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INNOVATION OR IMITATION - STRATEGIES FOR THE PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES

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CONTENTS

ABSTRACT

This paper focus on characteristics, trends and and strategies in the pharmaceutical industry world-wide. The patterns of R&D expenditures are surveyed and the implications of increasing costs for new drug development and reduced effective patent time is discussed. The factors behind the growth of the market for generic drugs are identified and discussed. The increasing demand for cost containment and efficiency in health care provision in combination with the fact that many commercially interesting drugs will come off patent in the near future will further stimulate generic competition.

The returns on investment in the research based pharmaceutical industry is compared with that in other industries and with generic companies. The high return on investments in the pharmaceutical industry can be explained by accounting principles and a higher than average risk. The returns on investment in R&D is less favourable, and the average new drug on the market will not pay its costs. The individual firms are increasingly dependent on a few drugs with very high sales. This creates an increased uncertainty, which the company tries to reduce through different strategies. Strategic alliances, mergers and acquisitions and diversifications into generics are business strategies used to reduce uncertainty and to position the company for the future.

The implications for the establishment of a domestic and/or export oriented pharmaceutical industry in less developed countries is discussed. The importance of the changing structure of health care markets is stressed, as well as the impact of regulations for quality and price control. Protection of property rights, for example patents, is not contradictory to the development of a domestic pharmaceutical industry. The existence of patent protection will not prevent a country from participating in the growing market for multi-source drugs and can facilitate the transfer of technology and the establishment of necessary alliances.

The paper ends with a description of a practical example of how transfer of technology, including R&D, can be organized and points out issues of central importance for success.

Key words: Pharmaceutical industry, developing countries, innovation, generics

INTRODUCTION

The pharmaceutical industry is characterized by big markets, big companies and big products. United States, Western Europe and Japan account for about two thirds of the world pharmaceutical market. Industrialized countries account for 80 per cent of a total pharmaceutical market of about 140 billion US dollars in 1988.[1]

The concentration of the world pharmaceutical industry is high. The 200 biggest companies had a sale of 106 billion US dollars in 1987, out of a total market, excluding the eastern block, of about 115 billion dollars. The sales from the 20 biggest companies accounted for 51 billion US dollars, or 44 per cent of the market. The 50 biggest companies for close to 75 percent of the the market.[2] However, the biggest company, Merck & Co, had a market share of only 3.7 percent with sales of 4.2 billion US dollars.

The two biggest products in 1987, Zantac and Tagamet, had a sale of 1.5 and 1.1 billion US dollars respectively. The 50 top selling drugs, all with sales over 200 million dollars, accounted for a total sale of 20 billion or 17 percent of the total market. An individual company is often very dependent on the sales of one of these leading products, often referred to as "cash cows". Of the top 50 selling products, 20 originated in the US, 10 in the UK, 6 in Switzerland, 7 in Japan, 5 in West Germany, 1 in Sweden and 1 in Italy. It is no coincidence

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1 If the planned economies in eastern Europe are included the market will increase 10-15 percent.
2 Estimates based on Scrip's Pharmaceutical Company League Tables 1988.

that the top 15 pharmaceutical companies in terms of sales, all come from the five countries with most top selling products.

The market is characterized by oligopoly rather than monopoly. A company can have a monopoly position in a defined market segment for a certain limited time period, but this position is continuously challenged by the competitors. Research and development is the key element for achieving a monopoly position as well as challenging existing monopolies in sub markets. Strategies for success in the international pharmaceutical market must therefore first of all focus on the role of R&D.

The discovery and development of new molecular entities and international marketing is the highest or final stage in the development of a pharmaceutical firm or industry. For most developing countries the strategy must be focused on production and domestic sales. We can distinguish three different steps in this process. The first is packaging based on import of bulk drugs. Most developing countries can set up facilities for packaging. Since this first stage is rather labor-intensive, it can also be good economy to do local packaging.

The second stage is production of tablets or injectables from imported substances. The technology needed for this stage is also rather simple and most countries can participate in this stage.

The third stage is the production of active substances. This requires a much more sophisticated technology and also access to raw materials (active ingredients). This is the stage that most developing countries aims at. One problem is that the technology is not only sophisticated, but also that there is significant economies of scale in production and that efficiency in production is very important for being competitive. The transportation costs are low, which means that it very often is more economical to buy from efficient producers than to produce domestically.

Even if the pharmaceutical industry in developing countries only to a limited extent is involved in R&D and international marketing, it is necessary to review the whole industry to see which strategies that best can serve the development of the pharmaceutical industry in less developed countries. There is a strong dependency between the research-based international industry and the opportunities for local production and sales.

A RESEARCH BASED INDUSTRY

The pharmaceutical industry invest on average nearly ten percent of total sales in research and development (R&D).[3] With a total sales in 1986 of 100 billion US dollars, the total investment amounted to about 10 billion dollars. The US pharmaceutical industry accounted for nearly fifty percent, or 4.6 billion US dollars of this investment.

Figure 1

R&D expenditures as a percentage of total sales has also increased over time. In 1986, 15 percent of the US pharmaceutical sales and export revenues were reinvested in research and development, up from 11.3 percent ten years earlier.[4]

Figure 2

A similar trend can be shown for other countries. In the UK research expenditures have increased substantially since 1970 and amounted to 13.8 percent of gross output in 1986.

Figure 3

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3 This is an average for research-based firms as well as firms without any research at all. For the research-based firms the average per cent of sales spent on R&D is of course higher.
4 A better estimate is R&D expenditures as a percentage of total world-wide sales, including sales by overseas subsidiaries. This figure was 12.7 percent in 1986.

Also the pharmaceutical industry in smaller countries like Denmark and Sweden spend about 13 percent of sales on R&D; significantly over the industry average.[5]

It is mainly the pharmaceutical industry in the developing countries that spend less on R&D. Most countries spend very little and even in countries like India and South Korea, countries with a fast growing production of pharmaceuticals, the share of sales invested in R&D does not exceed 2 percent.

Countries with significant investments in pharmaceutical research also spends a significant amount of public funds on investments in biomedical research. Figure 4 shows that in the United States, the total national spending on health R&D was close to 15 billion dollars in 1986.

Figure 4

Table 1 shows the private and public investment in biomedical research in different countries. It is not surprising that the countries with an important pharmaceutical industry also spend large public resources on biomedical research. The investment in basic biological research is an important source of knowledge for development of new drugs. The fruits of this research are available all over the world, through scientific journals and meetings. However, countries where the new

5 A recent publication, *The Pharmaceutical Industry in Perspective 1982-88: A detailed strategic analysis*, report the following figures: Companies in non-EEC European countries devoted 16.6 percent of sales to R&D in 1987/88, followed by the EEC (14.4%) the US (12.4%) and Japan (10.3%). See Scrip No 1433 July 28th 1989, p13.

knowledge is produced have an advantage of using this knowledge for development of new technologies.

PATTERNS OF INNOVATION

The number of new chemical entities (NCEs) is commonly used as an indicator of innovating activity. Figure 5 shows the world-wide introductions of new products since 1960. There was a continuous decline until the beginning of 1980s, but after that we can see a stabilization around 50 new products (NCE) introduced annually.

Figure 5

Data on world-wide NCE introductions by corporate nationality is shown in table 2. This table shows that the US pharmaceutical industry has originated about one quarter of the world's NCE since 1960. The percentage of NCEs originating from European firms has declined over the period. The Japanese industry originated approximately 10 percent of the world's NCE during the 1960s and 1970s. Its share increased to 27 percent during the 1980s, making it the leader in NCE introductions.

Table 2

The data in table 2 involve only simple counts of NCE introductions originating in each country. In Table 3 data are presented that provides some information on the importance or quality of NCEs originating in different countries. This table

includes only consensus NCEs, defined as NCE that were subsequently adopted in a majority of eleven major industrialized countries.

Table 3

The data on consensus NCEs in table 3 give a very different picture than those on total NCE introductions in table 2. They show that US drug firms accounted for 42 percent of the 170 consensus NCE introduced since 1970. Hence US firms account for a much larger share of consensus NCEs than overall NCEs. The same is true of Switzerland and the United Kingdom. On the other hand, Japan, France and Italy have a noticeably smaller share of consensus NCEs compared to all NCEs.

Another measure of innovating activity is the number of new products under development. Table 4 shows the number of self-originated drugs under development by corporate nationality. The table is based on data for the top one hundred pharmaceutical firms ranked by the number of drugs under development in 1986.

Table 4

Table 4 shows that the US industry is the world-wide leader in new drug candidates in 1986 with 938 selforiginated drugs under development, 37 percent of all candidates for the top one hundred firms. Japanese drug firms are second with 18 percent of all new drug under development.

It is difficult to make conclusions from only one year, but it is obvious that the US drug firms will be leading in product development also in coming years. The very rapid growth in R&D expenditures by US firms during the 1980s, close to 15 percent annually in fixed prices, is consistent with this development. It is also clear that Japan is emerging as a significant producer of new product introductions. The low share of consensus NCEs for the Japanese drug industry indicated that research efforts have been concentrated on imitative rather than innovative research. There is evidence, however, that this situation may be changing. Yamamoto[6] has recently surveyed the research projects undertaken by Japanese drug companies and finds that they are performing R&D projects utilizing new pharmacological concepts in a number of therapeutic areas. Grabowsky[7] also observes that the Japanese share of consensus NCE is growing over time.

A different view is presented by professor Lars Werkö, former head of R&D at Astra[8]. He points out that three of the four dominating groups of pharmaceuticals in the last decades, the beta-blockers, the H2-blockers and calcium-channel blockers come from European research, while the fourth, ACE-inhibitors, are a US discovery. He claims that European research is largely in the lead of the developments, while the American and the

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6 Yamamoto, Y. (1986) Investing in the Japanese Drug Industry 1987-91. New York. Prudential Bache Securities Inc.
7 Grabovski, H. (1988) Innovation and International Competitiveness in Pharmaceuticals. Paper presented at International Joseph A. Schumpeter Society, Sienna Italy (mimeo, revised version September 1988)
8 Svensk Farmaceutisk Tidskrift, No 7, 1989 and commented in Scrip No 1434, 1989.

Japanese pharmaceutical industries are stars of future development , possible modification and, probably mainly, at marketing. He thus points at the strong link between research and marketing. Bigger markets and companies can more rapidly and more effectively exploit new discoveries.

COSTS, TIME AND PATENTS

The costs for developing a new drug has rapidly increased over time. In 1986 a total of about 50 NCE were introduced, which can be related to a total investment in R&D of 10 billion US dollars. This means that each NCE "costed" about 200 million US dollars to bring to the market. This includes of course the costs for all other research as well as the costs for failures. This crude estimate of the costs to bring a NCE to the market is consistent with more precise estimates of the costs for developing a new drug. Figure 6 shows the rapidly increasing costs.

Figure 6

A new chemical entity probably costs its sponsor over 150 million dollars today to reach the marketplace if one counts, as one must, the failures as well as the successes and if one capitalizes the investment,I.e: calculates the return one would have got if, instead of investing in research with a long delay on return, the money had been invested in instruments guarantied to provide a prompt return.

