extensions, Office of Health Economics, London, 1988.

Wiggin S.N., The cost of developing a new drug, PMA, Washington DC, June 1987.

General:

ABPI, Blueprint for Europe, Association of the British Pharmaceutical Industry, London, 1988.

ABPI, A brief guide to the European directives concerning medicines, 1988.

Chew, Robert, The pharmaceutical industry and the nation's health, ABPI, London, 1988

Chew, Robert, George Teeling Smith and Nicholas Wells, Pharmaceuticals in seven nations, Office of Health Economics, London, 1985.

EFPIA, EFPIA in figures, 1985 -1986, EFPIA.

Grabowski, Henry G., An Analysis of U.S. international competitiveness in pharmaceuticals, 1987.

Green, David R., Medicines in the marketplace, Institute of Economic Affairs, London, 1987.

Hankin, Robert, European regulations, Association of the British Pharmaceutical Industry, 1988.

Macarthur, Donald, The EEC environment for medicines, PJB Publications, 1987.

Midland Bank, 'Prospects for the pharmaceutical industry,' Midland Bank Review, Summer 1985.

OHE, The impact of new medicines on health care costs, Office of Health Economics, London, 1989.

Redwood, Heinz, The pharmaceutical industry: Trends, problems and achievements, Oldwicks Press, 1987.

Walton, Jo, Stewart Adkins and Ian Smith, A controversial vision of the future: Challenges posed by pharmaceutical deregulation, Shearson, Lehman Hutton, London, 1989.

Wells, Nicholas, (ed.) Pharmaceuticals among the sunrise industries,