What helps the development of new vaccine products : an economic analysis of R&D spending in the vaccine industry, the productivity of biotechnological research and related issues in science and technology policy .

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What Helps the Development of New Vaccine Products?

An Economic Analysis of R&D Spending in the Vaccine Industry, the Productivity of Biotechnological Research and Related Issues in Science and Technology Policy

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Abstract

This thesis was motivated by concern regarding an alleged lack of investment in research and development of vaccine products which could offer considerable net benefit to societies, particularly in the developing world. The aim of this thesis is to provide decision support for science and technology policy which aims to promote private research and development in new vaccine products.

The literature suggests that markets fail to allocate sufficient resources to the development of new vaccines. Science policy can attempt to influence the direction of research through government subsidies, targeted fiscal support, regulatory measures or policies designed to influence human capital formation.

In order to assess the effectiveness of these measures in the context of the vaccine industry a R&D resource allocation model is empirically tested in Chapter Six. In a partial adjustment specification and error correction form, a relationship between the cost of funds and the allocation of R&D resources could be established for the US vaccine industry over a twenty five year period. It was also found that public sector research effort does not appear to 'crowd out' private sector R&D spending. Other factors emphasised in the literature, such as the relative market size and improvements in patent protection, were not significantly related to research intensity.

In the Second Part of this thesis the scope has been extended to include firms in the biotechnology industry which play an important role in vaccine innovation. The focus of research in Chapters Seven and Eight is on collaborative research which is believed to be a particularly productive way to bring new vaccines to the market.

In an empirical investigation of established US biotech firms it was suggested that companies which undertake more science or co-operate more closely with universities than their competitors are likely to show a higher level of

research productivity. What could not be established is whether scientific activity results in superior research outcomes or whether successful companies attract star scientists who are more likely to publish the results of their work.

This emphasises the importance of the promotion of scientific talent and the movement of scientists between the public and private sectors and internationally. It is suggested in Chapter Nine that the institutional structure of higher education has an important effect on the mobility of scientists: a country which imports highly-skilled personnel may maintain or improve its technological capabilities by this means. Using data from the British Higher Education Statistics Agency (HESA) it is suggested that contrary to belief, disciplines such as biological sciences experience a moderate net inflow of scientists from the private sector and abroad.

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This thesis touches upon the issue of 'informal research networks'. Such an exchange of ideas works exceptionally well with my colleague Peter Urwin. I would like to thank Peter especially, because he always finds time to discuss projects with fellow researchers.

Finally, I would like to dedicate this work to my parents who have supported me in all my ventures and have always shown remarkable faith in my abilities.

Statement of authorship: This thesis is the work of Stefan Kramer

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PART ONE

VACCINE RESEARCH AND DEVELOPMENT

1 Introduction

1.1 The problem and its setting

Innovative pharmaceutical companies invest heavily in research and development (R&D) of new products. Breakthrough innovations, or so called blockbuster drugs, offer large returns, guaranteed for a number of years by patent protection which legally prohibits the imitation of such a new product. The investment into innovative drugs will thus be guided by expected returns which in the light of many of today's as-yet incurable diseases is potentially very high.

Although today's large research intensive pharmaceutical companies are developing vaccines alongside therapeutical drugs, they are devoting comparatively little resources in vaccine R&D. Not only since the ongoing AIDS, Malaria, Tuberculosis and Measles epidemics, the public in general has realised that existing vaccines fall short of medical needs.

Physicians, world-wide, also remain frustrated by the death tolls caused by diseases against which vaccines are readily available and have in many cases been developed years, if not decades, ago. According to the World Health Organisation (2000a) Measles still kills 1 million children a year; Neonatal tetanus is responsible for 450,000 deaths among young children; Pertussis causes 355,000 deaths mainly among babies and young children; Meningococcal Meningitis is fatal in 35,000 cases, mainly among young children, and diphtheria still causes 8,000 deaths a year, with a huge proportion of deaths occurring in the developing world.

Improvements of existing vaccines such as combinations of vaccines to reduce logistics costs, to improve heat stability, and to improve immunogenicity are highly desirable (Baudrihaye 1992), while most of the existing childhood vaccines have undergone little modifications since they were first brought to the markets decades ago. Vaccine experts lament

that research into new vaccines has been stagnating during the past 30 years (Henderson 1994, p.4).

A number of factors are blamed for the underinvestment in preventive medicine: vaccination can adversely affect the sales of pharmaceuticals, vaccine markets are often much smaller than drug markets, or medical need arises where people cannot afford to pay for a new vaccine, in developing countries for example. In industrialised countries many parents are growing 'wary' of vaccination[1]; and during the 1980s US vaccine producers were made liable for injuries linked to vaccination. Patent protection on what is essentially a living organism is still disputed. Such was the perceived adversity of the market place that large US pharmaceutical companies such as Pfizer, Lilly, and Dow have in the past decided to leave the vaccine market for good (Galambos and Sewell 1996, p. 145).

Vaccine markets are also generally deemed to 'fail' in two respects. The individual vaccine user protects other members of society from contracting the disease and therefore conveys a benefit to them. In other words, vaccines carry strong positive externalities. Yet, the larger the percentage of the population vaccinated, the lower the individual's risk of catching the disease while the risk of adverse reactions remains unchanged. This gives a strong incentive for 'free-riding' on other people's use of vaccines leading to an overall underutilisation of vaccination.

Technologies for new vaccines are also considered 'international public goods' (World Bank 2000), which again creates a 'free-rider' problem, not of usage, but of investment in new vaccine technology. Individuals and

[1] At the time of preparation of this chapter, the alleged link between autism in children and the joint Measles Mumps Rubella vaccines has caused considerable controversy in the media, and the medical establishment, and this has led many parents not to immunise their children against these diseases.

governments will be paying less than the benefits they receive from other organisations' R&D inputs.

At the same time benefits in terms of saved treatment costs are in many cases estimated to be much higher than costs of developing, purchasing and administering the vaccine. Vaccines are thus often considered to be one of the most cost-effective measures available to the health care system and make better or even excellent use of resources. For example, in one of the reviews of the literature (Steering Committee on Future Health Interventions 1988, pp. 34-36) it was found that net savings from measles immunisation in the United States were US $ 1.3 billion during the period 1963-1972.

Albritton (1978), to mention another example, found a benefit-cost ratio of 10:1 with regard to measles vaccination. This means that the benefits in terms of saved treatment costs of the disease are ten times the costs of purchasing and administering the vaccine. In practically all cases vaccines can *reduce* health care costs provided that they are applied to the optimal population group (i.e. the population with a certain level of risk of contracting the disease). Mass immunisation campaigns throughout the 1970s and 80s reflected the belief of many health services that no better use could be made of their resources than investing in prevention and, ideally, eradication of diseases.

Since private investment may thus be falling far short of what is considered socially desirable, government has a potentially prominent role to play in influencing the outcome of the market. Governments in fact do make efforts either to develop vaccines themselves and/or to encourage the development of vaccines within the pharmaceutical industry. Quite how this is best achieved is subject to debate. The World Health Organisation has together with the Global Alliance for Vaccines and Immunisation (GAVI) established (WHO 2000b) that both 'push' and 'pull' factors will influence the pharmaceutical industry's investment

decision into new vaccines. Among the push factors, protection of property rights is cited as crucial for the successful development of a new vaccine. Public-private collaborations between academia and industry are also attributed a greater chance of success than industry effort alone to come up with a new formulation.

As far as pull strategies are concerned "one of the central issues is that of credibility. Specifically, "industry needs to be able to demonstrate that there is a credible market for the new products that it develops" (WHO 2000b, p. 24). The importance of a guaranteed market for future vaccine has also been emphasised by Michael Kremer (2000). The author acknowledges that drug companies are sometimes forced to sell products at a price not high enough to cover R&D costs. The small market in developing countries for vaccines -which amounts to no more than $200m a year- is not offering enough incentive to incur the huge costs of development. In Kremer's view a fund set aside for the purchase of a future vaccine would provide the right incentives, and, unlike R&D subsidies, public money would not be wasted should the industry's efforts to develop the desired vaccine not come to fruition. Acknowledging the importance of demand, the World Bank has recently pledged to set aside US$ 1 bn for the purchase of future vaccines.

While efforts are made to encourage industry investment, government has also become an increasingly important and, as a consequence, very cost-conscious purchaser of vaccines. Industry has repeatedly pointed out that lower vaccine prices present fewer incentives to invest in new vaccines (Baudrihaye 1992).

The following problem presents itself: for the reasons cited above, vaccine projects find it difficult to attract sufficient private R&D funds although more investment would, arguably, in many cases increase social welfare. Hence government wants to encourage vaccine R&D in the most cost-effective manner. In order to do this, policy makers need to

develop a clearer understanding of the factors influencing private R&D spending behaviour and research success in the area of vaccine products.

1.2 Aims and methodology

This study does not attempt to assess absolutely all factors relevant to the successful development of new vaccines. Its purpose is to focus upon, and clarify three distinct aspects of research and development into vaccine products. A first empirical study in Chapter Six investigates the determinants of R&D spending in the vaccine industry, controlling for regulatory and market forces and the cost of finance. This should help policy-makers to assess the effectiveness not only of 'pull' factors such as market demand and expected returns, but also regulatory influences such as patent protection and price regulation.

'Technology push' is at the centre of the second empirical investigation in Chapter Eight. Public-private collaboration is often seen as the most productive way to bring new medicinal products to the market although this has not been tested for in the field of biotechnological products. An empirical investigation of the biotechnology industry assesses whether those companies collaborating with the public sector are more productive researchers than companies 'going it alone'. This again might help policy makers to target public funds on R&D projects with the highest chance of success.

What comes to light in Chapters Seven and Eight is that the geographical location and movement of scientists appears to be associated with the research success of bio-pharmaceutical firms. Chapter Nine investigates the mobility of scientists further and looks at the wider implications for science and technology policy in Europe, in particular the funding of higher education institutions and the incidence of 'brain drain' and 'brain

gain' in biological sciences and a range of other relevant academic subject areas.

Ideally the thesis would conclude on the question of how a national or perhaps even an international system of biotechnology innovation should be designed. This would, however, be a near-impossible task, since many other factors also affect the effectiveness of such a system; their consideration is beyond the scope and size constraint of this thesis. Chapter Ten does, however, try to put the findings of the thesis in the wider context of Science and Technology Policy. Those aspects of Science and Technology Policy, which lie beyond the scope of this thesis, are discussed in outline.

1.3 Organisation of the remainder of the study

The thesis is divided into two main parts: Part One investigates the vaccine market and by reviewing the relevant literature aims to build a model of the determinants of private vaccine R&D spending. The model is introduced and empirically tested at the end of this part. Part Two looks at wider issues in science and technology policy specifically in the context of the biotechnology industry which is becoming increasingly important for vaccine innovation. An important aspect of research productivity in biotechnology is knowledge transfer and the associated movement of scientists, an issue which will be discussed in greater detail at the end of Part Two.

Part One is organised as follows: Chapter One introduces the subject. Chapter Two outlines the current state of world health and demonstrates how today's and future vaccines might control diseases in a very cost-effective manner. Chapter Three presents the economic rationale for government intervention in the vaccine market. This part will also investigate what is believed to be the most effective way to get industry to undertake research into the 'right' vaccines. Chapter Four reviews the

innovation economics literature for evidence that 'push' and 'pull' factors are at work when firms allocate R&D funds specifically in the context of the pharmaceutical industry. Chapter Five presents the little material there is about the economics of the vaccine industry, which will help to formulate a model of R&D investment, which is then introduced and tested empirically in Chapter Six.

Part Two starts with Chapter Seven, which reviews the literature assessing public-private cooperation in R&D and is followed by an empirical investigation of the biotechnology industry in Chapter Eight. Chapter Nine looks at the mobility of research scientists followed by Chapter Ten which reviews the broader context of science and technology policy. Chapter Eleven concludes the thesis and raises areas which could warrant further research.

2 Vaccines' contribution to world health

2.1 Background

Vaccines[1] are weakened or killed micro-organisms[2] which stimulate the body to produce antibodies against an infectious virus or bacteria. Vaccines can therefore confer immunity from an infection of that micro-organism and protect the vaccinated person form contracting the disease.

In this chapter it will be shown that vaccines are among the most cost-effective health care measure available to health services, and are best suited to prevent diseases which levy the heaviest burden on populations in particular in the developing world[3].

What will also be shown, is that the effective use of vaccines will in many instances *save* costs incurred by the health service. Despite all this, new vaccine development has in the past fallen short not only of medical needs but what is believed to be technically feasible by vaccine experts.

The apparent lack of firms' interest in new vaccine development has led many to believe that private sector research cannot exclusively be relied

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[1] 'Vaccinia' is the medical term for cowpox ('vacca', latin for cow). In 1796 the British country doctor Edward Jenner administered the first experimental vaccination with the cowpox virus to build immunity against smallpox. Jenner had observed that milkmaids which had previously contracted cowpox were no longer susceptible to contracting smallpox.

[2] Vaccines of weakened microorganisms are also called 'live' vaccines. Live vaccines, such as for example the Measles vaccine, will replicate inside the host and protection with a live vaccine often lasts a life-time (Ellis 1988, p. 568). They may, however, also revert to a more dangerous form and cause adverse reactions. Killed vaccines do not replicate inside the host and as a consequence are less efficient. In order to achieve long-term protection, booster doses are required.

[3] Many infective diseases are controlled though vaccination in the developed world so that heart disease and cancer have become relatively more important in terms of burden of disease.

upon when it comes to addressing the medical needs of those most severely affected by infectious diseases. While this chapter aims to outline the contribution vaccines can make in preventing diseases, the following chapter assesses whether vaccine markets do fail to allocate sufficient resources to research and development.

2.2 The state of world health

Infectious diseases represent the world's leading cause of premature death killing at least 17 million people in 1995, among them 9 million young children, who died from preventable causes such as diarrhoea, pneumonia and measles (WHO 1996). There was once a sense of optimism that the struggle for control of infectious diseases was nearly over. In October 1977 twenty-three year old Ali Maow Maalin was the last human ever to have contracted smallpox. Then a disease which caused widespread suffering and millions of deaths over many hundreds of years ceased to exist. Not only was immense suffering averted, hundred of millions of dollars of treatment and immunisation costs could then be allocated for the fight against other diseases. But why has smallpox been the only successful disease eradication so far? Will other diseases follow and can we look forward to a disease-free world with more powerful vaccines to be developed in the near future? What are the underlying biological, economic, and social criteria which seem to make eradication possible for some diseases and impossible for others?

Figure 2.1 shows the burden of the most devastating infectious diseases as identified in the World Health Report 1996 (WHO 1996), which is the most recent of the annual World Health Report series exclusively devoted

to infectious diseases[4]. Clearly marked with asterisks are those diseases which have been prioritised by the WHO.

[4] World Health Reports are published annually by the WHO and each report includes a detailed coverage of a specific global health issue, such as 'Fighting Disease, Fostering Development' in 1996 or 'Health Systems: Improving Performance' in the 2000 report.

Figure 2-1

Global Health Situation: mortality, morbidity and disability, selected infectious diseases of global and regional concern, all ages, 1995 estimates

		Number (000) of cases			
Selected infectious diseases by main mode of transmission	**Global priorities**	**Deaths**	**New (incidents)**	**All (prevalence)**	**Disabled persons (permanent and long run)**
Person to person					
Acute lower respiratory infections (not related to measles, pertussis or HIV)	◆	4,416	394,750	na	na
Tuberculosis	◆	3,072	8,888	22,000	na
Hepatitis B (viral)	◆	1,156	4,149	350,000	na
Measles	◆	1,066	Na	42,000	5,590
AIDS	◆	1,063	1,125	1,538	na
Whooping cough (pertussis)	◆	355	Na	40,000	na
Poliomyelitis, acute	◆	9	Na	82	85
Leprosy	◆	2	561	1,833	3,000
Sexually Transmitted diseases:	◆				
- Gonorrhoea		Na	62,000	na	na
- Syphilis, venereal		Na	12,000	na	na
- Chancroid		Na	7,000	na	na
Trachoma		Na	20,540	153,832	5,583
Diphtheria	◆	Na	Na	35	na
Food-, water- and soilborne					
Diarrhoea (not measles or HIV-related)	◆	3,115	4,002,000 (episodes)	na	na
Neonatal tetanus	◆	459	Na	na	na
Hookworm disease		65	Na	151,000	na
Ascariasis		60	Na	250,000	na
Schistosomiasis		20	Na	200,000	na
Cholera		11	384	na	na
Trichuriasis		10	Na	45,530	na
Nematode infections (foodborne only)		10	Na	40,000	na

Selected infectious diseases by main mode of transmission	Global priorities	Number (000) of cases Deaths	New (incidents)	All (prevalence)	Disabled persons (permanent and long run)
Person to person					
Dracunculiasis (guinea-worm infection)	◆	Na	122	122	na
Insect borne					
Malaria	◆	2,100	300,000 - 500,000	na	na
Leishmaniasis		80	1,750	12,000	
Onchocerciasis (river blindness)	◆	47	na	18,000	360
Chagas disease (American trypanosomiasis)	◆	45	800	18,000	na
Dengue/dengue haemorrhagic fever		24	592	na	na
Sleeping sickness (African trypanosiomasis)		20	Na	300	na
Japanese encephalitis		11	43	na	9
Plague		0.2	2	na	na
Yellow fewer		0.2	0.5	na	na
Filariasis (lymphatic)		Na	Na	120,000	43,000
Animal-borne					
Rabies (dog-mediated)		60	Na	na	na

Selected infectious diseases (total)	**17,312**

source: WHO (1996, p. 24)

Once a disease has been prioritised by the health service, any attempt to fight this disease would normally start at a national level, would then target a whole continent and finally attempt to eliminate the disease on a global level. A disease is only eradicated when the last samples of a virus kept in test tubes in laboratories are finally destroyed. For the smallpox virus this final step had originally been envisaged for the year 1999, but was subsequently delayed[5].

Many diseases have been prioritised due to their overall disease burden, but what are the criteria that can make a disease eradicable or at least controllable?

First of all an effective and easy to administer vaccine has to be available. Some of today's most widely used vaccines are only moderately effective. The BCG vaccine against tuberculosis, for example, is only effective in 60% of children. This will make eradication an impossible task because more than one out of four children who have received the vaccine remains unprotected against the disease. Given that only a certain proportion of children can be reached, the overall protection rate is even lower.

Second, the disease must be easily diagnosed, so that the spread of the disease can be averted by early treatment.

Thirdly, it is crucial than the agent which causes the disease only replicates inside humans. Some other agents live inside animals or soil/ water/air so they can survive effectively outside the human body.

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[5] It was believed at the time that the US and Russia are the only two countries to have retained samples of the smallpox virus. This is no longer certain and it is feared that a 'rogue state' may also have kept samples of the virus, for possible use in biological weapons. The two governments now consider it safer to keep their samples should the need for further research or the production of vaccines arise.

Finally, it is important that the biological variability of the virus is low so that an effective vaccine can be used at the same time at different locations. Should the genetic potential of the virus be large, so that the virus occurs with different strains and subtypes (such as HIV, with different sub-types in different continents), it is likely that a vaccine or treatment is ineffective against some of the sub-types.

Another key factor of success is the motivation of the population to participate in an immunisation campaign. Complacency, misperception of risk, and a general fear of adverse reactions to vaccines, have all caused some campaigns to fall short of their initial goal.

The WHO has set priorities according to the overall burden of disease and the feasibility of control. One has to bear in mind that the control of *infectious* diseases is only part of the agenda since:

> "the war against ill health in the 21st century will have to be fought simultaneously on two main fronts: infectious disease and chronic, noncommunicable diseases. Many developing countries will come under greater attack from both, as heart disease, cancer, diabetes and other 'lifestyle' conditions become more prevalent, while infectious illnesses remain undefeated" (WHO 1998, p. 2).

Here, only infectious diseases which could one day be effectively controlled by vaccination will be discussed below.

Half of all premature deaths from infectious diseases killing mostly children and young adults, are caused by six diseases - pneumonia, tuberculosis, diarrhoeal diseases, malaria, measles and HIV/AIDS (WHO 2000a). While effective treatment or prevention is not available for some of these diseases, many of the under-5 deaths in children, up to 2 million a year by some estimations, are preventable by existing vaccines (WHO 1998, p.3).

Infectious diseases are commonly classified by their main mode of transmission and the following will give a brief overview of the character, burden and potential treatment or prevention of diseases classified for global priority by the World Health Organisation.

2.3 Person to person transmission

Among the acute lower respiratory infections, pneumonia and the two agents which cause childhood pneumonia, streptococcus pneumonia and haemophilius influencae are the main cause of concern. Infants and young children, whose health is already weakened by low birthweight and malnutrition, have little resistance to it and show high case fatality rates. Millions of children are dying every year from these diseases which could be treated with antibiotics at very low costs (WHO 1996, p. 25).

However, the provision of antibiotics is sometimes prohibitively difficult in communities with little access to health care. The availability of an effective vaccine is therefore of great importance. According to the Childrens' Vaccine Initiative (CVI Forum, 13, 1996), a pneumococcal vaccine for children of all ages would bring the greatest benefit among all the vaccines which are likely to be developed within the next ten years. Four of the largest vaccine suppliers are currently undertaking clinical trials for conjugate pneumococcal vaccines. The outcome of these trials, however promising, is still uncertain.

Four airborne infections kill 1.4 million children each year world-wide, despite the availability of vaccines (WHO 1996, p. 25). These are measles, pertussis (whooping cough), meningococcal meningitis and diphtheria. Today, 1 million children a year still die of measles, the great majority in developing countries. An effective measles vaccine exists, although it cannot be administered before the age of nine months. A great number of children are affected by the disease before that age and therefore remain unprotected.

Pertussis became vaccine-preventable around 1960 and the number of deaths since then has dropped dramatically; however, 355 000 babies and children still die of it each year, most of them in Africa, Asia and Central and Latin America (WHO, 1996, p. 26).

A vaccine against diphtheria was introduced 50 years ago, although it is estimated that diphtheria still causes 8000 deaths a year. The recent outbreak in the countries of the former Soviet Union shows what can happen if immunisation levels are not maintained or do not keep track of large movements of population. 25,000 cases have been reported and up to 25% of those affected have died.

Tuberculosis, estimated to kill 2.9 million people a year (WHO 1998, p. 10), was declared a global emergency by the WHO in 1993. The WHO (WHO 1996, p. 27) warned that,

"if the effectiveness and availability of tuberculosis control measures do not improve substantially, more than 30 million tuberculosis deaths and nearly 90 million new cases are expected to occur in the last decade of this century. [...] To make the global situation worse, tuberculosis has formed a lethal partnership with HIV. The AIDS virus damages the body's natural defences - the immune system - and accelerates the speed at which tuberculosis progresses from a harmless infection to a life threatening condition. [...] Tuberculosis is already the opportunistic infection that most frequently kills HIV-positive people."

Tuberculosis can be treated but a growing number of drug-resistant strains appears world-wide, mostly due to incomplete or inappropriate treatment[6]. Tuberculosis is not restricted to developing countries.

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[6] Drug resistance occurs when treatments are stopped too early enabling the remaining cells to build resistance against that particular drug.

Outbreaks are occurring in the United States in prisons or hospitals including several forms of drug-resistant strains, involving people with HIV infections and health workers infected by patients. Partly due to the low effectiveness of the existing vaccine, Tuberculosis is most effectively prevented by early detection and cure. A new strategy where health workers make sure that all patients finish their course of treatment has been successfully adopted in many countries.

Leprosy does not kill but causes an immense physical and social burden. The breakthrough to cure leprosy came in 1981 with the adoption of a multidrug therapy which proved to be highly effective, although the target to eradicate the disease by the year 2000 (WHO 1998, p. 10) has been missed.

Poliomyelitis has also been targeted for eradication. The 'kick polio out of Africa' campaign is currently on top of the WHO agenda and thanks to an old but still highly effective vaccine the virus has already disappeared from the Americas and industrialised countries, with cases world-wide declining by over 90% since the start of the polio eradication campaign in 1988 (WHO 1998, p. 10). The disease, which is today prevalent mainly in the Indian Subcontinent, parts of West and Central Africa, some countries in the middle East and the Horn of Africa, affects mainly very young children, causing in one out of a hundred cases paralysis of the muscles. Although the existing vaccine is extremely cheap, the total costs of the eradication campaign are estimated at $2.5 billion between 1996 and 2000. However, the potential world-wide savings resulting from polio eradication are estimated to exceed $1.5 billion a year (WHO 1996, p. 36).

AIDS, unlike most other infectious diseases, kills young and middle-aged adults who are at their most productive and whose loss represents a particularly serious burden to developing countries. It has become one of the prime causes of adult death in some urban areas in Africa, the US and Europe with 1.8 million adult deaths in 1997 (WHO 1998, p. 3), and

swallows up to 80% of the health budget of some African countries. At the same time HIV could reverse some of the major gains achieved in child health over the past years with 590,000 children aged under 15 infected with the HIV virus in 1997 alone (WHO 1998, p. 3). Although a combination therapy using existing drugs can significantly reduce the viral load of HIV positive patients and thereby delay the progression of the disease, no effective cure or vaccine has been found. Any cure found is also most likely to be too expensive for health services in the developing countries, so that the adoption of safer sex practices appears to be the most appropriate strategy to control the disease in these countries in the medium term.

Hepatitis B is one of six different Hepatitis viruses (A,B,C,D,E, and G). Hepatitis B and C are the most serious due to their long term implications for the health of the people affected. More than 2 billion people alive today have been infected with Hepatitis B (WHO 1998, p. 11). The virus is transmitted by exposure to contaminated blood and blood products, semen and vaginal fluids. The infection is passed from the mother to her child, from children to other children, from children to adults and adult to adult which then infect their own offspring. Once infected, the carrier may either develop acute hepatitis and in a small number of cases die within days or weeks, or may recover and develop lifelong immunity, or develop the chronic carrier state. The chronically infected are at risk of serious illness and death from liver cirrhosis and liver cancer, and every year more than 1 million people die of these two conditions (WHO 1996, p. 33).

A highly effective vaccine was brought to the market in 1982 but has only recently been adopted in mass immunisation campaigns in developing countries, where most of the deaths occur, after the initially very high price has fallen significantly. However, some countries in sub-Saharan Africa, India, eastern and central Europe are still not able to afford the vaccine at the preferential price for developing countries of $0.50 to $1 per dose (WHO 2000b). Childhood immunisation is even more important

since young children affected have a higher probability of becoming chronic carriers than older children or adults. In industrialised countries mainly health workers are vaccinated against the disease.

Hepatitis C, similar in transmission and health consequences, was first identified in 1989 and it is estimated that today 170 million people are chronic carriers at risk of developing liver cirrhosis and liver cancer (WHO 1998, p. 11). No effective cure or treatment has yet been developed.

2.4 Food-, water-, and soil-borne diseases

The control of food- and water-borne diseases relies on the provision of clean water and food hygiene, which in turn depends on whether communities have an adequate system for disposing of their faeces, the availability of clean drinking water, and improving the hygienic quality of foodstuffs.

Diarrhoeal diseases, which caused more than 3 million deaths in 1995 (WHO 1996, p. 28) are caused by water and food contaminated most commonly with the organism Escherichia coli (E. coli).

Guinea worm disease may be eradicated in the near future. The disease which is transmitted through contaminated water and is associated with the emergence of guinea worms through skin of the hands, feet and other parts of the body, can be combated very easily by breaking the transmission cycle. An effective vaccine or cure is, however, not available.

Tetanus, being a soil-borne disease, is responsible for the deaths of at least 450,000 children a year (WHO 1996, p. 42). Tetanus cannot be treated; vaccination of pregnant women which prevents the transmission of the disease to their new-born babies is an effective measure to control the disease. Tetanus will never be eradicated since the organism will

always live in the environment and pose a threat of infection but the disease can be controlled by the widely available combination vaccine DTP (diphtheria, tetanus, pertussis). Up to five doses of DTP have to be given to insure sufficient immunisation, which makes the development of a slow-release tetanus vaccine desirable which could improve coverage and reduce costs by ensuring long lasting immunity with only one injection.

2.5 Insect-borne diseases

Among the insect-borne diseases, malaria is the most severe. It puts about 40% of the world population at risk, with 300-500 million of clinical cases of malaria each year and 1.5 - 2.7 million deaths caused by the disease (WHO 1996, p. 47). Malaria was thought to be controllable by the intensive use of insecticides, most notably DDT, but today epidemics are re-occurring in areas where transmission had formerly been interrupted. No vaccine has been developed yet and the elimination of mosquito breeding places and the prevention of mosquito bites (using bed nets) has been the most effective control strategy so far. Despite the availability of malaria drugs:

> "the greatest threat to the control of malaria in the near future is the loss of effectiveness of these drugs because of resistance. The potentially lethal malaria parasite, P. falciparum, has shown itself capable of developing resistance to nearly all antimalaria drugs now used. Chloroquine, perhaps the best ever antimalaria drug [...] is now failing against falciparum malaria in most areas of the tropical world" (WHO 1999, p. 52),

The predicted loss of effectiveness of anti-malaria drugs underlines the importance of developing a malaria vaccine as the only reliable means of preventing this disease.

River blindness is an infection with the filateral worm, which is transmitted by blackflies that breed in fast flowing rivers mainly in Africa. The worm matures inside the human host. Adult worms settle into visible lumps or nodules under the skin. Female worms then produce millions of microfilaria, which invade the skin and the eye, eventually destroying the skin and the retina of the eye, causing blindness. 17.5 million people are affected by the disease (WHO 1996, p. 52). The last 20 years have shown dramatic success in controlling river blindness either through insecticide spraying or the use of a newly developed drug.

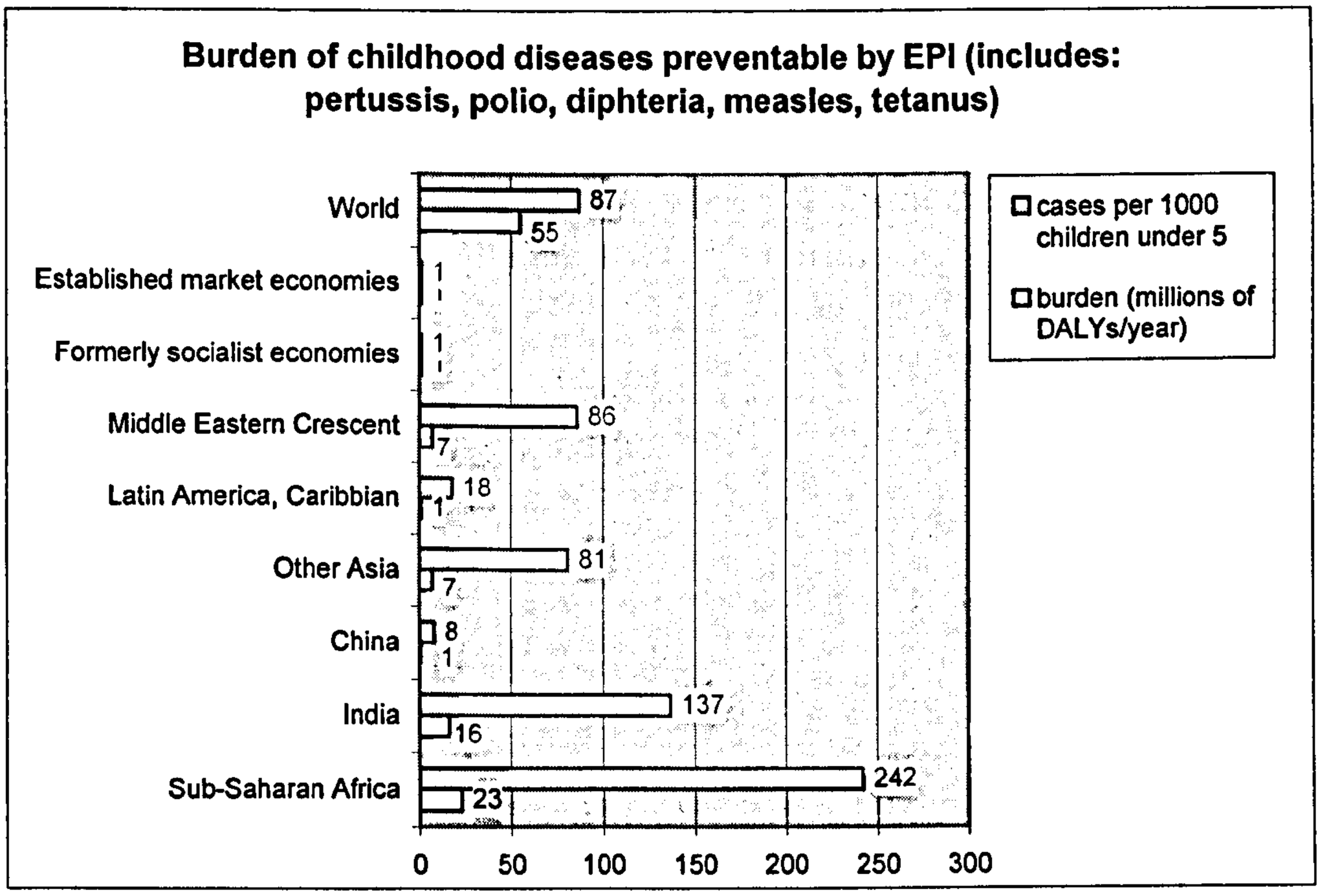
Chagas disease is caused by a parasite which is transmitted from domesticated or wild animals by a blood sucking triatomine bug. It occurs mainly in the Americas and is the leading cause of cardiac deaths among young adults in parts of South America. 45000 people a year die (WHO 1996, p. 53). Chagas, although untreatable, can be controlled by systematically attacking the vector and screening of donor blood in endemic countries. Remarkable success in this regard has already been made in South America where Chagas has been targeted for elimination as a public health problem.

In light of the devastating effect of the diseases described above, it becomes a difficult task to declare some of them as a priority. Given the limited health resources world-wide, calculating the burden of disease is however crucial for the cost-effective control of diseases and the minimisation of the overall burden of disease. Any evaluation of the burden of disease using the number of deaths has its merits since it is an easily measurable and indeed, by the statistical offices of most countries, widely measured event.

However, some diseases such as polio levy a heavy burden on society without necessarily causing death, hence the measurement of disease burdens will need to consider health states other than death. QUALYs (Quality Adjusted Life Years, explained in Box 2.1) and DALYs (Disability Adjusted Lifeyears) are used by the WHO and the World Bank (1993) to

measure the overall burden of disease taking different degrees of disability and quality of life into account. DALYs are computed by grouping diseases into six different classes of severity of disability in comparison with a loss of life. Blindness would, for instance, be assigned a severity weight of 0.6, and death representing the severity of 1 or a full year of life lost. Less severe conditions will be multiplied by the average duration of the condition. In this case allowances are also made for future life years lost, which are discounted by 3% a year and for age weights, so that life years lost at different ages were given different relative values[7] (World Bank 1993, p. 26).