The process of drug discovery is also a lengthy one. From start to finish it takes about 10 years on average to develop a new drug. Most of the costs and the time is for the testing of the safety and efficacy of the new compound. It takes also a considerable time to get approval for registration from regulatory agencies. Therefore the diffusion of new drugs into

the market place can be a lengthy one. Tables 5 and 6 shows estimates of the diffusion between six countries of NCEs registered since 1970.

Table 5

Average Delay after Licensing in the First Country is the average period of time that elapses between licensing in the first country and in the rest of them. All countries show a positive delay since the delay = 0 for the first country. Table 5 comprises all 301 NCEs licensed in Sweden and in at least one of the other countries, which results in an overrepresentation of Sweden. To balance this, a special study was made of the 132 NCEs licensed in all six countries (Table 6). There is, however, no great difference in the results. On average, an NCE was licensed in Sweden 2.7-2.8 years after approval in the first country, if licensed in Sweden at all. Approximately the same delay applies to France, Italy and the USA. The delays in West Germany and Great Britain are more than one year shorter.

The material was also broken down into the two periods 1960-69 and 1970-82 to see if any changes had occurred during this time. We can see from Tables 5 and 6 that Sweden, France and Italy lag considerably behind West Germany and Great Britain in the licensing of NCEs during both periods. The most conspicuous difference between the two periods is that during the 1960s the USA was on a par with West Germany and Great Britain, whereas during the latter period the delay there is the longest.

Table 6

The increase in the time of developing a new drug has reduced the effective patent life of new drugs. This has been shown in a number of studies. Eisman and Wardell[9] published the first comprehensive study of effective patent life. They studied all 191 NCEs introduced in the US during the period 1966-79, of which 88 percent had some patent protection. The effective patent time (EPT) was reduced from on average 13.6 years in 1966 to 9.5 years in 1979. The made the following conclusion:

"The effective patent life for new chemical entity drugs has fallen sharply in recent years as a result of an increase in the clinical testing period, later starting of clinical testing after patent application, and quicker issue of patents."

Walker and Prentis[10] report a reduction in EPT in United Kingdom from 13.2 years in 1960 to 9.5 years in 1970 and just under 8 years in 1982. Suchy[11] report similar results from West Germany. For Sweden, Andersson[12] report a reduction in effective patent life from 11.4 to 7.6 years (mean) between 1965 and 1987. See figure 7.

Figure 7

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9 Eisman, M.N. and Wardell,W.M. (1981)" The decline in effective patent life of new drugs". Research Management, No 21, 18-21.
10 Walker, A: and Prentis, R.A. (1985) "Drug research and pharmaceutical patents". The Pharmaceutical Journal, No 1, 11-13
11 Suchy, H. (1987) Effective patent term of pharmaceutical new chemical entities. Drugs Made in Germany, No. 3, 113-119
12 Andersson, F (1989) Effektiv patenttid för nya läkemedelssubstanser i Sverige 1965-87. CMT Rapport 1989:3

GENERIC DRUGS

Definition

The term generic is used to describe a class, kind or sort. The roots of the term is the word **genus**, a concept used in the biological classification of plants or animals with common distinguishing characteristics; a genus is the main subdivision of a family and is made up of a small group of closely related species or of a single species.

Even if this reference to biology could create associations to "survival of the fittest" it is at first sight difficult to understand why the innocent concept of generics, used for description and classification, can stir up so much heat in the discussion about competition in the pharmaceutical industry. Let us therefore start with a repetition of the different uses of the term "generic drug".

The first use is in **product nomenclature**. Drug products have three names; the brand name or trade mark which is owned by a company and used to identify and differentiate the product from competitors, the generic name which is the official name of the compound assigned to the product, and the scientific or chemical name of the product.

This classification is nothing new. What is new is the attempts to restrict or eliminate the use of the trademark in drug prescription. **Generic prescription** gives opportunities for

DIFFERENT USES OF THE TERM GENERIC DRUG

DEFINITIONS/USES	*POLICY IMPLICATIONS*
Product nomenclature	
Brand name/trade mark *Generic/assigned name* *Scientific name*	*Generic prescribing and generic substitution*
Product classification	
Originals/innovations *Transitional generic* *Branded generics* *Commodity generics*	*Price competition versus product competition* *Reimbursement*
Firm/industry classification	
Research-based industry *Generic industry*	*Different business philosophy*

generic substitution, which drastically changes the drug selection process. The value of the trademark is reduced or even eliminated and this will primarily hurt the innovative drug industry.

The second use is for **product classification**. The basis for the classification is market availability. The separation of the market in "generics" and "not generics" is not without its problems. We can first make the distinction between single-source and multi-source drugs. Single-source drugs can be both patented and not patented drugs. Let us however restrict the term generic to multi-source drugs. Not all multi-source drugs are generics. It is not uncommon that two companies jointly market a new drug. To characterize such a drug as a generic is more confusing than illuminating. We also have the situation that the innovator retains a large share of the market due to

previously attained brand loyalty, despite the existence of competitors. Such drugs are sometimes called transitional generics[13] . Usually the price differential is smaller than 20 percent and the imitator does not market his product very aggressively.

The classification "generic drug" should be restricted to such drugs where the competitor prices his drug significantly lower than the innovator, and actively tries to take the market. Dependent on the market strategy of the imitators a distinction is often made between branded generics and commodity generics.

The policy implication of the classification of drugs as generics is first and foremost an increased price competition in the market. However, this price competition is different from the traditional price competition due to reduced production costs. The reason that the imitator can reduce his price is not that he has a superior method of production or distribution but that he has no expenses for research and development. The key policy issue is therefore the balance between incentives to innovate and incentives to cut current costs. A second policy implication of the classification is that it can determine the reimbursement status of the drug. This further enforces the price advantage of the imitator.

There is no official statistics about the generic market that allows for comparison over time and between countries. Definitions differ between studies and there are great

13 James, B.G. (1981) The marketing of generic drugs. Associated Business Press, London.

variations between countries. But we can conclude that the generic market increases faster than the total drug market.

Table 7

Table 7 shows an estimate of the generic share of the total retail prescription drug market in different countries. The figure refers to number of prescriptions and not value.

The third use of the concept generic drug is in the classification of a firm or industry. Even if this concept is commonly used ("the generic drug industry is here to stay") it is not very helpful for analysis. First, a number of research-based companies are involved in supplying generic drugs. Second, the generic companies are of different kind. Some are pure manufacturers, some manufacturers and marketers and some only marketers. Some are working with a salesforce and also have ambitions to do research. The important conclusion is that there is a number of very qualified companies whose business idea is to manufacture and market drugs that come out of patent. This will reduce the margin and shorten the profitable segment of an original product's life-cycle.

Generics and technological innovation

Generic drugs are best understood as an integrated part of the process of technological change or innovation. This process of technological change is rather new in the pharmaceutical industry. Before 1945 there were very few drug innovations. The

majority of the products consisted of natural substances without patent protection. The pharmaceutical industry at that time can best be described as a commodity industry where cost of goods accounted for 65-70 percent of sales. Very little was spent on R&D. Margins were low and could only be slightly increased by branding and creation of proprietary products.

A number of research successes beginning with antiinfectives and antibiotics changed the strategic position of the pharmaceutical industry. The management and funding of R&D became one of the critical factors for the competitive position of the company. Changes in business strategy led to the development of the decentralized multidivisional enterprise and the institutionalization of a new function, research and development (R&D). This can be described by the simple model presented in the figure below.

Figure 8 in here.

The model describes the main environmental factors which contribute to innovative decisions, and the principal departments of the firm which participate in them.

There is an unfortunate division in the literature on innovation between analytical work and prescriptive work. The analytical work is concerned with such questions as: Why do firms innovate; what are the social costs and benefits of innovation; are the returns to innovative behaviour adequately distributed? The prescriptive work ask questions like: How can

innovation be better managed and controlled; what is the "right" way to fight generic competition etc.

Although the prescriptive work seems relevant for a manager there are two major disadvantages to only rely on this type of studies. First the prescriptive work is taking some answers from the analytical work as given. If these premises are wrong the prescriptions could be wrong. Second the prescriptive work cannot produce a "no loser" strategy. If everybody followed the prescriptions they would not all end up as winners.

Most studies are concerned with the development and early diffusion of innovations. A fairly small number of studies address the problems related to the later stages in the process of innovation.

The appearance of a new technology creates an **adjustment gap**, defined by the difference between the equilibrium market demand and the actual demand at a particular instance during the diffusion process.[14] The size of the gap depends on the price and the advantage of the new technology over the old one. The adjustment gap will have its maximum value for the first innovator and will gradually decrease as more imitators enter the market. A decreasing adjustment gap is reflected in a decreasing proportional rate of growth of demand. Assuming constant or increasing costs of production the profitability for the innovator will decline together with the adjustment gap and the proportional rate of growth of demand. The existence of

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14 See Coombs et al (1987), chapter 5.

post-innovation improvements can increase the adjustment gap during the diffusion process.

A major goal for an innovator is to maximize the area under the adjustment gap. The effect of generic competition can be described as reducing the adjustment gap and the return to investments in technological innovation. The aim of policies to counteract generic competition is to defend and/or increase the adjustment gap.

The firm, the market and the government

The three most important institutions in the process of technological innovation are the firm, the market and the government. The outcome of the process is dependent on the actions at all three levels. There is a strong interdependence in the actions at the three levels.

We will first have a look at the factors behind the growth of the generic drug market. We will make a distinction between:
-factors on the supply side
-factors on the demand side

The influence of government policy and regulation on the changing market environment will also be discussed.

Supply factors behind the growth of the generic market

Earlier successful innovations

The growth of the generic market is a result of earlier successful innovations. If there are no innovations, there are no generics. It is not surprising that many of the important drugs that were introduced during the 1960th and early 1970th today form the body of the generic market. And still a number of important drugs are coming out of patent every year, providing fuel for a further increase of the generic market. However, unless the innovative industry continues its success there will be fewer opportunities for new generic competition. Sooner or later the market will stabilize with a new balance between innovations and generics.

Reduced rate of innovation

The opportunities for generic competition are particularly favourable when a period of rapid innovation is followed by a period of fewer introductions. We can see from figure 5 that this was the case during the 1970th. If there is a continuous high rate of innovation, the opportunities for generic competition are small since new drugs replace the old ones before the patent has elapsed. This was the situation between 1945 and 1965. After that period the pace of technological change was slower, thus creating the opportunities for generic competition in the mid 1970th.

Increased life expectancy of new drugs

The stricter control of new drugs introduced in the 1960th also improved the possibilities for generic competition. Stricter controls means fewer and better drugs and therefore a longer life for the drug on the market. Empirical studies on the average life expectancy for NCE on the market in Sweden shows that drugs introduced in the 1970th on average had 6 years longer time on the market than those introduced in the 1960th.

Table 8 in here

Reduced effective patent time

Stricter regulatory control, often a result of increasing scientific demands, also increase the time taken to develop a new drug. As a consequence, the period the innovation is protected by patent on the market will be reduced. Since at the same time the average market life increased, the period that a drug is attractive for generic competition will increase in both ends.

Reduced barriers to entry

There are also a number of factors that have reduced the barriers to entry for generic firms. Simplified registration procedures have reduced the time if takes to register a synonym to a previously registered NCE. The documentation needed for registration has also been reduced which have reduced the cost for registration. Marketing costs have also been cut due to the emergence of institutional buyers, mainly interested in the price of the drug. It can also be added that manufacturing

costs often is low for new drugs and there are a number of suppliers for those generic firms that only aim at establishing themselves as marketers. During the 80s it has not been difficult to find capital for entering the market and the investment is comparably small.

Demand factors behind the growth of the generic market

Growth of health care expenditures

For all OECD countries taken together, the share of total health spending in GDP rose from just over 4 percent in 1960 to nearly 7.5 percent in 1985. This represents a growth rate of nearly twice that of GDP.

The public share of the total health care expenditure increased even faster, from 2.4 to 5.6 percent of GDP, and now about three quarters of total health outlays are publicly financed.

Since 1975 there has been a slow-down both in the growth of total health expenditures and in the public component. This has been associated with the slower economic growth since mid 1970s and with conscious policies to restrain the growth of health care costs, with respect both to prices and to utilization/intensity of care.

The increased resources has mainly been directed towards an increase in the quantity and/or quality of resources for each individual patient. The number of physician visits or number of

patient days per head of the population has increased slowly or not at all.

Changing goals for health policy

Until the mid 1970s the main goal for health policy was to increase the provision and access to medical services. To achieve this goal public provision and financing of health services was increased. This was done because of difficulties in providing these services adequately through purely commercial mechanisms and because this approach was considered to reflect normative judgments concerning equal access to necessary care.

Since mid 1970s policies have shifted towards efficiency in the use of resources. There are two reasons for this. The first is the necessity to restrict the growth of public expenditures. This policy is usually described as cost containment. The second is the concern about effectiveness of health care expenditures. Questions have been asked if the drastically increased intensity in the use of resources really pays off in terms of better health. A lot of studies have been published showing that the marginal benefits of health care spending are small if not even negative. This has focused the interest on technology in health care. Health care technology is defined as the drugs, devices and medical and surgical procedures used in medicine and health care and their support systems.

The health policy related to health care technologies is not very well developed yet. However, it is possible to identify three different components of such a policy.

The first component concerns the array of policies affecting the R&D phase. They include the level of funding, priority-setting in funding, the private/public mix in funding, and patent policies. It has been suggested the an international system for collecting data on R&D expenditures should be set up.

The second component concerns the array of policies affecting the diffusion of health care technology. These can broadly be divided into regulatory and reimbursement mechanisms. Regulatory intervention in the drug market has a long tradition. Premarket regulation for medical devices will be a natural second step and then probably also an increase of regulatory policies directed towards the R&D phase can be expected. However, there is a general awareness that regulatory policies have limitations.

During recent years reimbursement policies have been used to stimulate appropriate and cost-effective technology use. Financial incentives can be directed at various levels of the health care system, for example:

- at patients, for instance by requiring partial payment by the patient for selected services
- at physicians, for instance by changing payment from "fee-for-service" to capitation systems

- at health care teams, by introducing hospital ward or departemental budgeting
- at hospitals by introducing prospective payment systems or annual hospital budgets
- at population groups not defined by region (HMOs and PPPs)
- at geographical regions

In the case of drugs, financial incentives can also be directed towards pharmacies.

The third component concerns the role of **technology assessment** as a major source of information for public policy making in the area of health care technology. Technology assessment can be defined as "the systematic study of the effects on society that may occur when a technology is introduced, extended, or modified, with special emphasis on the impacts that are unintended, indirect, or delayed". Public and private technology assessment activities are rapidly increasing in a number of OECD countries. Coordinating bodies have been set up in the Netherlands, Sweden and the US.

Drug reimbursement systems

The increased emphasize on efficiency as a goal for health policy generally favours generic competition. It is difficult to communicate the argument that new drug innovations also can improve efficiency. Substitution to a lesser priced generic drug is a simple way to show improvements in cost-effectiveness. The effect is the same but the costs are lower.

Even if the total expenditures as well as the share of public expenditures is smaller for drugs than for hospital and physician services, the public expenditures on drugs are significant. Therefore drug reimbursement has been the target of different cost containment policies.

When we discuss the effect of reimbursement policies on the competition between innovators and imitators it is appropriate to make a distinction between neutral and discriminatory policies.

Examples of neutral policies are general reductions in the reimbursement level, ceiling for the total (public) pharmaceutical expenditures or the introduction of transparency lists for price comparisons. These measures stimulate the prescribing of cheaper drugs but they do not directly discriminate against the innovators.

The discriminatory policies changes the relative price of the original in comparison with the copy. The most effective of these policies are when only the cheapest product is reimbursed. A milder variant of this policy is when reimbursement is limited to a fixed cost, equal to or smaller than the cost of the generic product. Among these policies should also be included the practice to use reimbursement status as a leverage to influence to outcome of price negotiations in systems with price control on drugs.

Bureaucratization of the drug selection process

The decision-making power of the prescribing doctor has been diluted over time. He is increasingly sharing the influence over the selection of drugs with members of formula committees that set up a restricted list of products he can prescribe and pharmacists that are allowed to substitute the product he is prescribing.

The most important consequence of this is that the barriers to entry for generics are reduced. First, costs play a significant role when deciding which drugs to put on the formula and which drugs to substitute. Costs are usually not a very important concern for the prescribing physician. Second the marketing efforts can be limited to a small number of decision makers which make the costs of marketing lower.

Increased vertical integration in the health care industry

One special case of changes in the decision making about drug purchasing is represented by the health maintenance organizations (HMOs) which are growing in importance and today have 28 million members in the US and account for 1.5 billion dollars in ethical drug purchases. The growth of HMOs is a response to the struggle for containing health care costs. The HMOs represent a total vertical integration of insurance, primary care and secondary care. Not all HMOs operate pharmacies and buy their own drugs, but those that don't

contract with pharmacy chains, which in turn negotiate with drug companies.

This type of "managed care" will probably continue to increase as a response to calls for greater efficiency in health care. If this i the case, drugs will become an input (factor of production) to the health care industry instead of a product that is selected of the prescribing physician as an agent for the patient. Noting that generic drugs have had more success in hospital than in primary care, the consequences for the innovative industry are obvious.

Generic prescribing and substitution

The practice of generic prescribing and substitution is dependent of legality and incentives. Beginning with the elimination of anti-substitution laws in the different states in the US, several countries now are in a process of introducing legislation that allows generic substitution. Unless some medical disaster will occur, we will probably see this legislation introduced in most countries very soon.

However, legality is not enough to introduce substitution. Incentives are also necessary. These can be directed towards consumers or pharmacists. Many different models for such incentives have been created, usually as a result of a compromise between different parties involved. The enthusiasm from doctors, pharmacists and consumers for substitution has been limited, but if the proper economic incentives are there,

the opportunity will be used. Reimbursement and substitution policies are very closely linked.

RETURNS ON INVESTMENT

The accounting rate of return on equity is relatively high in the pharmaceutical industry. Over a longer time period it has been in the order of twenty percent, nearly double that of other industries. Table 9 shows an estimate for the United States firms.

Table 9

Most studies of the rate of return comes from the United States. However, there is reason to believe that the situation is similar in other countries. Figure 9 shows a comparison of the rate of return on total assets between the Swedish Company Astra and a sample of competitors from US and Europe. It is also clear from the figure that the profitability of Astra is significantly higher than for other public companies, listed on the Swedish Stock exchange, during the same period.

Figure 9

However, there has been a long debate of potential bias in comparing accounting rates of return in the pharmaceutical industry with other industries. The reason for this is the asset nature of advertising and R&D expenditures.

Advertising (market investments) and R&D expenditures amount to between 30 and 45 percent of the sales of a research-based

pharmaceutical firm. If these investments grows fast and the depreciation of this intangible capital is slow, the bias in accounting profit can be substantial.

Many authors have discussed this bias and tried to estimate its magnitude. The results differ but all conclude that accounting rates of return may be significantly biased upward. The reasons for this is that the industry's intangible capital assets are high relative total assets and there is a long time lag between the investment and the return on the investment.

When accounting rates of return are corrected the difference between pharmaceuticals and other industries is much smaller. However, the profitability is still higher for pharmaceuticals. The general explanation for this is that the risk is higher. If this is the case, higher than average profits are not inconsistent with a high degree of competition. However, it is difficult to measure the degree of risk or uncertainty of investments in different industries, so the argument is based on the characteristics of the investments (the combination of technical (medical) and commercial risk) and not empirical studies.

The high profitability in the pharmaceutical industry is often assumed to stem from a highly profitable research and development. However, this must not necessarily be the case. Product differentiation and barriers to entry could explain the higher return on equity. In fact, several studies have pointed out that the return on R&D to produce NCE is very low, see

Schwartzman[15], Virts and Weston[16] and Grabowski and Vernon[17]. These findings are not consistent with the increasing investment in R&D by the pharmaceutical industry during the 1980s.

In a more detailed study, Joglekar and Paterson[18] have challenged earlier estimates and produce significantly higher rates of return.

Table 10

The "average" NCE gives a higher return than a corporate bond. However, this is not the case for the "median". The industry is dependent on a few big winners to pay back the investments. See figure 10.

Figure 10

This makes investments aiming at producing NCE a very risky business. The company needs high profits over a long period of time to finance the investment and still there is no guarantee for success. If the new product takes long time to come out of the pipeline, or if the pipeline dry out, the company rapidly

15 Schwartzman, D. (1975) The Expected Return from Pharmaceutical Research, Washington, D.C.: American Enterprise Institute.
16 Virts, J.R. and Weston, J.F. (1980) "Returns to Research and Development in the US Pharmaceutical Industry" Managerial and Decision Economics, Vol 1, 103-11
17 Grabowski, H. and Vernon, J. (1982) "A sensitivity analsysis of expected profitability of pharmaceutical research and development", Managerial and Decision Economics, Vol. 3, 36-40
18 Joglekar, P. and Paterson, M. (1986) "A closer look at the returns and risks of pharmaceutical R&D", Journal of Health Economics, Vol. 5, 153-177.

goes into financial problems. In the next chapter we will have a closer look at different strategies to reduce uncertainty and increase the probability of survival for the company.

STRATEGIES

Competition in the pharmaceutical industry is a dynamic process in the Schumpeterian sense. Firms in the market constantly look for opportunities to compete by improving their products and production processes and by introducing new products. This process of competition is fueled by scientific breakthroughs that create opportunities for development of new technologies and by an increasing demand for new technologies. During the last decade we have seen a revolutionary development in biomedical science with the birth of new technologies like genetic engineering and monoclonal antibodies and new disciplines like molecular biology,virology,neurobiology and immunology. There are also still major medical challenges like cancer, aids, Altzheimers disease and other diseases related to aging. There is no reason to assume that the era of product competition in the pharmaceutical industry has come to an end.