Figure 2-2



Source: World Bank 1993, p. 73

As shown in figure 2.2, among the childhood diseases which are preventable by the Expanded Programme of Immunisation (EPI), developing countries carry the heaviest toll. The burden of disease

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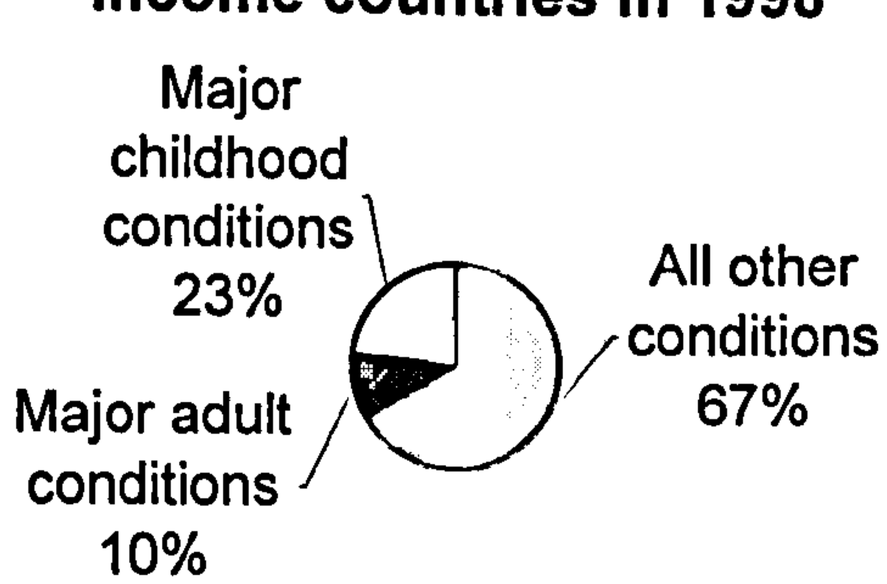
[7] The relative value of a year of life is at its maximum of 1.4 at the age of 25 and declining to 0.4 at the age of 90.

expressed in DALYs is many times greater in the developing world than in the developed world where childhood immunisation has been well established for many years. Targeting diseases prevalent in these countries is likely to generate a higher health gain overall. Of all diseases prevalent in low and middle income countries, six diseases - pneumonia, tuberculosis, diarrhoeal diseases, malaria, measles and HIV/AIDS impose a disproportionately high burden on these societies (WHO 2000a).

Of all conditions, five major childhood conditions cause 23% of all Disability Adjusted Lifeyears (DALYs) in low and middle income countries, three major adult conditions cause 10% of all DALYs, here shown in figure 2.3.

Figure 2-3

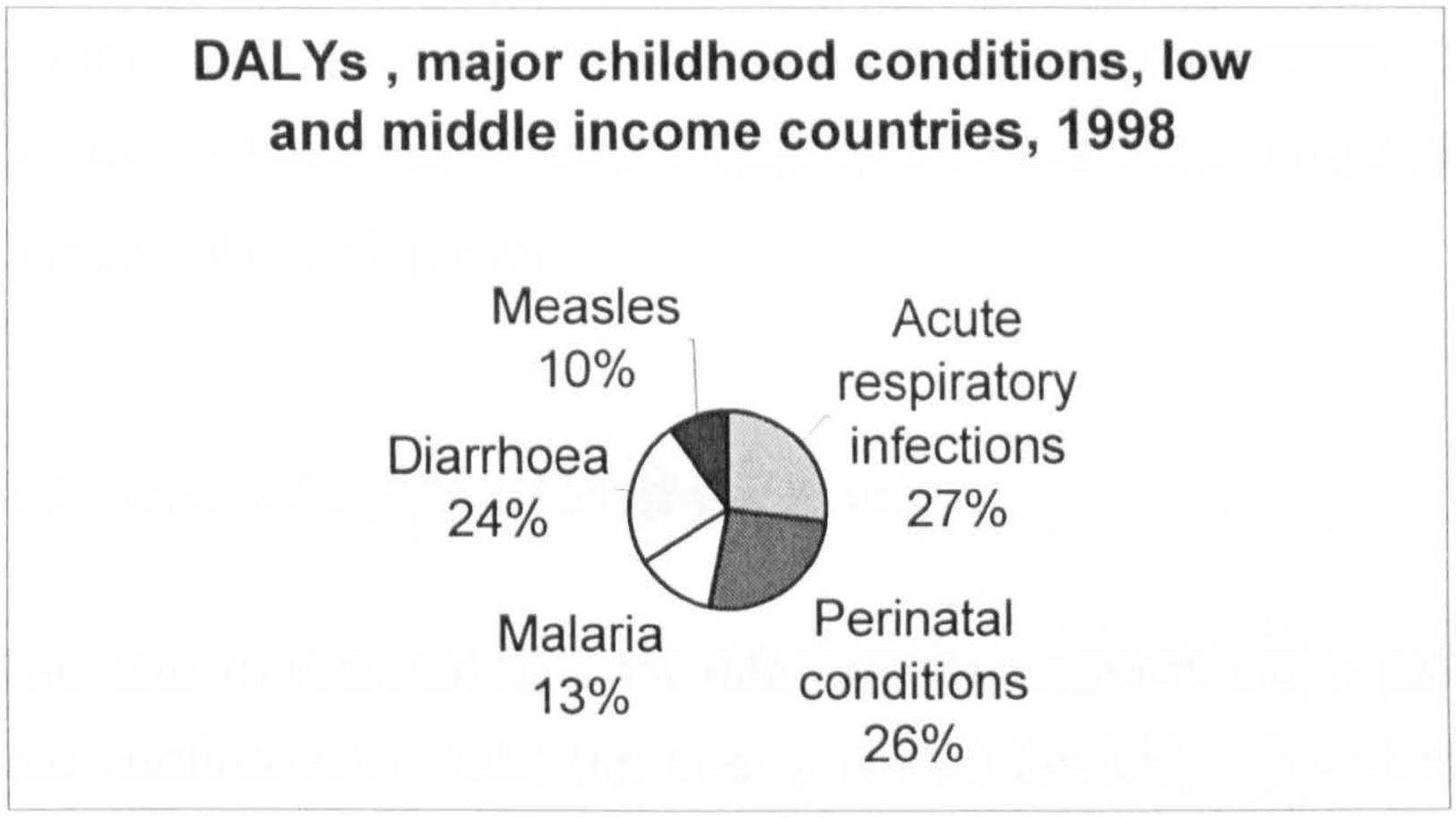
DALYs , all conditions, low and middle income countries in 1998



Source: WHO 1999, p. 21

The relative disease burden of the five major childhood conditions (acute respiratory infections, perinatal conditions, diarrhoea, Malaria, and Measles) is shown in figure 2.4.

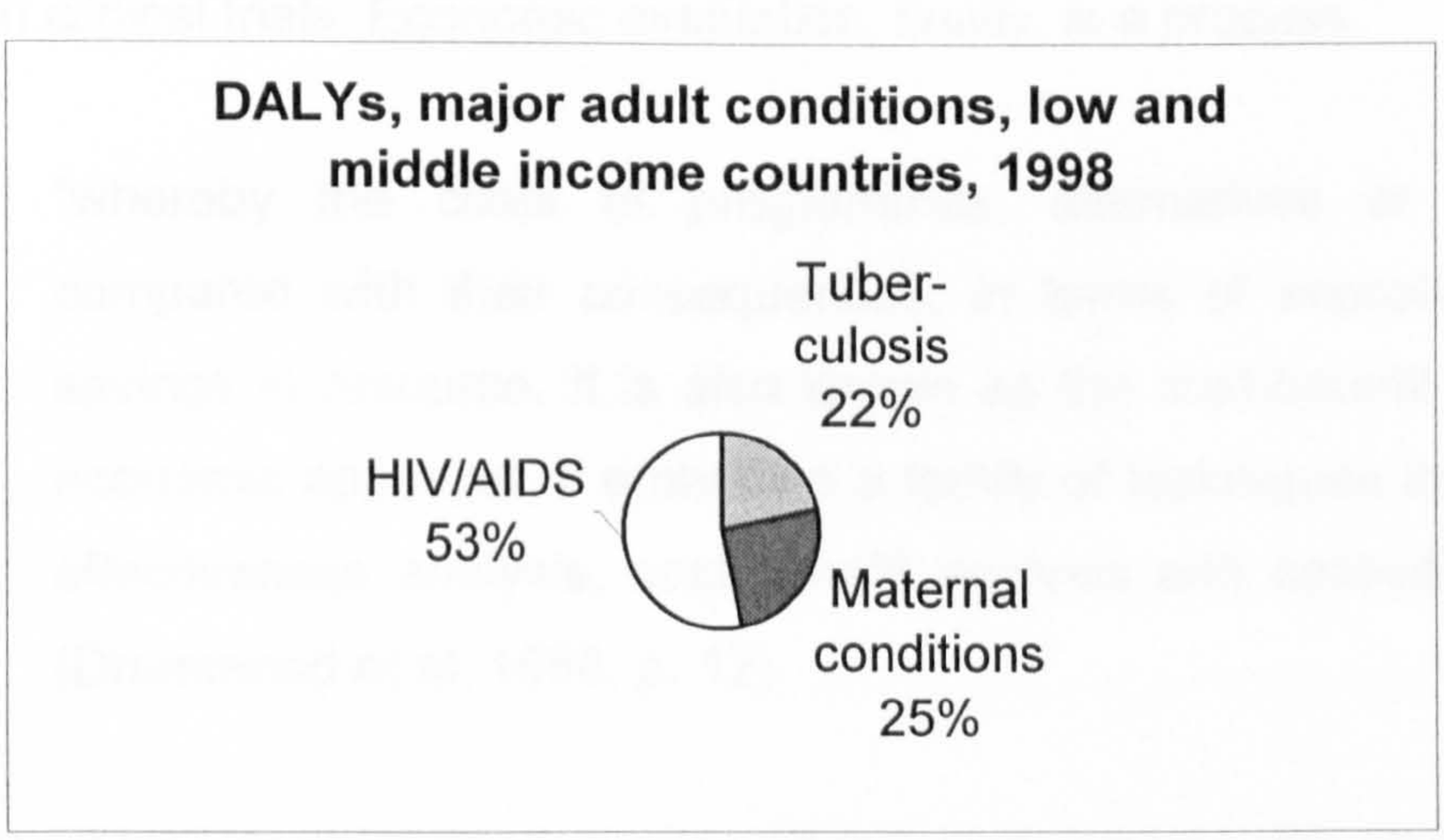
Figure 2-4



Source: WHO 1999, p. 21

Among the major adult conditions HIV causes 54%, maternal conditions 25%, and Tuberculosis 22% of all DALYs, here shown in figure 2.5.

Figure 2-5



Source: WHO 1999, p. 21

Using adjusted lifeyears for the calculation of disease burdens improves the targeting of diseases and the setting of priorities for health intervention measures. At the same time health policy would need to be guided by what is technically possible or indeed affordable to the health service. A particular disease may be high on the agenda in terms of overall health burden, the treatment or prevention might however come at

a disproportionately high cost compared to other forms of health interventions. Prioritising certain interventions would therefore have to be guided by the cost effectiveness of health measures. The following section will demonstrate how cost effectiveness may be calculated in the context of health policy.

2.6 Cost-effectiveness of vaccines

The aim of calculating cost effectiveness figures for a particular health intervention is to make the best possible decision about the allocation of resources for the purchase of a particular drug or vaccine or the investment into the development of new products. There are three stages of evaluating a new drug or vaccine. First of all it must be effective, i.e. it must prevent the target disease and only those substances which show the highest probability in doing so will be used and/or further developed. Secondly, it must be safe. Effectiveness together with safety is measured in clinical trials. Economic evaluation, finally, is a process

> "whereby the costs of programmes, alternatives or options are compared with their consequences, in terms of improved health or savings in resource. It is also known as the cost-benefit approach or economic appraisal. It embodies a family of techniques including cost-effectiveness analysis, cost-benefit analysis and cost-utility analysis" (Drummond et al. 1988, p. 12).

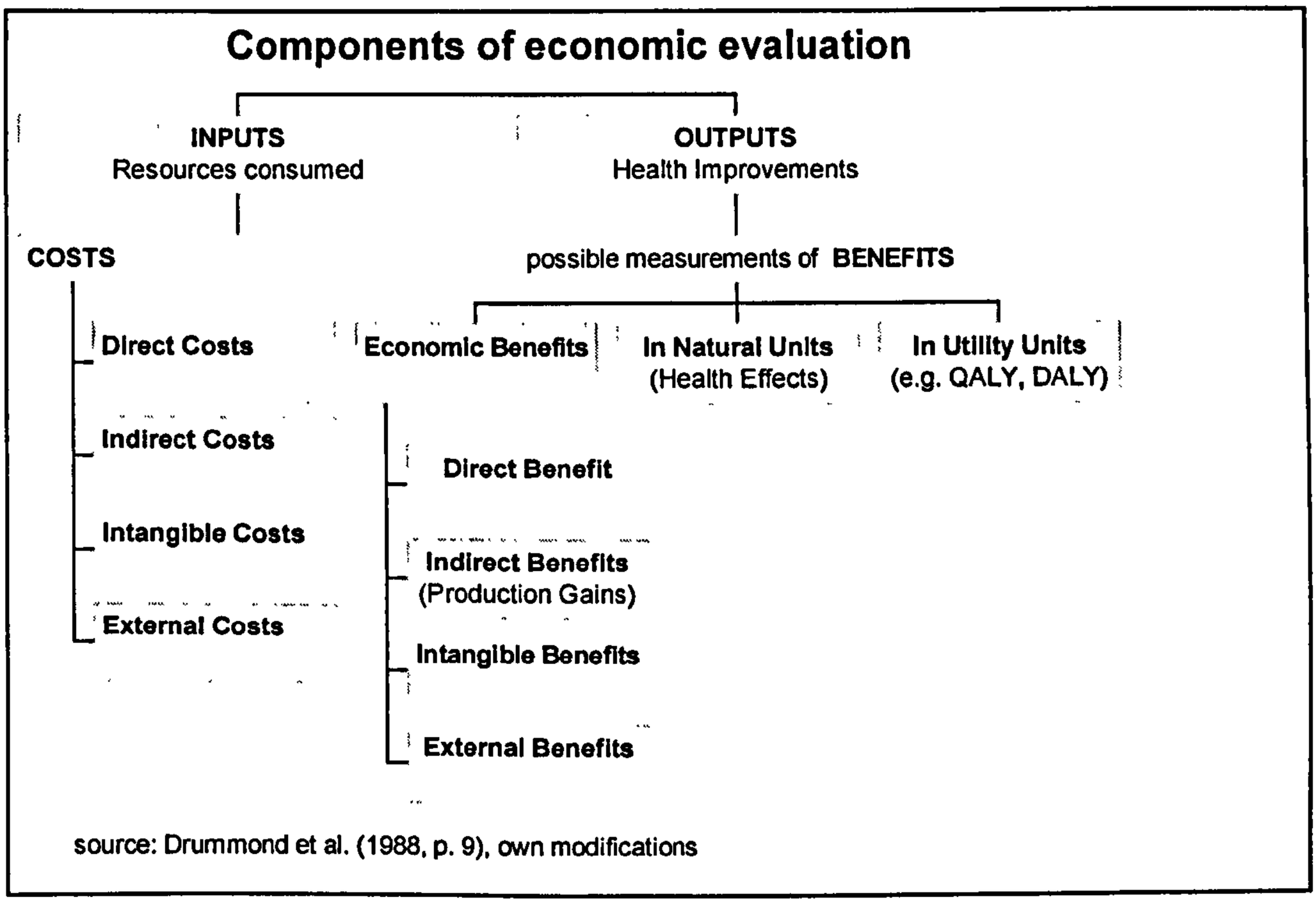
Cost-benefit analysis measures all the cost and benefits attributed to e.g. a vaccination programme in *money* terms. Estimation difficulties, however, often reduce cost-benefit analysis to a consideration of those costs and consequences which are *expressed* in money terms.

Cost effectiveness studies are a form of economic evaluation where costs are expressed in money terms but where some of the consequences are expressed in physical units (e.g. lives saved). Cost-utility analysis is a

form of cost effectiveness analysis and expresses some of the consequences in utility units (e.g. quality adjusted life years)[8].

Figure 2-6 presents a general framework for economic evaluation.

Figure 2-6



source: Drummond et al. (1988, p. 9), own modifications

All types of economic appraisals compare inputs, usually the money costs of a health measure, with the outputs of that measure, the main distinction being whether the output is measured in money terms or health effects. What are the costs and benefits which should be taken into consideration?

Drummond et al. (1994, p. 21) gives an overview of the types of costs and benefits involved. The direct costs include the cost of organising and operating the programme, i.e. the variable costs (staff time) and fixed

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[8] Some authors do not differentiate between cost effectiveness and cost utility analysis, so some of the work written on e.g. QALYs may appear under the heading 'cost-effectiveness analysis'. The main distinction between the economic evaluation techniques is indeed whether outcome is measured in money terms or not.

costs (light, heat, rent, capital costs, etc.). Direct costs also include the costs borne by patients and their families, i.e. out-of-pocket expenses or other resources they use up in the treatment process. Loss of time from work, the so-called production losses incurred by patients and family members, are referred to as indirect costs[9]. There may also be 'intangible' costs in the form of pain or suffering resulting from therapy. It may also be the case that the operation of a health programme causes costs outside the health service; these are external costs. Health and safety measures in a factory may, for example, reduce productivity and hence increase prices for other members in society.

Direct economic benefits signify changes in resource use within the health sector; an effective vaccination programme averts the future costs of treating the people who would have contracted the disease. Patients and their families may also use less resources; these benefits are also included in direct benefits. Any gain in working time in that group accounts for the indirect benefits. Since Drummond et al. (1994) added external costs to the earlier framework (Drummond et al. 1988), external benefits should logically be included as well. External benefits as part of the measurement of economic benefit of a health measure would comprise any benefits incurred outside the health system. Vaccination would be the prime example of this type of externality. Vaccination, as opposed to most other treatments, incurs a benefit to other members in society which although unvaccinated will not contract the disease due to the vaccination of their peers. These benefits are therefore part of the outcome of the health measure, although in many cases extremely difficult to measure.

Apart from benefits expressed in money terms, benefits can also be expressed in natural units or health effects. These benefits are usually

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[9] Drummond (1994, p. 24) points out that "care must be taken however, when including this cost item in an analysis, since its inclusion implies that the cost was incurred as a result of participation in treatment and therefore that the individual's condition was not of a type which would have prevented productive activity anyway."

described as changes in physical functioning, e.g. the wound healed. The last category comprises benefits expressed in utility units, an attempt to attribute a common utility to a variety of health outcomes and therefore make comparisons between different interventions possible. One possible utility measure is explained in box 2-1.

Economic evaluations will then provide benefit (effectiveness, utility) - cost ratios which can be compared with alternative vaccination programmes, medical interventions or even other forms of public spending, for instance an anti-alcohol campaign.

Box 2-1

The use of QUALYs

Extending life is hardly ever the prime aim of a treatment or preventive measure. It is in the physician's interest to make the patient feel well. If the cost-effectiveness of a range of treatments or vaccines is to be compared, an outcome which would describe solely life years gained could be misleading. Some of the patients might live five years longer but suffer from restricted mobility and pain while others gain only three years but enjoy reasonable health and mobility. Which one is more cost- effective? What the economic evaluator aims to look at is the utility derived from a particular intervention. This can in principle be measured by letting the patient or health professionals assign values usually between 0 (death) and 1 (perfectly healthy) to certain health states and add them up to a weighted total. Let's assume the utility value for person A after receiving treatment X would be 0.5 meaning that the patient is about half as well off as he or she would be had the patient never suffered from the disease. Person B after receiving treatment Y has a utility value of 0.8. Treatment X costs $1000 per person and prolongs life by 5 years, treatment Y cost $2000 and saves 3 years of life. Which treatment is more cost effective? The answer is given in the term 'cost per quality-adjusted life year gained'. Treatment X saves 5 years at a value of 0.5 each which is the equivalent of 2.5 QUALYs (or healthy life years, to use a simpler term). The cost per QUALY gained is then $1000/2.5 QUALYs = $400. Treatment Y saves 3 years at a value of 0.8 which corresponds to 2.4 QUALYs gained, the costs per QUALY gained sum up to $2000/2.4 QUALYs = $800. Treatment X is the better buy since it saves a quality adjusted life year at half the cost. The World Bank (1993) considers health interventions which cost less than $50 per QUALY a 'good buy'.

Some evaluations try to take into account that a life year gained in the distant future has a smaller value to the individual than a life year gained in the near future. This is of particular importance for the evaluation of vaccines against diseases such as Hepatitis B which affect the individual at a late stage in life. Obviously, if people grow up in conditions where life expectancy is generally low, a life year gained at the age of 55 might not have the same utility value as a life year gained at the age of 18 when they become income earners and have to look after their family. The easiest way to account for this is to discount life years gained by a certain percentage - the World Bank (1993) uses a discount rate of 3% - so that e.g. next year's healthy life is only worth 1/1.03 = 0.97 QUALYs.

Economic evaluation serves as a guideline on how to spend scarce health care resources most effectively. The most straightforward

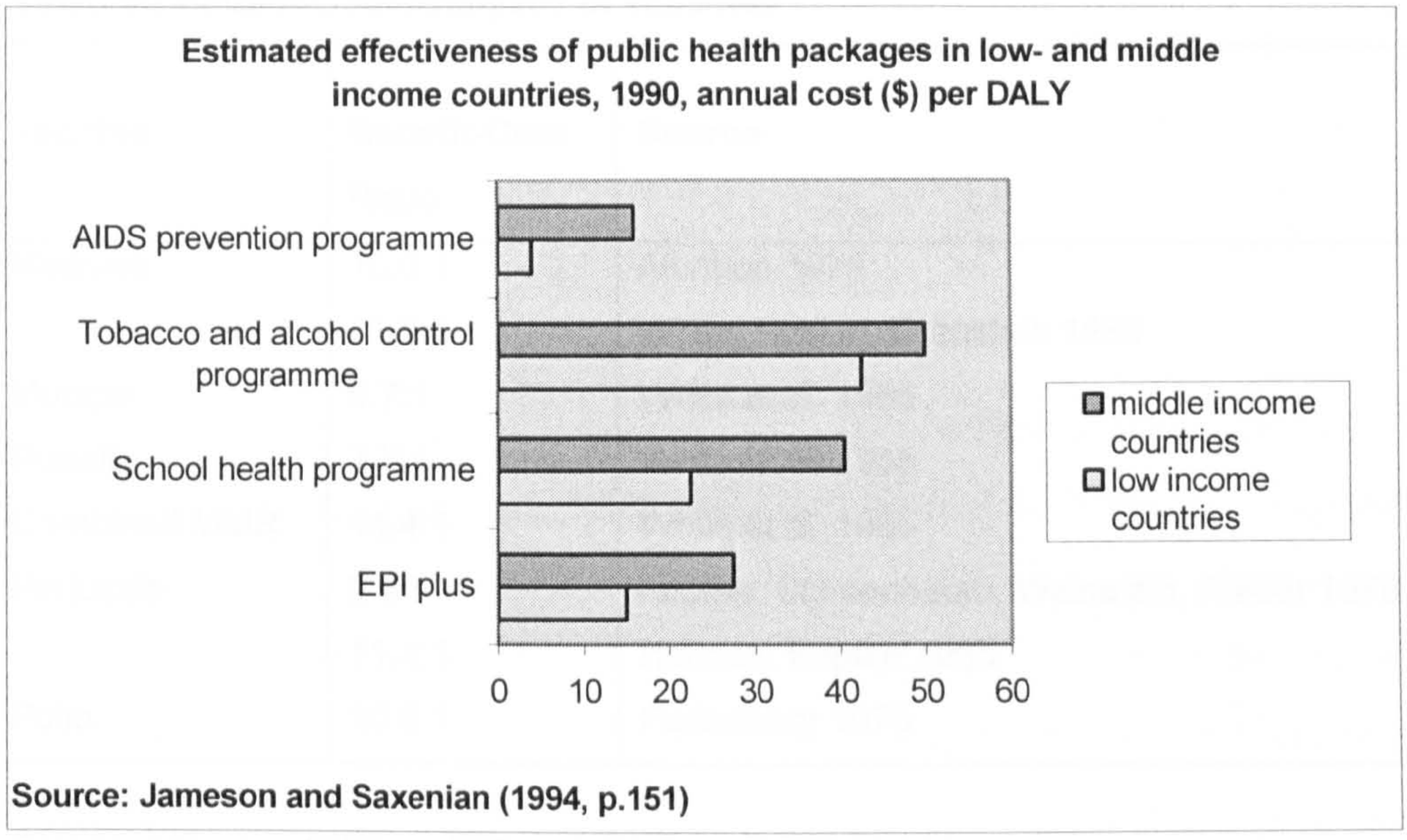
approach is to compare alternative treatments, preventive measures, which are designed to achieve the same therapeutic aim, then judge which one does the job at least costs. The broader the outcome is defined, the broader can be the choice of compared alternatives. With regard to vaccines, for instance, the way public health providers look at cost-benefit figures has undergone considerable change. Waddington and Goodman (1994, p.165) note that:

"In the 1980s the argument went like this. [...]. For the money available, vaccinations can save more lives than most other interventions. There is thus a moral imperative (as well as an economic logic) to vaccinate as many people in the target age groups as possible, as quickly as possible. [...] Substantial amounts of resources were devoted to single issue mass vaccination campaigns. [...] The 1990s question is rather different. It is concerned with health as a whole, rather than merely with vaccine-preventable diseases, and the timeframe is longer. The question is 'what does a cost effective health care system look like?' More particularly 'What role does vaccination play in this system'."

If the outcome is to be the improvement in quality of life for the general population, a number of public health measures with different target groups may be compared. Vaccination compares favourably with other measures in terms of cost-utility-ratios. The study by Jameson and Saxenian (1994) compares UNICEF's Expanded Programme of Vaccination (EPI plus) with measures such as tobacco and alcohol control. Together with AIDS prevention, vaccination belongs to the programmes which achieve the greatest health effect per dollar spent[10].

[10]DALYs (disability adjusted life years) used in this study are based on the same idea as QUALYs outlined above, i.e. they adjust life years saved for any reduction in the quality of life (degree of disability).

Figure 2-7



Source: Jameson and Saxenian (1994, p.151)

Cost-*effectiveness* measures, which allow comparison of treatments and other public policy measures[11], are popular in the economic literature and practice. However, measures of that kind do not give an indication whether the measure is actually affordable to the health service concerned, and what the financial incentives are of using a particular health intervention. Only cost-*benefit* figures can reveal that in most cases an immunisation campaign saves money as well as lives. The literature justifying immunisation on the basis of favourable cost-benefit figures is vast and can only be outlined briefly at this point. It is a reasonably accurate simplification that the benefits of any of the childhood vaccines exceed the costs of immunisation, sometimes up to more than tenfold.

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[11] Many cost-effective measures to improve people's health are found outside the realm of the health service. The quality of nutrition, housing and the prevention of alcohol and tobacco consumption often have a greater impact on people's health than medical intervention.

Table 2-1

Selected Benefit-Cost Analyses of vaccines

Vaccine	Benefit-Cost Ratio	Source
Measles	10.0:1	Albritton 1978
	11.9:1	White, Koplan, Orenstein 1985
Mumps	6.7:1	White et al. 1985
Rubella	7.7:1	White et al. 1985
Combined MMR	14.4:1	White et al. 1985
Pertussis	2.6:1	Koplan, Schoenbaum, Weinstein, Fraser 1979
	11.1:1	Hinman, Koplan 1985
Polio	10.0:1	Fudenberg 1973

Source: Hinman, 1988, p. 597

This is why the emphasis today has shifted away from justifying immunisation in general towards the evaluation of incremental cost-effectiveness in form of improvement of existing childhood vaccines, combination of vaccines or the development of entirely new vaccines against so-far unpreventable diseases.

2.7 Candidate vaccines for development - success stories and shortcomings

UNICEF's Expanded Programme of Immunisation is one of the most successful public health campaigns of the Twentieth century. Since its establishment in 1974 the programme had managed to raise immunisation rates against the six most common childhood diseases from an initial 5 per cent in 1974 to up to 80 per cent by its target date of 1990.

In 1990, the World Summit for Children did, however, express concern about the lack of new and improved children's vaccines. Shortly afterwards, the Children's Vaccine Initiative (CVI) was established. Its

prime aim was to promote the development and implementation of new and improved children's vaccines for use in developing and industrialised countries. The CVI was based at the WHO headquarters in Geneva with a small number of permanent staff. The CVI had a three-fold mission according to its Executive Secretary Dr. Jong-Wook Lee (CVI Forum 9/1995, p.8):

"First to build consensus among its many collaborators over vaccine needs, opportunities and priorities. It will do this through a number of mechanisms, in particular its strategic plan and its Consultative Group meetings. Second, to provide cohesion and co-ordination for the work of its collaborators so as to speed the development and introduction of priority vaccines. Third to play an advocacy role for the CVI's goals. This it will do through its communications and public awareness activities, which include the newsletter and other publications, media seminars, the creation of national CVI committees and so on."

An identification of candidate vaccines for development was undertaken by Shepard et al. (1995) to help the CVI to achieve its goal of new and improved children's vaccines. The results can be seen in figure 2.8:

Figure 2-8 - CVI candidate vaccines (Shepard et. al. 1995, p. 709)

Vaccine	*Cost/ quality adjusted life year ($)*	*additional delivery costs/ child ($)*	*additional vaccine costs/ dose ($)*
highly cost effective			
Measles - early single dose	5	-0.58	0.84
Slow release tetanus toxoid versus existing	9	-0.46	0.93
Measles - early two dose versus one dose	13	1.36	0
Typhoid versus none	20	1.87	2
HBV-DTP combination versus DTP alone	21	0	0.35
Rotavirus versus none	39	0.35	2
moderately cost effective			
Pneumococcal pneumonia versus none	57	0.35	2
Hib-DPT combination versus DPT alone	78	0	1
Enterotoxogenic E.coli versus none	159	0.35	2
Dengue versus none	399	0.70	2
Thermostable OPV versus current OPV	1005	0	0.12
Meningococcal meningitis: conjugate versus polysaccharide meningitis (A,C)	1355	0	1.63
Not especially cost-effective			
DT with acellular pertussis (DTaP) versus existing DTP	113208	0	2

To measure health outcome in quality adjusted life years (QALYs) allows selection among a wide range of possible investment and more importantly to compare the incremental effect of an investment against the 'do nothing and stick to the old technology'-option. The QALYs in this model are discounted meaning that individuals prioritise immediate over future health gains.

Measles vaccines clearly rank among the three most urgently required improvements. According to a CVI-Forum (4/1993), measles causes more deaths in children than all other diseases preventable by vaccination taken together. The fatality rate in developing countries ranges from 3% to 15%, depending on age, being highest when contracted early in life. Many deaths at little extra cost could be prevented if only vaccination could be administered before the age of six months.

According to the World Bank (1993), vaccines with costs below the $50 per QALY mark are considered a good buy even for the poorest countries. If developed, they should be included in the Expanded Programme of Immunisation. Vaccines between the $50 and $2000 mark are considered moderately cost-effective and suitable for adoption in most of the middle income countries and most developing countries. Vaccines above $2000 per QALY are not cost-effective for most of the developing countries.

Box 2-2

Combination and single-shot vaccines

The CVI aims to develop a single heat-stable[12] vaccine which can be given orally soon after birth and which would protect children before the age of highest risk of infection and reduce vaccination programme costs by reducing the number of contacts needed to complete the vaccination schedule (Cutts, 1992, pp. 274-275). Views differ about how long this is going to take; 10 years is the most optimistic and 25 years the most pessimistic estimate. Steps towards this goal would involve the combination of an increasing number of vaccines in one shot following today's DTP example, one vaccine against three diseases - Diphtheria, Tetanus and Pertussis. The CVI believes that DTP could be the backbone for all the future combination vaccines (CVI Forum, 10/1995). Combination vaccines based on a new *acellular* DTaP (less impure and therefore causing less side effects than the old Pertussis component in DTP, which consisted of a crude preparation of the whole Bordatella Pertussis organism) have already been launched in the US. They now combine DTaP and Haemophilius influencae type b and may soon link hepatitis B and an injectable polio vaccine to the DTaP component. In the future a multi-antigen vaccine could link Hib, HepB, and even HIV and pneumococcal antigens to the DTP vaccine.

However, some concerns are expressed about the economics of such a powerful vaccine (Cutts, 1992, pp. 275-276). Would such a vaccine be affordable for developing countries, and if not, would the old and therefore affordable vaccines still be available once the single shot vaccine was launched? And would such a new vaccine not discriminate against diseases in the developing world since those countries are unlikely ever to be able to afford it? Not necessarily. According to the CVI (CVI Forum 5/1993) about 60 to 70% of DTP used in developing countries is manufactured locally. A technology gap could however occur whereby developing countries, through lack of resources, are forced to hold onto their old technologies. Whether the encouragement of these countries to adapt to new technologies and transferring such technology to developing countries is a good idea remains to be seen. It might well prove to be an obstacle to further investment into R&D if developed country innovators could not keep the sole right to manufacture and sell new technology vaccines at large volume.

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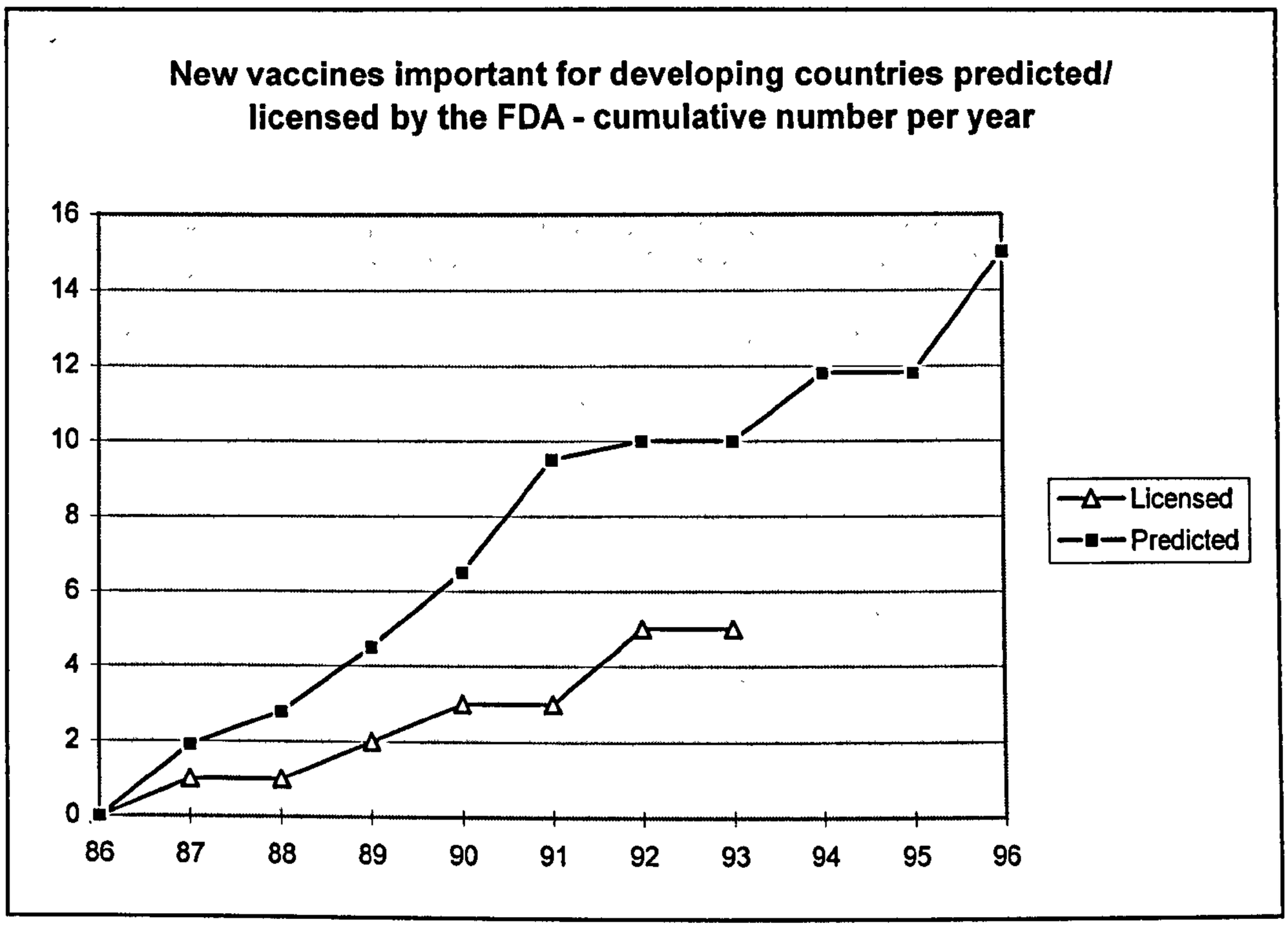
[12] Vaccines which remain active in hot conditions are particularly important for developing countries. Many of today's vaccines need to stored below a certain temperature and the 'cold-chain' needs to remain intact during transport to guarantee effectiveness.