But the increasing costs and time of new product development in combination with increasing governmental cost containment have increased the risks for the participants in the market. The major pharmaceutical firms have responded to this new situation with a series of strategic alliances and mergers. We will first look at different types of strategic alliances and then review

the merger activity in the industry. Then we discuss the pros and cons of diversifying into generics.

Strategic alliances

There are several types of strategic alliances:

1. Co-marketing[19]
2. Co-promotion agreements[20]
3. Cross-promotion agreements
4. Jointly owned company agreements[21]
5. R&D partnerships
6. Licensing agreements
7. Supplier agreements
8. Quid Pro Quo agreements

Strategic alliances is not a new feature on pharmaceutical markets. There are many examples back in the 1960s and 1970s. But the magnitude of these activities is new. This can be seen from the following survey of recently announced strategic alliances.

Recently announced strategic alliances (1987/88)

Sandoz and Glaxo	*- Sandoz will develop Zantac OTC* *- Glaxo to co-market DynaCirc a calcium*

19 Two or more companies market different brands of the same product

20 Two or more companies market the same brand

21 An example is the Merck&Co and Jonsson and Jonsson joint venture, Jonsson & Jonsson Merck Consumer Pharmaceuticals Co, for development and marketing of OTC products, based on Merck's existing prescription drugs.

	channel blocker
Squibb and Boehringer Ingelheim	*- Co-marketing Squibb's second generation ACE inhibitor Fosinopril* *- Co-marketing Boehringer's PAF antagonist*
LyphoMed and California Biotechnology	*- Licensing agreement for a micro-emulsion drug delivery technology*
Roche and Miles	*- Co-marketing Baypress, long-acting calcium antagonist*
Schering and Sandoz	*- Co-marketing spirapril, long-acting ACE inhibitor*
Merch and Stuart	*- Co-marketing lisinopril* *- Co-marketing an aldose reductase inhibitor*
Upjohn and Sankyo	*- Co-marketing and oral cephalosporin*
SmithKline and Bristol-Myers	*- Co-marketing Tagamet OTC in the U.S.* *- SmithKline received exclusive rights to an H2 receptor antagonist*
Abbott and Burroughs Wellcome	*- Co-promotion of Hytrin (one-a-day alpha-blocker)*
SmithKline and DuPont	*- Co-promotion of Tagamet*
Sandoz and Genetics Institute	*- Supply agreement for biotechnology products*
Sterling and Advance Polymer Systems	*- Agreement for topical controlled release OTC products*
Johnson & Johnson and Centocor	*- Marketing and distribution agreement for biotechnology products*
Squibb and McNeil	*- Co-promotion of Capoten, co-marketing of zofenopril and a Johnson & Johnson product*
Roche and Glaxo	*- Co-marketing: Cipralin, an anti-arrhythmic; Inhibace and Diuretic combination.*

There are many reasons for establishing strategic alliances. One is to increase marketing power. Examples of this is the co-marketing of Zantac by Glaxo and Roche and Capoten by Squibb and McNeil. A second reason can be to reach new target

customers or market segments. Many companies have for example been interested in entering the OTC market, which is of growing importance. Alliances between SmithKline and Bristol-Myers and Sandoz/Glaxo have been formed with this goal.

An alliance can also be formed to get access to new therapeutic categories or new technologies. Examples of the former is the cooperation between Merck and ICI on aldose reductase inhibitors. This cooperation also gave ICI access to an ACE-inhibitor developed by Merck. Examples of the latter is the cooperation between Sandoz and Genetics Institute on biotechnology and Jonsson & Jonsson and Centacor on monoclonal antibodies.

Alliances to obtain local market presence and leverage are also common, for example between Squibb and Menarini(Captopril) and Merck /Sigmatau (Enalapril) in Italy. Similar agreements can be found in the H2-receptor antagonist market between SmithKline, Glaxo and local companies. Often a multinational company acquires a local company. Merck AG has for example recently acquired a majority shareholding in the Spanish pharmaceutical company, Biologicos Organicos Industriales (BOI).

Strategic alliances are assumed to increase in the future. The following forecast was presented by one leading pharmaceutical executive.

Strategic Alliances - Major similarities and differences among Japan, Europe and the US

Japan	*- Well established/accepted strategy within Japan*	*- Alliances will increase as Japan seeks to penetrate worldwide markets*
	- Japanese distribution systems encourages alliances	
U.S.	*- Becoming very popular as a strategic weapon*	*- Alliances expected to experience a quantum increase*
	- After used to gain a quid pro quo	
Europe	*- Acceptance varies greatly by country*	*- Harmonization in 1992 will greatly accelerate transnational alliances*

Source: Presentation by Jan Leschly, PMA International Meeting, 1988

There are however not only advantages with strategic alliances. Co-marketing can encourage generic prescribing,loss of brand loyalty, substitution and price competition. This will intensify the competition and reduce profits. In the long term, the link between a company's R&D efforts and marketing can be broken and create a change in business philosophy. This can have a negative impact on the company's image, both internally and externally.

Mergers and acquisitions

During the last years we have seen an increasing number of mergers and take-overs between major pharmaceutical firms. One example is the merger between SmithKline(US) and Beechham(UK) creating the second largest pharmaceutical company in the world. SmithKline has experienced decreasing sales for their

major product Tagamet and the merger broadens the product base for the company.

Just recently (July 27th) Bristol-Myers and Squibb announced an agreement to merge to form a global healthcare company with annual sales of 8.6 billion dollars. It will be the second largest pharmaceutical company in the world, with sales of 4 billion dollars, after Merck&Co and pushing the newly merged SmithKline Beecham into third place. The new company will have an annual R&D budget of about 600 million dollars and a sales force of about 8000.

The merger between the Danish companies Novo and Nordisk is an example that this tendency can be found in Europe and in smaller countries as well. This merger, which was approved by the shareholders in April 1989 creates one of the largest biotechnology companies in the world. The merged company account for about 50 percent of the world insulin market. The intention with the merger is to co-ordinate and integrate the companies'production and research departments, while marketing will continue under their existing brand names and through the same sales organizations.

These are only a few example of attempts to consolidate the pharmaceutical industry for the future. During 1988 there were over 200 mergers and acquisitions in the pharmaceutical industry world-wide.[22]

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22 For more details, see Scrip Yearbook 1989.

Diversifying into generics

With increasing costs and risks of investments in R&D and increasingly cost conscious buyers, diversifying into generics is an attractive business opportunity. It represent a business that is closely related to the research based companies'core business. There is also an increasing number of very important pharmaceuticals coming off patent.

Table 11

If we look at the leading products world-wide, 14 out of 15 products will lose patent protection by the end of 1995.

Table 12

The rate of return has also been very high for some generic companies, higher than the average for research based pharmaceutical firms.

Figure 11

However, the competition in the generic market increases over time and success is not guarantied. There is a need for a very

clear business strategy including when to enter, which generics to market and how to enter the market. Since manufacturing represents a much greater share of costs for a generic product than for a pioneer product, it has a much greater impact on profitability.

The generics business is in general more local than development of new drugs. But the future can very well see one or more world-wide generic companies. As a step on that road, we will probably in the near future see all-european generic firms.

IMPLICATIONS FOR THE ESTABLISHMENT OF A DOMESTIC AND/OR EXPORT ORIENTED PHARMACEUTICAL INDUSTRY

Development of a researchbased industry

The trends and developments presented in this study indicates increasing difficulties for companies who like to compete in the market for new drug candidates. The high costs of performing innovative drug research makes this activity prohibitive for most pharmaceutical companies, particularly those from developing countries. These countries also lack the infrastructure necessary for supporting such research.

But the high costs for R&D are mainly for the testing of safety and effectiveness of new drug candidates. The discovery and selection of new drug candidates is more depending on creativity and new ideas than financial resources. In many developing countries you will find good scientists that are

capable of performing innovative research. This is a potential resource for development of the pharmaceutical industry in developing countries. However, there is the problem of keeping the researchers in their home country. Many good researchers from developing countries moves for education and work to developed countries and never return.

For testing and marketing of new drug candidates domestic research based pharmaceutical firms must collaborate with multinational firms. The necessary investments to bring a new drug candidate to the world market are so large that new companies cannot finance them alone. There is a need for strategic alliances between domestic and multinational firms. Also the very successful Japanese pharmaceutical industry, with a very strong home market and capital base, have found it necessary to use this strategy during the development of the industry.

In order to form such alliances it is an advantage, even a prerequisite, that there is a protection of property rights within the country. Patents and protections of trade marks makes it much easier to make agreements. Strengthening of the patent system helps the development of a researchbased pharmaceutical industry. Since most partners for strategic alliances are private companies, there is an advantage if the domestic companies have the same ownership structure. The past international as well as domestic policy has been of a different kind.

The development of a researchbased pharmaceutical industry must be a long-term goal, which will take decades to achieve. The development of the pharmaceutical industry in Japan is a good example both of the time it takes and that it is possible to achieve. The development of a researchbased industry should not be mixed up with goals about independence. A successful research-based industry will always have the majority of sales on the international market. This is particularly true for industries in small countries like Switzerland and Sweden. There has over time been a development towards increased inter-dependence between the developing countries. The share for domestic firms in the domestic market is decreasing and the percentage of exports of total sales is increasing for domestic firms. It is not realistic that a country can be independent or self-sufficient in the supply of new pharmaceutical products. The international division of labour and specialization is a more effective strategy.

However, it is a problem if too few countries are involved in new drug development. The dominance of a handful of countries in the development of new drugs is a fact, but there is so far no clear tendency towards concentration.[23] There is also a debate about the relative competitiveness of the European, Japanese and United States pharmaceutical industry. There are no signs that one party will lose or win in this market battle. The most likely future is that the relative strength will change over time and that more countries will enter the scene. It is an advantage if more countries enter the competition in

23 However, the recent wave of mergers can be a sign of a new era.

this market because it opens up the opportunities for reciprocability and reduces the risk for protectionism and restrictions in international trade. It is therefore in the long term interest of all countries that a true multinational researchbased industry can develop.

Production of generics

Many important pharmaceuticals have come off patent during the last years and many more are to come during the next five year period. Even if patented drugs are the big sellers if we compare drug by drug, more than two thirds of the pharmaceutical market is for non-patented drugs. For developing countries this share is even greater. It is therefore not necessary to infringe with patent protection to find modern, effective and import drugs for national production. On the contrary, if patent protection is given to the newest technologies, so important for the individual companies depending on the sales of a few "break-through drugs", this will make it easier to transfer technology for those products that just got off patent.

Even if the product is off patent, the technology for its production is not generally available. The knowledge about production, quality control, efficacy and marketing of the product is held by one or several companies, often multinational, that have been involved in developing the drug. The most obvious strategy for technology transfer is to cooperate with these companies. All transfer of technology is

from one company to another. For this to take place, an agreement has to be made that makes both parties a winner. It is not possible , or at least not efficient, to make a transfer of technology, if one party is unwilling to participate.