The current EPI includes vaccines against six diseases: measles, tetanus pertussis, diphtheria, polio, and tuberculosis. One of the lessons learned from the selection of candidate vaccines[13] above, is that improvements in vaccine technology would reduce multidose vaccines to a single dose, improve heat stability, simplify administrative requirements (greater use of oral vaccines as compared with injections for example), create combinations of vaccines to reduce patient contacts, integrate new vaccines into EPI and allow vaccination at an earlier stage in life to reduce deaths of very young infants (see measles as an example).

Six years into the launch of the CVI, questions were raised again as to how industry could be encouraged to develop vaccines. In the past vaccines developed by industry were not necessarily the most cost-effective or the most urgently required by developing countries. Based on the new vaccine launches anticipated by the Institute of Medicine (1985), Shepard et al. (1995) compared the predicted number with the cumulative number of vaccines actually licensed by the US Food and Drug Administration (FDA). The results are shown in Figure 2-9.

[13] see also World Bank 1993, p.153

Figure 2-9



source: Shepard et al (1995)

Among the vaccines which were licensed and expected was Hib in 1987, HBV (recombinant) in 1989, typhoid in 1990, Japanese acellular pertussis (for booster doses only) and Japanese encephalitis in 1992. These five vaccines represent only 50% of the ten vaccines expected to be licensed by the FDA through 1993. Shepard et al. (1995) cite low immunogenicity (affecting four vaccines), licensing delays due to uncertain benefits (three vaccines), excessive side effects (two vaccines), inadequate demand to justify investment (two vaccines), problems in large scale development (two vaccines) as the major factors responsible for the difficulties.

The United State's National Institute of Allergy and Infectious Diseases (2000, p. 131) concedes that:

> "by early 1998 it had become apparent that there were serious limitations in global vaccine programs. Immunisation coverage had plateaued at about 80 per cent in 1990 and, in some countries, was actually dropping [...] the World Bank, having identified vaccines as the

> most cost-effective public health tool, was doing very little to help immunisation [...]. Research into vaccines of interest predominantly to developing countries was lagging and in clinical trials was proving increasingly difficult to finance".

In two subsequent meetings in 1998 and 1999, all major stakeholders in world vaccination, i.e. WHO, UNICEF, the World Bank, the five largest vaccine manufacturing companies and big donor organisations such as the Rockefeller foundation, agreed to wind up the CVI and to replace it with a Global Alliance for Vaccines and Immunisation (GAVI) supported by a small secretariat and a number of working groups, one of them concerned with research and development issues.

GAVI was officially launched at the January 2000 World Economic Forum in Switzerland. What really made GAVI possible was a substantial donation of $750 million by the Bill and Melinda Gates foundation. These $750 million are designated for the purchase of non-traditional EPI vaccines, such as hepatitis B, and are supplemented by smaller donations by the same foundation for the accelerated development of malaria and HIV vaccines and the assessment of disease burdens in developing countries. Eventually GAVI will raise more money from a variety of individual and institutional donors to achieve four broad aims: the global eradication of polio, the improvement of the infrastructure and equipment currently available in countries participating in EPI, the introduction of newer vaccines into EPI routine use, and the promotion of research and development of new vaccines (National Institute of Allergy and Infectious Disease 2000, p. 133).

Assessing the global needs for vaccine research and development was at the centre of a GAVI/WHO conference held in November 1999 in Geneva. The conference proceedings (WHO 2000b) distinguish between 'impeded' and 'developing market' vaccines. The former are vaccines which have substantial markets but are not prioritised for investment by the industry for reasons of scientific, ethical or public perception obstacles

such as the fear of adverse reactions. Developing market vaccines are lacking substantial markets in industrialised countries and therefore dissuade industry from making investments. GAVI agreed that its initial effort should focus on developing market vaccines and "GAVI's involvement in championing the development of vaccines against AIDS, malaria and tuberculosis is specifically instructed in its charter" (WHO 2000b).

GAVI's research and development taskforce will undertake a systematic analysis to select candidate vaccines for development. Although large gaps exist in the quality of disease burden data, it was agreed that

> "at least for tuberculosis, malaria and HIV/AIDS, current disease burden data were sufficient to validate their high priority as a focus for GAVI. Diarrhoeal diseases, acute lower respiratory infections and parasitic infections have been recognised as important public health targets for intervention" (WHO 2000b).

Two approaches are seen as exemplary for future economic appraisals and identification of candidate vaccine for development and will form the base for GAVI's own methodology for the selection of candidate vaccines: Kotloff et al's (1999) calculation of the global burden of diarrhoeal diseases and dysentery caused by Shigella and the work undertaken by the Institute of Medicine (2000) to prioritise vaccine development in the Unites States.

Research efforts currently undertaken include the first large-scale human trial of a HIV vaccine in the United States and Thailand. If these efficacy trials are successful, a similar vaccine could be developed to protect against HIV/AIDS in Africa (WHO 2000a).

Pneumococcal vaccines already exist but they are not effective in children under two, which is the highest-risk group. At the same time the low-cost drugs available to treat pneumonia are becoming less effective

due to drug resistance and not all children can get treatment when it is needed. To date four manufacturers are carrying out clinical trials on new pneumococcal vaccines (WHO 2000a).

A large number of malaria vaccines are also under development and being tested in Asia, Africa and the United States although so far no breakthrough has been announced.

A detailed review of vaccine research currently undertaken is provided by the annual Jordan Report published by the National Institute of Allergy and Infectious Diseases (2000).

What has happened to the vaccines initially targeted for development by the CVI and identified by Shepard (1996)? Already in 1996, the CVI (CVI Forum 11, 1996, p. 18) had sensed a "renewed buoyancy and vitality of industry's vaccine development activities. [...] The industry has all reason to believe that the vaccine market is taking off." The industry's development efforts were certainly rewarded with respect to the three new vaccines against Hepatitis B, Hib and Hepatitis A which have outperformed all other vaccines in terms of annual sales. Hep B alone accounts for 20 % of the world vaccines market. This hardly comes as a surprise since Hep B is not only one of the most innovative products, it is also patent-protected and has for a long time been the most expensive product on the market. Only recently has the price declined far enough for the vaccine to be considered part of immunisation campaigns in the developing world. These vaccines do however not belong to the group of vaccines which were initially identified as the most cost effective (such as a single dose measles vaccine, a heat-stable OPV, a slow release tetanus toxoid or typhoid vaccine) and therefore do not seem to emphasise the most urgent needs of the developing world. Indeed, research for a early dose measles vaccine is today conducted primarily in the public sector, according to the CVI (CVI Forum 10, 1995).

The public sector project to make the oral polio vaccine more heat-stable, originally very high on the CVI agenda, was brought to a standstill in 1995. WHO experts expressed reservations about the necessity of such a vaccine since the existing vaccine seems to have done such a good job and there appeared to be no real need for a more stable OPV.

A public sector working group was formed in 1994 to undertake development of a single dose tetanus vaccine (CVI Forum, 10, 1995).

The involvement of the public sector in the development of these vaccines does not come as a surprise. Many of the most cost effective vaccines are variations of older vaccines which were never, or are no longer, patent-protected. Any investment in these vaccines could not be safeguarded against copying and is therefore unattractive for the industry. Compounds in the current vaccine pipeline do at least contain one modern or entirely new vaccine, whose technology can be effectively protected and promises some return on investment for the industry.

2.8 Concluding remarks

This section has outlined how vaccines could help avert millions of deaths in the developing world as well as fight newly resurgent diseases in industrialised countries. Vaccines do that in a very cost-effective manner with the benefit in terms of saved treatment costs almost always outweighing the costs of purchasing and administering the vaccine.

Despite this, the most cost-effective new vaccine projects have not attracted the funds necessary for their development. Public sector organisations, most notably the Global Alliance of Vaccines and Immunisation, have recently accelerated their efforts to promote the development of the most urgently needed vaccines.

The following chapter will look more closely at what kind of market imperfections could lead to the alleged underinvestment in vaccine products, whether these imperfections justify government intervention at least on theoretical grounds, and what is currently proposed to correct the outcome of this market.

3 Market failure and government's role in promoting vaccine R&D

3.1 Background

The material discussed so far suggests that there is a strong economic rationale to use vaccine technology as an overall cost-saving measure available to health services worldwide. If the economic rationale is strong, what keeps market forces from allocating funds towards new vaccine projects? One possible reason could be market failure as a result of lack of information or uncertainty among the actors in the market. Another cause of market failure could be positive externalities, and goods which are underprovided or not provided by the market at all due to non-excludability and non-rivalry in consumption: vaccines might be so-called public goods. Each of these characteristics may play a role in the market for new vaccines.

Some market failure arguments appear very straightforward in the context of vaccines and government intervention readily accepted as is indeed often the case with products of an 'ethical' nature. However, whether government intervention will move the market anywhere closer to a socially optimal level, what 'socially optimal' actually means, and how much and what sort of intervention is required are questions far more difficult to answer.

An analysis of market failure in innovative industries should probably have Kenneth Arrow's (1962) article on 'economic welfare and the allocation of resources for invention' and Demsetz's (1969) response as a starting point and a brief review of their arguments will be presented here. Once a framework for the analysis of market failure is laid out, the question arises whether an optimal level can be determined with reasonable accuracy and what means society has at its disposal to move towards this, if not optimal but possibly more desirable, level. Later on in the Chapter the occurrence of market failure in the vaccine market will

be investigated before the Chapter finishes with a brief summary and outlook over the rest of the thesis.

3.2 Issues in resource allocation: the Arrow-Demsetz debate

Arrow's (1962) argument is based on three reasons for possible misallocation of resources for invention: uncertainty, indivisibilities[1], and inappropriability.

Uncertainty in Arrow's view is an impediment to the allocation of resources to inventive activity because inventive activity is a risky activity with uncertain returns, and the economic system has only limited devices to insure against the risk of failure. Arrow describes how the outcome of a particular production decision is uncertain and depends on a particular state of nature (e.g. weather conditions in agriculture). In the ideal system, commodity options would be traded in which the buyer agrees to pay a certain sum for a certain quantity only if a certain state of nature has occurred. The revenues of the firm are completely determined and the firm can choose its inputs so as to maximise profits. In the absence of commodity options, firms will make input decisions and outputs are produced depending on the state of nature. Prices will be set to clear the market and these prices are a function of the state of nature. Should firms be unwilling to bear the risk of not knowing which state of nature will occur and hence face uncertain returns, then, according to Arrow, the allocation of resources will not be optimal.

Arrow admits that optimal allocation could be achieved if insurance against any conceivable event was available. Individuals could also shift their proprietary interests among a large number of firms or large firms could internally spread risk across a large number of projects. Insurance does however change the incentives of the insured and could cause a

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[1] More often referred to as public goods

decrease in the technical efficiency of the project undertaken, people simply won't try as hard once they are not bearing the consequences of failure (moral hazard).

Interestingly Arrow claims that risky activities of any sort, including investments in innovative products, are characterised by a suboptimal allocation of resources. As it turns out, Arrow's article seems concerned not only with inventive activity but leads –taken to its ultimate conclusion- into a general critique of the incentives to invest, produce or indeed undertake *any* risky economic activity in a free enterprise system.

Besides uncertainty, inappropriability of information is the second reason for the misallocation of resources for invention. Arrow (1962, p. 614) claims that if the cost of transmitting a given body of information is zero, then optimal allocation would call for an unlimited distribution of the information because it has the character of an indivisible commodity (public good) and the owner should not extract the economic value. Arrow admits that this would not present any incentive for investment in research.

But even if the inventor tried to charge a non-optimal positive price, "the inventor will in any case have considerable difficulty in appropriating the returns from information produced" (Arrow 1962, p. 617). Arrow outlines two reasons why selling information may not be possible. Any purchaser could undermine any monopoly power of the seller since he could reproduce the information at practically no cost. Also "no amount of legal protection can make a thoroughly appropriable commodity of something so intangible as information" (Arrow 1962, p. 615). Even if it was possible to protect information with suitable legal measures such as property rights, demand for information would be difficult to establish because the "value for the purchaser is not known until he has the information, but then he has in effect acquired it without cost" (Arrow 1962, p. 615). This in Arrow's view is a good thing since the optimal allocation would require

a free distribution under some regime of centralised decision-making anyway.

What is particularly relevant in the context of this study is Arrow's notion that *basic* research is especially unlikely to be rewarded. Arrow states (1962, p. 618) that information is not only the product of inventive activity but also an input into further productive activity or indeed the production of information. This however causes much greater appropriability problems and makes the value of its use much more 'conjectural' and likely to be underestimated. As a result basic research is "especially unlikely to be rewarded" (Arrow 1962, p. 618).

Arrow concludes that "for optimal allocation to invention it would be necessary for the government or some other agency not governed by profit or loss criteria to finance research and invention" (Arrow 1962, p. 623). This has of course already happened where it is most needed, in basic research, which is undertaken at universities or government organisations. But some more applied fields such as medicine or aeronautics have also received strong government support, Arrow claims. Although desirable in principle, two problems arise from government participation, "how shall the amount of resources devoted to invention be determined and how shall efficiency in their use be encouraged?" (Arrow 1962, p. 623). Arrow suggests that equating marginal social benefits across all projects might prove impossible in the face of uncertainties but the estimation of future rates of return from those in the past and that investment allocated to those projects with a definitely superior rate of return could be achieved.

Arrow is well aware that awarding research contracts on a cost-plus fixed-fee base is not encouraging to efficiency, even if contracts were only awarded if a firm has operated efficiently in the past. He admits that there is "clear need for further study of alternative methods of compensation" (Arrow 1962, p. 624), although the firm may not be so important after all

because "there is plenty of reason to suppose that individual talents count for a good deal more than the firm as an organisation", and "other forms of organisation, such as research institutes financed by industries, the government, and private philanthropy, could be made to play an even livelier role than they now do" (Arrow 1962, pp. 624-625).

It must have been the general nature of Arrow's critique of the free enterprise system as an efficient allocator of resources which triggered a vehement reply from Demsetz (1969) whose response focuses not so much on invention but Arrow's critique of free enterprise as such.

Demsetz (1969, p. 2) argues that even though free enterprise may not be able to allocate resources optimally, it does not follow that government or other non-profit institutions would necessarily achieve a superior outcome without actually examining how government would go about to achieve it. Demsetz refers to Arrow's reasoning as 'the grass is always greener fallacy' and proposes the following alternative formulation to Arrow's statement: "the previous discussion leads to the conclusion that for optimal allocation to invention it would be necessary to remove the non-optimalities" (Demsetz 1969, p.4).

Beside this fundamental critique Demsetz questions some of Arrow's more specific assumptions. Demsetz (1969, p. 4) believes that commodity options exist in the real world and quotes labour contracts linked to the Consumer Price Index as one of many examples. What is more important, the market may not use commodity options because they are not free. Adjustment to risk may be incomplete as a result, but incomplete and non-optimal are very different concepts. Non-optimality suggests that a situation can be improved upon while incomplete risk adjustment is an economic decision as a response to scarcity.

Demsetz also disagrees with Arrow's understanding of the optimal level of risky investment in invention. Arrow believes that "inventive activities

should be undertaken if the expected return exceeds the market rate of return, no matter what the variance is" (Arrow 1962, p. 613). Demsetz believes that this understanding of optimality is flawed, at least in a Robinson Crusoe economy, since people are generally risk-averse and risk reduction is an economic good. People are prepared to pay the price of a lower return for a reduction in risk and a lower variance is a good indicator of risk reduction. Once it is accepted that people act economically when they try to avert or reduce risk it becomes clear that an efficient economy would allow people to reduce risk if the economic gains exceed the cost and that risk shifting can never be complete because it comes at a cost.

In Arrow's view one important obstacle to risk shifting is moral hazard, people acting inefficiently in the presence of insurance. Demsetz argues that moral hazard is just another cost of producing insurance which is partly borne by people taking out insurance and the sellers of insurance. Moral hazard in Demsetz's understanding is no different from the decision of not bringing iron ore to surface because it is too costly to exploit (Demsetz 1969, p. 7). The fact that not all risks can be insured due to moral hazard doesn't make the market inefficient, it simply accepts that people tend to commit moral hazard and calling 'optimal' a world where moral hazard doesn't exist means in Demsetz's view to commit the 'people could be different fallacy' (Demsetz 1969, p. 7). Assuming moral hazard away certainly doesn't answer the question as to what exactly the governing principles of the alternative and 'optimal' regime should be.

Concluding the debate about the ability of the free enterprise system to shift risk and the ability of governments to take a risk-neutral attitude, Demsetz admits that government can be less risk-averse in some of its activity, as for instance shown in its attempt to send a man to the moon, although in other activities the political risk to be borne could make government more risk averse, for instance when some technical innovation causes the redundancy of workers.

Demsetz is equally dismissive of Arrow's analysis of the appropriation of the returns from knowledge. The detection of theft of knowledge may be more difficult compared to other commodities -after all the owner is not deprived of the use of knowledge after the theft has occurred- but it is not impossible since the subsequent use of stolen information will reveal it. If theft becomes detectable then "a harsher schedule of penalties always can be used to enhance the appropriability of knowledge" (Demsetz 1969, p. 10).

As far as Arrow's indivisibilities or public goods argument is concerned, Demsetz claims that the production and dissemination of information cannot be regarded separately. "Since one of the main functions of paying a positive price is to encourage others to invest the resources needed to sustain a continuing flow of production, the efficiency with which the existing stock of goods or information is used cannot be judged without examining the effects on production" (Demsetz 1969, p. 11). In other words it may well be optimal to disseminate existing information free of charge, but if as a result the pool of knowledge dries up, this cannot be desirable from the viewpoint of society. Government could of course take over the production of knowledge as well but whether decisions on resource allocation at government level would necessarily be superior compared to an enterprise system is again questionable in Demsetz's view:

> "He [Arrow] finds the capitalistic system defective. The socialist ideal however solves static allocation problems rather neatly. But this is only because all the dynamic problems of production are ignored. The comparison of a real capitalistic system with an ideal socialist system that ignores important problems is not a promising way to shed light on how to design institutional arrangements for the production and distribution of knowledge" (Demsetz 1969, p. 12).

The Arrow-Demsetz debate has been presented in some detail here because it is from a theoretical viewpoint the most thorough analysis of the market failure framework in the allocation of resources for invention and will as such help to develop a more structured approach to the analysis of the market for preventive medicines. There are however limitations to the applicability of this theoretical framework. According to Demsetz, Arrow is using a 'nirvana' approach to real world problems which was possibly influenced by the feeling at the time that America was falling behind the Soviet Union in the technology race. Some radical measure seemed required and Arrow delivered what must be one of the more substantial critiques of the enterprise system this side of the former Iron Curtain. By the time Demsetz published his critique, the belief in the suitability of the existing institutions to catch up with the Soviet Union in the arms race or the race to conquer space had probably been at least partly re-established.

The following discussion whether or not the market for vaccine innovation fails is influenced by both authors' arguments, and will also expand some viewpoints and introduce new arguments.

3.3 Market failure in vaccine innovation

While Arrow and Demsetz are primarily concerned with investment decisions concerning new products, Musgrove (1999) investigates public spending decisions on existing health interventions. The author distinguishes nine different criteria which could justify public financing of current health measures, and by analogy, could also guide public investment into new treatments or preventive medicines. These criteria are summarised in table 3-1.

Table 3-1

Criteria for public spending on healthcare

Efficiency criteria	• Cost-effectiveness • Catastrophic cost • Externalities • Public goods
Equity or Ethical criteria	• Poverty • Vertical equity • Horizontal equity • Rule of rescue
Political criterion	• Public demands

Source: Musgrove 1999, p. 209

Efficiency criteria describe possible reasons for market failure in health interventions and show some parallels to Arrow's argument. Equity criteria are more concerned with the fairness of health care provision while political criteria are considering public demands which may or may not be guided by economic or equity considerations. Musgrove (1999) points out that none of the above criteria can be viewed in isolation from the cost-effectiveness criterion, which has already been discussed in the previous chapter. The remaining criteria for public spending on healthcare, such as externalities, the public good aspect of vaccines and equity and ethical criteria will now be discussed in greater detail.

3.4 Externalities

Possibly the most important argument for government intervention is the existence of externalities, not explicitly discussed in Arrow's work[2]. Vaccination of an individual carries a benefit for other members of society by protecting them against the disease as well. Therefore the total benefit

to society from a programme of vaccination will exceed the sum of the benefits to each individual. The existence of externalities implies that producers cannot capture those external benefits to society i.e. they will not be remunerated appropriately for their investment in a particular preventive measure. The fact that vaccination is a source of positive externalities could justify a public research effort in the development of a new vaccine, although Demsetz would argue that an inefficient government may not be able to improve the outcome of the market.

Government intervention should ultimately depend on how large the potential social gain is and whether it justifies the cost (Musgrove 1999) which again shows the importance of cost-effectiveness as an intimately related criterion. There is indeed some evidence that cost-effectiveness of vaccines is compromised by incomplete vaccination. Phillipson (1993, p.129) states that epidemiologists assume that vaccination even if incomplete (either because the vaccine is not one hundred per cent effective or because not everyone in the population at risk is vaccinated) reduces the prevalence of the disease. Prevalence, however, may fall much less than expected as a consequence of incomplete vaccination, because the reduction brought about by the vaccine in the probability of infection may increase the demand for risky activity by lowering its relative price. The prevalence of a disease may in an extreme case also rise due to the reduction in the relative costs of the disease to the victims (ibid., p. 129). There is, for example, some evidence that the existing AIDS drug treatments have led to a return to unsafe sex amongst some groups. The overall net welfare gain to society could thus become ambiguous.

Externalities could, however, also be even stronger than expected. Dow et. al. (1995) show that the incentive to invest in the prevention of one

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[2] Of course Arrow discusses the extreme case of externality: the Samuelson public good which is both non-rival and non-excludable. See point 3.5 for further discussion of the public good character of vaccines.

kind of disease positively depends on the level of survival from other diseases. Observing the effects of the Extended Programme of Immunisation (EPI) in Zaire, a one per cent drop in mortality was expected if tetanus vaccination simply avoided tetanus deaths. However, the effect measured was significantly larger. The authors suggest that

> "mothers whose children are more likely to survive neonatal tetanus as a result of an immunisation campaign may have an incentive to increase other health inputs such as nutrition, now that such inputs are less likely to be wasted on children who otherwise would likely have died (ibid., p. 4)".

Externalities from vaccination are certainly an important argument for government financing. People's behaviour as a response to vaccination is, however, just as important for the outcome of a preventive health measure and a government will thus need to carefully assess this overall outcome before deciding on financing a project.

3.5 Are vaccines a public good?

Quite closely linked to the externalities debate is the question whether vaccines are in fact a public good. This is certainly not so as far as the characteristic of non-rivalness in consumption is concerned, however consumption is at least to some extent non-excludable. The Institute of Medicine (1985, p. 52) states:

> "as the percentage of the population that is immunised increases, an individual's chance of contracting a particular disease lessens, but the risk of adverse reactions remains unchanged. Many individuals in this situation will be tempted to be 'free riders', hoping that others will choose to be inoculated but concluding that it is not in their own best interest to do so."

People can only be free riders if they cannot be excluded from the benefit of avoiding disease due to other people's vaccination. Vaccination can therefore be seen as a partial public good in which case the market fails to provide the right quantity or in an extreme case does not provide any of the good at all. If demand becomes unpredictable then uncertainty is greatly increased which is likely to lead to a reduction in investment into vaccine products.

Simply being a (partial) public good is of course not a good enough reason for government to intervene into the provision or development of a new vaccine product. Only if the product is cost-effective, as is the case with most vaccines, should government money be allocated, otherwise this money might be spent more effectively on another health intervention. The rationale for intervention is even stronger if there is no private market at all and hence no risk that government finance crowds out private finance (Musgrove 1999, p. 210).

3.6 Public demands - uncertainty and underutilisation of vaccines

The Institute of Medicine (1985, p. 34) blames underutilisation of preventive treatment as one of the causes of inadequate demand for vaccine use. The market size for a particular vaccine is substantially smaller than the population for whom it would be cost-effective to use the vaccine. Hence, the users do not send enough signals to producers that the development of a new vaccine would pay off. Three factors influence underutilisation: system factors, client factors and provider factors[3].

System factors describe the impact of the health care system and reimbursement practices on the utilisation of vaccines. Health care professionals are said to be geared towards the use of therapeutic

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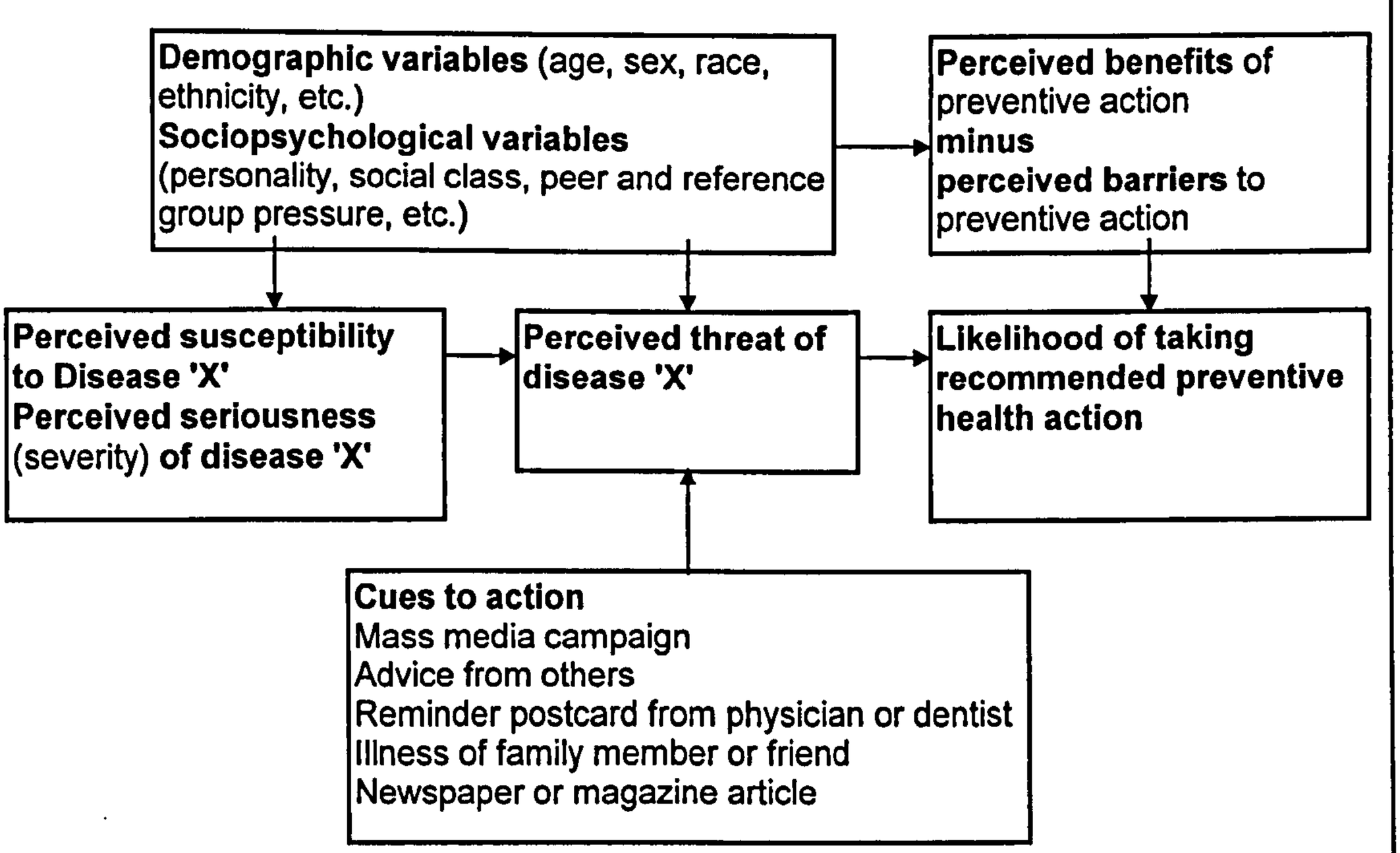
[3] The description of these three factors is based on work by the Institute of Medicine (1985, pp. 34-40).

medicines rather than prevention, with the reason for this lying partly in medical education and attitudes. Health care systems generally provide relatively little information on the benefits of vaccination to clients or health professionals. Another important factor is that, much in contrast to therapeutic care, health insurance policies or national health services are reluctant to cover some preventive procedures.

The second factor which causes underutilisation of vaccines is their undervaluation by individuals or 'clients'. Becker et al. (1977) was the first systematically to outline factors of influence on the perceived threat of a disease independently of its actual threat.

Figure 3.1

Becker's Health Belief Model



source: Becker et al. (1977)

Becker's model is based on the assumption that the willingness to use a vaccine depends on the individual's state of readiness to take action which is influenced by the individual's perception of the likelihood of

susceptibility to the disease and the perception of the severity of the consequences of contracting the disease. The willingness also depends on the individual's estimate of the vaccine's potential benefits in reducing susceptibility and/or severity weighed against perceptions of barriers to preventive action, such as financial, psychological and physical barriers.

Cues to action determine the willingness to take preventive action and stimulate feelings about the disease.

Demographic and sociographic variables are believed to influence the willingness to take preventive action, but only indirectly. Depending on the type of vaccination programme, factors in the health belief model affect the individual's willingness to prevent to a varying degree.

This can be illustrated by the fate of the first Hepatitis B vaccine, an effective, plasma-derived vaccine which became available in 1982. Its acceptance in the targeted population of health workers has been quite low. According to the Institute of Medicine (1985, p. 261) this may be "because of costs concerns related to its source, i.e. plasma from donors who may be at high risk from other infections", most notably the HIV virus. Media coverage of possible adverse reactions and the general attention HIV received in those years has certainly contributed to an overtly cautious use of the Hepatitis B vaccine. Although safety procedures were elaborate, the vaccine had to be abandoned and a new vaccine which wouldn't be perceived to be quite as risky had to be developed.

Another more recent example is the combined measles mumps rubella (MMR) vaccine whose alleged association with autism and irritable bowel syndrome in children has been widely reported in the press. Although these claims have yet to be scientifically substantiated, immunisation rates have dropped, not least because single vaccines against each of the diseases are not approved in the UK.

The case of preventive and therapeutic medicine alike is further complicated by the role of the provider of treatments. As already seen, the provider features in the health belief model as one of the cues to action, i.e. the willingness to take preventive procedures. But the provider itself, which could be the family doctor, the local health authority or UNICEF which purchases well over 100 million doses of vaccines a year has to decide whether or not to use an existing vaccine or signal the importance of a new vaccine.

The theory (Institute of Medicine 1985, p. 36) suggests that three variables are important: the characteristics of the providers and their patients, the characteristics of the innovation and the norms, values and policies of the target population and health service. With regard to the characteristics of the provider, the role of the opinion leader has been stressed in the literature and efforts of persuasion once a new vaccine is introduced have to be concentrated on these opinion leaders. Innovations also possess characteristics which determine the speed of diffusion of a new vaccine. The following is a list of factors which will affect acceptance of a vaccine innovation based on the Institute of Medicine (1985, pp. 37-39) and WHO (2000b, p. 12):

Table 3-2

Factors which aid diffusion of future vaccine
• Magnitude of disease burden • Public perception of disease and need for its control • Existence of alternative treatment or public health measure • Relative advantage – the degree to which the innovation is perceived as being better than existing medication (Cost-benefit/ utility figures play an increasing role in that respect) • Observability - are the results of vaccination visible to others and how long does it take until the benefits and risks can be assessed? • Compatibility - does the innovation fit in with existing procedures, e.g. in case of a vaccine which requires new skills and training from the personnel? • Maturity of science to generate the vaccine • Complexity of innovation - is it difficult to understand, in particular its mode of operation? • Risk - what are the risks involved for the vaccine users and is mode of delivery attractive to users (e.g. mucosal or transcutaneous, number of doses required)? • Ease of combination and delivery with other vaccines through existing immunisation services • Suitability for pilot studies
Source: Institute of Medicine (1985, pp. 37-39) and WHO (2000b, p. 12):

Box 3.1 shows a fictional conversation which aims to outline some of the problems which an even extremely cost effective innovation might face before being adopted by a national health service.

Box 3-1

- Does sound economics affect vaccination policy?

The following (shortened) dialogue, taken from Waddington et al. (1994, pp. 167-168), illustrates the decisive role of the provider of treatments. An economist tries to convince the head of a national department of health service to adapt hepatitis B vaccination on the ground of excellent cost-benefit figures:

E: I've just read a paper about hepatitis B vaccination. Evidence suggests that a death can be averted for between US$ 150 and $200.

DHS: I suppose this is one of your cost-effectiveness analyses. They always seem to smooth over the practical difficulties. How much money are we talking about?

E: The addition of the hepatitis B vaccine to the Expanded Programme of Immunisation (EPI) represents a 65% increase over total cost of the EPI programme. For us that means about $1 Million per year.

DHS: I hope not all of it will be required in foreign exchange.

E: Almost all of it. In fact, 82% of the additional costs is for the vaccine itself.