The multinational companies today supply about 70 per cent of the drugs consumed in developing countries. About 60 per cent of the supply comes from subsidiaries in developing countries. There is a need for strengthening the role of local production and joint ventures for supply of pharmaceuticals. The technology for production of generic drugs is available from many sources, not only multinational firms. More advanced developing countries such as India,Egypt,Mexico and Brasil can export the technology as well as some countries from the eastern block. Many small companies in industrialized countries, with a limited amount of international operations, are able and willing to sell the technology for production of generic drugs.[24]

It is therefore possible to transfer the technology to national companies with no foreign ownership at all. However, it can be effective to form joint ventures with foreign firms. For many foreign firms it is a long-term goal to have a presence in the market of a developing country. Participation in a joint venture is a way to establish contact and create knowledge about the market. Since this has a value, the foreign partner

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24 It is maybe surprising that several firms that were set up in the beginning of the 1980s to sell pharmaceutical production technology to develping countries have gone out of business due to lack of profitable projects. This indicates that the problems of technology transfere is not only a problem with supply of technology.

is prepared to pay for this investment in a future market in the form of financial resources and expertise. Therefore a joint venture can be a more economically way to transfer technology than a pure local company. Appendix 1 gives an example of a model for a joint venture of this kind.

A joint venture can also be a way to solve the difficult problem with supply of raw materials. This is a well known problem for developing countries and there is a need for international agreements and contracts.

Health care and the national market for pharmaceuticals

The domestic market for pharmaceuticals is of central importance, also for an export oriented pharmaceutical industry. One important restriction for the pharmaceutical industry in developing countries is the very low per capita consumption of drugs. In 1983 the average consumption per capita was 75 US dollars in industrialized countries and less than 6 dollars in developing countries. The low per capita consumption is of course balanced by the fact that developing countries account for three quarters of the worlds population.

A characteristic of developing countries is also that pharmaceuticals account for a larger part of health care expenditures than in industrialized countries. In many industrialized countries, pharmaceuticals account for less than 10 percent of total health care expenditures, while in developing countries the share can be 40-50 per cent. The costs

for pharmaceuticals are therefore of much greater importance for the total health care expenditures.

The lack of infrastructure for health care and lack of trained manpower, doctors, pharmacists and nurses, is a major problem for developing countries. The solution to this problem is not the establishment of a local pharmaceutical industry. Regardless if the market is supplied by local production, multinational subsidiaries or import there is a need for an efficient system for procurement and distribution of pharmaceuticals. The role of government is much more important in creating an efficient and just "demand" for pharmaceuticals, than participation in the direct supply or production of drugs. There are no evidence that public ownership of production facilities is advantageous in the development of a domestic pharmaceutical industry.

The establishment of an effective counterpart to the suppliers of drugs is essential for the sound development of the pharmaceutical industry. If the market is imperfect on the demand side it will be imperfect on the supply side. An efficient use of drugs, within the limited resources of a developing country, is also important for minimizing the conflict between health policy goals and industrial policy goals. If the production is inefficient and the costs therefore higher, the health services will produce less health with the resources available. Most developing countries will accept higher prices for domestic production, at least for a limited period of time, but the costs in terms of health benefits

foregone is proportional to the excess price, and this gives limits for "subsidization" of local production. More than 25 percent higher prices for local production is probably not accepted.

Regional cooperation

Most developing countries have small home markets. With economies of scale in production, marketing and regulation there is an obvious case for cooperation between countries. If the different cooperating countries each specialize in different product the advantages of division of labour can be achieved. But there are problems with this strategy. First it is difficult to establish an agreement. The cake is bigger if everybody cooperates, but still each participant looks for the size of his peace. If it is possible to form an agreement, it can be difficult to keep it in the long run. If a producer outside the coalition, supplies the product at a lower price, it can be to the advantage of one partner to break the coalition.

Despite these problems there are so significant gains from regional cooperation that this strategy should be further pursued. The development of the European "internal market" can provide an example of both the problems and opportunities from regional cooperation and the establishment of a common market for pharmaceuticals.

Regulations - benefits or costs?

The pharmaceutical industry needs regulations to work efficiently. The most important regulations are those for quality control. There are many examples that local production will fail, even if it is protected from outside competition, if the quality control does not work. Regulatory agencies for control of safety and efficacy of medicines as well as good manufacturing practices and good laboratory practices must be established before a domestic industry can be developed. Such regulations are of great value for improving the efficiency and rationality of the health services as well. Regulations of this types are costly, both for the government and the pharmaceutical companies.[25] But without knowledge about quality control and adequate resources for carrying it out, the long run development of the industry is handicapped.

But there are other regulations that are of dubious value, for example price control. There is an obvious conflict between low regulated prices and the development of the industry. If low prices of pharmaceuticals is the overriding aim, the consequence can very well be the killing of a developing national industry. Stifling bureaucratic controls and interventions in the activities of the industry in detail and at all levels can also be a significant drawback in the development of the industry. See for example Lall[26] for an

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25 The WHO document "Guiding principles for small national drug regulatory authorities" suggests a solution to this problem.
26 Lall, S. (1979) "Emerging trends and future prospects in the less developed countries" in Medicines for the year 2000, OHE, London and Lall, S. (1982) "The pharmaceutical industry in India: The economic costs of regulation" in Papers presented at the eleventh IFPMA assembly, Washington.

example of how regulations and controls can be a threat for the future development of a pharmaceutical industry.

CONCLUSIONS

The strategy for establishing a domestic or import oriented pharmaceutical industry is dependent on the basic goals for and functioning of the health care system in the country. First when these goals are clearly specified it is possible to define the most effective strategy for establishing or re-structuring a pharmaceutical industry. There are conflicts between health policy goals and goals about industrialization and it is fruitless to assume that industrialization can solve health policy goals, for example reductions in drug prices. But it is a clear advantage for establishment of a local pharmaceutical industry if health care has a high priority and the public as well as private spending on health services is stimulated. The experience from developed countries is that the pharmaceutical industry, particularly in small countries, can benefit from a health care system of high quality.

The role of government should first of all be to create a functioning procurement and distribution system and an appropriate system of regulations, particularly the regulation of safety,efficacy and quality of drugs. However, excessive regulations of details of pharmaceutical production and a stifling price control, can be counterproductive to the establishment and development of a national pharmaceutical industry. There are no evidence that government ownership is advantageous for the development of a national pharmaceutical industry.

Protection of patents and trade marks is a prerequisite for the development of a researchbased pharmaceutical industry. Without such legislation it is very difficult to establish the necessary strategic alliances to develop a research based industry. For developing countries with a good education system and qualified researchers in biomedical sciences there should be opportunities to form alliances with multinational companies for the establishment of local research and development aimed at developing new drug candidates. This is however a very long term strategy for making the country a source of innovation in the future by creating the necessary biomedical infrastructure.

The existence of patent protection will not prevent the establishment of production of valuable drugs of high quality. Many important drugs developed and introduced during the 1970s and 1980s have recently come off patent and more are to come during the coming years. This gives an opportunity for the developing countries to participate in the creation of a national,regional and global market for multi-source ("generic") drugs.

Local production can be achieved through domestic firms, joint ventures and investments (subsidiaries) of multinational companies. There is no reason to rule out any of these forms for ownership. They can exist together and the potential areas of conflicts must be solved on a case per case base. Today the multinational companies account for the majority of pharmaceutical production in developing countries. There is a need to establish a better balance and increase the share for

joint ventures and local ownership. This is possible since the technology for production of non-patented drugs is available, not only from multinational companies, but also from smaller companies in developed countries, from eastern European countries and from more advanced developing countries. All parties are interested in participating in transfer of technology to developing countries. The development of a regional cooperation is one way to achieve economies of scale and share the costs for the necessary regulatory institutions.

Appendix 1

SINO-SWEDE PHARMACEUTICAL COOPERATION Ltd - A MODEL FOR TECHNOLOGY TRANSFER?

Background

Chinese legislation on establishment of joint ventures from 1 July 1979 gives an opportunity for foreign companies to establish production in China, on the condition that technology is transferred and part of the production is exported. After three years of discussions and negotiations between a group of Swedish pharmaceutical firms and China National Pharmaceutical Industry Cooperation (CNPIC), a joint venture agreement was signed on September 15, 1982 to establish SINO-SWEDE PHARMACEUTICAL CORP. LTD (SSPC).

Ownership

The partners from China are China National Pharmaceutical Industry Corporation (CNPIC), Beijing, Jiangsu Provincial Pharmaceutical Industry Corp (JPPIC), Nanjing and Mashan Industry Corp (MIC), Wuxi. CNPIC is the representative for the government level, JPPIC for the provincial government and MIC is a state owned corporation under Wuxi municipality, where the plant and head office of SSPC are located.

From Sweden a Consortium of five pharmaceutical firms, Astra, Kabi, Leo, Ferrosan and Ferring together with Swedfund, a government organization for industrial cooperation with developing countries are the partners.

The total registered capital is 12 million USD with 50 percent from each side. The duration of the joint venture is 20 years and extendible. The capital was payed in USD from the Swedish side and for China one million in USD and the rest in local currency.

Business idea

The business scope of SSPC is to:

- produce in China (according to WHO rules for GMP) Swedish original pharmaceuticals for sale in China

- produce generics for export from China

-produce active substances and basic material for export to mainly Sweden

-develop cooperation in research and development

Examples of products are the cardiovascular agent BETALOC for hypertension and angina pectoris, BRICANYL for treatment of astma and bronchitis and 18 cristal amino acids solution VAMIN and fat emulsion INTRALIPID.

Production, employment and training

The building of the production plant, 20.000 sq m, started in 1984 and was completed in 1987, one year later than planned. The production unit will employ about 350 persons. Of these were 50 persons employed two years before the planned start of production. Since there was one years delay the total pericd of training was three years. Part of the training was located in Sweden, and a significant part of the training is for fulfilment of GMP criteria for quality and hygiene. The plant will be the most advanced, and probably the most expensive, in China.

A market organization has been build up and also the necessary administrative competence for economic planning and management.

The creation of a complicated, comprehensive pharmaceutical company in a new environment is a difficult undertaking and some problems must be expected. The most important were:

- recruitment of a qualified labour; a well functioning labour market is an important factor for success

- more education than expected was necessary for the transfer of technology

- difficulties to procure raw materials and material for packages. Standardization and specifications for material is often lacking. Lack of foreign currency to procure raw material from other countries.

-problems with licensing agreements and protection of property rights;

-problems with currency regulations and bartering agreements

-problem with bureaucracy and administrative delays

-problems with the quality of construction workers and construction material for the building of a according to GMP standards

Cooperation for new drug development

Related to the joint venture was an agreement between The Swedish Association of Pharmaceutical Industry(LIF) and the State Pharmaceutical Administration of China(SPAC) on co-operation in the development of new drugs. The co-operation is

coordinated by a steering committee with three representatives from each party. The Swedish representatives includes one from the pharmaceutical industry, one from medical science and one from the government.The cooperation is supported financially by the Swedish government and the Swedish pharmaceutical trade association (LIF).