DHS: So you are asking for money I haven't got in a currency I haven't got. But where there is a will there is a way. It sounds like the sort of thing donors might be interested in. But are you sure it is really that simple? We just add hepatitis B vaccine to the vaccine supplies? Won't our health workers need some training about hepatitis B and the administration of the vaccine?

E: The paper doesn't consider that. But I bet it's technically very simple. We could probably just add on a 10-minute lecture to existing training programmes.

DHS. The person I was talking to before called himself a Pedagogical expert. We all know that the technical knowledge and skills of our primary health care workers are poor. He argued that we had to prioritise the messages we want to get across. He convinced me that if we concentrated on five to begin with, we might expect some real improvement within a year. How does knowledge about this hepatitis B vaccine compare with the skill of preparing oral rehydration solution, or administering measles vaccine, or prescribing rationally for malaria? Are those not all cost effective interventions that we haven't got right yet ?

E: You seem to have a point. I'll look into it.

DHS: If this hepatitis B vaccine is as good as you say, I can try to woo the powers that be with thoughts of fewer child deaths next year. That's always popular.

E: Oh dear, I'm afraid it doesn't work like that. We are talking about averting adult deaths in 30 or so years time.

DHS: And democracy is to be restored here next year? You do need to go away and do some more homework.

Most of the above factors correspond very closely to the health belief model. This does not come as a surprise since the provider's role is to understand the user's needs as objectively as possible, so when the provider decides upon the willingness to use an innovation the determining factors should in some respects come close to those of the end user.

As far as the last factor, the norms and values of the health service and the target population, is concerned, religious beliefs or other attitudes and schools of medicine may also be opposed to a particular innovation.

All these factors taken together simply increase the level of uncertainty faced by the potential innovator. An apparent health need may or may not be transformed into actual demand depending on the strength of the individual factors outlined above. What seems to make vaccine demand particularly unpredictable is the diffusion process of new vaccine technology and the extent to which a new technology gets accepted by the medical profession and the individual user (WHO 2000b, p.24). Uncertainty can be an impediment to innovation and a certain degree of guidance of the innovation process from initiating research up to propagating the use of the finished product would reduce uncertainty significantly.

3.7 Imperfect Information

Besides factors influencing actual private demand, the perception of potential demand by the industry is just as important for the allocation of resources. The lack of certainty about future vaccine sales due to imperfect information increases the risk of investment with predictable consequences for vaccine research. CVI co-ordinator Roy Widdus, for example, claims (CVI Forum 10/1995, p. 6) that the CVI should "provide commercial vaccine manufacturers with an evaluation of Third World

markets for their vaccines and thereby enhance the predictability of their R&D investments in products destined mainly by such markets." Information does play a major part in the R&D process and the clearer the information on the absolute size and purchasing power of a market the more precise will the R&D resource allocation decision be. What is most likely to happen is once knowledge of a potential market is established certain desirable vaccine projects will first of all become candidates for development. Secondly, more accurate information may correct a formerly underestimated market size, improve the ranking of the candidate vaccine and may eventually lead to its development.

The World Bank (1993, p.153) agrees that providing information on potential markets for new products, including epidemiological data about the disease, the target population, and technical requirements of desirable innovations, would help to make innovations more viable. The WHO (2000b, p. 24) concedes that industry needs to know that there is a credible market for the product it develops. Government or some other non-profit institution such as the CVI could reduce uncertainty in the development process by providing reliable information on future market size. Whether such information would be trusted when the providers are aiming to increase investment in vaccines is another matter.

3.8 Equity and altruism

The existence of catastrophic cost could normally be resolved by insurance which, if adequate[4], covers the cost of treatment and no

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[4] Only in the case of insurance failure, resulting for instance from moral hazard problems, should government provide cover for the uninsured. This is for instance the case with public health insurance for the elderly and poor in the US (Medicaid and Medicare), while the rest of the population relies on private health insurance. In such a system universal coverage is however impossible to achieve, which led some countries to introduce either compulsory membership in health insurance funds or a tax financed National Health Service.

government intervention is needed. The absence of health insurance for certain groups of individuals and very high prices for cost-effective vaccines would however call for some form of government help. It also happens that

> "some though not all of the diseases which differentially affect the poor, are also diseases for which relatively cost-effective interventions exist [...] because the non-poor either do not need those interventions, or would benefit less of them, or have already benefited, while the poor still suffer a reducible burden" (Musgrove 1999, p. 212).

This does not imply that money spent on the poor is always the most cost effective, but is likely to have a greater impact on reducing the burden of disease. To mention just one example, measles disproportionately affect malnourished children and measles immunisation prevents more childhood deaths among the poor than the non-poor.

Providing the poor with access to cost-effective health interventions also conforms with the principle of *horizontal equity* which implies equal treatment to people with equal health conditions. Unless the effectiveness of vaccination differs among children, all children should thus have access to the same immunisation package.

The effectiveness of vaccination does however differ between individuals, as the measles example has shown. Giving preferential treatment to those most in need then becomes an issue of vertical equity. In its simplest form, the *rule of rescue* implies that those who will die without an intervention will receive treatment first. As long as the expense to save a life is justifiable and the person recovers fully, this principle seems to intuitively conform with efficiency. But what if the cost of saving a life are unacceptably high and the person does not recover fully? These considerations will lead straight to quality of life measures such as QALY and DALY and the original premise of *vertical equity* to do more where

the effects in terms of healthy life years gained are greater. The most efficient intervention is an intervention which helps most, ie. saves most healthy life years, per dollar spent.

Musgrove (1999) discusses these aspects of vertical and horizontal equity at some length although the relevance for the decision on how to finance certain interventions is somewhat limited. The key question remains whether those affected are poor and cannot afford a cost-effective intervention, either because no insurance or other funds are available at all and/or the costs are 'catastrophic'. Only in these cases should the public finance the health measure.

In the framework discussed so far, cost effectiveness is the litmus test for public finance. The most cost effective health measures by far involve very simple interventions mostly in developing countries which satisfy horizontal and vertical equity criteria. The money spent on projects in the developing world will, however, only to a small extent benefit the donors of that money, either raised through taxation in donor countries or voluntary donations by private individuals. Rotary International, the Rockefeller foundation, and the Bill and Melinda Gates Children's Vaccine Programme, for example, sponsor WHO's mass vaccination programmes and research on new vaccines important for countries in the developing world.

Why are donors financing mass vaccination in the developing world? Three possible answers can be given. One is that the *perceived* risk of individuals in the donor countries is actually higher than the real risk of catching the disease. The recent outbreak of plague in India and Ebola in Zaire have sharpened the public mind and the perception of individual risk to an extent which doesn't reflect the actual risk.

Secondly, the *actual* level of risk to donor countries arising from diseases prevalent in developing countries is increasing. Today's world is rapidly

'globalising' –with both legal and illegal migration and travel increasing continuously. This, inevitably, means a lot of people moving from the developing to the 'developed' world countries and vice versa. This raises the prospect of the re-occurrence of some eliminated diseases re-emerging in donor countries, which might be at least partly controlled through an increase in vaccination rates in developing countries. A current case is Tuberculosis, which was thought to have been virtually eliminated by a variety of policies many years ago. Tuberculosis is now generally on the increase in most donor countries in particular among the prison population in the US and as an opportunistic disease among people suffering from AIDS.

The third motive for donor financing is horizontal equity. The argument that no individual, regardless of income, should be denied access to medical care can be extended to individuals in other countries. Stiglitz (1986, p. 288) explains that "the view that there are goods and services, such as health care, whose availability to different individuals should not just depend on their income, is known as specific egalitarianism". Stiglitz also outlines the main criticism of that view. The relationship between medical care and life, according to some critics, appears to be weak, and other behavioural factors such as smoking, drinking, food, education and sexual behaviour play an equally important role in determining an individual's health. Few people would argue that food, perhaps as important as medical care in influencing a person's health status, should be provided free of charge.

Today's vaccination policies provide a certain degree of prevention to the developed world (WHO's Expanded Programme of Immunisation, EPI), although below the standard of the industrialised world. This seems to fall short of specific egalitarianism, but encompasses the view that everyone should have the right to a certain minimum of medical care in excess of what national health services in poor countries could afford to provide.

Motives to provide such care are perhaps best described as altruistic motives. Altruism has an increasingly important role to play in the provision of new vaccines, not least since the Bill and Linda Gates foundation kick-started the Global Alliance for Vaccines and Immunisation (GAVI) in Spring 2000 with the substantial donation of US$750m.

Donors want to spend their money effectively and a considerable proportion of resources is spent on identifying good causes. The question remains whether altruistic behaviour can achieve a higher level of health provision than the market alone. If donors really were less risk-averse than private investors then one could expect more money overall to be invested in vaccine research because charitable money would invest in areas which are too risky for private investors. As outlined above, Arrow (1962) believes that charitable organisations are well equipped to take over that extra risk. The character of charitable funds may allow for more risk taking because people do not necessarily expect a market rate of return.

Charitable institutions are, however, becoming ever more competitive and increasingly accountable for the cost-effectiveness of their programmes in order to attract money. Charities may worry even more about their donors than firms worry about their shareholders and as a result are more risk averse than firms. If this was the case, charitable money might simply chase similar development projects and replace some private funds.

An overall increase in research funds might only be achieved, if investments go into projects with an expected private rate of return below the market rate but with a high social rate of return[5]. Careful targeting and sound economic evaluation of new vaccine projects are required if these extra social gains are to materialise.

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[5] Which, if the externality argument holds, would apply to many new vaccine projects.

3.9 Is government intervention justified in vaccine innovation?

If there is market failure in inventive activity in general as Arrow suggests then there is also market failure in vaccine innovation. Even for those who do not subscribe to Arrow's view of systematic underinvestment in R&D there is ample evidence that vaccine markets are more prone to failure than, for instance, the market for therapeutic medicines.

The Arrow-Demsetz argument really is an argument about the notion of 'social optimality' as used in traditional economics. This is of course a very hard, if not impossible, criterion to make decisions by. As Demsetz (1969) rightly argues, the notion of social optimality emerged from welfare economics and assumed a static, certain world. Neither businesses nor governments operate in such a world and do not know what really is 'socially optimal'. In reality, both markets and governments are imperfect, but decisions still have to made using decision making criteria other than the optimality criterion. Decision makers then fall back on decision criteria such as cost-effectiveness, feasibility, social acceptability given that social optimality is elusive whilst random decisions are also clearly undesirable.

Musgrove's (1999) decision tree, shown here in figure 3.2, provides a clear and unambiguous set of criteria, which can support the decision whether or not to publicly finance a particular health intervention in the world of real decision making instead of the static and certain world assumed in orthodox welfare economics.

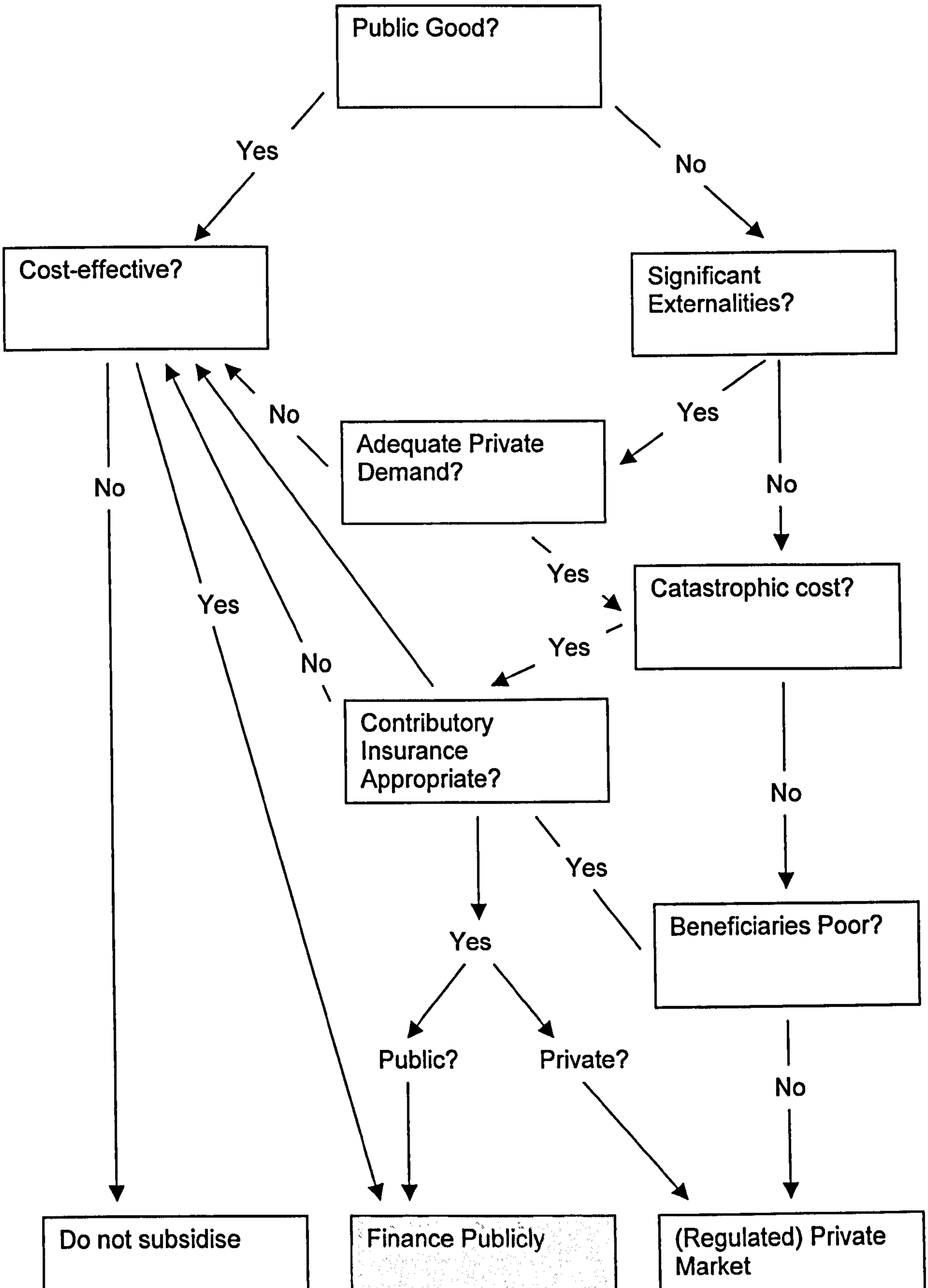

Figure 3.2: Public resources for health care, source: Musgrove 1999, p. 220

Positive externalities (although potentially weakened by incomplete vaccination), the impure public good character of vaccines, and the uncertainty of demand are part of a strong argument for government intervention. As outlined in Chapter Two, vaccines are considered one of the most cost-effective health measures which in the present scheme is a prerequisite for at least some public financing of existing or new vaccine projects. Even where significant externalities do not exist, the cost-effectiveness of vaccine products implies public financing where consumers are facing catastrophic costs, and are too poor to be insured to afford the purchase of vaccines via an insurance scheme.

The above discussion also indicated that in the presence of market failure, government may *potentially* achieve a higher level of social benefit. Government action could, however, also have a negative effect on the delivery of new vaccines, depending on the way the health service and vaccination policies are administered. With a theoretical justification of government intervention in place, the effectiveness and focus of government policy will become a central issue in the latter part of this thesis.

3.10 What is currently suggested to correct the outcome of the market for vaccine innovation?

At a recent meeting of WHO, GAVI and industry representatives in Geneva it was acknowledged (WHO 2000b, p. 12) that:

"although most of the basic scientific breakthroughs that made new vaccines possible were generated in the public sector (academic and government) research institutions, most of the cost for their clinical development, including the support of extensive phase II and phase III clinical trials, was borne by the 'big pharma' vaccine industry in industrialised countries".

These investments to bring a new vaccine to the market, which according to Wyeth-Lederle vaccines (WHO 2000b, p. 6) amounts to anything between 200 and 400 million US dollars, requires companies initially to charge a high unit price in order to recoup investments in those markets which can afford the product. Return on investment and the avoidance of unnecessary risks in doing so is undoubtedly influencing R&D decisions for new vaccine projects.

However, as far as developing market vaccines are concerned, public-private partnerships seem to be of vital importance. The two typhoid and two cholera vaccines which have been licensed in the last 15 years underwent phase I to III clinical trials financed by the public sector, whereas vaccine companies provided formulations of the vaccines for the clinical trials[6]. GAVI believes that at the least the very costly phase II studies can be performed by public sector investigators at a fraction of the expense (WHO 2000b, pp. 16-17).

GAVI will therefore consider two different approaches to synergise the development of new vaccines, a 'pull' mechanism which predominantly addresses the need of the industry to recoup investments, and a 'push' mechanism which emphasises the role of the public sector in partnering with industry to aid the development of high priority vaccines (WHO 2000b, p. 21).

The following table summarises the views expressed by representatives of the public and private sectors at the Geneva meeting on what push and pull strategies GAVI should employ to encourage industry to invest in developing market vaccines (WHO 2000b, p. 22):

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[6] The manufacture of formulations for clinical trials (pilot lot formulations) is a very costly procedure due to strict Good Manufacturing Practice (GMP) guidelines imposed by regulatory authorities. More about regulatory costs of vaccine development in chapter 5.

Table 3-3

Ways forward to encourage industry to invest in developing market vaccines

Push strategies	*Pull* strategies
- allow intellectual property coverage - target vaccines which will also be purchased by tourists from industrialised countries who travel in developed countries - public sector needs to quantify extent of future vaccine use - shared costs of early pilot lot formulations (formulations for clinical trials) - costs of phase I and II trials borne by public sector - shared costs of phase III trials - formation of joint public-private not-for-profit companies dedicated to specific vaccines - increase access to pilot lot formulations for research teams	- stimulation of national demand - developing guaranteed purchasing mechanisms - providing realistic forecasts for vaccine use - protection of intellectual property rights - increasing government ownership/responsibility for national immunisation systems including the introduction of new vaccines - availability of infrastructure for vaccine distribution - advocacy of the vaccine - demonstration that developing countries are credible and sustainable markets for new products - vaccine prices that provide reasonable margin of profit

Source: WHO 2000b

Among the push strategies, access to pilot formulations and protection of property rights appear crucial for the successful development of a new vaccine. Public-private collaborations between academia and industry were also attributed a greater chance of success than industry effort alone to come up with a new formulation (WHO 2000b, p. 23).

This view is shared by the US Pharmaceutical Manufacturers Association (Pharmaceutical Manufacturers and Research of America, 2001, p. 112), who, in a different context, stated that

> "we also need to keep the public-private partnership in pharmaceutical research strong. Attempts to harm this partnership- for example, by

putting restrictions on co-operative research agreements between drug companies and the National Institute of Health- should be rejected. [...] Strong world-wide protection of pharmaceutical patents is essential to spur vigorous investment."

As far as 'pull' strategies are concerned the GAVI-industry working group states that "one of the central issues is credibility. Specifically, industry related its need to be able to demonstrate that there is a credible market for the new products that it develops" (WHO 2000b, p. 24).

The importance of a guaranteed market for future vaccine has also been emphasised by Michael Kremer (2000) in a recent National Bureau of Economic Research (NBER) publication. The author acknowledges that drug companies are sometimes forced to sell products at a price not high enough to cover R&D costs. The small market for developing countries vaccines which, as indicated earlier, amounts to no more than $200m a year, is not offering enough incentives to incur the huge costs of development. In Kremer's view a fund set aside for the purchase of a future vaccine would provide the right incentives, and, unlike R&D subsidies, public money would not be wasted should the industry's efforts to develop the desired vaccine not come to fruition. US$ 1 bn set aside by the World Bank for the purchase of future vaccines is currently awaiting approval by the bank's board.

3.11 Concluding remarks

This Chapter has outlined under which circumstances it makes possible economic sense for the public sector to promote the development of vaccine products. This results mainly from market imperfections, such as the existence of externalities, the public good aspect of vaccines and equity considerations. The issue of government failure was also briefly addressed, most notably in the context of incomplete vaccination which

could under certain circumstances lead to an overall increase of health care costs.

The Global Alliance for Vaccines and Immunisation will be instrumental in encouraging industry to develop new vaccines for the developing world and a number of push and pull strategies will be employed which have been outlined above.

Although these strategies were formulated in consultation with industry representatives, little is known about the likelihood of success of the individual measures. The relationship between property protection, market size and public-private cooperation, to name the most important factors, and firms' R&D behaviour in the field of biological products is, as yet, largely unexplored.

This is, broadly speaking, the task of the following five chapters of the thesis. While Chapters Four, Five, and Six will be investigating relationships between market size, property right protection and other factors on the R&D behaviour of manufacturers of pharmaceutical and vaccine products, Chapters Seven and Eight will examine evidence on the question of whether public-private interaction in research in the specific area of biological products is more productive than private R&D alone. The related issue of knowledge flow and the associated mobility of scientists will be investigated in chapters nine and ten.

4 Innovation economics and R&D resource allocation in the pharmaceutical industry

4.1 Background

The literature on both innovation economics and pharmaceutical R&D is extensive, reflecting the fact that innovation is seen as one of the driving forces of economic growth. Further to that, pharmaceutical manufacturers are the biggest R&D spenders in some economies[1].

Compared to the aircraft and defence industries (two other R&D-intensive sectors), the vast majority of R&D investments in the pharmaceutical industry are financed by the industry itself with very little government aid, and are paid for primarily out of profit contributions from its current products.

Pharmaceutical R&D is a very cost-intensive undertaking. It is estimated that today the development of a new molecular entity[2] (NME) costs 500 million US$ on average, which is largely due to the extremely costly screening process of newly synthesised compounds[3], and will take on average 14 years from the moment of discovery until market launch of a new drug (Pharmaceutical Research and Manufacturers of America 2001).

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[1]According to the Department for Trade and Industry (2000), the pharmaceutical sector is the most R&D intensive of all the main industrial sectors with average spending equivalent to 12.8 per cent of sales. The pharmaceutical sector carries out 40% of all corporate R&D in the UK with Astra Zeneca, Glaxo Wellcome and SmithKline Beecham topping the table in 2000.

[2] The more familiar term New Chemical Entity (NCE) has been replaced with the term New Molecular Entity (NME) since new drug technology is no longer exclusively based on chemical processes but increasingly derived from the manipulation of living organisms (biotechnology).

[3]On average only one out of 6000 of these compounds are considered to be safe and effective enough to be brought to the market.

Contributions in the microeconomic branch of innovation economics, and pharmaceutical economics in particular, aim to explain the determinants of R&D spending by focusing on industry-specific characteristics, usually classified under the headings 'appropriability conditions', 'technological opportunities' and 'demand factors'. This literature is the starting point of the analysis since these three factors have inspired the debate on whether 'technology push' or 'demand pull' are responsible for bringing new vaccine products to the market (see chapter three).

Before these specific microeconomic approaches are reviewed in greater detail, the section immediately following will give a brief overview of how innovation has entered both macro- and microeconomic thinking over the past 60 years. Later on, this chapter also reviews some contributions made by the finance literature which has lately influenced the work of pharmaceutical economists.

The subsection 'resource allocation at the individual firm level' presents information on how individual companies allocate R&D resources. These case studies, although difficult to generalise, will help in assessing some of the assumptions made in industry studies.

The chapter concludes with some reflections on the welfare effects of pharmaceutical pricing, trying to put allegations of 'unfair' pricing of innovative drugs into perspective.

4.2 The scope of innovation economics

Innovation economics can be broadly separated into a microeconomic and macroeconomic approach. In macroeconomics, growth theorists use

the production function to explain economic growth[4]. According to early Keynesian growth theory[5] an economy's output and its rate of growth depends on the relative input of two factors of production: labour and capital. According to this view the transition from slow to rapid growth required a sustained rise in the rate of savings and investment. Use of this idea diffused rapidly to the planning agencies of newly independent countries. This model was also interpreted as:

> "consistent with the view that achieving sustained growth would be more difficult for capitalist economies than for economies in which the central planning apparatus would have more direct access to the instruments needed to force a rise in the savings rate and to allocate investment to its most productive uses[6]" (Ruttan 2001, p. 24).

Solow (1957) introduced technical progress as a third factor into the production function. Whatever proportion of growth is not 'explained' by the conventional production function would then be picked up by that third factor, technical progress. This appears to be a useful explanation for differences in growth rates in periods with comparable relative factor inputs such as the post war surge in economic growth in the United States, where according to some authors only one third of the observed growth in output could be explained by the growth in the traditional inputs labour and capital (Beije 1998, p. 30). The remaining two thirds, sometimes called the 'measure of ignorance', were then attributed to factors which improved efficiency of the use of capital and labour, with technological change seen as the most important contributing force.

The explanation of differences in growth rates and per capita income between countries was further pursued by what is now known as neo-

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[4] See Dornbusch and Fischer (1994, pp. 261-293) for a comprehensive introduction to the macroeconomics of growth and productivity

[5] See the work of Harrod (1939) and Domar (1947).

[6] A view which proved rather far from the truth

classical growth theory. Considering diminishing returns in the production function then an increasing number of workers added to a given rate of capital will result in a declining growth rate. With the growth rate of capital depending on savings which in turn depend on income and income depending on the stock of capital this interdependence required further analysis. Neo-classical growth theory makes a number of important predictions. Once the economy has reached a so called steady state the *growth rate* of output is exogenous, i.e. independent of the savings rate. An increase in the savings rate increases the steady state *level* of income but not the rate at which income grows (Solow 1988). The steady growth rate of income per capita remains dependent on the rate of technical progress and the rate of population growth. Unless a new general purpose technology were to result in another spurt in the rate of productivity and output growth, the economy would remain at the steady state. This theory reverses the conclusions of the earlier Keynesian growth theories: technological change has replaced growth of capital equipment as the primary source of growth (Ruttan 2001, p. 24).

Differences in growth rates between countries shouldn't persist in the long run according to this theory if each country has the same rate of population growth and access to the same technology. Although there is some evidence of convergence in growth rates between countries, this prediction proved unsatisfactory in the light of different growth experiences of different countries in the world over longer periods.

Hence 'exogenous' neo-classical growth theory of the 50s and 60 was followed by a second period of research starting in the late 1980s creating neo-classical 'endogenous' growth theory[7]. In endogenous growth theory, the growth rate becomes determined *within* the theory.

[7] See Grupp 1998, p. 62 for a brief introduction into endogenous growth theory or original contributions by Romer (1986) and Romer (1994).

According to this theory the rate of technical progress is determined by the share of the economies' resources devoted to research and development, and the growth rate is determined by the savings rate via its effect on the rate of capital accumulation.

What neo-classical growth theory does not attempt to explain, however, is what influences a firm's decision to devote more or less of its resources to innovation in any given year.

Answers to this question are more likely to be found in microeconomic theory, and Joseph Schumpeter (1942) was one of the first economists to investigate factors influencing technological change at the firm level. In his work he emphasised the role of the entrepreneur in the application of knowledge and new technologies. Schumpeter also focuses on the relationship between innovation and market structure which confirms his position as the pioneer of the competition-theoretic branch of innovation theory. In Schumpeter's view, perfectly competitive markets are suitable for static resource allocation. Large firms operating in concentrated markets are however much more conducive to rapid technological change and long-run expansion of total output. Schumpeter challenged traditional antitrust ideology, claiming that welfare advantages derived from large firms operating in concentrated markets could outweigh welfare derived from perfectly competitive markets.

Schumpeter's two main hypothesis, that a) innovation increases more than proportionately with firm size and b) innovation increases with market concentration, have been tested extensively. In a survey of the literature Cohen and Levin (1989, p. 1061) found that:

> "the empirical results bearing on the Schumpeterian hypothesis are inconclusive, in large part because investigators have failed to take systematic account of more fundamental sources of variation in the innovative behaviour and performance of firms and industries."

More important in the context of research policy is Cohen and Levin's (1989, p. 1061) statement that:

> "the more general task of identifying and evaluating other, perhaps more fundamental, determinants of technological progress in industry has received little attention relative to the effort devoted to exploring the effects of size and market structure."

One of these efforts came from game-theoretical contributions which offer some insight into interdependencies between firms' R&D decisions. Among others, Dasgupta and Stiglitz (1980) have looked at patent races where the value of one firm's patent depends on how much another firm spends on R&D. In a deterministic setting[8] the first firm to win a patent gets the entire market and the more money is spent on R&D the shorter is the time to develop the product. If two firms have the same research capabilities then it can be shown that in a Nash equilibrium only one firm will undertake R&D at all. If two firms spend the same amount they both have the same chance of winning the race and one firm is bound to be frustrated because it gets no return at all. In equilibrium a firm will spend exactly the amount it expects as a return on its investment. If the firm spent any less, the other firm could outspend it and win the patent race while still earning a positive profit.

In a probabilistic setting an increase in R&D spending no longer guarantees that the firm will win the patent race but increases the probability it does win the race. The individual firm's decision by how much to increase its R&D spending will then depend on a number of factors, such as absolute R&D productivity, its productivity relative to that of other firms, the other firm's response to an increase in outlays and the total number of firms undertaking R&D.

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[8] See Besanko, Dranove, Shanley (1996, pp. 589-593) for a brief, non-technical introduction into deterministic and probabilistic patent races.

Outside the realm of game theory the most encompassing approach to explaining firms' R&D behaviour is offered by Dosi (1982, 1988, 1997) who regards innovations as a problem-solving process which is initially built upon a key scientific principle, for example genetic engineering. The innovation process then follows along a 'technological trajectory', a term originally used in Nelson and Winter's (1982) evolutionary theory of economic change.

Along the way, two factors influence R&D decisions, appropriability and technological opportunity. In Dosi's view these two conditions differ from industry to industry but also between firms within an industry. Hence his approach attempts to explain not only inter-industry differences but also intra-industry differences in technological innovation. This is of course relevant for the purpose of this study which aims to model R&D behaviour with regard to a product group within an industry.

4.3 From technological opportunities to technological trajectories

Explaining the role of technological opportunities, Dosi (1988, p.1136) states that:

> "scientific knowledge plays a crucial role in opening up new possibilities of major technological advance. In this century, the emergence of major new technological paradigms has frequently been directly dependent and directly linked with major scientific breakthroughs; see for example the origin of synthetic chemistry...".

Clearly industries differ in terms of opportunities they face for technical advance. It is, however, difficult to make differences in technological opportunities a testable hypothesis. In his quantitative studies Scherer (1965, 1982) has classified industries into a small number of technology

groups, such as chemical, electrical, mechanical, and was able to explain variance in patenting activity in these industries.

One of the most extensive qualitative surveys measuring technological opportunities and appropriability[9] conditions was undertaken by researchers at Yale University and discussed by Levin et al. (1987). R&D personnel in 650 firms in 142 sectors of activity were asked to rate the importance of variables representing technological opportunities and appropriability conditions on a semantic scale. Among the factors stated as having a varying but significant impact on innovative activity were a) the contribution of basic and applied science, b) contribution of other sources of technical knowledge, e.g. upstream suppliers or downstream users of technology, c) university research, d) institutional factors such as public agencies research (e.g. the military) and e) independent inventors.

Subsequent studies have looked at each of these factors individually. Dosi (1988, p. 1136) emphasises the "nature and interest of bridging institutions" between pure research and economic applications, or technology transfer as it is often called, a factor which has become very influential in biotech industries, where a large number of today's firms are commercial spin-offs from university research departments. Also the role of government in financing or undertaking its own research has been widely acknowledged.

Case study literature has further supported the notion of technologies developing along 'natural trajectories'. Cohen and Levin (1989, p. 1086) suggest, that "technological development proceeds along a relatively clear path, as if moving toward some physical limit. ... Engineers ... repeatedly focus on a particular class of engineering problems, drawing upon or strengthening a familiar method or solution."

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[9] A detailed explanation of appropriability conditions will follow in the next section.

This is what Teece (1988) refers to as a 'lock-in' phenomenon, doing what has been done in the past. David (1985) explains how the QWERTY keyboard arrangement became locked in through the forces of *technical interrelatedness* between a typist's memories and the typewriter design, *economies of scale* due to a decline in user costs once QWERTY becomes standard, and *quasiirreversibility* of investment once typists have been trained on the specific keyboard[10].

Nelson and Winter's Evolutionary Theory of Technological Change (1982, p. 14) also claims that behaviour patterns of a firm are replaced by 'routine':

> "a term that includes characteristics that range from well-specified technical routines producing things, procedures for hiring and firing, ordering new inventory, or stepping up production of items in high demand to policies regarding investment, research and development (R&D), …."

Ruttan (2001) claims that most technological trajectories will eventually come to an end. Once scale economies are exhausted and profits decline, pressure will focus scientific and technical effort on breaking technological barriers that lock technology into inferior or obsolete trajectories.

This is called the S-curve effect in some accounts (Foster 1986). The standard hypothesis is that eventually diminishing returns set into a technical trajectory, yielding an S-curve like the one shown in figure 4.1.

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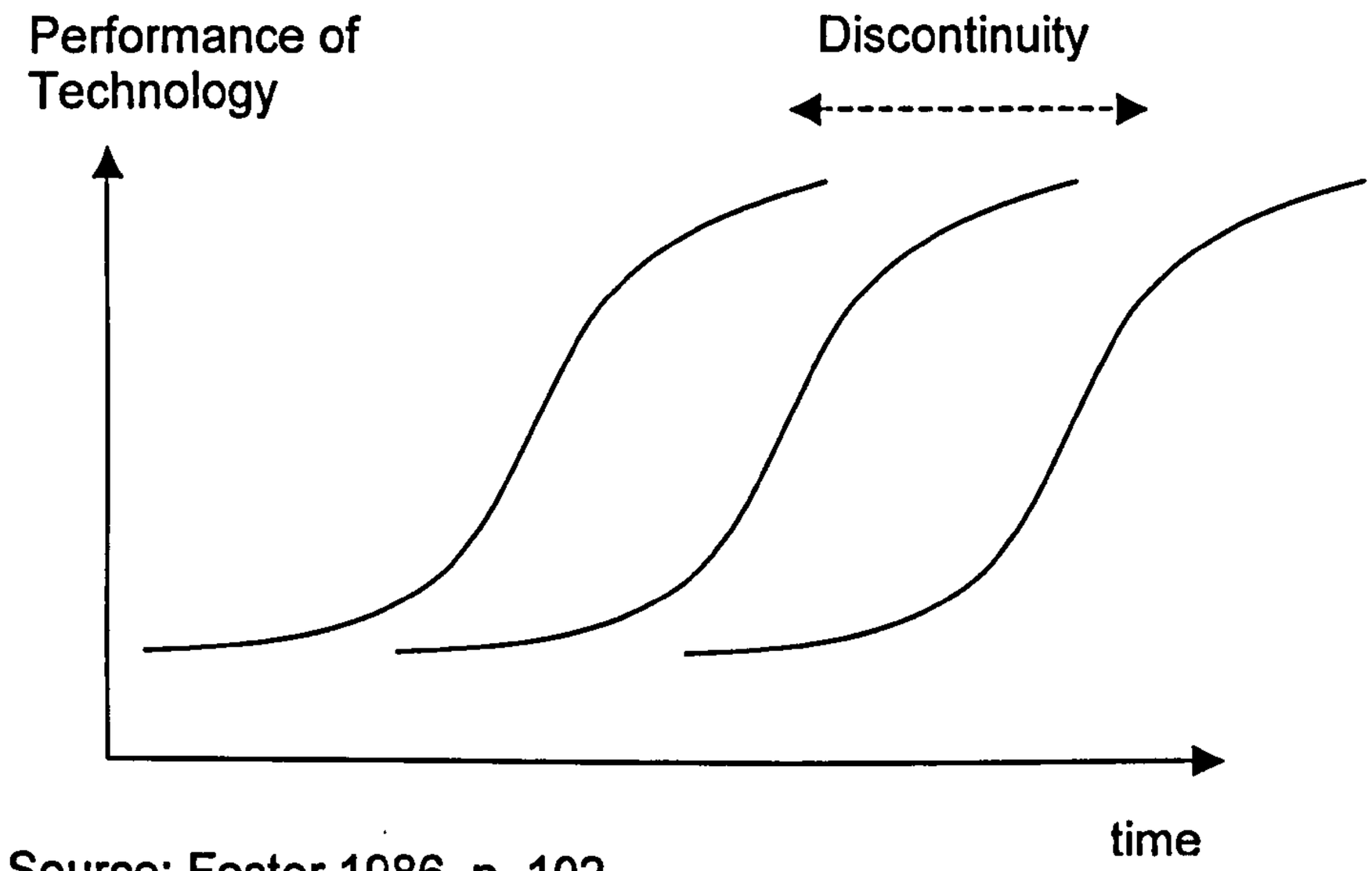
[10] Ruttan (2001, p. 112-116) points out that these characteristics are sometimes bundled under the rubric of 'positive network externalities' and gives further examples of what he calls the 'path dependence' of technical change.