The guide-lines for the co-operation are as follows:

1. The Chinese side may provide preliminary research results and the successful experience from the traditional medicine, such as

- Synthetic compounds worth to pursue further.
- New structures identified from herbal drugs which could be used as leads.
- Herbal drugs shown to be active by preliminary pharmacological studies.
- Compound herbal prescriptions of definite therapeutic efficacy.

2. The Swedish side may provide up-to-date facilities and scientific experiences for further research, such as

- sending experts to China to give lectures and to hold seminars for both pharmaceutical and medical audiences
- to accept and support selected Chinese scientific workers for further training in Swedish universities and institutions. The duration may last 1-3 years.

3. When the co-operation has progressed to the point where a new drug candidate has been selected through mutual agreement, the Swedish side will

- take the responsibility for patent application and New Drug Registration of the resulting new drug
- to provide according to GLP requirements Swedish industrial research facilities in the areas of pharmacology, toxicology, biopharmacy and clinical evaluation in the co-operative project

4. According to the progress of co-operation and to the interest of both sides joint ventures in the formation of Research Units in China may be considered.

The co-operation has not so far resulted in any new drugs. If some interesting new substances were found, the problem with limited opportunities for patent protection of drugs based on "herbal plants" is a major obstacle for rising the necessary resources for developing the product to a marketed drug.

LIST OF TABLES

Table 1. Biomedical Research and Development Funding in 1980 (1975 U.S.$) per caput

Country	Total/caput	Public/caput	Private/caput
Switzerland	32.56	8.36	24.21
Sweden	24.18	16.69	7.49
United States	19.95	13.36	6.00
FRG	17.89	9.78	8.11
Netherlands	15.94	11.14	4.81
Japan	14.62	5.77	8.85
Norway	12.33	10.53	1.81
France	11.53	7.02	4.51
Denmark	11.22	7.94	3.28
Belgium	10.18	5.54	4.64
United Kingdom	9.71	3.76	5.96
Canada	8.25	5.99	2.26
Finland	6.78	3.98	2.79
Italy	6.71	4.12	2.60
Australia	4.51	3.73	0.78
New Zealand	3.55	3.03	0.52
Spain	1.71	0.93	0.79
Ireland	1.70	0.83	0.87
Portugal	1.15	1.07	0.08
Austria	n.a	n.a	n.a
Luxembourg	n.a	n.a	n.a
Greece	n.a	n.a	n.a

Source: Shephard, D. and Durch, J.S. (1986). International Comparison of Resource Allocation i Health Sciences: An Analysis of Expenditure on Biomedical Research in 19 Industrialized Countries. Boston. Harvard School of Public Health (mimeo).

Table 2. Worldwide NCE Introductions by Nationality of Originating Firm, 1961-86.

Period	Number of new entities	Share distribution (%)						
		USA	Japan	West Germany	France	Italy	Switzerland	UK
1961-70	863	24	9	13	20	6	7	5
1971-80	635	23	12	14	16	11	7	5
1981-6	281	23	27	10	8	8	6	3

Notes: Classification is based on the country where company discovering the drug is headquartered rather than that where first synthesis of the drug occurred.

Source: Grabowski, H.G. (1989). "An analysis of US international competitiveness in pharmaceuticals", Managerial and Decision Economics, Special issue, 27-33.

Table 3. Distribution of Consensus NCEs by Nationality of Originating Firm, 1970-83.

Country	Number of NCEs	(%)
United States	71	41.7
Switzerland	22	12.9
West Germany	17	10.0
United Kingdom	17	10.0
Sweden	12	7.1
Italy	8	4.7
Japan	7	4.1
France	4	2.4
Others	12	7.1
	170	100

Note: Consensus NCEs are defined as new drugs introduced in at least six of eleven major markets over the period 1970-83.

Source: See table 2.

Table 4. Drugs under Development by Corporate Nationality for the Top Hundred Ranked Firms in 1986.

Country	Number of firms	Self-originated drugs under development	Percentage of total
United States	27	938	36.5
Japan	24	462	17.8
West Germany	11	350	13.5
United Kingdom	5	182	7.0
Switzerland	4	164	6.3
France	6	157	6.0
Italy	6	94	3.6

Source: See table 2.

Table 5. Average Delay after Introduction in First Country for NCEs Licensed in the Respective Countries during 1960-82. NCEs Licensed in 2-6 Countries, including Sweden.

	Licensed in the respective countries					
	1960-69		1970-82		Total 1960-82	
Country	No of NCEs	Delay(yr)	No of NCEs	Delay(yr)	No of NCEs	Delay(yr)
Sweden	150	1.8	151	3.6	301	2.7
France	113	1.9	122	3.8	235	2.9
West German	149	1.0	121	2.2	270	1.5
Italy	105	2.1	132	3.8	237	3.1
Great Britain	127	1.2	128	2.3	255	1.7
USA	87	1.1	103	4.2	190	2.8

Source: Berlin, H. and Jönsson, B. (1986). "International Dissemination of New Drugs: A Comparative Study of Six Countries". Managerial and Decision Economics, Vol. 7, 235-242.

Table 6. Average Delay after Introduction in First Country for NCEs Licensed in all Six Countries during 1960-82.

	Licensed in the respective countries					
	1960-69		1970-82		Total 1960-82	
Country	No of NCEs	Delay(yr)	No of NCEs	Delay(yr)	No of NCEs	Delay(yr)
Sweden	64	1.8	68	3.7	132	2.8
France	63	1.7	69	3.8	132	2.8
West Germany	75	1.2	57	2.1	132	1.6
Italy	60	2.0	72	3.6	132	2.8
Great Britain	70	0.8	62	1.9	132	2.8
USA	60	1.2	72	4.2	132	2.8
				All:	132	2.4

Source: See table 5.

Table 7. Generic Share of the Total Retail Rx Market.

Country	1980	1983	1987
Germany	2%	3%	8%
France	1%	2%	5%
United Kingdom	3%	6%	8%
Italy	6%	10%	13%
Spain	30%	34%	36%
Brazil	28%	33%	38%
Japan	12%	15%	21%
Canada	13%	19%	24%
United States	21%	22%	26%

Source: 1987 Script Yearbook.

Table 8. Life Expectancy for Pharmaceutical Specialities by Foreign Pharmaceutical Companies in Sweden.

Period	Number	Life expectancy Median (months)	Percent with longer life than 30 mo	60 mo	120 mo
1960-64	879	172	92%	82%	61%
1965-69	616	184	95%	80%	62%
1970-74	306	253*	96%	89%	75%
1975-79	306	263*	95%	89%	--

*extrapolation

Source: Berlin, H. and Jönsson, B. (1985). "Market Life, Age Structure and Renemal - an Analysis of Pharmaceutical Specialities and Substances in Sweden 1960-82". Managerial and Decision Economics, Vol. 6, 246-256.

Table 9. Average accounting rates of return on net worth, by industry, 1959–73.

Industry	*Rate of Return Where R & D and Advertising Are Expensed*	*Rate of Return Where R & D and Advertising Are Capitalized*
Pharmaceuticals	18.29	12.89[a]
Electrical machinery	13.33	10.10
Foods	11.81	10.04
Petroleum	11.23	10.77
Chemicals	10.59	9.14
Motor vehicles	10.46	9.22
Paper	10.49	10.12
Rubber products	10.11	8.69
Office machinery	10.48	9.90
Aerospace	9.23	7.38
Ferrous metals	7.55	7.28

a. It should be noted that sales promotion investments other than advertising were not capitalized for any industry for lack of data. In the case of pharmaceuticals, nonadvertising sales promotion spending is much larger relative to total earnings and to total equity than for any other industry.

Source: K. Clarkson, *Intangible Capital and Rates of Return* (Washington, DC: American Enterprise Institute, 1977), table 10, p. 63.

Table 10. Internal rate of return of NCEs vs that of corporate bond after taxes of 35%.[a]

NCEs ranked in declining order of average annual worldwide sales	Nominal IRR (%) through years after marketing				Real IRR (%) through years after marketing				Break even year after market introduction
	10	15	20	24	10	15	20	24	
3 7 percentile	17.67	20.75	21.22	21.21	11.01	13.91	14.36	14.35	7
14 2 percentile	9.87	13.96	15.74	16.47	3.65	7.51	9 19	9.87	10
20 6 percentile	6.94	10.83	13 45	14.83	0.88	4.56	7.03	8.33	12
Average	7.22	10.73	12.08	12.44	1.16	4.46	5.73	6 07	12
28 0 percentile	6 66	9.24	10.11	10.18	0.62	3.06	3.88	3 95	14
31 7 percentile	2.16	5.94	8.32	9.56	−3.62	−0.06	2.19	3.39	21
Corporate bond	8.45	8.45	8.45	8.45	2.31	2.31	2.31	2.31	
35 3 percentile	6.67	6.44	6.28	6.18	0.63	0.42	0.27	0.17	not within 24
44 0 percentile	−0.42	3.80	5.55	5.96	−6.06	−2.07	−0 42	−0.05	not within 24
50 0 median	−2.91	2.58	4.20	4.21	−8.40	−3.22	−1.70	−1.69	not within 24
57 3 percentile	−2.39	0.62	2.08	2.60	−7.91	−5.08	−3.70	−3.21	not within 24
67 0 percentile	6.41	−3.86	−3.71	−3.63	−11.71	−9.31	−9.16	−9.09	not within 24
75 7 percentile	−10 89	−8.69	−7.75	−7.45	−15.53	−13.86	−12.98	−12.69	not within 24
86 7 percentile	−15.57	−12.89	−10.60	−8.95	−20.35	−17.82	−15.66	−14.11	not within 24

[a] Real rate (%) = $\left(\frac{100 + \text{Nominal rate (\%)}}{100 + \text{Inflation rate (\%)}} - 1\right) 100$.

Table 11. Drugs Selling More than $10 mio in the EC and Coming out of Patent Between 1986 and 1990.

1986	Albuterol	Anti-Asthmatic
	Diflunagil	NSAI
	Dobesylate calcium	Vasotropic
	Gliclazide	Anti-Diabetic
1987	Albutalol	B-Blocker
	Cefazolin	Antibiotic
	Clotrimazole	Antifungal
	Indapamide	Diuretic
	Methyldigoxin	Cardiotonic
	Parlodel	Enzyme Inhibitor
	Pindolol	Vasodilator
	Prazosine	Antihypertensive
1988	Amineptine	CNS Stimulant
	Econazole	Antifungal
	Flunarizine	Vasodilator
	Metoprolol	B-Blocker
	Miconazole	Antifungal
	Naproxen	NSAI
	Piroxicam	NSAI
	Timolol	B-Blocker
	Triazolam	Hypnotic
1989	Atenolol	B-Blocker
	Ketotifen	Anti-Asthmatic
	Tiaprofenic acid	NSAI
1990	Captopril	Antihypertensive
	Loperamide	Antidiarrheal

Source: W.P. von Wartburg (1988). Present and Future of Generics (mimeo).