Figure 4-1



Source: Foster 1986, p. 102

Foster (1986) also argues that we often see S-curves coming along in succession, old sources of competitive advantage being replaced with by new ones as indicated in the above diagram. This, of course, corresponds to Schumpeter's creative destruction and more recent strategic management work, for example by d'Aveni (1994).

This could cause the problem of an increasingly empty pool of knowledge and hence a historical decline in research efficiency identified by Grabowski in the case of the pharmaceutical industry. Grabowski quotes former FDA Commissioner Schmidt (Grabowski 1978, p.139):

> "As the gaps in biomedical knowledge decrease, so do the opportunities for the development of new or useful related drugs. This does not reflect a loss of innovative capacity, but rather reflects the normal course of a growth industry as it becomes technologically more mature."

As shown by the declining number of new single entity drugs approved in the U.S., England, France and Germany, this is an international and still

ongoing phenomenon. According to the Centre of Medicines Research (CMR International News 19/2001, p. 10) the year 2000 witnessed the launch of only 32 new molecular entities, down from 41 in 1999 and the lowest number since 1979. In 1991, a total 53 new molecular entities were launched.

The notion of an emptying pool of knowledge in medical research has been met with some criticism. Some have argued that the rate of development of significant and truly useful new drugs has remained stable over the years. Others claim that massive expenditure on basic biomedical research could indeed create a renewed pool of knowledge which could offset the trend toward a depletion of opportunities. Dosi in particular (1988, p. 1138) has shown that decreasing returns to research did not emerge historically. Especially in the pharmaceutical industry biotechnology has had great effects on the efficiency of search for new drugs.

Margaret Sharp (1990) has investigated Dosi's notion of technological trajectories in the context of biotechnology. Sharp explains (1990, p. 94), that:

> "much innovation is continuous and incremental within the firm, resulting from a combination of demand and cost pressures, on the one hand, and learning by doing on the other. However from time to time radical innovations emerge, which ... far from being a part of a continuous stream of innovation, represent a major jump, or discontinuity in technological progress."

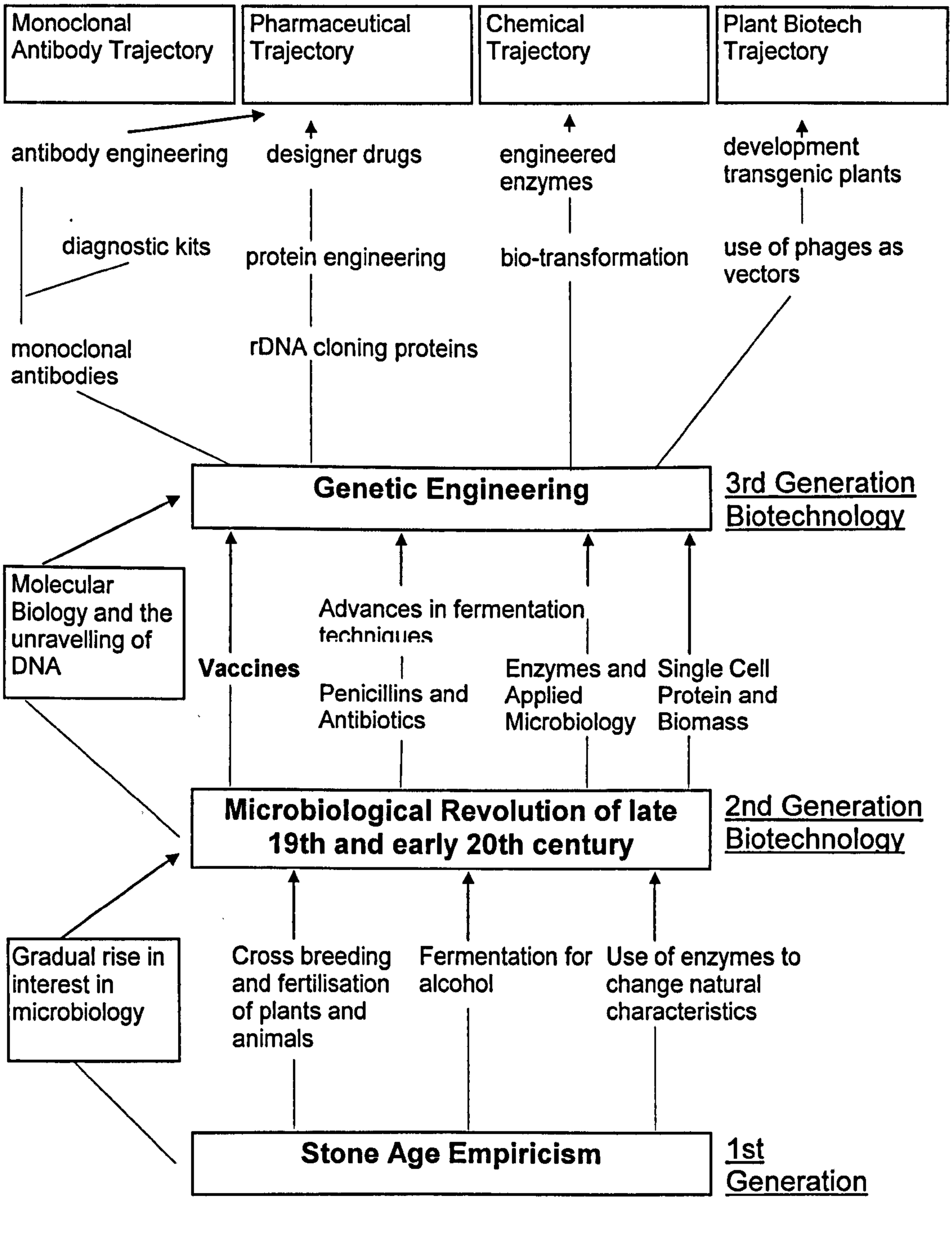
The former continuous process of innovation emerges along a technological *trajectory* while the latter technological jump establishes a new technological *paradigm*. Firms tend to undertake research along lines which are familiar to them and build in-house expertise in these areas and reinforce that expertise (ibid., p. 95). This continues until the

existing technological paradigm or routine is superseded by another one, which again offers a new set of technological trajectories to be pursued by firms. While firms are able to protect their competitive position in the process of building up expertise along an existing trajectory, the complete change of paradigm or the fundamentals of science offers an opportunity for new firms to enter the market.

In Nelson and Winter's view (1982), in order to survive firms search for better techniques and those which succeed are 'selected' by the market, a process which, again, resembles Schumpeter's concept of creative destruction. According to Ruttan (2001, p. 116) once scale economies are exhausted and, as a result, profits decline, the "pressure of growth in demand will focus scientific and technical effort on breaking the technological barriers that lock technology into inferior or obsolete trajectories".

In biotechnology Sharp (1990) identifies three of these distinct paradigm changes, the First, Second and Third Generation Biotechnology, here shown in figure 4.2.:

Figure 4-2 Three generations of Biotechnology and trajectories evolving from third generation Biotechnology (taken from Sharp 1990, p. 99)



While Second Generation Biotechnology led scientists to discover cures for life-threatening diseases caused by micro-organisms and prevention of diseases through vaccination, it is the Third Generation Biotechnology which has created the new technological paradigm of genetic engineering.

The cutting and splicing of genes has opened up a range of new trajectories in the fields of medicine, chemistry and agriculture. In agriculture, genetically modified plants and seeds, or GM crops, have caused considerable controversy. Despite the fact that these seeds or plants have certain desirable characteristics, such as resistance to particular herbicides or indeed the pest itself, the public (at least in Europe) has been reluctant to accept genetically-modified foods which in turn has severely hampered the commercial prospects of the new technology.

It is the field of pharmaceuticals which is the most important new trajectory, because it offers the prospect of finding cures for diseases previously untreatable and as a result potentially large commercial rewards for those companies at the forefront of the new science.

Historically, pharmaceutical firms' research capabilities consisted of large-scale screening of new substances for potential therapeutic properties. Piachaud and Lynas (2000, p. 11) outline how the process of discovery of new substances has changed with the advent of biotechnology: "New substances were instead identified through the examination of the basic function of cells. This then signalled the shift toward biology as the primary science as opposed to organic chemistry." Identifying new drugs now required competencies well beyond the traditional skills of the pharmaceutical industry and more likely to be found in the vicinity of research-active university departments.

Gambardella (1993, p. 188) explains the importance of the new field of drug design:

> "The growth of basic information about the biology of the human body offers more solid knowledge about the nature of altered equilibria before developing an appropriate remedy. Scientists can then design an 'ideal' compound that is expected to counteract the undesired state."

Drug design in turn is greatly facilitated by development of recombinant DNA (rDNA), the ability to combine genetic material from different sources, e.g. from two different micro-organisms, to create a DNA sequence with specific properties. The initial discovery of the rDNA technique by Stanley Cohen and Herbert Boyer[11] in 1973 started not only the foundation of commercial biotechnology but also a burst of scientific innovation (Zucker et al., 1998, p. 291).

The discovery of monoclonal antibodies originally resulted in a separate technological trajectory (see chart) with important applications in the field of diagnostics. Monoclonal antibodies are derived from the fusing of an antibody with for instance cancer cells and can be used for in vitro diagnosis of diseases since the growth characteristics of one cell are combined with the specificity of the other (Sharp 1990, p. 100). Subsequently it was discovered that monoclonal antibodies also allowed drugs to be delivered to specific targets without harming healthy cells and tissues. The combined benefits of the two techniques (DNA and monoclonal antibodies) presented a new set of opportunities for medicinal research, and formed the basis for targeted pharmaceutical R&D (Piachaud and Lynas, 2000, pp. 5-6).

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[11] Herbert Boyer founded in 1977 one of the first Biotech companies, Genentech, together with the venture capitalist Robert Swanson.

Certainly the discovery of rDNA techniques marks the beginning of a new era of drug discovery and a new technological trajectory. The extent to which genetic engineering has influenced innovative activity in firms is difficult to verify, at least empirically. Zucker et al (1998, p.291) believe that:

> "at least for the first 10 or 15 years, the innovations which underlie biotechnology are properly analysed in terms of naturally excludable knowledge held by a small initial group of discoverers .... Ultimately the knowledge spread sufficiently widely to become part of routine science which could be learned at any major research university."

This view is shared by Sharp (1990, p. 101), who believes that "cloning genes is now regarded as everyday experience to such a degree that every graduate student in molecular biology knows how to do it." From the above it becomes obvious that the new knowledge diffuses only gradually within the scientific community and any surge in innovative activity would be just as gradual as firms start to tap into the scientific community in search of personnel who can master the new technique.

One well-known phenomenon has been the emergence of a large number of small biotech companies dedicated to the commercial exploitation of the new technological paradigm. To what extent the emergence of this new technological trajectory may have *caused* a surge in investment in the field of vaccines will be evaluated in greater detail in Chapter Six.

No matter what opportunities or trajectories arise, the sole consideration of what is technically possible, i.e. supply conditions, would ignore another important determinant of commercial success, demand. Given any level of technological opportunity "the incentive to commit resources to their discovery and development will depend [...] on the incentives that interested motivated agents perceive in terms of expected economic

returns", as Dosi (1988, p. 1139) pointed out, and the ability to appropriate these returns will depend on so-called appropriability conditions, which we turn to next.

4.4 Appropriability conditions

According to Dosi (1988, 1997) and Dosi and Nelson (1994) 'appropriability' concerns the properties of technological knowledge, technical artefacts, markets, and the legal environment that permit innovations and protect them as rent-yielding assets against competitors' imitation.

As in other industries, the state protects the innovative activities of the pharmaceutical industry by granting patents so that the imitation of products is prohibited for the duration of the patent. Without effective patent protection, imitators could use the R&D efforts of the innovative firm without having to compensate the innovator for R&D expenses incurred. Investment in innovation would not pay off since any imitator could offer the same product immediately after the development at a lower price.

Levin et al's qualitative survey (1987) suggests that patents are of varying importance for industry. In general patents have been quoted by R&D personnel as the least effective means of securing a competitive advantage achieved through innovation. Secrecy, the ability to move quickly down the learning curve, cost advantages and superior sales and service all score higher on industry average. Patents are, however, significant for the pharmaceutical industry, and some branches of mechanical and electrical engineering. These findings are confirmed by Mansfield (1986) who asked a sample of 100 firms from different industrial sectors about the percentage of innovations that would not have been developed over a given period without patent protection in place. According to this survey, 65% of pharmaceutical inventions would

not have been introduced in the absence of patent protection. The figures were much lower for the chemical industry (30%), petroleum, machinery, and metal products (10-20%) and less than 10% for electrical equipment, instruments, primary metals, office equipment, motor vehicles, rubber and textiles.

In Europe patent protection is usually granted for 20 years. Inevitably a pharmaceutical company applies for a patent at a very early stage in the research process. The component will then have to undergo non-clinical and clinical trials and the final licensing procedure of the national drug administration so that on average another 14 years pass by until a patented NCE can finally be launched (Pharmaceutical Research and Manufacturers of America, 2001, p. 112). The effective patent protection during which the product is making valuable contribution to current R&D programmes is then only 6 years on average.

Another feature of pharmaceutical innovation is the empirical character of research. An element of chance is highly significant in the process of pharmaceutical R&D since there is still only limited understanding of how drugs work. This causes problems when it comes to patent protection of New Molecular Entities (NMEs). Usually a large number of similar molecules are protected together with the molecule that proved to be effective. But there remains a number of molecules which also work but which are not covered by the patent. This makes imitation possible for the competitor and it is believed that patent protection alone is not sufficient to protect a newly developed product for the duration of the patent. Innovative manufacturers have to devise other means to protect their profit contribution at least for the duration of the patent, the most important one of which is the ability to move quickly down the learning curve.

This role is fulfilled by the firm's R&D department which constitutes a dynamic barrier to entry into the market (Schellhaass 1986). The R&D

department is obliged to speed up technical progress to the extent that the imitator cannot catch up. Ideally the imitator will be unable to develop a copy of the original drug before the innovator has launched an improved follow-up product. The imitator should then be unable to develop the original product at the same pace as the innovator. The only way the imitator could match this performance is to have a similarly powerful R&D department at its disposal as the innovator. Due to the lack of experience and the concentration of knowledge in the scientific community, this is highly unlikely.

A second advantage for the innovator results from this creation of a knowledge gap. Once the innovator is unchallenged for a number of years, a substantial proportion of the necessary profit contribution has already been generated. The imitator now faces a dilemma. Any investment in a powerful enough R&D department would incur cost which are potentially sunk in case of exiting the market. The imitator may also face the threat of a limit-pricing strategy by the innovator which could potentially drive the imitator out of the market. The R&D department is called a 'dynamic entry barrier', since it requires a continuous investment in R&D facilities by the innovator. Should it cease to do that the barrier will erode. But only static barriers (patents) and dynamic barriers together enable the innovator to pursue a pricing policy which is not primarily designed to fight off competitors but serves the purpose of yielding profit contributions significant enough to finance current R&D projects[12].

The existence of patent protection (or the lack of it) is, however, not the only appropriability condition. Many attempts have been made to test the

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[12] Whether an innovator has a 'first mover advantage' will not only depend on the strength of protection from patents and lead time, but also the uncertainty of the R&D project, the existence of network externalities and the need of the buyer to invest in complementary resources. Sometimes leaders do stumble: the IBM PC springs to mind, but also De Haviland's first commercial jet engine (the Comet) which proved to be unstable. The follower, Boeing (successfully launching the 707), dominated the market for commercial jet planes for many years subsequently.

impact of other regulatory measures on the pharmaceutical industry. Early studies date back to the 1960s, when the regulations imposed by the Food and Drug Administration (FDA) in the US were amended in 1962. New drugs had previously been tested for toxicity alone; they were now required to show improved efficacy as well. The FDA was also given greater influence over the drug evaluation process[13]. The decline in new drug introductions which followed was widely believed to be a direct result of the amendments and provided valuable testing ground for the new discipline of pharmaceutical economics.

Martin Bailey (1972) attempted to separate technological opportunity factors from regulatory factors using pre- and post- amendment data in his sample. His results supported both the research depletion and regulation hypothesis. Grabowski and Vernon's (1978, p. 143) re-estimation of Bailey's study is reproduced here (t-statistics in parentheses) as an example of an early model used to illustrate the effect of regulatory changes specifically in the pharmaceutical industry:

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[13] The reason for this was a health scare resulting from an investigatory drug and more importantly the belief that the US pharmaceutical industry over the years had used its monopoly power to keep prices well above cost of goods sold. Furthermore the commission which led the inquiry argued that little of social value arose from industry research. Molecules were simply manipulated and the resulting new drugs presented little therapeutic advantage over the old ones, but could however be sold at higher prices due to patent protection.

$$\text{Log } (Nt/Et) = -0.88\ (2.40) - 2.26Dt\ (8.63) - 0.003Pt\ (0.23)$$

$$R^2 = 0.88 \qquad DW = 1.60$$

Nt = number of NCEs introduced and discovered by US firms in year t

Et = average industry deflated R&D expenditure for ethical drugs in the US in years t-4, t-5, and t-6 (assumed fixed five year lag form R&D outlay to introduction)

Dt = a zero-one dummy variable representing the effect of regulation (=1 after 1961)

Pt = 1/7 ΣM t-v v ranging from 7 to 13, where Mt is total number of new drugs introduced from all sources (seven year moving average of past introductions as proxy variable for depletion)

While Bailey could show that R&D productivity (expressed as NCEs per dollar of R&D invested) was statistically significantly related to proxy variables for regulation and research depletion, Grabowski and Vernon's re-estimation (ibid.) using additional and more recent data finds that the depletion variable becomes statistically insignificant.

Wiggins (1983a) examined the effects of the 1962 drug amendments on the level of research spending in the pharmaceutical industry. His findings indicate that regulation had a major impact on new drug introductions in the US. Regulation influenced new introductions directly and indirectly via its impact on research spending. Wiggins estimates that introduction rates have been reduced by as much as 60% due to the 1962 amendments. In another study Wiggins (1983b) shows that the response of pharmaceutical research expenditure to regulation is not immediate but lagged by a number of periods.

In a subsequent study, Wiggins (1984) used disaggregated data to show how development in different therapeutic classes has been affected by the 1962 amendments. The decline was significantly more pronounced in the areas of anti-infectives and drugs affecting the Central Nervous System (CNS) than in other therapeutic classes although these two areas were not more strictly regulated than other classes. Wiggins argues that

about half of the decline in new introductions could be explained by regulatory factors.

Grabowski (1997, 2000) has subsequently expanded this basic framework and introduced cost of finance effects; these models will be discussed further below, in Section 4.6. and Chapter Six.

4.5 Demand factors

Griliches (1957), Schmookler (1962), and Vernon (1966, 1979) emphasise the importance of demand factors in explaining technological change.

Schmookler (1962) showed that output of capital goods and capital expenditures led output of relevant capital goods patents, Griliches (1957) demonstrated the role of demand for the invention and diffusion of hybrid maize, while Vernon (1966, 1979) attempted the same for consumer durables.

This set off the debate whether 'demand pull' (or demand for innovation), or 'technology push' (or supply of innovation), was the driving force behind technical change.

The view behind Schmookler's demand pull hypothesis is that a common pool of scientific knowledge and technological opportunity is available at any time and that it takes large and growing markets for industry to start investing in applied research and the exploitation of this pool.

In response Cohen and Levin (1989, p. 1080) argue, that Schmookler:

> "never attempted to test the maintained hypothesis that the supply conditions for innovation (technological opportunities) were uniform across industries. Schmookler's proposition that demand almost alone

determines the rate and direction of technical change has not survived empirical scrutiny. The consensus, after dozens of case studies, is that the Marshallian scissors cuts with two blades."

Scherer (1982) found in comparing technology and demand variables that both were significant in four different industries. Technology variables however explained more of the variance.

The relationship between market demand and innovative activity, which seems to have at least some significance, needs further clarification. Demand for an innovation would be estimated before the product is actually developed. The relationship is likely to be stronger where an innovation would substitute an existing product or process for which data about market size is available. Entirely new products, such as a cure against a previously untreatable disease, would be developed in the knowledge that a 'need' exists and that a market could be created.

Mowery and Rosenberg (1979, p. 140) point out that demand-pull hypotheses must base themselves on the precise concept of a systematic relationship between prices and quantities i.e. demand, devolving from the constellation of consumer preferences and income. In their view most empirical studies rarely make a distinction between 'needs' and 'demand' "as a result of which the relationship of the need recognition category to market demand as a motivating or controlling influence is tenuous indeed" (ibid., p. 140). The authors also point out that the most radical of innovations were the least responsive to needs and that the demand-pull case is weakest for the most significant innovations.

This is not necessarily at odds with the demand-pull hypothesis. It is the less dramatic innovations, replacing already existing products in the same category, for which reasonable demand estimates exist and which are plausibly developed as a response to expected demand. Dramatic

innovations by comparison are scarce. They are often unexpected, discovered by accident, and life-changing to an extent that consumers may not even have expressed a need because they were unaware that such a need existed. Think for instance of the Personal Computer, and the VCR. The fact that demand-pull cannot be established for the most dramatic innovations (which would create their own markets) does not mean that is has no influence on the majority of minor ones.

Mowery and Rosenberg's criticism does, however, indirectly address the real shortcoming of the demand pull/supply push framework, the lack of recognition of the role of the entrepreneur. The entrepreneur foresees demand, and then creates an entirely new product that does not yet exist. Both are entrepreneurial acts of visualisation and implementation. The Sony Walkman is an often cited example of sheer entrepreneurial persistence to meet potential demand in the face of tremendous technical difficulties.

Another conceptual criticism of the demand-pull hypothesis is the identification problem raised by Mowery and Rosenberg (1979). Demand-pull would assume a rightward shift in the demand curve. The resulting observed increase in the quantity may of course have been a result of that shift but could also have been caused by a shift of the supply curve, e.g. because technological improvements or cost reductions in general make it possible to sell the product at a lower price. In other words, any empirical study establishing a relationship between the quantity demanded and R&D investment may mistakenly interpret the quantity increase as a result of a demand shift, when in reality it has been caused by technology push. Most quantitative empirical studies (Schmookler's for example) are looking at changes in revenue, and an increase in revenue can of course be associated with a shift in demand, a decrease in prices resulting from a shift of supply, or both.

4.6 The R&D investment decision and capital market imperfections

Outside the realm of innovation economics, conventional investment theory has acknowledged that investment is influenced not only by the expected future profitability of a project but also the cost of capital. Modigliani and Miller (1958) maintained that real firm decisions are independent of purely financial factors such as internal liquidity, debt leverage, or dividend payments. In line with this argument, neo-classical investment theory postulates that firms' investment decisions are influenced by the cost of capital as set in centralised securities markets that does not depend on the financial structure of the firm. More recently Fazzari et al. (1988) and Hubbard (1998) have highlighted information imperfections in credit markets, which has led some authors to argue that problems of asymmetric information (in particular in the case of smaller and less established firms), leads to a gap between the cost of external and internal financing. As Hubbard (1998) points out:

> "in the presence of incentive problems and costly monitoring of managerial actions, external suppliers of funds to firms require higher return to compensate them for these monitoring costs and the potential moral hazard associated with managers' control over the allocation of investment funds".

The extent of what is essentially an agency problem, will depend on the degree of newness of the product and the size of the firm. Consider the matrix of possibilities in table 4.1:

Table 4-1

	Large/established firm	Small/entirely new firm
Well-known, existing product	*Modigliani-Miller: low monitoring costs*	*Hubbard: higher monitoring costs*
Entirely new product	*e.g.: Sony Walkman; UMTS mobile phones*	*e.g.: Dotcoms; Small Biotech firms*

Hubbard attributes monitoring costs mainly to small or new firms. Monitoring costs could also be high if an established firm launches entirely new products. Large firms have in the past introduced some disastrous new products; the Ford Edsel is the classic example. More recently, mobile telephone companies have seen their credit ratings reduced after their successful bidding for fourth-generation mobile telephone licenses. As a result, the cost of external finance is likely to go up since a lower rating reflects a higher probability of the firm defaulting on its debts.

The case of small firms launching entirely new products is perhaps the most interesting and applies particularly to small biotech firms and Internet start-up companies. Banks could be backing complete failures or the next Microsoft, and expected returns are extremely difficult to estimate. 'Bubbles' -as well as bursting bubbles- in the stock of such companies are particularly likely. For some of these firms debt finance will be prohibitively expensive or is simply not available and they rely on venture capitalists to provide the necessary equity capital.

Empirical studies of firm investment support the link between changes in net worth and investment due to information problems in financial markets, as for instance Auerbach (1984), Fazzari et al. (1988) and Hubbard (1998) have demonstrated. This is consistent with a difference in cost of external and internal funding and a positive relationship between cash flow and investment spending given investment opportunities are constant.

Grabowski has, for the pharmaceutical industry, expanded his earlier empirical work and introduced such cash flow effects alongside demand effects. In a recent study Grabowski (1997) estimated the following equation for the period 1974 - 1989 using a sample of 11 US pharmaceutical companies (t-statistics in parentheses):

R = -0.20 (-7.00) + 0.74Imarg (6.58) + 0.27 Cashfl (9.88) + 0.005 Pcpharm (4.57)

$R^2/F = 0.71/140.8$

R = Companies' R&D expenditure deflated by sales

Imarg = Industry margin, average pre-tax profits as percent of sales

Cashfl = profits after taxes, plus depreciation, plus R&D costs, divided by sales, lagged by two years

Pcpharm = percentage of total firm sales accounted for by pharmaceutical sales

All coefficients are significant and support the hypothesis that a firm's research intensity is sensitive to expected returns (expressed as the industry's profit margin and the relative importance of pharmaceutical sales) and the relative cost of funds expressed as cash flow.

In a further study, Grabowski (2000) demonstrated that research intensity, defined as R&D divided by sales, also depended on past sales of new introductions as a proxy for expected returns, besides the industry profit margin and cash flow as a proxy for the availability of internal funds. Grabowski's model will be used in a modified form in the empirical section in chapter six and is hence referred to in greater detail further below.

4.7 Allocation of R&D resources at the individual firm level

Although these empirical studies make some reasonable and often statistically significant assumptions about the determinants of R&D spending in the industry, relatively little is documented about how *individual* firms organise the process of R&D allocation.

One industry representative explains that at Pfizer pharmaceuticals the

> "decision making process is based on epidemiology, on medical need and scientific do-ability. The therapeutic areas we wish to focus on are those with high populations and high medical need, based on the burden to the patient and/or to the health service by virtue of there being no adequate treatment" (Samuels 1997, p. 16).

This confirms the importance of demand/need and technological opportunity in the innovation economics framework discussed above.

The following chart illustrates how Pfizer has set priorities at the time. Except for an AIDS vaccine and Hepatitis no other vaccine-preventable diseases are listed. The HIV vaccine is however ranked higher than a cure for HIV, simply because the number of people vaccinated would exceed the number of people treated. This however also illustrates the importance of market size. While undoubtedly the number of people in *need* of vaccination is a significant proportion of the world adult population, most of these would be found in countries unable to pay for an expensive vaccine, i.e. result in insufficient *demand* for the product. This may partially explain why anti-AIDS drugs have been marketed successfully and are already administered in the developed world while an effective vaccine is still years away from commercialisation.

Figure 4-3

Medical need and patient population as driving forces of R&D allocation (source: Pfizer Pharmaceuticals and Lehman Brothers)

Patient Population			
High	Hypertension Arthritis Bacterial Infection Sedation Analgesia Lipid Lowering	Asthma Anxiety Depression Osteoporosis Prostate Hyperthrophy Diabetes type 2 Male pattern baldness Acne Influenca	Obesity Dementia Arthritis (disease modifying) Arteriosclerosis Periph. Vascular Disease Oral peptide delivery AIDS vaccine Urinary Incontinence Stroke/MI prophilaxis Cancers
Medium	Allergies Herpes Haemophilia Chlamydia Infection Emesis	Epilepsy Migraine Diabetes type 1 Endometriosis Thrombosis Fungal infection	Heart failure Chronic bronchitis Schizophrenia Parkinson's Psoriasis Drug/alcohol abuse Sexual dysfunction Wound healing Arrhythmia Cirrhosis Hepatitis
Low	Gaucher's	Irritable bowel syndrome Crohn's disease Ulcerative colitis Unstable angina	AIDS Multiple sclerosis Emphysema Cystic fibrosis Transplant rejection Septic shock
	Low	Medium	High

Medical Need

At Pfizer, investment projects will compete for funding internally and multidisciplinary groups (including scientists, marketing and market research personnel) will allocate resources to specific research opportunities which will be reviewed regularly. Cockburn and Henderson (1997) have found this kind of peer review process for resource allocation in other pharmaceutical firms as well.

Projects are no longer pursued when the science proves 'too difficult' to master or when a competitor's research makes the pursuit of the company's project irrelevant (Samuels 1997). Industry representatives also emphasise the importance of partnerships with the science base, such as universities, the heavily research-oriented biotech sector and institutions such as the National Institute of Health in the US or the Medical Research Council in the UK.

The second case is Glaxo Wellcome, which uses six criteria to select a development portfolio (Sully 1997). The first three address the commercial opportunities of a product; they are: net present value, unmet need (derived from market research with opinion leaders) and what is referred to as "strength of value proposition", a preliminary assessment of cost versus income profile, and as such a rough indicator of profitability.

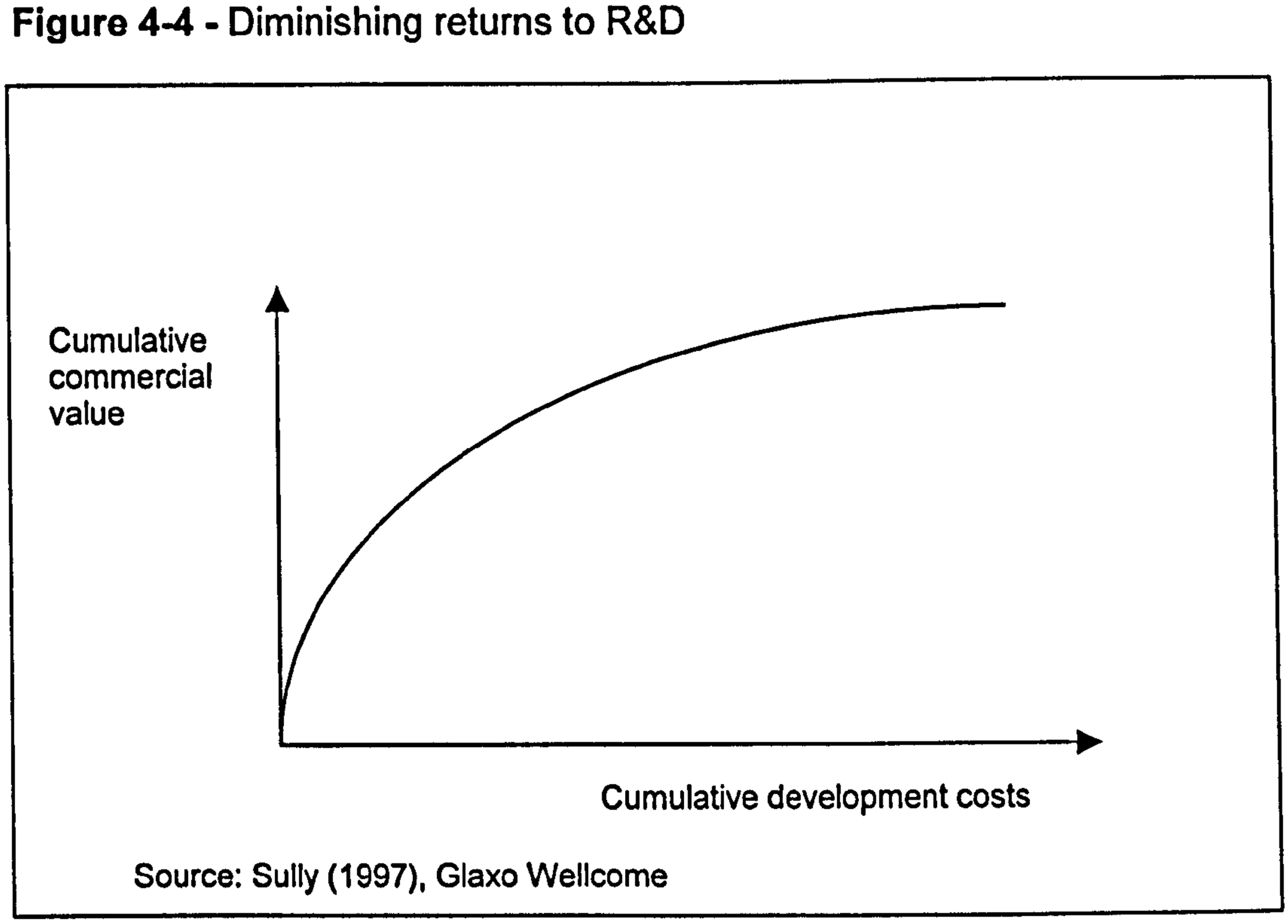
Another two criteria correspond to Pfizer's notion of scientific do-ability. Glaxo Wellcome uses the terms strength of scientific rationale and development probability, assessing the ability to meet the defined product profile for the former, the latter attributes a probability of successful development to each stage of the development process. Measure number six assesses the extent of strategic fit with the current portfolio and general strategic direction of the company.

A computer spreadsheet will then create an overall score and a rank order of individual projects. Different weightings are used for different stages of the development process. While early stages are more likely to

be driven by scientific rationale, during later stages net present value becomes more important. This also reflects the fact that the quality of commercial estimates increases in the later stages of a project. Unmet need, for instance, is a more reliable proxy for market size during the early stages, than an estimate of income streams. As the project moves towards market launch more market research is undertaken which in turn improves the quality of cash flow estimates. Another important aspect is the overall balance in the research portfolio. The relatively few high-return, high feasibility projects must be complemented with high-feasibility, low-return projects (such as variations on existing products) and high-risk, high-return projects, such as promising new compounds at very early stages of the development cycle.

Glaxo Wellcome finds that returns to R&D projects are diminishing (Sully 1997). This is illustrated in the following figure:

Figure 4-4 - Diminishing returns to R&D



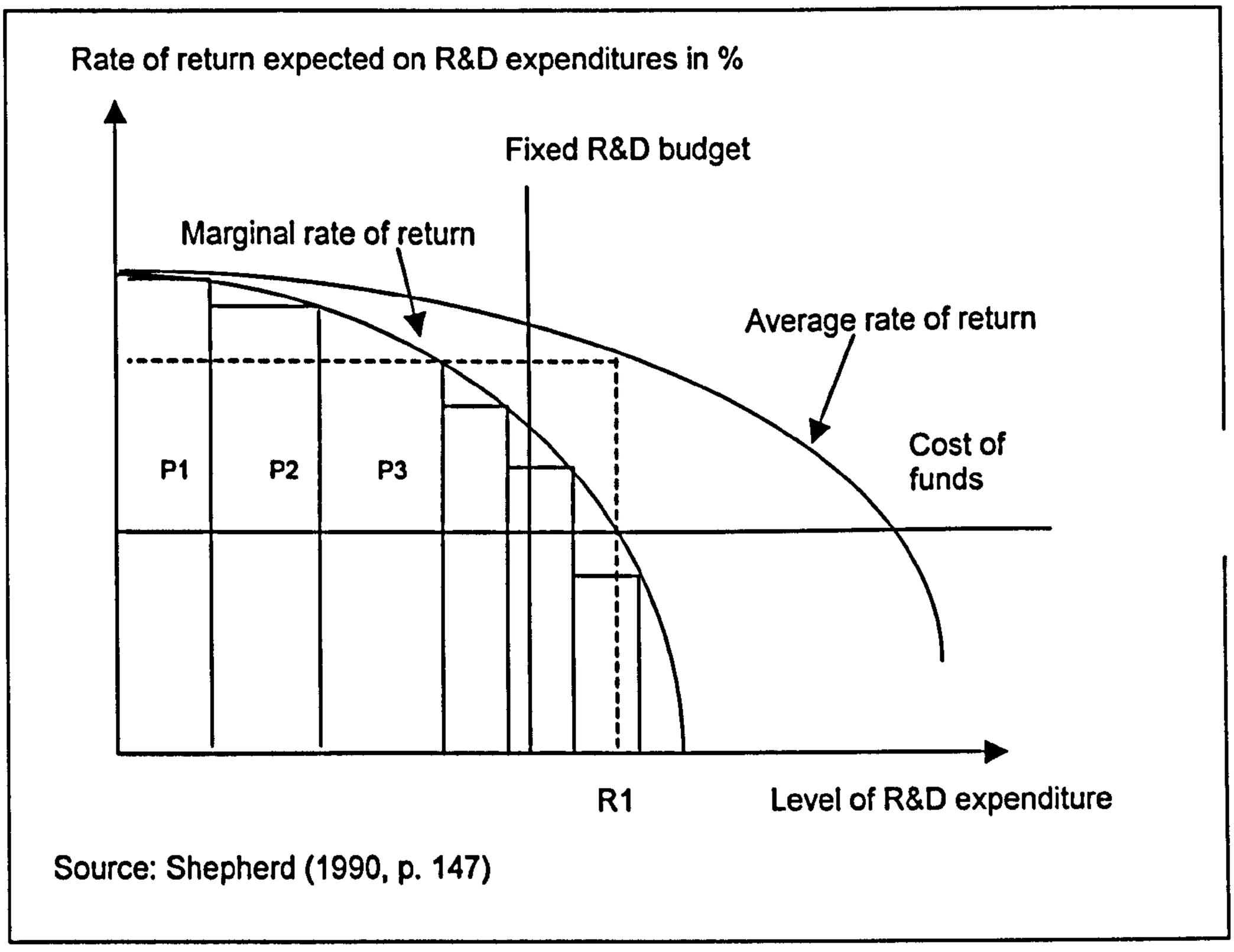
Source: Sully (1997), Glaxo Wellcome

Sully (1997) notes that if the above curve should ever start to dip, this would be a logical point to cut back on R&D spending. The notion of

diminishing returns to R&D is important because once costs of finance are taken into consideration, the cut-off point for further funding would be where the cost of the last project is equal to the return of the last project.

This kind of marginal analysis is proposed by Shepherd (1990), here presented in figure 4.5:

Figure 4-5



Source: Shepherd (1990, p. 147)

In Shepherd's view all R&D projects (P1, P2, P3 etc.) are listed from left to right according to the expected return on investment. Firms will spend money on additional projects as long as the return on investment is positive and up to the point until either the fixed R&D budget is exhausted or the cost of funds are equal to the return on the last R&D project, in the latter case resulting in the level of R&D expenditure R1.

While Shepherd assumes constant cost of funds, Grabowski's (2000) marginal analysis of the R&D spending decision shows a rising cost of

funds curve, reflecting the higher cost of external finance when compared to internal sources of finance (see section 4.6 above). Grabowski's model will be referred to in greater detail in the empirical part of this thesis in chapter 6.

4.8 Some comments on 'excessive' returns on R&D and welfare

The ability to appropriate returns on R&D investment will also depend on whether the innovator is able to set prices freely or whether a regulator sets a limit on drug prices.

Prices are regulated in most countries, except the United States[14]. Possibly resulting from that the United States has one of the most vibrant and R&D intensive pharmaceutical industries in the world, shortly followed by the British, which is allowed a substantial return on capital on its business with the National Health Service.

Those countries with stringent price regulation, such as France and Italy, are believed to offer too few incentives for pharmaceutical R&D and, as a possible consequence, have a smaller and less innovative national pharmaceutical industry. This, in a simplified form, is the picture presented by some industry representatives. Although plausible, the effect of regulation is difficult to verify, since there are so many more contributing factors to industry success than the price level of prescription medicines in the domestic market[15].

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[14] Most European countries operate a system of price regulation, where new drug prices will have to be approved by a regulator, Britain operates a system of profit control, while the United States allow manufacturers to set the price for new drugs freely.

[15] Most countries allow free pricing of Over-The-Counter (OTC) medicines and price differences are common between the domestic and increasingly important overseas markets.

On a theoretical level, the impact of price regulation can be demonstrated quite easily: An innovator would need to determine the price/output mix of his products so that research and development costs are covered. In order to do that, prices must exceed marginal costs of production. The question is: how great should this excess be and should it vary from drug to drug?

From society's point of view common costs, or R&D cost in this case, should be allocated so that social losses resulting from prices being higher that variable costs are minimised. The Ramsey pricing rule[16] implies that in order to minimise excess burden in a two-product environment, tax rates should be inversely proportional to price elasticities of demand, i.e.:

Equation 4-1

$$\frac{t_x}{t_y} = \frac{\varepsilon_y}{\varepsilon_x}$$

Since t_x and t_y are percentage increases in the prices of the two goods, by analogy the total welfare loss will be minimised if the mark-ups on marginal costs follow the rule:

Equation 4-2

$$\frac{P_1 - MC_1}{P_1}\varepsilon_1 = \frac{P_2 - MC_2}{P_2}\varepsilon_2$$

and:

Equation 4-3

$$\frac{\frac{P_1 - MC_1}{P_1}}{\frac{P_2 - MC_2}{P_2}} = \frac{\varepsilon_2}{\varepsilon_1}$$

which indicates that in order to minimise excess burden in a two-product environment, mark-ups on marginal cost should be inversely proportional

to price elasticities of demand, i.e. the less elastic the demand the higher the mark-up should be. This means that the more innovative and often more urgently required product should be sold at a higher price.
Another form of the Ramsey rule , where:

Equation 4-4

$$\frac{P_1 - MC_1}{P_1} = \frac{k}{\varepsilon_1}$$

and:

Equation 4-5

$$\frac{P_2 - MC_2}{P_2} = \frac{k}{\varepsilon_2}$$

shows a constant k whose value depends on the amount of common fixed costs that must be covered. This formula corresponds to the Lerner index of market power, where k=0 when the market is competitive and k=1 when the market is monopolised, because:

Equation 4-6

$$\frac{P - MC}{P} = \frac{1}{\varepsilon}$$

states that the price/cost margin of the profit maximising firm should be equal to the reciprocal of the elasticity of demand. The similarity between the welfare loss-minimising and profit-maximising rules implies that structurally the same decision rules apply, i.e. a firm which aims to maximise contributions to R&D would price their products in a way that welfare losses are minimised. If prices are above the level necessary to cover R&D costs, a regulator would aim to reduce mark-ups to the point where these costs are covered. Rather than applying the same price

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[16] See for Instance Cullis and Jones (1998) for mathematical proof of the Ramsey pricing rule

restriction across all products Ramsey prices imply that the percentage change of the quantity demanded of the two goods as a result of a price reduction must be equal, since substituting ε in 4-2 gives:

Equation 4-7

$$\frac{P_1 - MC_1}{MC_1}\frac{\frac{dQ_1}{Q_1}}{\frac{P_1 - MC_1}{MC_1}} = \frac{P_2 - MC_2}{MC_2}\frac{\frac{dQ_2}{Q_2}}{\frac{P_2 - MC_2}{MC_2}}$$

and therefore:

Equation 4-8

$$\frac{dQ_1}{Q_1} = \frac{dQ_2}{Q_2}$$

must hold for a welfare loss minimising regulation, i.e. the quantity change in per cent must be equal in the two markets.

Exact cost and demand schedules are often not known to the regulation authorities, and without such information imposing optimal pricing behaviour will prove futile (Reekie 1997). Rather than legislating for uniform mark-ups on all products, the authorities should allow for price discrimination, i.e. higher prices on the less price-elastic product. The system best suited to allow this is a profit regulation system[17], which would limit the maximum amount of recoverable R&D costs, rather than a uniform price limit which, as could be shown above, would result in a higher welfare loss than necessary.

Cocks (1975) expands Clemens' (1957) analysis to introduce a multiproduct firm in a dynamic environment, here shown in figure 4.6.:

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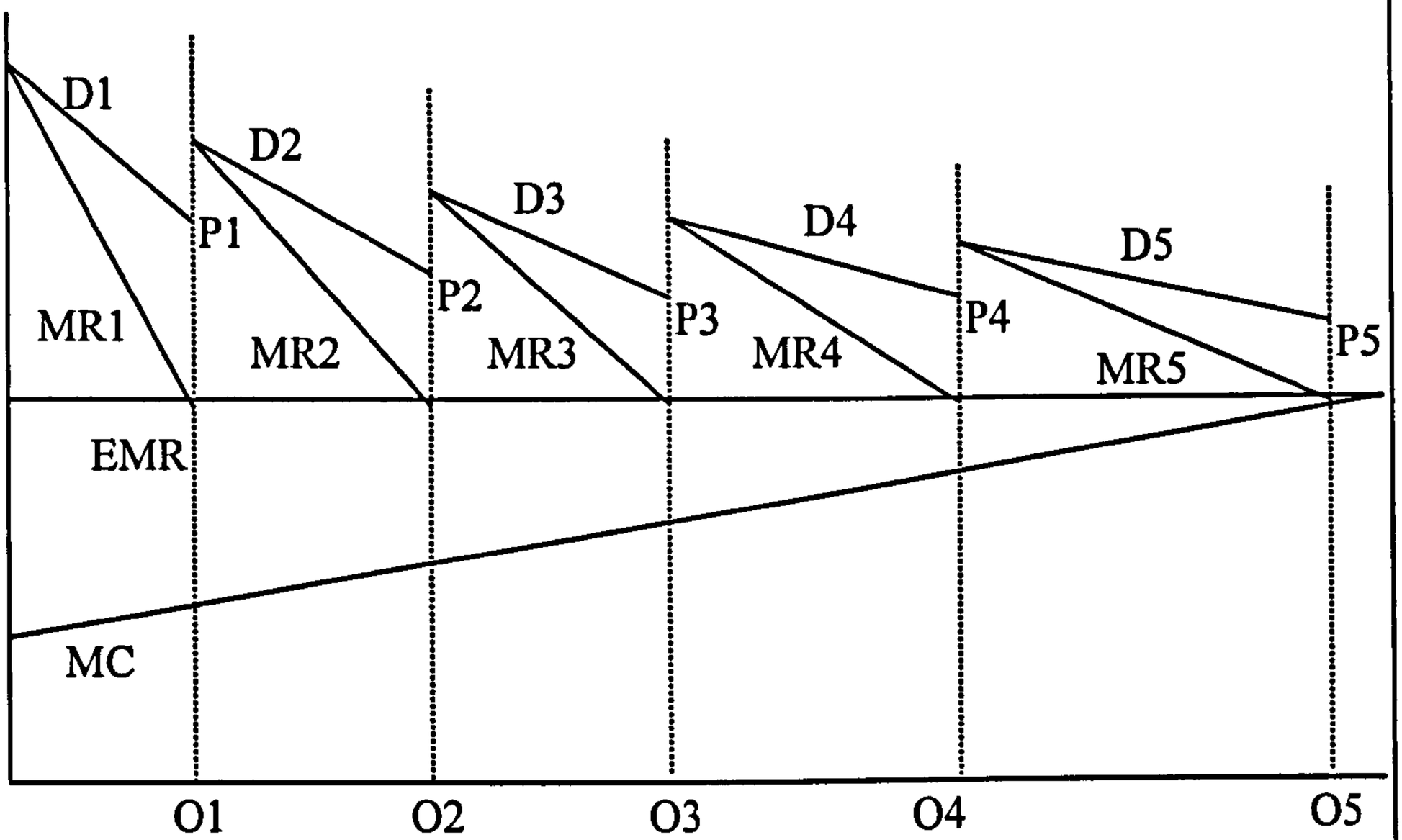
[17] The British PPRS (Pharmaceutical Price Regulation Scheme) is in fact a profit regulation scheme, which allows for a fixed profit margin to be generated with drugs sold to the NHS. Most European countries would regulate individual drug prices, while the US does not impose any price restrictions on drugs.

Figure 4-6



Source: Cocks (1975)

This model can be interpreted as follows: most firms would start off as a single product firm with idle capacity at a point where marginal cost equals marginal revenue. At this point the firm increases production seeking new markets where demand exceeds marginal costs. A firm would explore new markets in order of their profitability. Equilibrium will be reached if there are no more markets where demand is greater than marginal costs.

The above graph shows five markets. Profits will be maximised where production is allocated along the five products so that marginal revenue is equal in all markets and equal to marginal costs. The EMR line is the line of equal marginal revenue. Each market has its own output axis which is the origin of its demand and marginal revenue curve. The markets are lined up according to their profit potential, shown by the extent of profit (falling from left to right) and/or the elasticity of demand (increasing from left to right). It can be seen that markets on the inside

make a larger profit than the markets on the outside since the mark-up on marginal costs is higher on these inside markets.

Cocks (1975) looks at this model over time: Recently-launched highly innovative products start on the inside markets and gradually move outside being replaced by new more recent innovations in the process. These products start off with a high price and relatively low volume and, facing increasingly tough competition in their life cycle, will gradually lower prices and expand on volume not dissimilar to a skimming pricing strategy. The firm will attempt continuously to create new inside markets to replace the products which are moving outside towards higher volume and higher elasticity. This process would move towards an equilibrium which embodies a price close to marginal cost at least for some of the older products (Reekie 1997). Scherer (1980) argues that this process is not unlike a tendency towards Paretian optimality, where the monopoly rents on the inside markets are sources of funds for the R&D which develops new products in the future. For any individual existing drug these contributions are transitory as prices are eroded over time, and new products must be introduced continually in order to provide R&D funds on a continuing basis (Reekie 1997).

Linking this to the initial hypothesis that mark-ups should be inversely proportionate to elasticities the model can make some predictions about the rate and direction of innovative activity[18]. The initial high price of innovation at the beginning of the product life cycle secures the current level of innovative output by the firm. Should highly innovative products not be able to yield sufficient return on R&D the direction of innovative activity may change towards me-too products which are less risky, less prone to intervention by regulatory bodies and cheaper to develop. Should the firm anticipate a price intervention in its highly innovative market segment it could also attempt only to gradually improve products in order to justify a price rise which seldomly represents a real increase in

[18] See also Schellhaass (1982)

the value of the product. The implications of this dynamic model are the same as the earlier static analysis. Price regulation should neither be uniform, nor should it target the particularly profitable products. In order to minimise welfare losses and guarantee a constant stream of new drug innovations, the most profitable products must be allowed to contribute more to R&D than older products with a higher demand elasticity.

4.9 Concluding remarks

The microeconomic branch of the innovation economics literature lists three determinants of R&D spending, technological opportunities, appropriability conditions and demand factors and much of the debate is related to the relative importance of these factors.

Some authors attribute technical change to the supply of innovation (technology push), others argue that demand induces industry to innovate (demand pull) while at least some empirical evidence suggests that both factors are equally important.

Most empirical studies will however be compromised by the unclear distinction between need and demand which reflects the lack of consideration of the role of the entrepreneur to foresee potential demand.

Pharmaceutical economists believe that regulation can once and for all alter the rate of innovation in the industry, either negatively through more stringent drug approval regulation, or positively through improved patent protection, both affecting what is referred to as appropriability conditions.

Appropriability conditions will also be improved, if companies can set prices in such as way, that R&D expenses in excess of cost of production will be covered. It could also be shown, at least on a theoretical level, that the practice of setting higher prices for products with a low elasticity of

demand will conform with the social objective of welfare loss minimisation.

At the firm level companies are believed to face diminishing returns to R&D and would aim to equate the return on the last R&D project (marginal return) with the cost of funds. Once the rising cost of funds (due to differences in the cost of internal and external finance) is taken into consideration, the optimal level of R&D spending is where marginal return to R&D equals marginal cost of R&D.

The following Chapter will aim to identify those technological opportunities, demand and appropriability factors specific to the vaccine industry before developing and testing a model of R&D spending in Chapter Six.

5 Vaccine industry analysis

5.1 The global vaccine market

As explained in more detail in chapter two, vaccination may effectively control or even completely eradicate a disease. This makes vaccination one of the most powerful and widely used health interventions available today.

If all diseases could be completely eradicated through vaccination, then vaccines will no longer be needed. Epidemiological data indicate, however, that despite a few such total success stories -the eradication of smallpox for example- many diseases continue to circulate making it essential to continually vaccinate young children and people newly exposed to these diseases. The European Vaccine Manufacturers (1994, p. 12) identify four factors which influence the demand for vaccines:

1) The nature of disease against which the vaccine is required: Only viral and not bacterial diseases can be eradicated[1]; and some vaccination programmes are more difficult to administer than others; whilst achieving herd immunity[2] requires different effort (e.g. the number of doses necessary) for different viral diseases.

2) The importance of vaccination for national or supranational health policy, most notably the existence, or prioritisation of immunisation programmes. For example, even under given existing immunisation programmes, falling birth-rates could reduce the demand for a vaccine.

3) The successful transformation of epidemiological data into actual demand and which crucially depends upon the existence or quality of the data itself.

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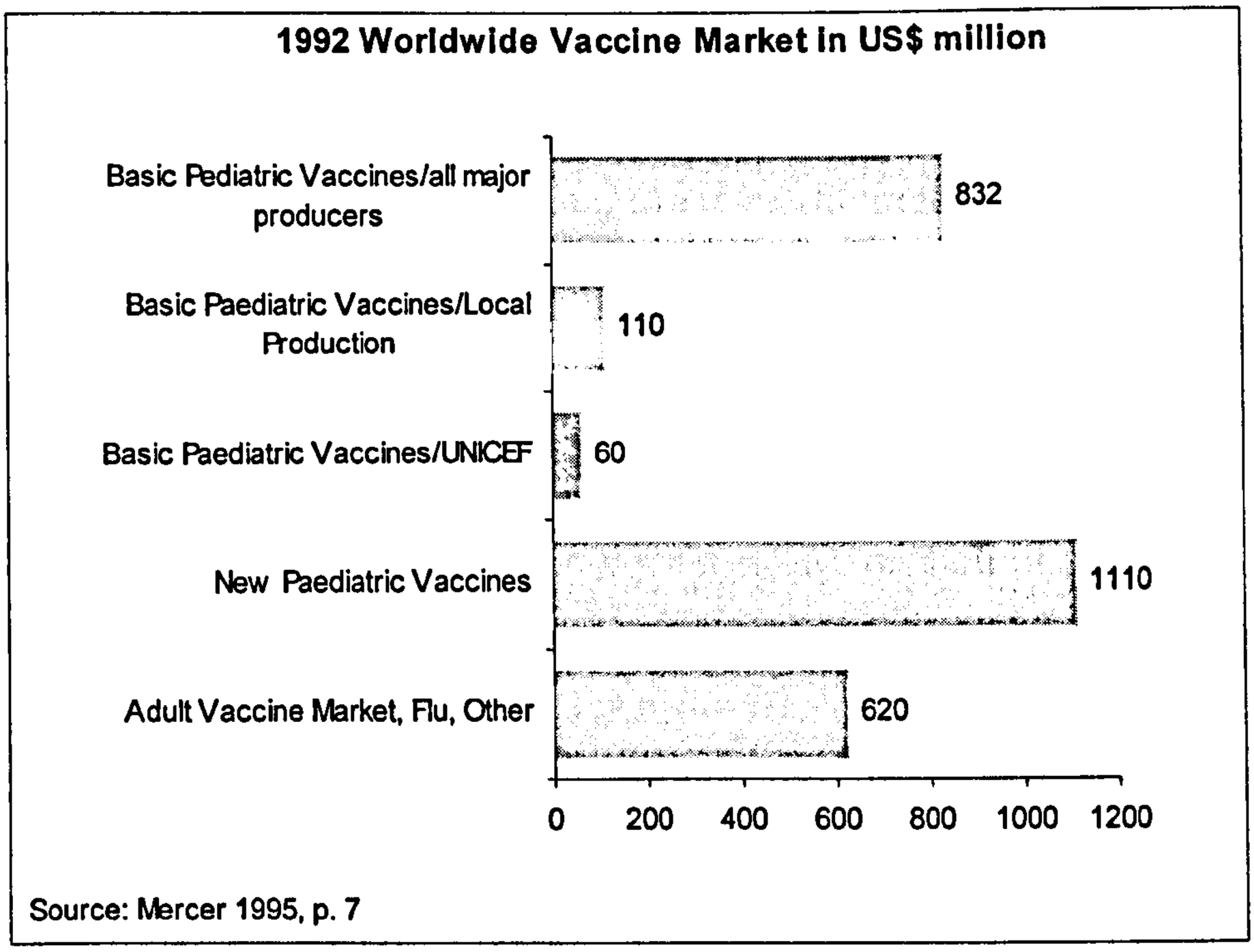
[1] Bacteria survive outside the human body and can therefore never be fully eradicated.

[2] Herd immunity denotes a situation where "the population susceptible to a disease falls below the critical threshold required for the disease to perpetuate itself" (European Vaccine Manufacturers 1994, p. 12)

4) The market for vaccines is often split into a private segment, where prices are established by market forces, and a public segment, which is characterised by a government agency buying large volumes at comparatively low prices.

The most comprehensive and most recent study on the vaccine market has been undertaken by Mercer Management Consulting in 1995 and was commissioned by the US Department of Health and Human Services. According to this study the world-wide vaccine market generated 2.73 billion US$ in 1992[3] of which paediatric vaccines[4] accounted for 77% or approximately 2.11 billion US$ as can be seen in figure 5.1.

Figure 5-1



Source: Mercer 1995, p. 7

Basic paediatric vaccines, such as Diphtheria, Tetanus and Pertussis (DTP), Polio, BCG (vaccine against Tuberculosis) and Tetanus Typhoid (TT) account

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[3] In its 1996 annual report SmithKline Beecham expects the worldwide vaccine market to reach $7 bn by the year 2001 (SmithKline Beecham, 1996).

[4] Vaccines for children

for about 30 per cent of the market. In general there are multiple suppliers of these products. The above chart (Fig. 5.1) indicates that more than 80% of the total turnover ($832 million) of basic paediatric vaccines is generated by major vaccine producers, which are all located in Europe and the United States. Roughly 10% of turnover is generated by local producers outside Europe and the US and under 10% are purchased by UNICEF tender mainly for use in the least developed countries.

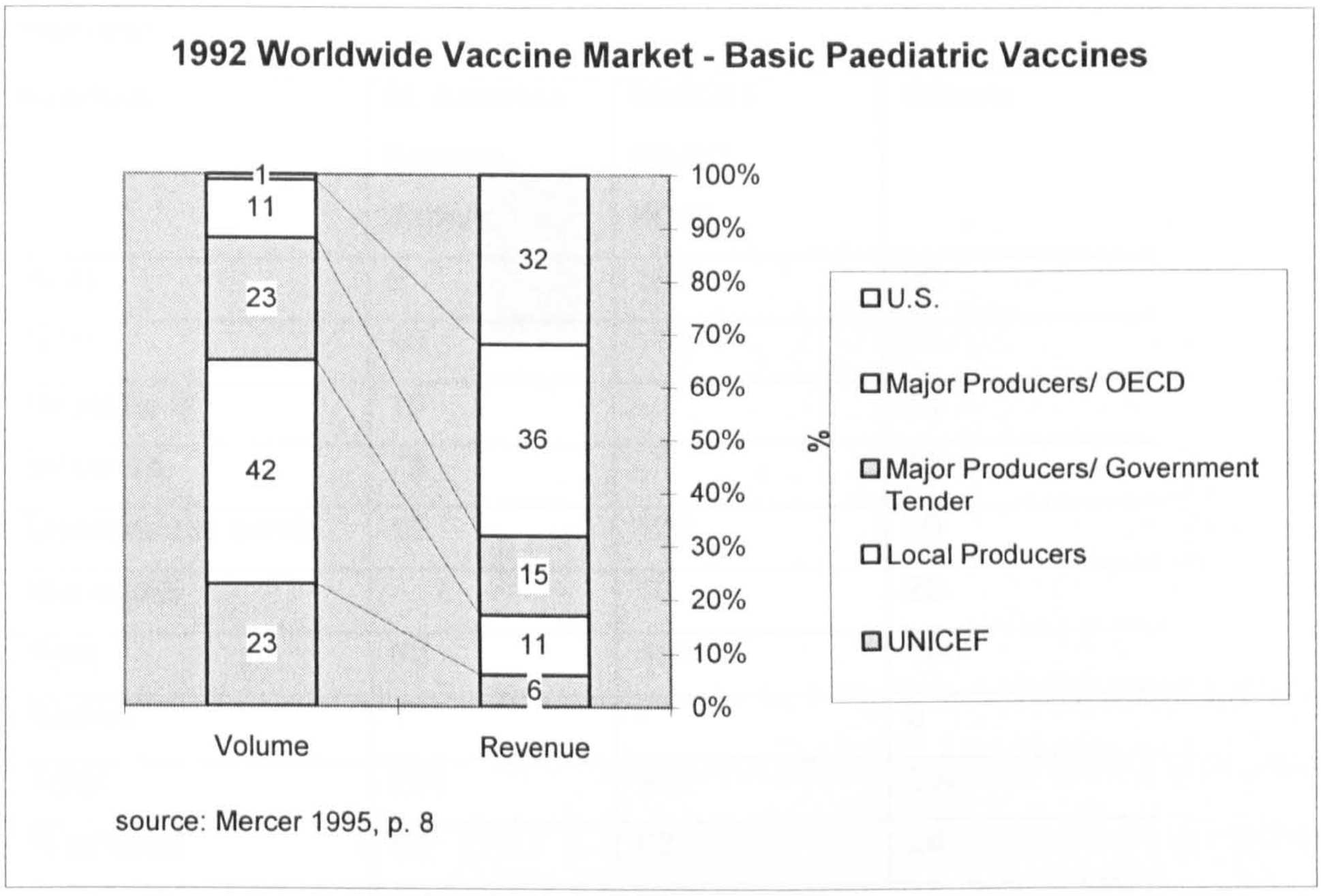
The technology of making basic paediatric vaccines is well known. Most of these vaccines were developed more than thirty years ago and are no longer or never have been protected by patents. They are often sold at prices near costs of production. National suppliers dominate the markets for these basic paediatric vaccines, not because their quality is superior but because they enjoy privileged relationships in their home markets (Mercer 1995, p. 8). There is little incentive to penetrate export markets since prices for basic paediatric vaccines are generally very low. One notable exception according to Mercer (1995, p. 7) is the Measles Mumps Rubella vaccine (MMR) produced by the US manufacturer Merck, which is thought to be the safest and most effective of its kind and therefore enjoys a significantly higher price and market share than other MMR vaccines on the market.

The market for basic paediatric vaccines can be further segmented: Besides UNICEF purchases and local producers (which have no international exposure), figure 5-2 breaks down the 'major producer' category into major producers winning government tenders, the OECD market (without the US), and the US market.

Although UNICEF purchases and local production account for a very small share of the basic paediatric vaccine market in revenue terms, figure 5-2 shows that the volumes associated with these two groups are far more significant. 42% and 23% respectively of paediatric doses used world-wide are either locally produced or purchased by UNICEF. The large-revenue US market accounts for less than 2% of paediatric doses used world-wide. Revenue is mainly generated in industrialised countries markets supplied at

relatively higher price by major European and American vaccine manufacturers.

Figure 5-2



source: Mercer 1995, p. 8

Figure 5.1 also shows that in 1992, 41% of the global vaccine market is represented by the more recently introduced new paediatric vaccines such as Haemophilius Influencae Type B (Hib), Hepatitis B (Hep B), Hepatitis A (Hep A) and Varicella. These vaccines are still patent protected and their prices are higher than for basic vaccines since considerable investment in R&D is still to be recovered. These products are sold in an increasing number of overseas markets and their market share is growing compared to the older paediatric vaccines.

Baudrihaye (1992) further emphasises the importance of UNICEF, PAHO (Pan American Health Organisation) and WHO purchases in volume terms, which accounted for 62% of the doses sold world-wide between 1985 and 1991.

Table 5-1

Estimated world usage of vaccines in 1990 (millions of doses)

Product	N. America Europe, Japan	UNICEF PAHO WHO	Others
BCG	5	160	20
DTP	40	170	50
Hepatitis B	15	-	35
Influenza	75	-	10
Measles and comb.	15	120	30
Meningitis	-	10	20
Polio	60	450	190
Rabies	1	-	3
Total	211	910	358
% of total	**14**	**62**	**24**

source: Baudrihaye, (1992, p.894)

These numbers emphasise that the developing countries account for a large percentage of *doses* sold each year, but considerably less in *revenue* terms as was shown before.

On the supply side seven private European companies share the vast majority of the production of vaccines used by Europe and much of the rest of the world.

Table 5-2

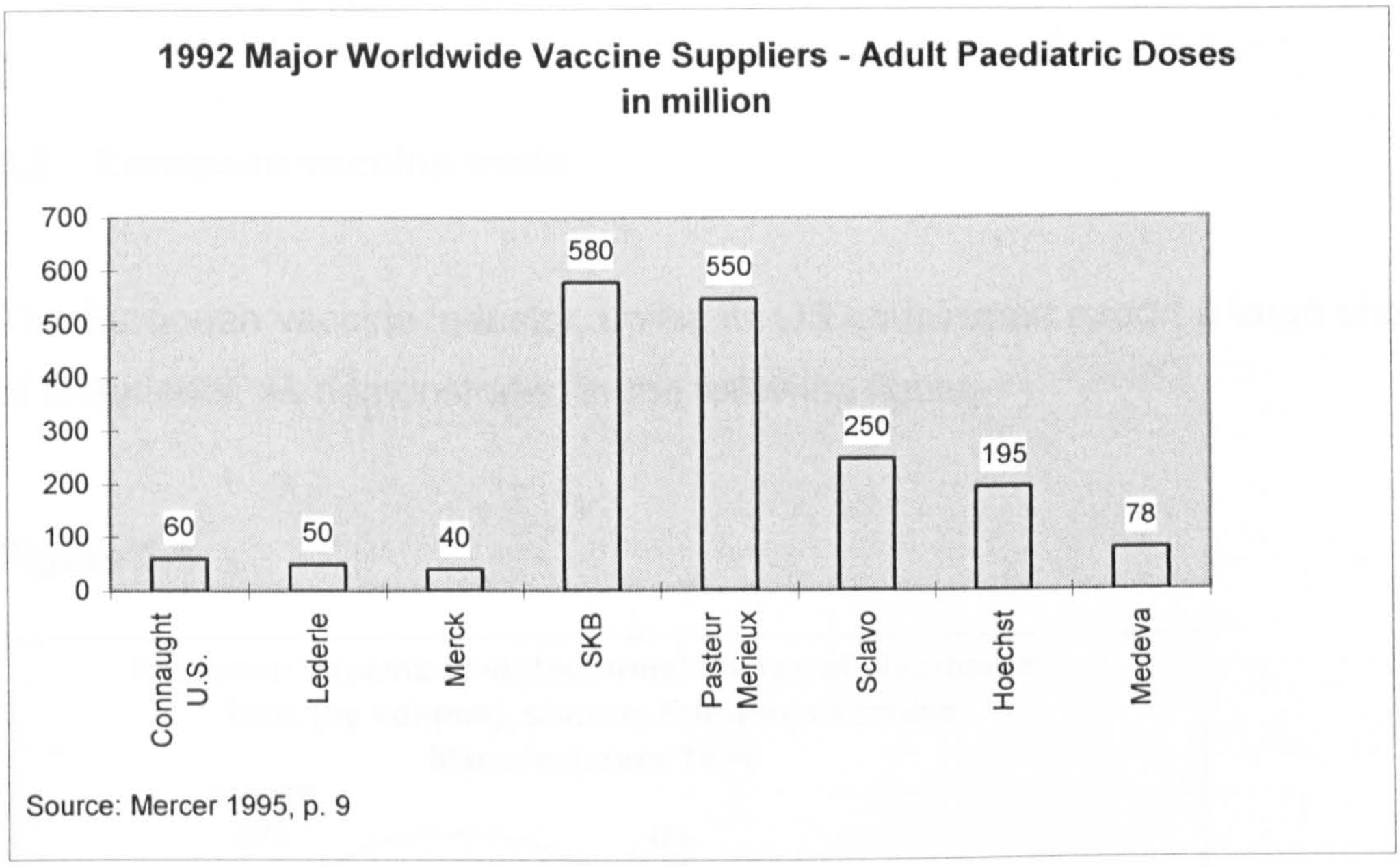
Vaccine suppliers to UNICEF

Origin	BCG	DTP& TT	Measles	Polio	% of UNICEF total
European Vaccine Manufacturers	●	●	●	●	67
Eastern Europe		●	●	●	
Japan	●		●	●	33
Others		●		●	
USA					

Source: Baudrihaye 1992, p.894

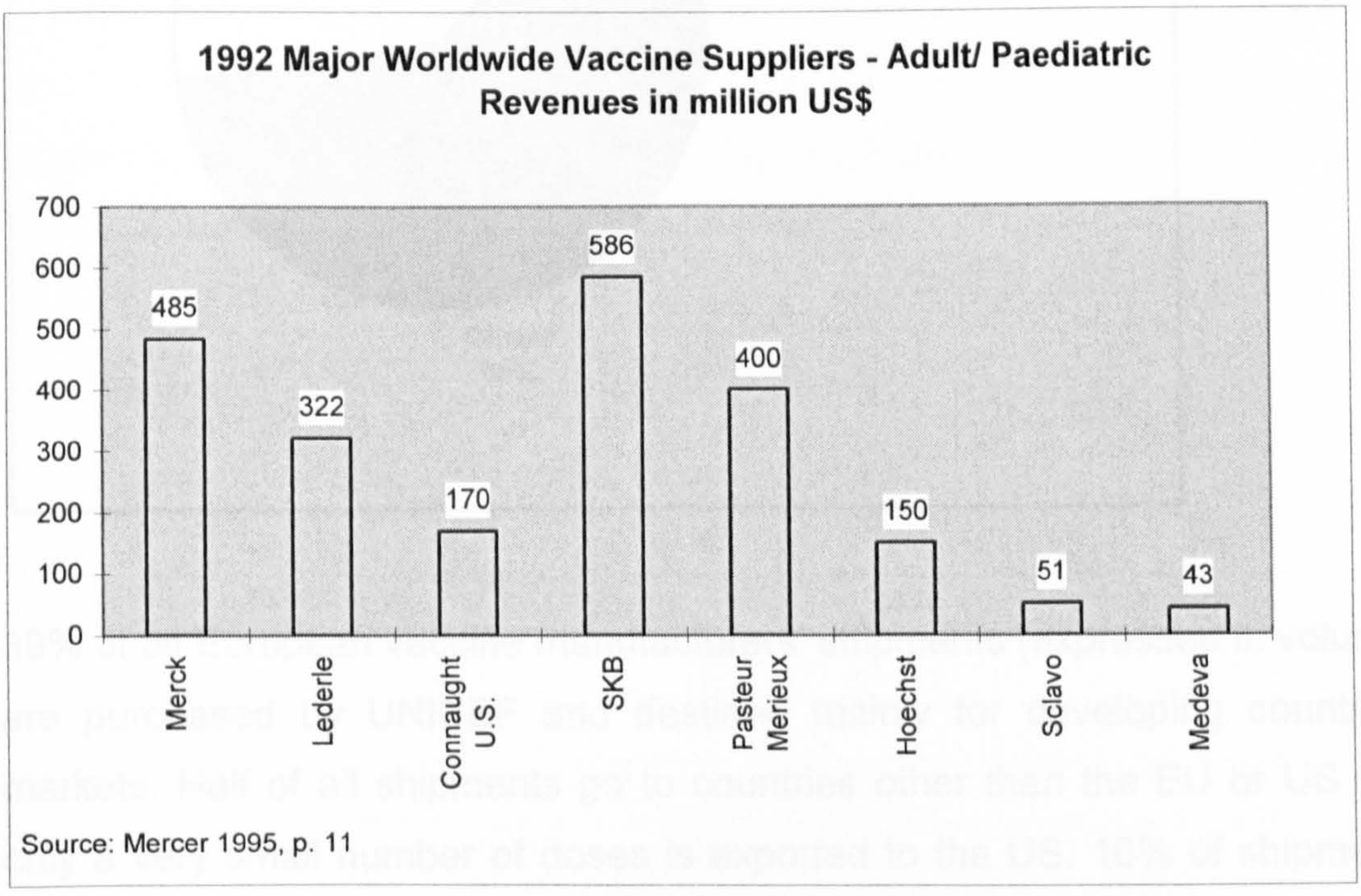
The discrepancies described above between market volume and revenue also reflect differences in the strategies of American and European Manufacturers. As can be seen from figures 5-3 and 5-4, US manufacturers generate large revenues with relatively low volumes whereby European manufacturers sell large volumes generating relatively smaller revenue.