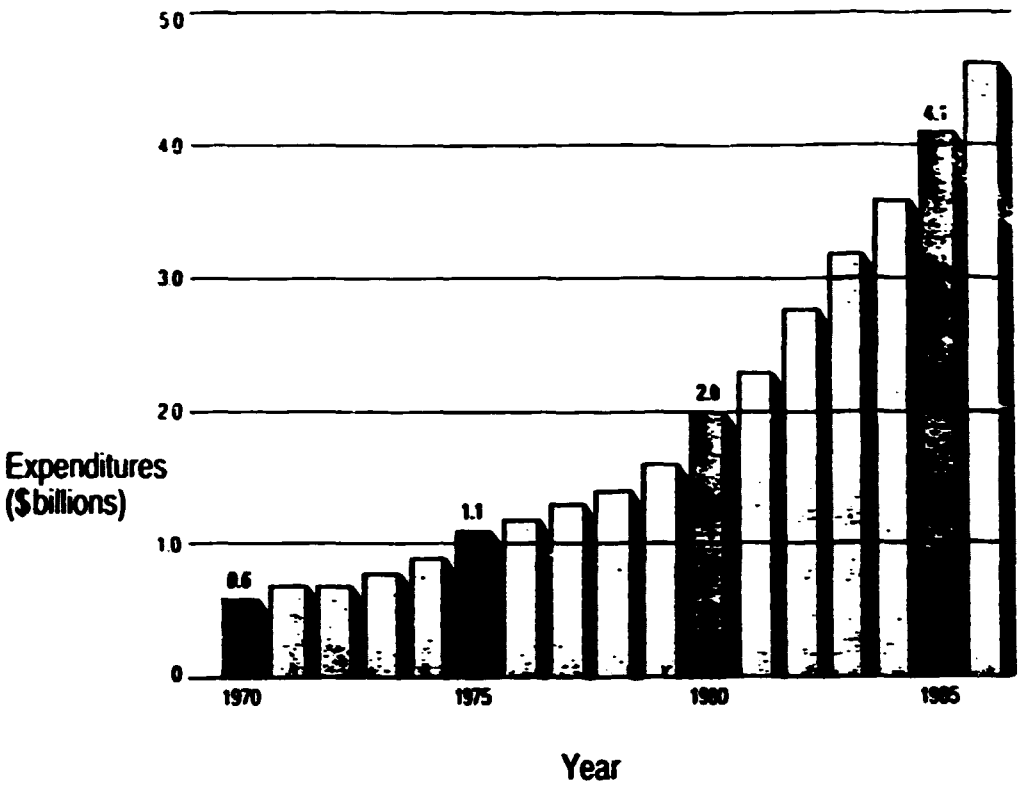
Table 12. Patent Expiration Dates for Leading Products Worldwide.

Rank	Product	Estimated Expiration Date
1	Zantac	1995
2	Tagamet	1994
3	Adalat	1989
4	Capoten	1995
5	Tenormin	1993
6	Renitec	2000
7	Naprosyn	1993
8	Voltaren	Expired
9	Feldene	1992
10	Kefral	1990
11	Cardizem	1992
12	Ventolin	1989
13	Ceclor	1992
14	Krestin	Expired
15	Amoxil	Expired

Source: Presentation by Jan Leschly, PMA International Meeting, 1988.

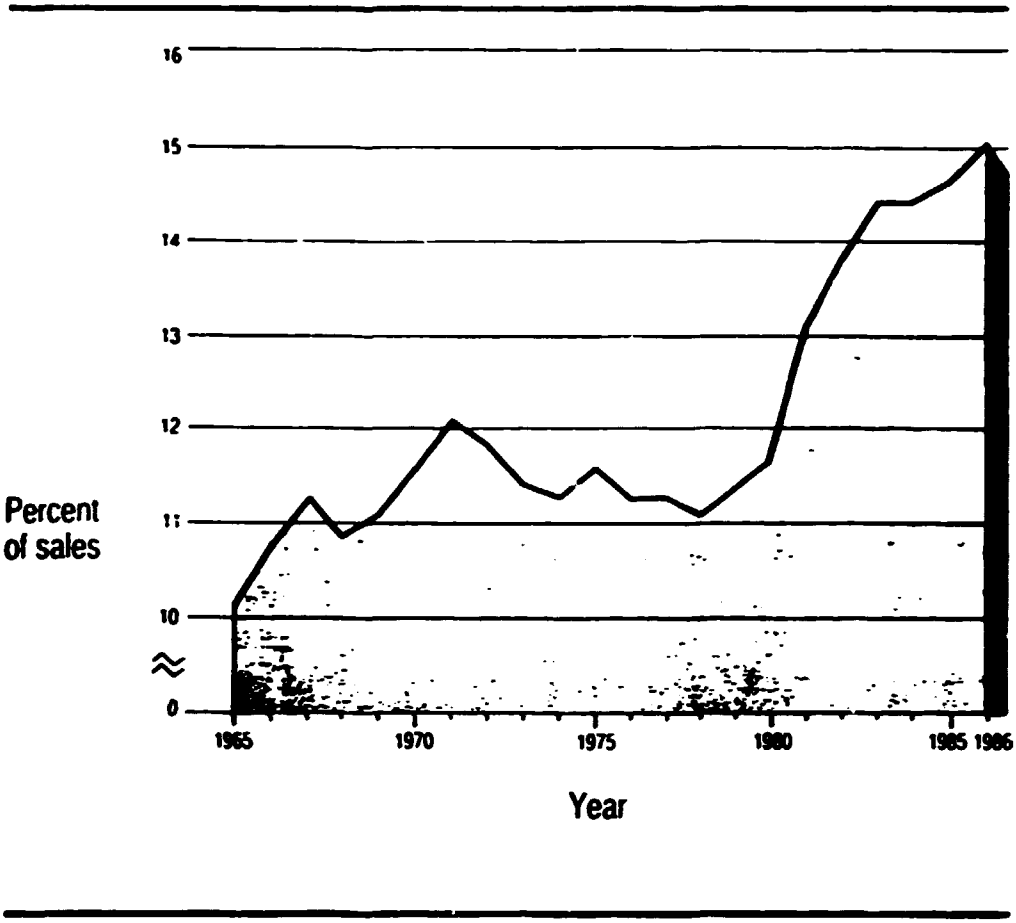
LIST OF FIGURES

Figure 1. R & D expenditures for PMA member firms.



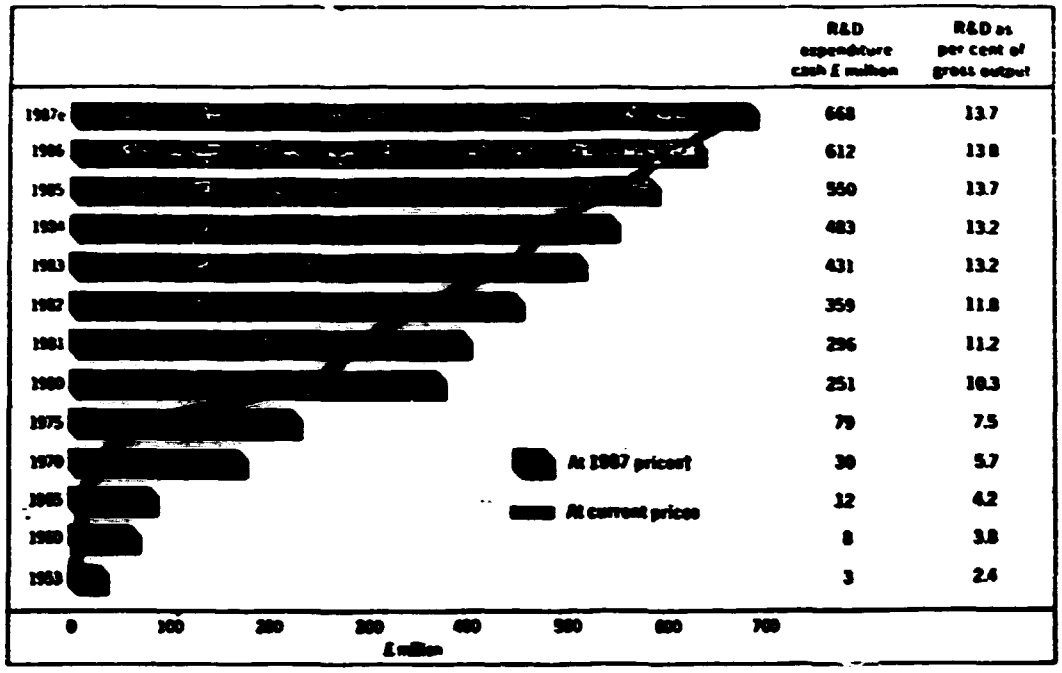
Source: Facts at a Glance, PMA (1987).

Figure 2. R & D expenditures for PMA member firms as a percentage of sales 1965-86.



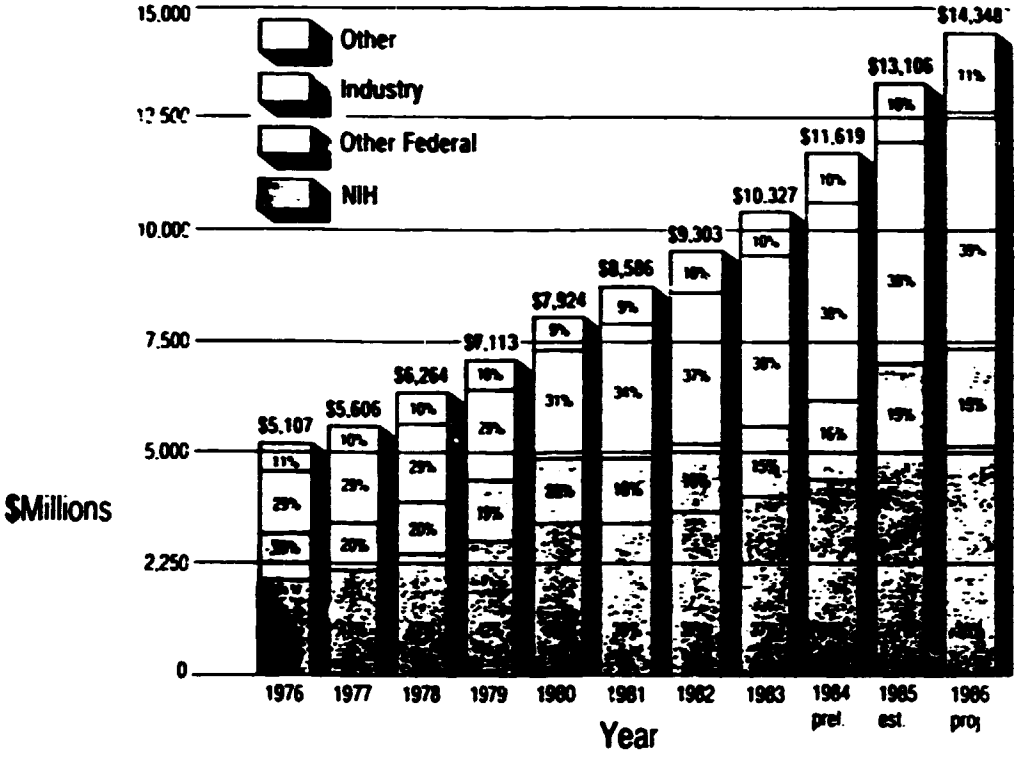
Source: See figure 1.