Figure 5-3



Source: Mercer 1995, p. 9

Figure 5-4



Source: Mercer 1995, p. 11

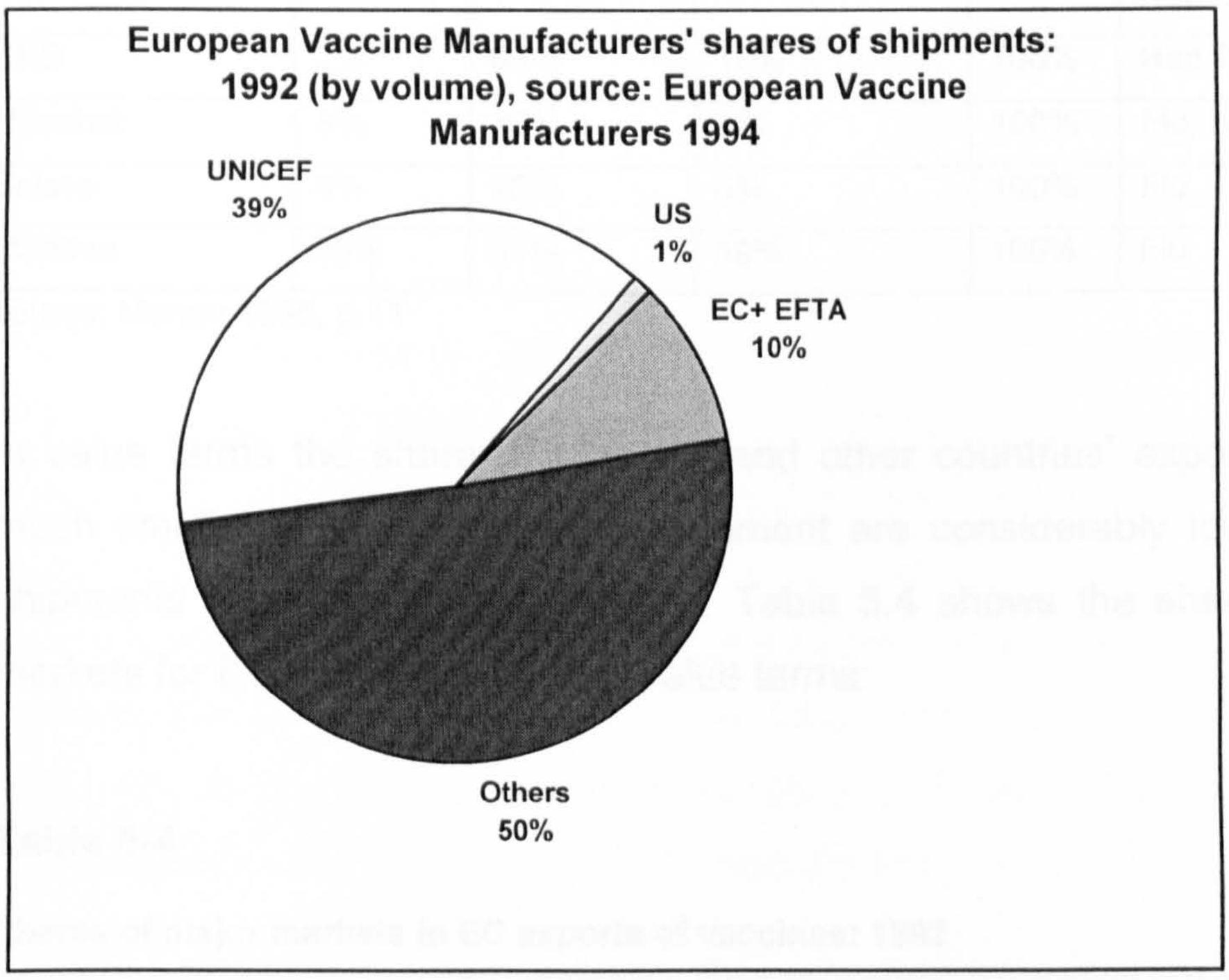
US manufacturers concentrate almost entirely on their home markets while European manufacturers operate on a much larger scale selling large quantities of vaccine in overseas markets. The following section investigates further European vaccine manufacturers' export trade. The subsequent

section also explains why American vaccine manufacturers are reluctant to export their products.

5.2 European vaccine trade

The European vaccine industry, unlike its US counterpart export a large share of shipments, as demonstrated in the following figure:

Figure 5-5



39% of all European vaccine manufacturers' shipments (expressed in volume) are purchased by UNICEF and destined mainly for developing countries' markets. Half of all shipments go to countries other than the EU or US and only a very small number of doses is exported to the US. 10% of shipments remain in Europe.

The large volumes generated by European suppliers are mainly basic paediatric vaccines included in the EPI (Expanded Programme of

Immunisation). Up to 90% of exports in volume terms is supplied to non-OECD countries at very low prices and usually tendered out by organisations such as UNICEF (United Nations Children's Fund), WHO (World Health Organisation) or PAHO (Pan American Health Organisation).

Table 5-3

European Vaccine Suppliers' Export Ratios, % of shipments in volume terms					
	EPI to OECD	**EPI Export Tender**	**Non-EPI OECD/Export**	**Total**	**Non-EPI vaccines**
Pasteur Merieux	7%	80%	13%	100%	Flu, Hib, Rabies, Hep B
SKB	2%	86%	12%	100%	Hep B, Hep A
Hoechst	8%	89%	3%	100%	Flu, Hib, Rabies
Sclavo	4%	90%	6%	100%	Flu
Medeva	20%	61%	19%	100%	Flu

source: Mercer 1996, p.11

In value terms the share of UNICEF and other countries' export tenders is much smaller since prices in this segment are considerably lower than for shipments to industrialised countries. Table 5.4 shows the shares of major markets for EC vaccine exports in value terms:

Table 5-4

Shares of major markets in EC exports of vaccines: 1992

Market	**export share (by value)**
intra-EC	33.9
EFTA	4.0
Eastern Europe	1.6
US and Canada	24.6
Japan and Australia	0.65
other countries	35.2

source: Eurostat 1996

The above table shows the importance of intra-EC trade in vaccines and also confirms that in revenue terms the US market is an important destination for

European vaccines. The US market is attractive for European manufacturers because the price level is higher than in Europe. Especially novel vaccines such as IPV (Intravenous Polio Vaccine), Influenza and Hepatitis B are exported to the US. Although Europe is potentially a huge market for US manufacturers, with the exception of MMR, Hepatitis B and Hib, they largely abstain from exporting to Europe.

5.3 Regulatory impact on export behaviour

One of the reasons why US manufacturers are reluctant to export outside the US is that prices in Europe are generally lower. Even if US manufacturers wanted to export some of their vaccines at a lower price in order to generate economies of scale then elements of the US government (such as the Anti-Trust Division of the US Justice Department, if not Congressional Enquiries) would probably take a 'very critical' look at prices charged in the US. Congress has decided to challenge the high domestic prices of US manufacturers on the grounds of much lower export prices. The US industry thus probably prefers not to set a precedent, and avoids supplying low-price markets altogether. However, US manufacturers sometimes try to circumvent interference by Congress by entering foreign markets through a range of alliances, as was the case with Connaught and Pasteur Merieux -respectively an American and French vaccine manufacturer- and which subsequently merged.

Other regulatory procedures may also be held responsible for low US exports of vaccines. The FDA licensing-process in the US requires not only the vaccine itself to be validated but also the plant that will be used for commercial production. Strict GMP (Good Manufacturing Practice) regulations require the preparation of pilot lots already for phase one clinical trials in a GMP approved facility (Gupta 1997, p. 1). So already before the product is licensed a decision has to be made about the scale of production. The costs of building the production plant are therefore incurred already at the development stage of the product. These costs are sunk, should the American

firm not be able to sell the envisaged capacity. Any organisation without a GMP-approved facility will find it impossible to conduct the phase one trials and is thus discouraged from undertaking development of the product.

According to Mercer (1995, p. 13) it is precisely this licensing procedure which discourages manufacturers from entering other markets. Lack of harmonisation and country-specific requirements make it far too costly to obtain multiple licenses. In the case of US manufacturers it appears that concentrating on their large, unified domestic market alone has been more attractive than incurring the risk and uncertainties of building plants which could supply international markets. Matters are further complicated by the plant relicensing requirements for vaccines. Once a US manufacturer has decided on the plant size sufficient to serve a particular market, it is not viable to consider expansion since resizing the plant requires a costly plant relicensing process (Mercer 1995, p. 9).

In Europe too, manufacturers claim (European Vaccine Manufacturers 1994, p. 14) that increasingly stringent quality control and GMP rules, the latter introduced with EC directive 91/356, have a damaging impact on competitiveness. They fear that manufacturers in other regions with less stringent rules could obtain a cost advantage in the cost-sensitive segment of international procurement.

As far as the licensing of new vaccines is concerned, Europe has recently undertaken steps to make sure that a new vaccine will only have to undergo one licensing procedure to be successfully marketed across Europe.

Since 1995, there have been two EU procedures for obtaining marketing authorisation for medicinal products: the centralised procedure, and the mutual recognition procedure. The first one is designed for biotechnological products or high-tech products, the second one is for all other products. Vaccines can follow either one of these depending on their nature (biotech/ high-tech or not). In the centralised procedure companies submit new products to the European Agency for the Evaluation of Medicinal Products

(EMEA), which can grant a European marketing authorisation by the Commission. The decision is assisted by a scientific advisory committee, the Committee for Proprietary Medicinal Products (CPMP).

Under the decentralised (mutual recognition) procedure applications are made to the Member States of the EU selected by the applicant and the procedure operates by subsequent mutual recognition of national marketing authorisations. Where this is not possible, the EMEA is called on to prepare a binding arbitration again based on recommendations or 'opinions' by the CPMP. These new procedures should lead to a faster process of registration and reduce the cost of repetitive tests and paperwork under the old system. Although a system of mutual recognition existed before CPMP, opinions were not binding under the old procedures.

New vaccines are likely, increasingly, to fall into the category of biotechnology products. Two directives, 90/219 and 90/220, the former referring to the use of genetically-modified organisms, the latter governing the deliberate release of genetically modified organisms (GMO directives) are applicable to vaccines. European Vaccine Manufacturers (1994, p. 64) believe that both directives

> "represent major constraints to the development of sophisticated vaccines, especially if they use recombinant technology and genetically modified organisms. New constraints could limit the development of vector vaccines, either at the level of contained use in the laboratory or at the level of deliberate release for clinical trials. Such constraints must not become barriers to their development or to trade, thus placing manufacturers in the US or Japan in a more advantageous position".

Once a product has received marketing authorisation, in Europe as well as the US, each individual batch of a vaccine is required to undergo quality and safety testing before being released on the market. Since 1993, once a batch control follows guidelines published by the Commission, the batch is accepted for sale within the Common Market without further testing. This procedure is however not mandatory and some countries, most notably the UK, France and

Germany have continued to submit all vaccine imports to a second batch testing (European Vaccine Manufacturers 1994, p. 76). This double control incurs further costs and is time- consuming for the manufacturer. The CPMP has now introduced a new procedure covering some vaccines. Seven appointed control authorities within the EU have the competence to issue batch release certificates for vaccines to be marketed on a EU-wide base, which are then subject to mutual recognition without further testing.

Single-batch testing within the EU is, however, accepted by UNICEF and Eastern European countries partly because their authorities do not possess the required equipment, and partly because further testing would increase the costs of price-sensitive UNICEF tenders. The US still requires additional tests to be carried out.

A further harmonisation in regulatory requirements regarding plant licensing and marketing approval would allow manufacturers to exploit economies of scale and improve profitability which would attract additional resources into vaccine R&D. Quite why scale economies are so important for vaccine products will be explained in the following section.

5.4 Scale economies and contributions to R&D

The vaccine industry's value chain can be broken down into five main cost categories: production, distribution, product returns, sales marketing, and administration. In the table below, the difference between the price of the product and these costs will contribute to covering the costs of R&D, interest, taxes and earnings, and is called contribution.

Figure 5-6

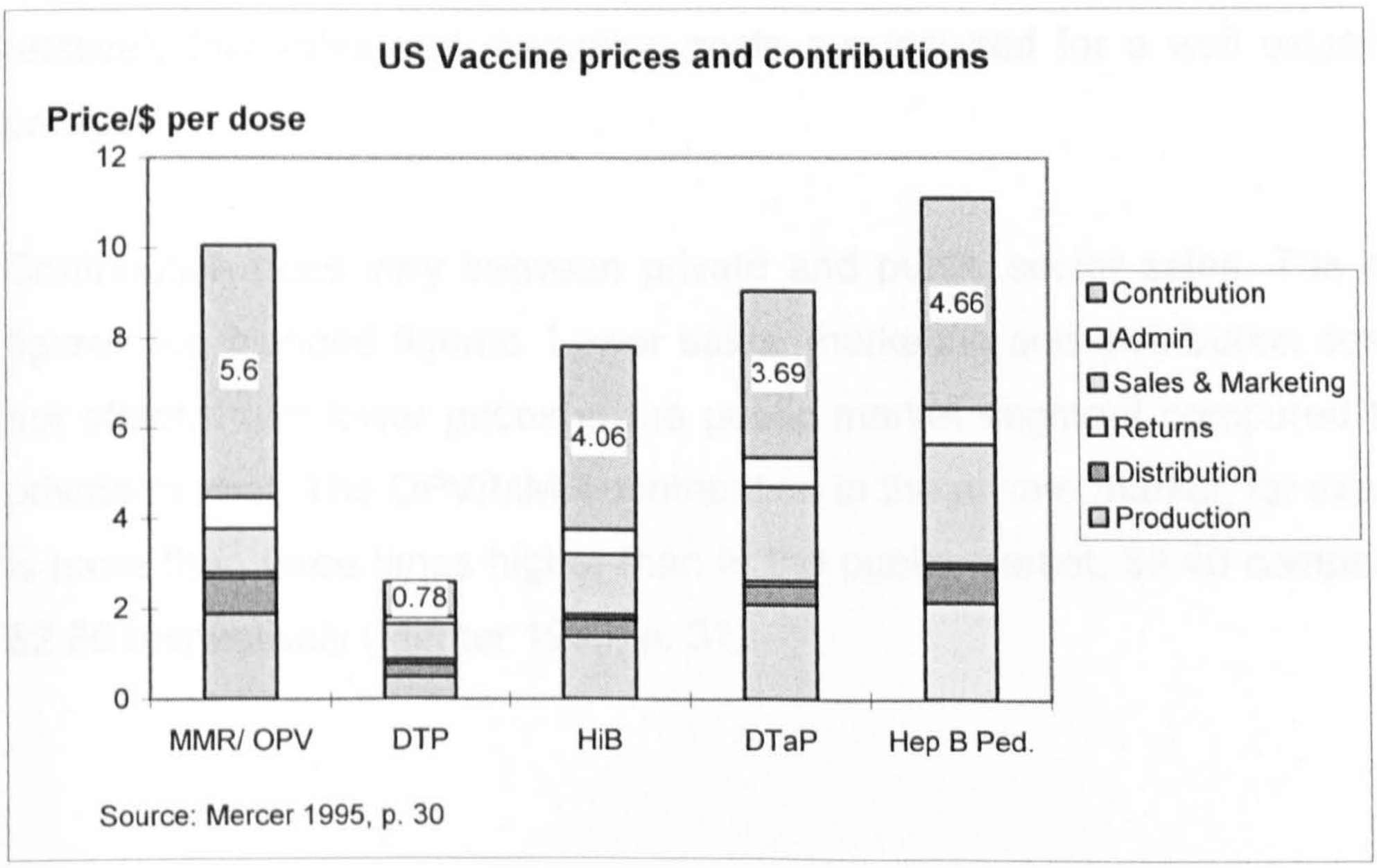
***Contribution* to** -R&D -interest -taxes -earnings
Production costs -bulk production -filling/finishing -Quality assessment/quality control -royalties
Distribution costs -shipping -storage -pick and pack -materials
Returns of faulty products costs
Sales and Marketing costs -sales force -promotional discounts -promotional materials
Administration costs -corporate overheads -legal/liability management

Price/dose

Source: Mercer 1995, p.25

The costs and contributions of six different childhood vaccines produced in the US (MMR and OPV are combined in the original report for reasons of confidentiality) varies significantly as shown in figure 5-7.

Figure 5-7



Source: Mercer 1995, p. 30

Differences in production costs are down to differences in complexity and scale; royalties are also high especially for the newer vaccines. DTP, being the oldest and simplest vaccine among the six, and being produced at a large scale, has predictably the lowest production costs. Royalties account for a high percentage of the costs of production for the newest vaccine in the field, Hep B (13-15 % of sales according to Mercer, 1995, p. 27). Since they are calculated on a percentage base of sales revenue, royalties double when revenue doubles. In the case of Hep B a number of organisations hold a total of 14 different patents. Owners of intellectual property could be educational or research institutions, private companies (e.g. a biotech firm) or both.

Sales and marketing costs depend on the number of suppliers in the market. MMR and OPV are supplied by two single suppliers and hence do not need the same promotional effort as DTaP and Hep B, the latter reflecting substantial investment in sales force. Mature products such as DTP are marketed less heavily since prices and contribution are already low. As the relatively young products Hep B, DTaP and Hib are still penetrating the market, sales and administration costs are high.

Surprisingly the old products MMR and OPV yield the highest contribution in the field. These two vaccines hold a monopoly position in the US due to their high safety and efficacy. Prices are therefore high while at the same time relatively low sales and marketing costs are incurred for a well established product.

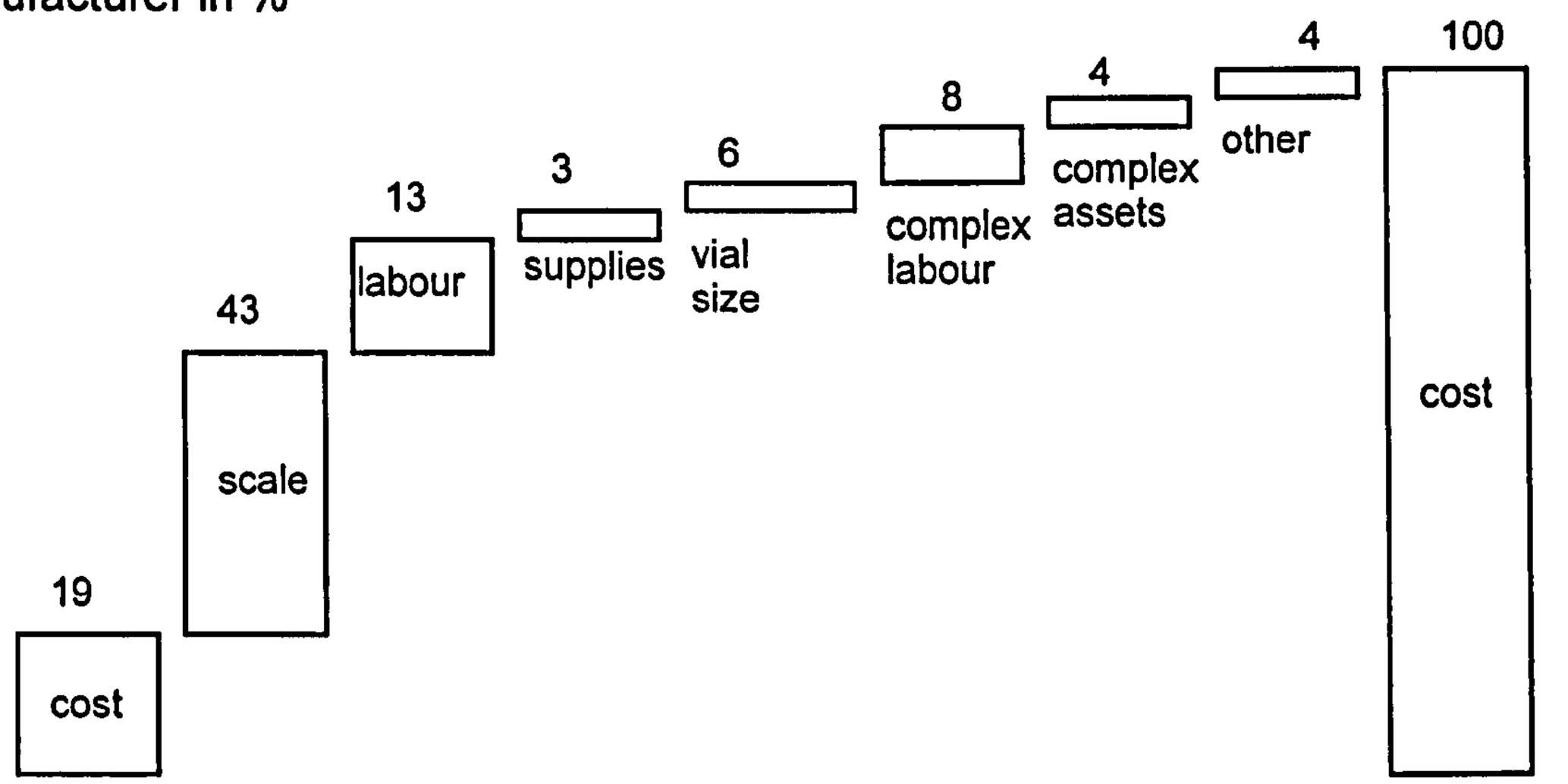
Contribution does vary between private and public sector sales. The above figures are blended figures. Lower sales, marketing and distribution costs do not offset much lower prices in the public market segment compared to the private market. The OPV/MMR contribution in the private market, for example, is more than three times higher than in the public market, $8.40 compared to $2.90 respectively (Mercer 1995, p. 31).

Contribution is therefore determined by costs, which vary considerably between vaccines, and price, which in turn depends on market structure, i.e. competitive forces, and the degree of government interference.

What is true for all vaccine products is that lower volumes result in significant cost disadvantages since economies of scale are important in vaccine production. Production cost for OPV (oral polio vaccine) in Europe, for example, is 16% of US costs; 36% of the cost difference is attributed to scale economies (Mercer 1995, p. 13). Whitehead (1997) finds that on average only 10% of production costs are variable, the remainder is fixed, 19% of them R&D, 31% selling, distribution and overheads, 16% site costs, and 24% batch fixed costs.

In Whitehead's (1997) study the costs of a high volume European and a low volume US producer both producing the same unnamed vaccine are compared.

Figure 5-8 – Cost differences of a high volume and low volume vaccine manufacturer in %

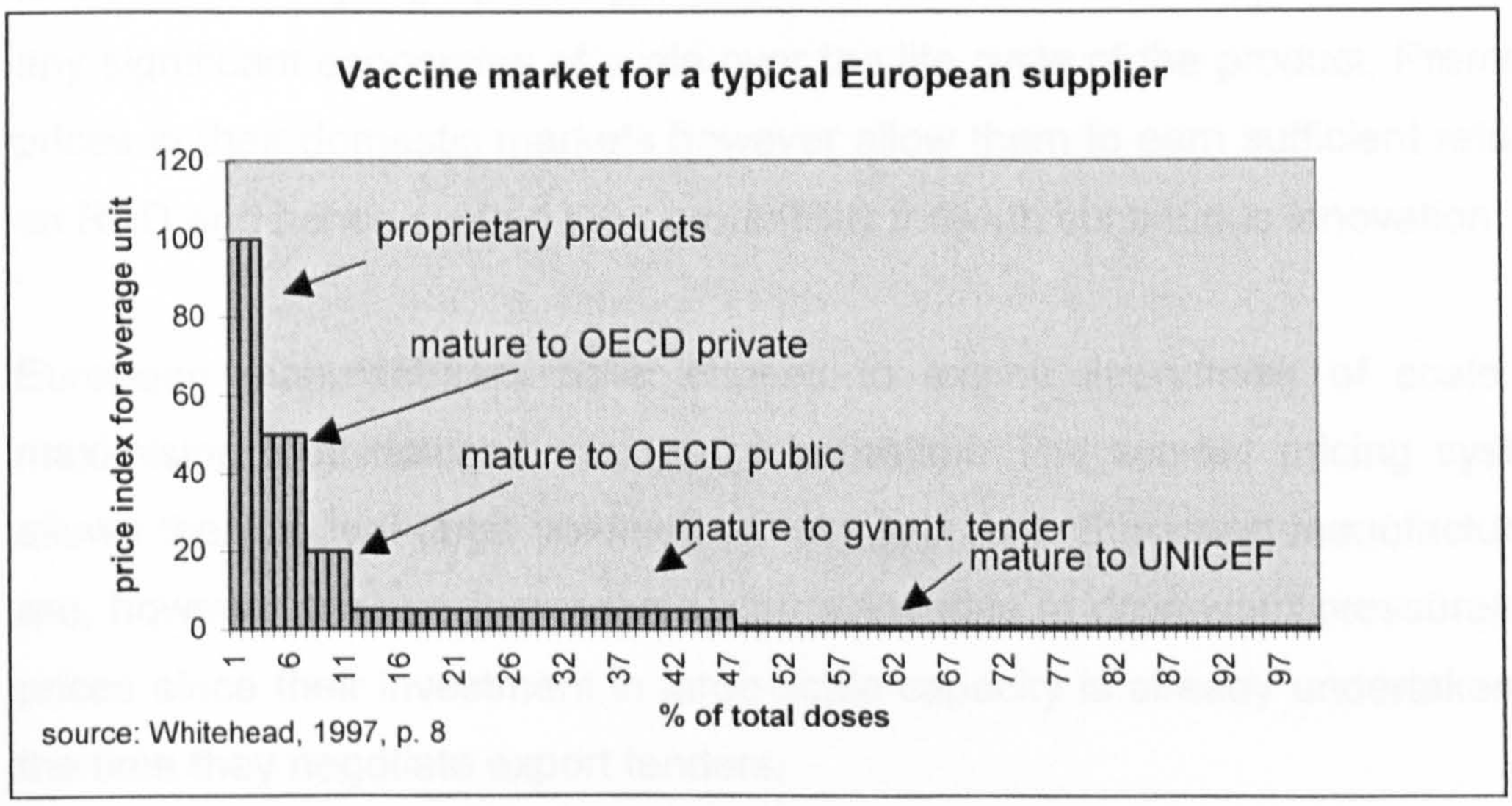


Source: Whitehead (1997, p. 3)

Figure 5.8 Can be interpreted as follows: The high volume vaccine manufacturer operates at a cost level equivalent to 19% of the cost level of the low volume manufacturer. About 43 % of the cost advantage are attributed to being a low-scale manufacturer. Other cost differences result from the higher cost of labour and supplies in the US plus the cost of complexity due to what Whitehead (1997) describes as a stricter regulatory environment in the US.

However, a cost advantage alone will not result in greater profitability. It also depends on the ability to charge an adequate price for the product. Despite the confidential nature of exact pricing information, vaccine prices are believed to be higher in the US than in Europe. What is more important is that European suppliers are facing a large price difference between European and export markets, in particular for export tenders to WHO and UNICEF. The following figure shows the typical vaccine market profile for a European supplier having in its portfolio a proprietary product such as Hepatitis B and a standard EPI vaccines such as OPV. For reasons of confidentiality the name of the supplier and products have been omitted in the original study.

Figure 5-9



source: Whitehead, 1997, p. 8

The above market profile shows how contributions to individual vaccines are driven by elasticities of demand which in turn depend on where a product is sold. Proprietary products are skimming the domestic markets for high returns. Mature products are marketed internationally, typically at a relatively higher price in industrialised countries -compared to UNICEF prices which are near marginal cost. The above also represents the life cycle for any of today's new vaccines. Starting as a proprietary product with a single high price it will penetrate the market and finally reach maturity. While the technology gets diffused, capacity increases and prices will come down and become tiered across markets. Many of the EPI vaccines are sold at low average prices and can only be marketed profitably due to significant scale effects.

This is certainly the case with the Hepatitis B vaccine, which when it was first introduced in 1986 cost US$ 25 per dose. Since then the price has come down to under $US1 today (GAVI 2000). In 1998, Latin American health authorities were purchasing the new Hib vaccine for $US 8.50 per dose. Two years later the vaccine is available at about $US 3.00 per dose.

The above analysis shows how US and European vaccine manufacturers have chosen two very different dynamic pricing strategies to maximise contribution. US manufacturers focus on their core markets which allows them to earn relatively high prices per dose. At the same time they cannot exploit any significant economies of scale over the life cycle of the product. Premium prices in their domestic markets however allow them to earn sufficient returns on R&D and hence sustain their profitability through continuous innovation.

European manufacturers have chosen to exploit economies of scale by maximising total demand through globalisation. The two-tier pricing system allows them to sell large volumes at very low cost. European manufacturers are, however, making themselves very vulnerable to downward pressures on prices since their investment in large-scale capacity is already undertaken by the time they negotiate export tenders.

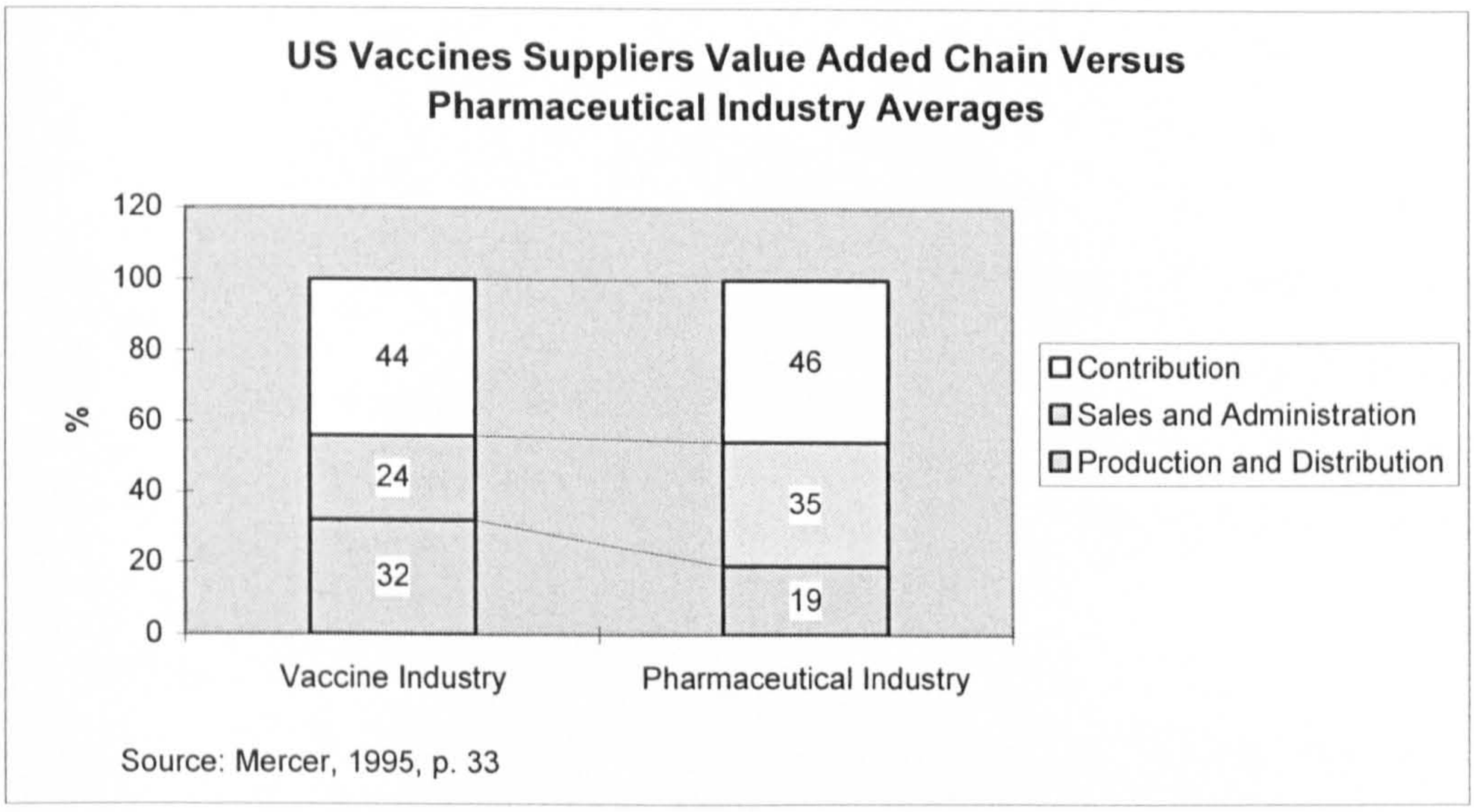
Which of the two pricing strategies contributes more to R&D and therefore results in greater innovative activity is difficult to assess. Besides the specific scale/price trade-off outlined above, vaccine products are often developed alongside pharmaceutical products in the same companies and compete for funding with a product group with an often superior marketing potential.