Figure 3. UK pharmaceutical industry R & D expenditure.



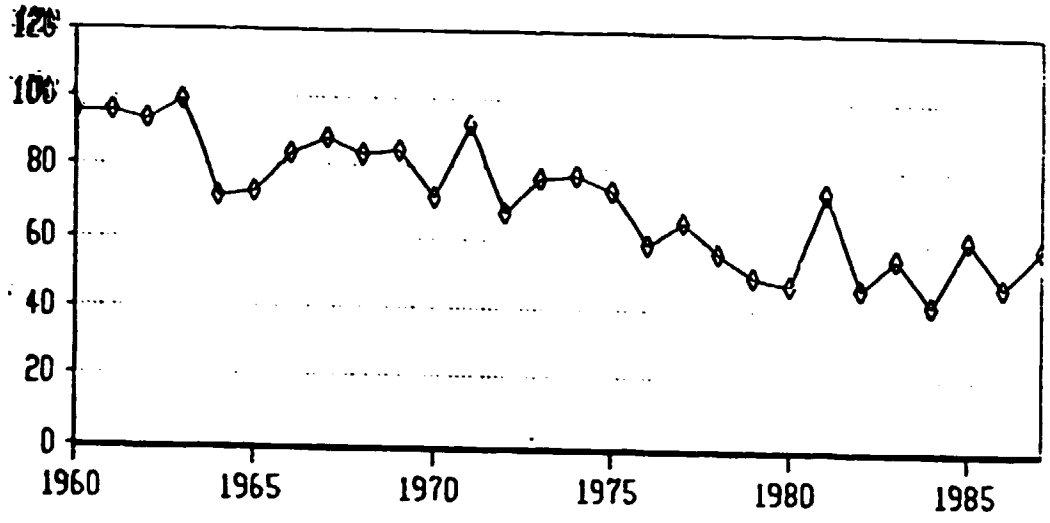
Source: British Medicines Research 1988. ABPI (1988).

Figure 4. National Support for health R & D in the United State by source; 1976-86.



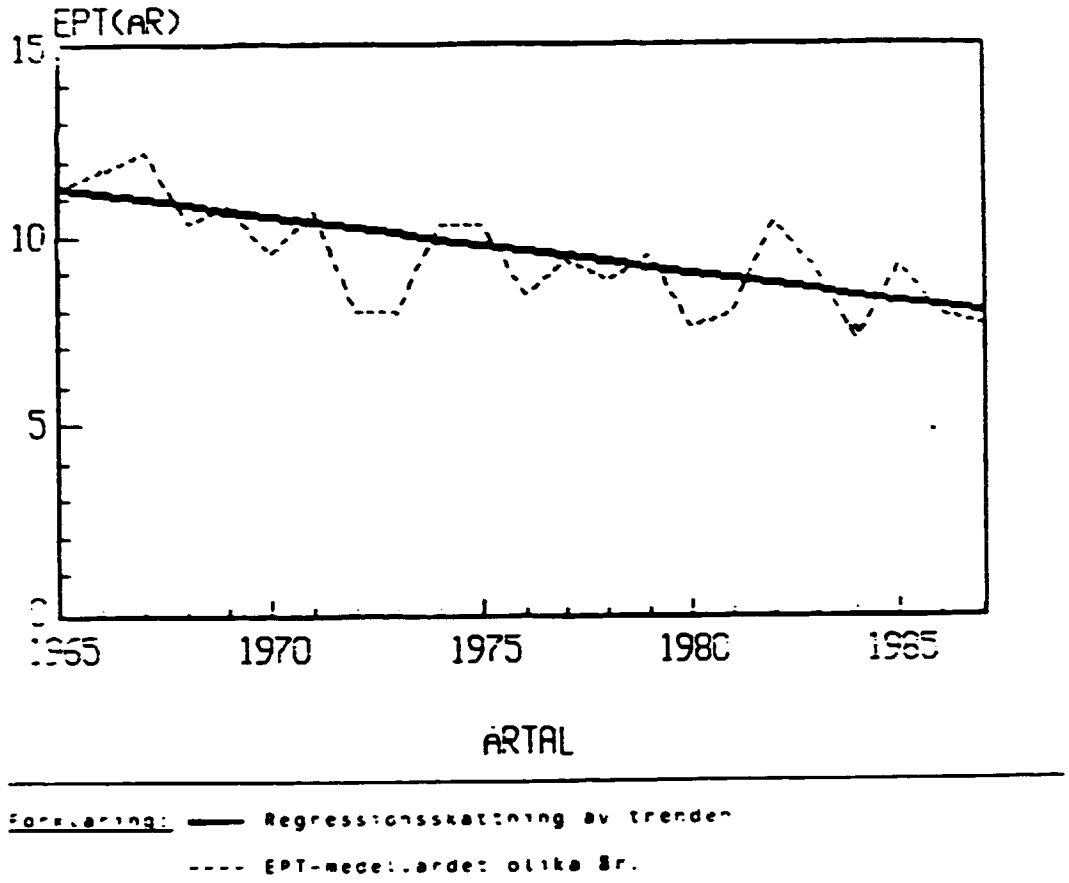
Source: See figure 1.

Figure 5. Registered NCE in the world 1960-87.



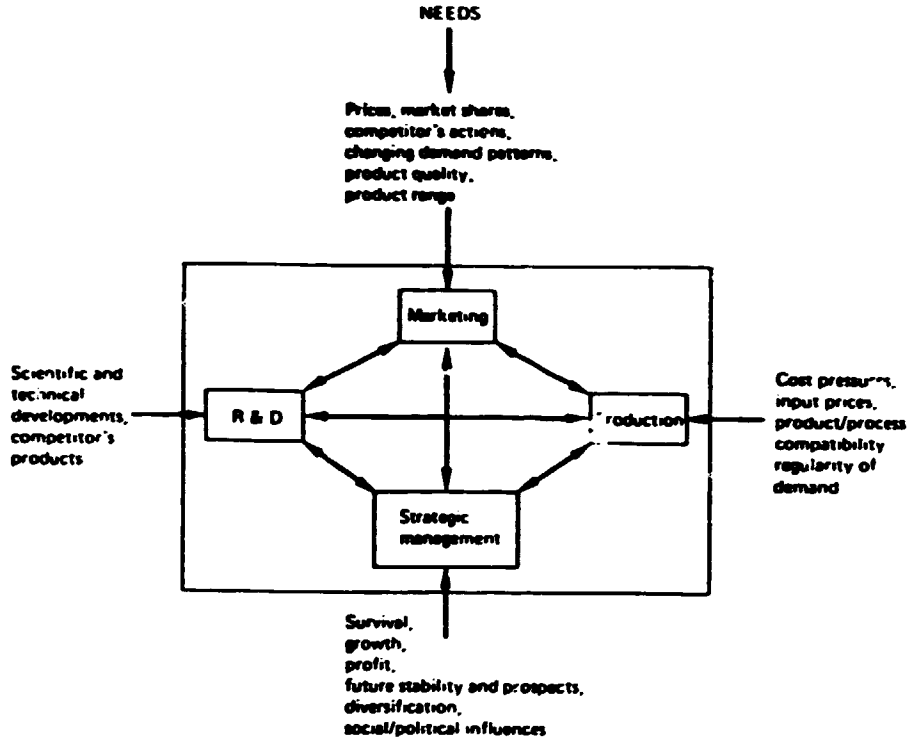
Source: Data base, Department of Health and Society, Linköping University.

Figure 7. Average effective patent time and estimated trend for NCE registered in Sweden 1965-85.



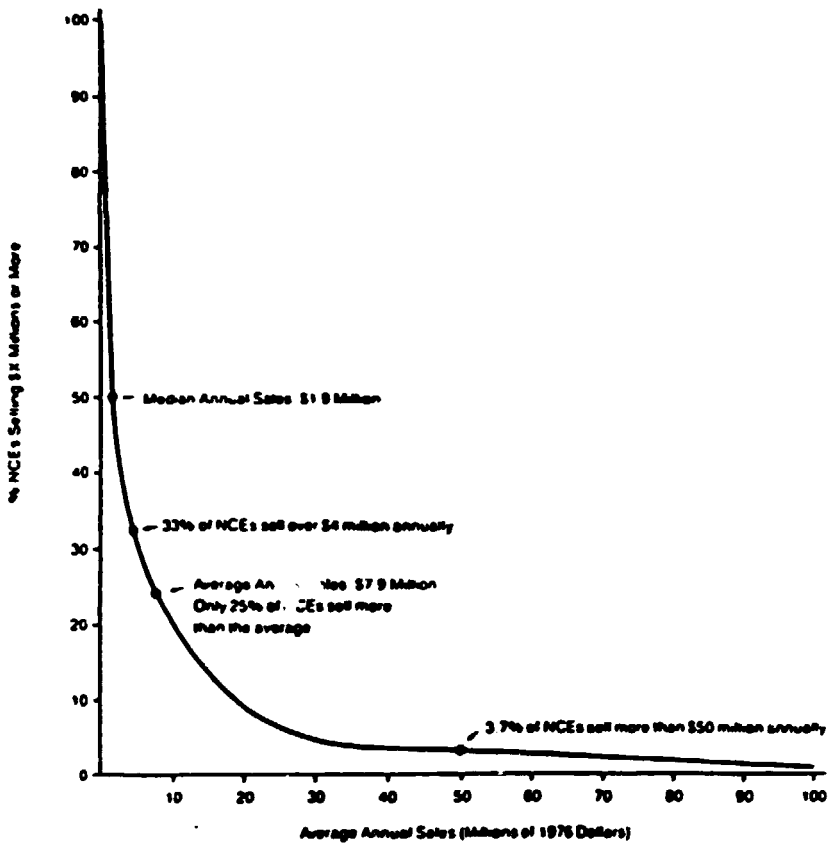
Source: Andersson, F. (1989). Effektiv patenttid för nya läkemedelssubstanser registrerade i Sverige 1965-87. CMT Rapport 1989:3.

Figure 8. A simplified model of the relationship between the innovating firm and its environment.



Source: Coombs, R., Sariotti, P. and Walsh, V. (1987). Economics of Technological change. Rowman & Littlefield Totowa, NS.

Figure 10. Per cent of NCEs exceeding a given level of average annual U.S. sales.



Source: Joglekar, P. and Paterson, M. (1986). "A closer look at the returns and risks of pharmaceutical R & D". Journal of Health Economics, Vol. 5, 153-157.