Historically, the US vaccine industry experienced a very difficult phase in the 1970s when some major manufacturers such as Pfizer, Lilly and Dow left the vaccine industry for good. This was due to a number of factors: The world market for vaccines was small compared to pharmaceuticals, margins were tight and many vaccines were selling as commodities (Galambos and Sewell 1995). 'National champions', such as Behringwerke in Germany and Pasteur Merieux in France, were firmly controlling their respective domestic markets. By contrast many of the new antibiotic drugs developed at the time were assured patent protection and significant market share abroad.

The 1970s were also marred by a number of technological and commercial setbacks. Merck's new vaccine against Meningitis for example, was soon after its launch confronted with competition from generic vaccine producers, encouraged by the US government's efforts to reduce vaccine prices. Merck decided to leave the market within a year after the launch of the new product. Another example was Merck's new swine flu vaccine introduced in 1976, which raised liability concerns when deaths among elderly recipients were linked to Merck's vaccine.

Today, these problems have been largely overcome and, for those manufacturers who remain in the industry, contributions of vaccine products (defined as prices minus sales, administration and manufacturing costs) match contributions of pharmaceutical products at least in the case of the US industry (Mercer 1995). This is largely the result of profits generated by new patent protected recombinant vaccines launched since the mid 1980s, as suggested in figure 5-10.

Figure 5-10



Despite the similarity in contribution, there are big differences in the cost structures of vaccine and pharmaceutical manufacturing. Production and distribution costs are significantly higher in the vaccine industry (more costly process control and sterilisation standards; higher distribution costs because many vaccines require an uninterrupted cold-chain during transport; smaller shipments to individual physicians). Sales and marketing costs are, however, much lower in the vaccine industry, mainly because well defined sales to government -usually on a longer term base- incur less promotional costs than pharmaceuticals.

Judging from the findings above it is not clear whether the US vaccine industry, which in general charges higher prices but also operates at higher costs than its European counterparts, has the higher contribution and therefore better incentives to undertake R&D in the vaccine field. No data are available on the profitability of European manufacturers[5].

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[5] Because of the integration of the vaccine business into pharmaceutical and other divisions, profitability figures for vaccine operations can generally not be obtained through company reports. For the United states this was only possible because Mercer (1995) and Whitehead (1997) gained access to confidential information at company level.

What appears to be clear is that a decision about the scale of a vaccine plant is taken very early in the development process. Any manufacturer will face a low-scale/high-price versus large-scale/low-price trade-off. Once the manufacturer is tied into a large-scale operation, the capacity has to be used since exit costs are huge. Because of these sunk costs, manufacturers are facing a potential hold-up problem. Export tendering may bring prices down to an extent which leaves very little or no return on the initial investment and may discourage further R&D investment. US manufacturers who have opted for the low-scale/high-price option experience less pressure on their contribution due to a supportive domestic market.

US innovations will in some instances be licensed out to European manufacturers which will eventually supply them to developing countries. The delay until an innovative product can be priced competitively[6] by the licensee and subsequently introduced into immunisation schedules such as EPI will have to be accepted as an integral part of the diffusion process.

However, for the reasons explained above, US innovations are highly likely to be targeted at their home market and diseases prevalent in the United States. The development of some of the most cost-effective modified and new vaccines such as early-dose measles, the single shot tetanus, Malaria; or against certain subtypes of the HIV virus, may not be pursued by these manufacturers because there is no lucrative home market. The Guardian newspaper writes (Guardian, 21/6/99, p. 21) that "drug companies have developed expensive anti-HIV treatments for the rich western markets but argued that the failure of cash-strapped developing countries to buy vaccines for diseases such as hepatitis means they would not be able to recover the high cost of Aids drugs."

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[6] Such as the Hep B vaccine whose price has only recently fallen sufficiently to be included in developing countries' immunisation programmes

Specifically, the pharmaceutical (especially vaccine) industry needs to be able to believe that there is a credible market for the new products that it develops (WHO 2000b, p. 24). The importance of a guaranteed market for future vaccine has also been emphasised by Michael Kremer (2000). The author acknowledges that drug companies are sometimes forced to sell products at a price insufficiently high to cover R&D costs. The small market for developing-country vaccines -which amounts to no more than $200m a year- is not offering enough incentive to incur the huge costs of development. In Kremer's view a fund set aside for the purchase of a future vaccine would provide the right incentives. The World Bank has recently pledged to set aside $US 1 billion for the purchase of future vaccines.

What the World Bank needs to take into consideration though, this dissertation suggests, is that besides the need to cover R&D costs, manufacturers are facing a potential hold-up problem if they commit capacity to the large scale production of such a vaccine. Large-scale production will make the manufacturer vulnerable to price pressures in the high-volume segment of the market. Any attempt to offset the downward pressure on prices through tiered pricing may induce regulatory authorities to push for lower prices in home markets which in turn undermines contributions to R&D. All this presents a considerable risk which some manufacturers may not be prepared to take.

5.5 Property rights and new technological opportunities

One aspect of dynamic pricing has not been fully explored in the above analysis: the longer a manufacturer can command prices above the cost of production, the higher the contributions will be. The duration of this time period will depend on the length of patent protection and whether patent protection is complete.

In the case of vaccines, property rights were weak until in 1980 the US Supreme Court ruled that biological products[7] are a patentable subject matter. Until then process patents were more common than product patents and a large proportion of vaccines were not covered by patents at all. The availability of patent protection coincided with a new phase in technological opportunities based on new developments in DNA technology, which made it possible for researchers to use fragments of DNA to produce specific antigens in microbial cells (Galambos and Sturchio 1998). With the transformed cells dividing, antigens could now be replicated. This recombinant DNA technology may well explain the surge of new vaccine projects with the world's first recombinant vaccine against Hepatitis B launched in 1986.

All the modern vaccines launched since then are in effect patent protected. This is particularly 'good news' for the biotech industry which plays an increasing role in vaccine R&D and whose main source of income is generated through royalties or the sale of innovations to pharmaceutical manufacturers and which undertakes little or no production and distribution activity in itself.

Some countries could, however, decide to disregard a patent and produce a patent protected vaccine or purchase a generic vaccine from a country which does not respect patents[8]. As Francis E. Andre, SmithKline vice-president claims (CVI Forum 11/96, p. 19), " we have several patents on our hepatitis B vaccine but of the 140 million children born every year, only about 15 million of them are born in countries that respect our patents." And as a legal adviser on patents points out (CVI Forum 11/96, p. 19), "without adequate protection for intellectual property in developing countries, there has been no financial or other incentive to devote scarce resources to developing new technology."

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[7] Vaccines are based on living organisms and hence classified as biologicals.

[8] One case widely discussed in the media in the first half of 2001 was the South African Pharmaceutical Manufacturers Association's attempt to prevent the South African Government from purchasing cheap generic versions of patent protected anti-Aids drugs from India. The lawsuit was subsequently dropped after some of the US-based pharmaceutical companies, whose patents were infringed, withdrew their support.

R&D investment which could be of any, or possibly exclusive, use for these countries is impeded.

While vaccines enjoy patent protection in principle, the ability to appropriate returns on investment can also be compromised if patent protection is incomplete. This may be the case if a product has seen significant public sector input during the development stage. According to the CVI Forum (10/1995) this is becoming increasingly common: "In pre CVI days, for example, the organisation never dreamed it would be taking on vaccine development from basic research of candidate molecules right up to the almost finished product stage." The interest of such an involvement is to make the vaccines widely available at low costs, which could not be achieved if a firm has to recoup its R&D costs through high prices for a considerable period of time.

Although public-private collaborations between academia and industry are attributed a greater chance of success than industry effort alone of coming up with a new formulation (WHO 2000b), extensive public sector research effort may also crowd out private sector investment. Many new vaccines or combination vaccines, which can be effectively patent protected since they include at least one new compound, are developed in the private sector. For 'old' vaccines however, which urgently require modifications (e.g. early single dose measles vaccine) research is limited in the private sector, since it appears unlikely that a new compound which has seen heavy public sector input would ever gain effective protection. Multiple patents simultaneously held by public and private institutes also create practical difficulties for access to patents and processes (EVM 1994, p. 14). Obtaining licenses may be significantly delayed and at the same time innovators may shy away from undertaking R&D when the commercialisation of the results is uncertain.

Above all, the industry receives little respect for its attempts to protect property rights and hence investments. Intellectual property rights are sometimes made responsible for the limited access to new technology developed by the biotechnology industry. According to the CVI (CVI Forum

11/96, p. 19), "[property rights] increase the unit cost of new vaccines and delay their introduction into the third world immunisation programmes." This problem, the CVI believes, can be solved by a tiered royalty system, bulk filling[9] of vaccines by developing countries and joint private-public venture arrangements. A tiered royalty system would be acceptable since it may pay off for the firm to sell at lower prices in mass markets. However, filling of vaccines in developing countries would raise concern of easy property right violation. Countries advanced enough to run a vaccine filling plant might also be capable of imitation. Public-private joint ventures could create some crowding out and could be discouraging particularly for biotech manufacturers which depend to a much larger extent on the commercialisation of innovations, than the traditional pharmaceutical industry. In any case, should new technology be licensed out, a secrecy- or a non-disclosure agreement included in the licensing contract is absolutely vital (European Vaccine Manufacturers 1994, p. 64).

As figure 5-11 shows, overall patenting activity has increased remarkably since the late 1980s, which may reflect the increasing importance of biotechnology in the vaccine area[10]. A closer look at vaccine patents held by the public sector compared to the total number of patents[11] in figure 5.12. reveals an increase from around 17% in 1976 to 35% in 1999 with some variation over time.

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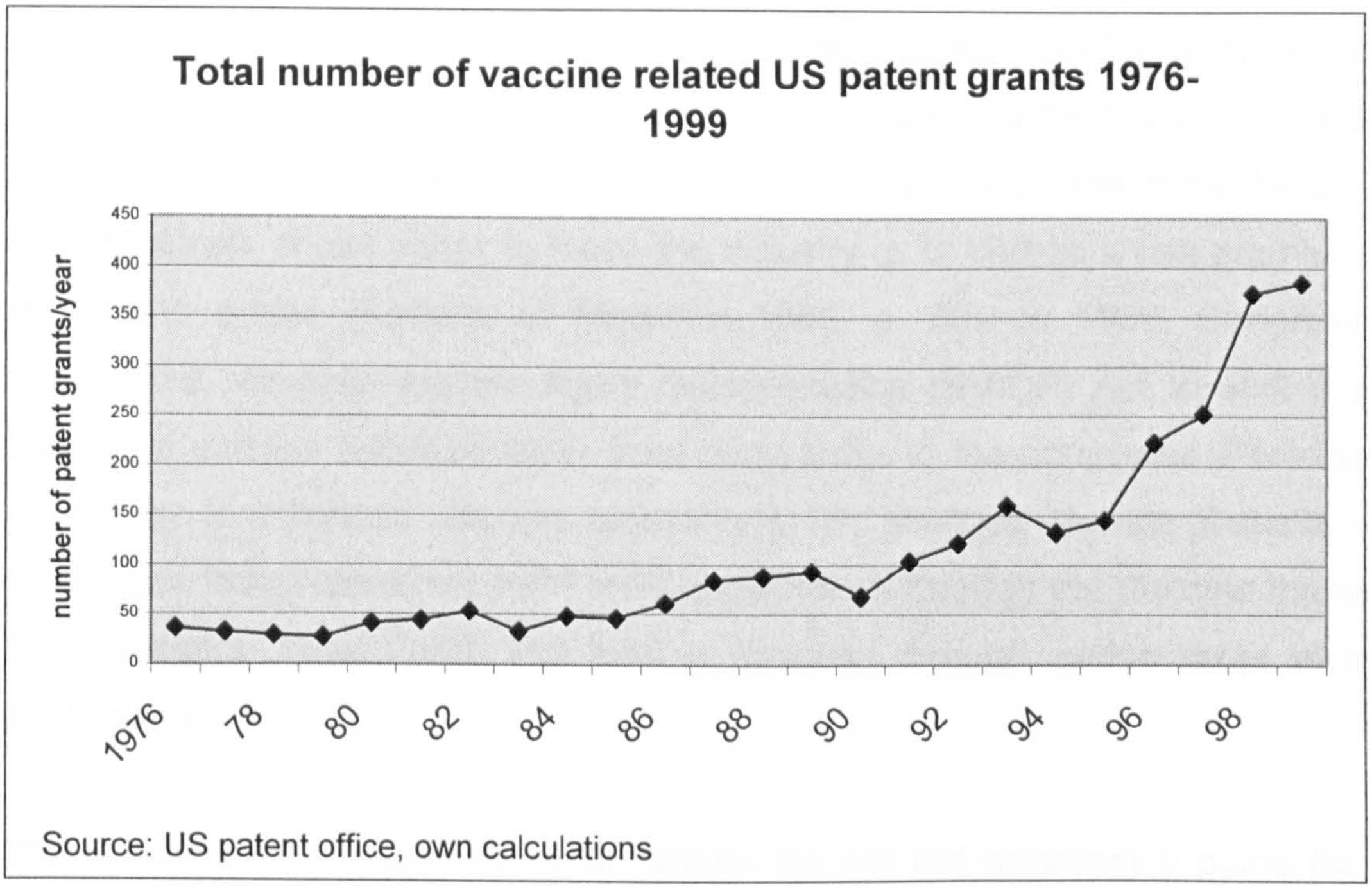
[9] Bulk filling implies that the vaccine is produced elsewhere and then shipped to a developing country where it is filled into smaller containers and distributed to the end-user.

[10] Biotech and vaccination alike are based on the manipulation of living organisms for therapeutic or preventive use.

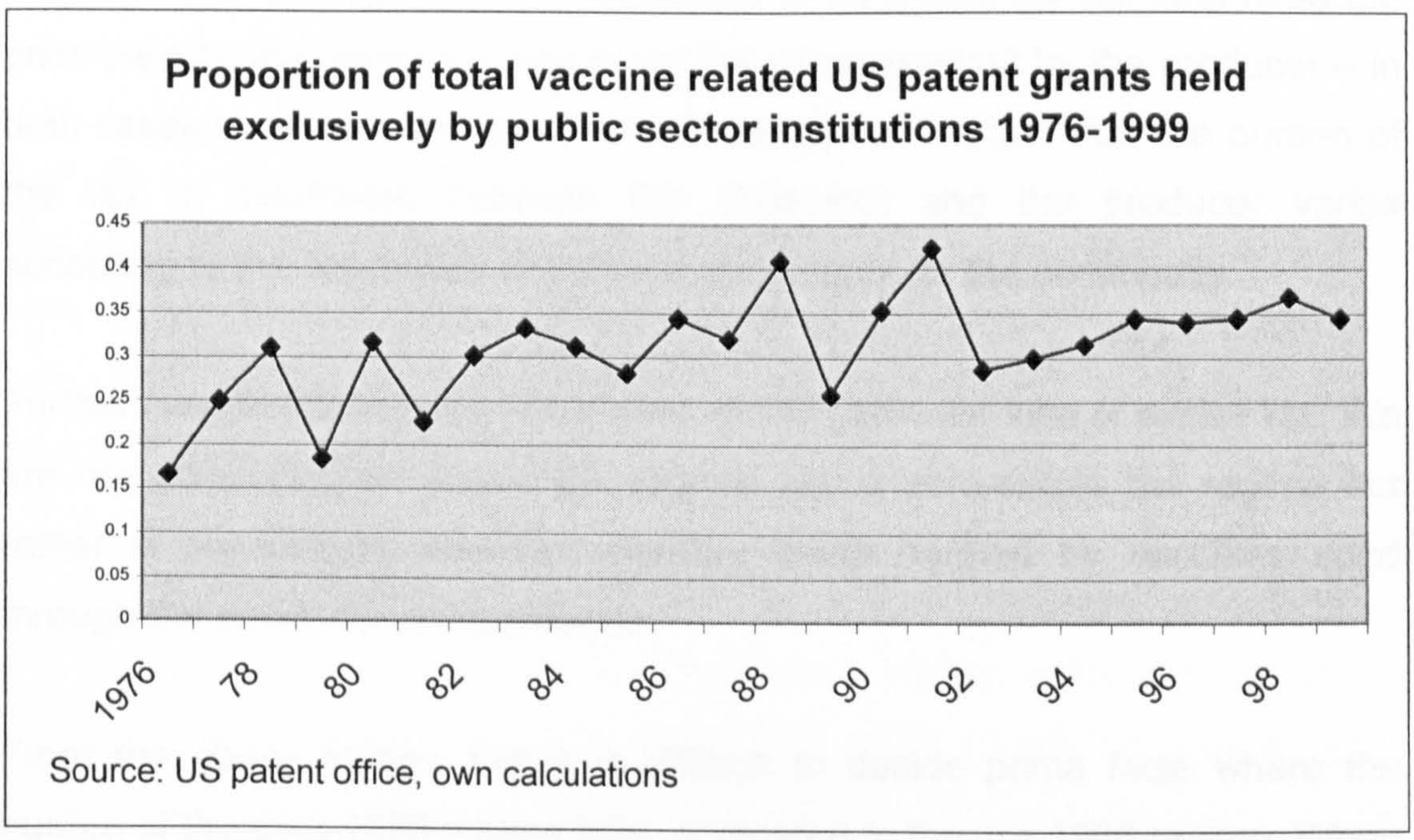
[11] All US patent grants since 1976 are available on-line (www.uspto.gov) and can be searched by key word such as 'vaccine'. All vaccine patents over this period were separated into two groups: patents exclusively held or co-owned by public sector institutions and vaccine patents held exclusively by the corporate sector.

Figure 5-11



Source: US patent office, own calculations

Figure 5-12



Source: US patent office, own calculations

5.6 Liability and Vaccine Pricing

As outlined above, potential liabilities for vaccine injuries have for many years hampered innovation in vaccines. The number of product liability cases filed against manufacturers were sharply on the increase since the early 1980s. Manufacturers chose either to leave the industry or to charge a risk premium in vaccine prices (Institute of Medicine 1985, p. 53). In 1986, Congress passed the National Vaccine Injury Compensation (NVICP) Act to shift the burden of vaccine liabilities away from companies to the consumer. Persons injured by a childhood vaccine (primarily DTP, Measles Mumps Rubella - MMR, and Polio) can since 1988 receive payments through the Vaccine Injury Compensation Trust Fund. The fund is financed through excise taxes also implemented in 1988.

The effects of the imposition of an excise tax will not necessarily place the burden of the tax on the consumer. The tax incidence literature suggests, that as long as the demand curve slopes downwards and the supply curve of the commodity slopes upwards the imposition of an excise tax will both raise the price paid by the consumer and lower the price received by the producer – in both cases by an amount less than the amount of the tax. How the burden of the tax is distributed between the consumer and the producer varies according to the elasticities of demand and supply for the commodity.

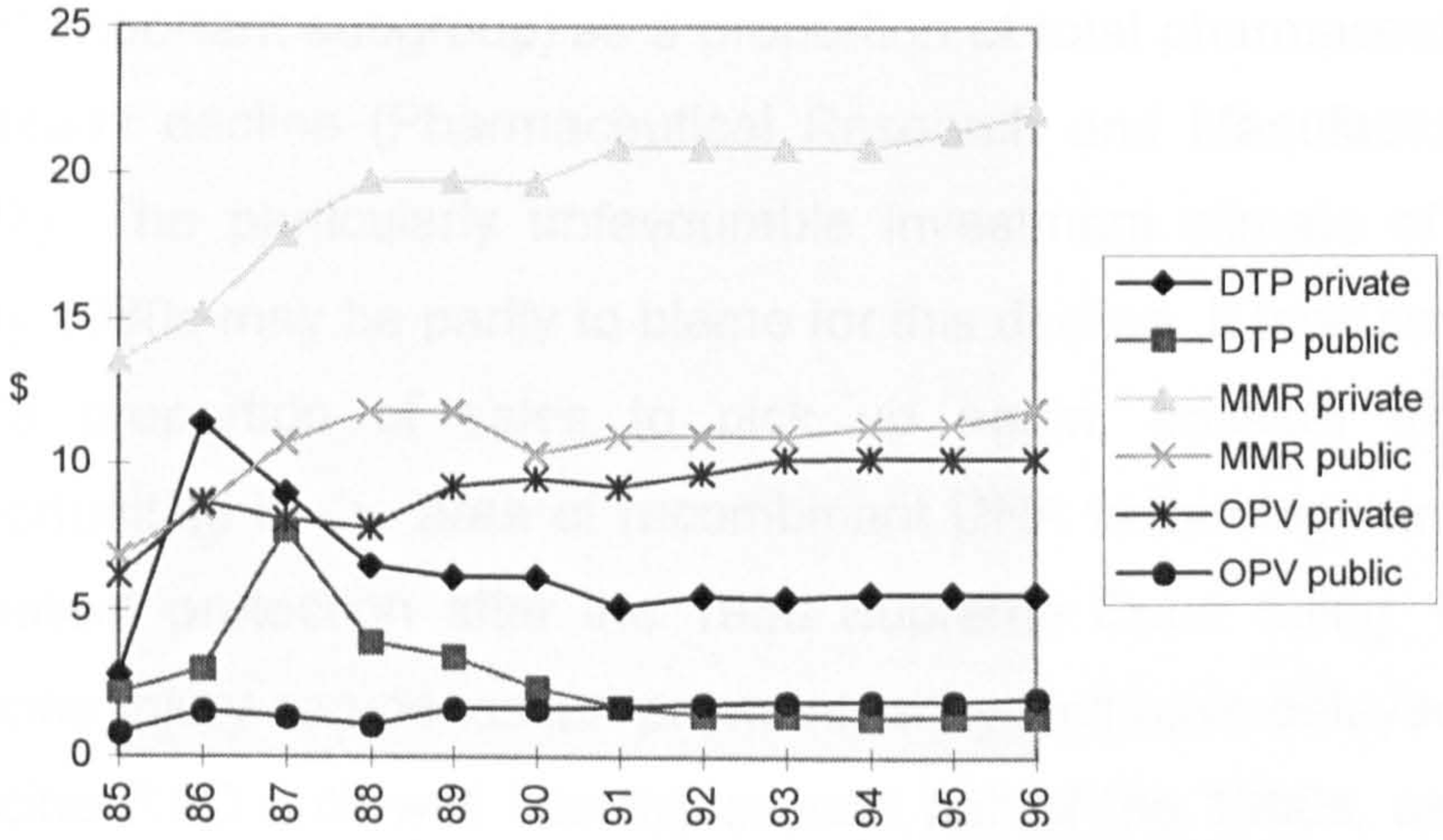
Further complications arise in the case of this particular kind of excise tax: We are not comparing an excise tax regime with a zero-excise tax regime but rather a pre-existing situation whereby those harmed by vaccines sued through the courts for compensation.

From the above follows that it is difficult to decide prima facie where the burden of the post-1988 regime falls, compared to the pre-1986 regime. When observing the actual development of vaccine prices the NVICP Act appears to have resulted in significant downward pressure on nominal vaccine prices in both the private and public segment of the market. Fig. 5-12 shows the

resulting price development in the private and public sectors of three important childhood vaccines from 1985 to 1996 in the USA.

Figure 5-13

Private catalog and public contract prices for children's vaccines, 1985-1996 in $



source: Grabowski 1997, Centre for Disease Control and Prevention

This is in line with the objective of the NVICP Act. Since the passing of the NVICP Act the number of DTP suits filed against manufacturers has declined from its peak of 255 cases in 1986 to 4 in 1997 (Department of Health and Human Services 1999) and hence government could argue that a risk premium was no longer justified. The impact on profit contributions is somewhat ambiguous. The reduction in law suits may well have compensated manufacturers for lower prices.

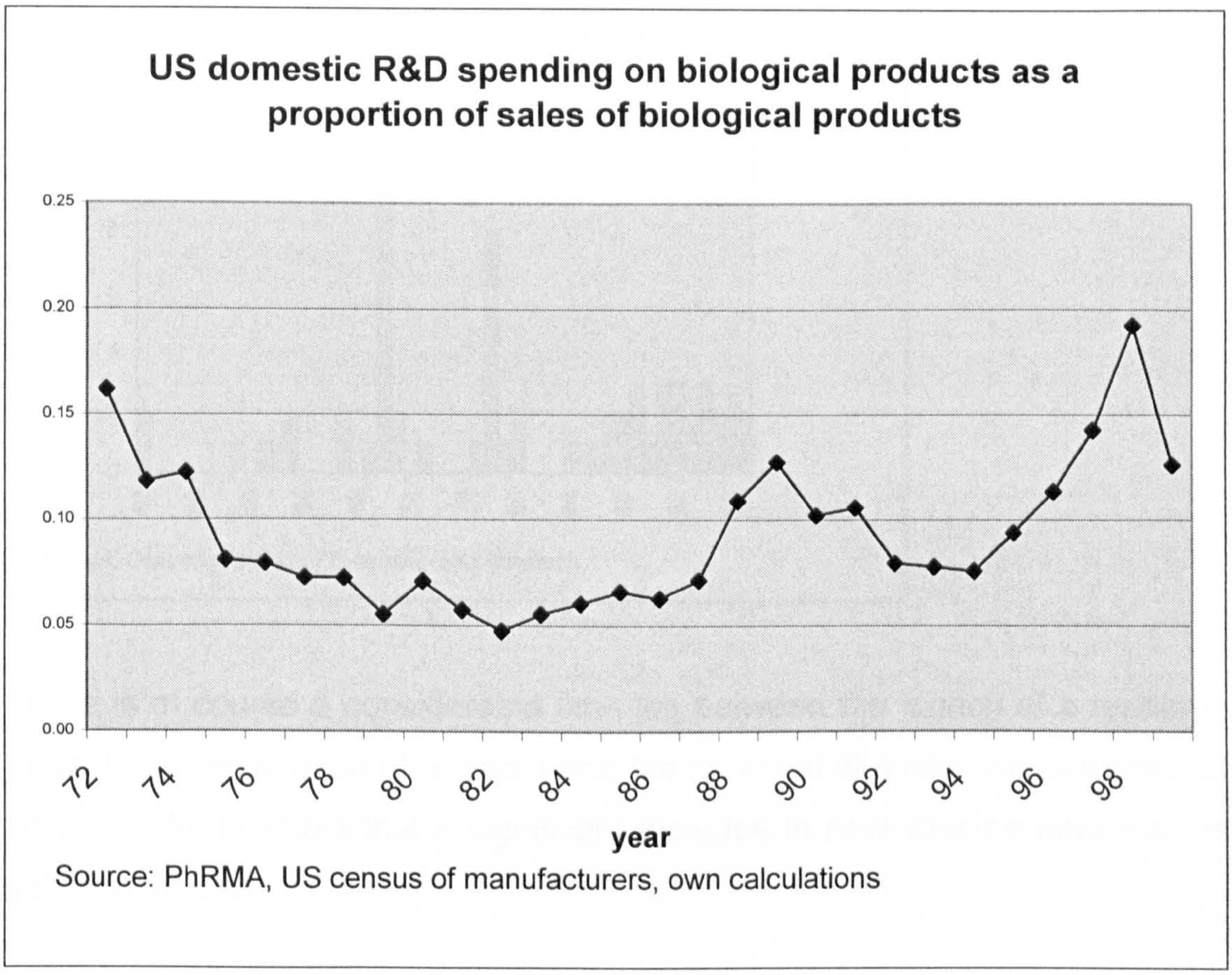
A second important development in the vaccine market has been the Vaccines for Children programme (VFC) which started in the US in October 1994 and its impact on the industry is likely to be significant. The scheme provides publicly purchased vaccines to eligible children 0-18 years of age free of charge as long as they are either enrolled by Medicaid, without health insurance, American Indian or Alaskan native or for children with health insurance which does not cover immunisation. Because this scheme is increasing the proportion of doses purchased by the state, the resulting

downward pressure on prices could reduce the expected return on R&D and as a result R&D spending.

5.7 R&D activity

Until 1982 R&D investment in biological products (of which vaccines are the most important subgroup) as a proportion of total pharmaceutical R&D shows a steady decline (Pharmaceutical Research and Manufacturers of America 1997). The particularly unfavourable investment climate of the 1970s and early 1980s may be partly to blame for this decline. It took some time for R&D as a proportion of sales to pick up again, possibly triggered by new opportunities in the area of recombinant DNA technology and the availability of patent protection after the 1980 Supreme Court ruling. Uncertainty over vaccine injury compensation payments may well have delayed the recovery of vaccine R&D until well into the second half of the 1980s, as can be seen in Fig. 5.14. This positive trend was again reversed in 1990 which saw a temporary fall in R&D intensity which lasted until 1994. After 1995, R&D intensity has increased steadily to reach a new high in 1998, only to drop again in 1999.

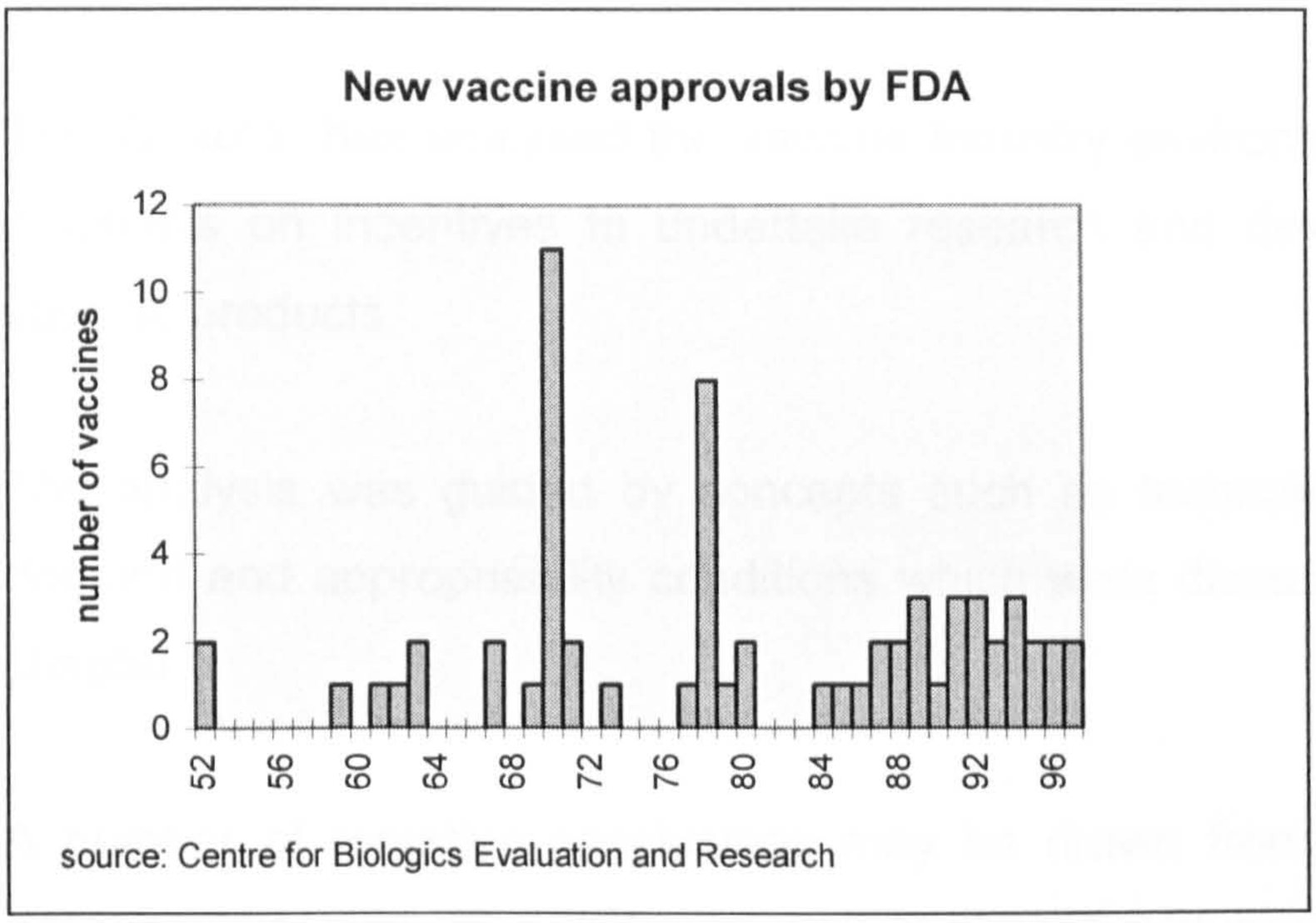
Figure 5-14



Source: PhRMA, US census of manufacturers, own calculations

Whether the increase in R&D spending and patenting activity has fed through to new product development is unclear. As Fig. 5.15 shows, new vaccines have been introduced at an almost constant rate of two to three vaccines per year over the 1984-1997 period.

Figure 5-15



There is of course a considerable time lag between the launch of a research project, the registration of a patent and the approval of a new vaccine product so it is quite possible that a significant increase in new vaccine approvals is yet to materialise.

R&D investment is likely to be more immediately responsive to changes in the environment and was therefore chosen over the number of New Molecular Entities (NMEs) as the dependent variable in the following empirical investigation. To what extent R&D investment has been influenced by patent protection, new technological opportunities, market size and public sector research activities will also be examined in the next chapter.

5.8 Conclusions

This Chapter has analysed the vaccine industry environment, with particular emphasis on incentives to undertake research and development into new vaccine products.

The analysis was guided by concepts such as technological opportunities, demand and appropriability conditions which were discussed in the previous chapter.

A number of tentative conclusions may be drawn from this analysis here: American vaccine manufacturers supply almost exclusively to their domestic market. The US vaccine market allows a return on investment similar to pharmaceutical products. This is partly due to a new breed of genetically engineered paediatric vaccines launched in the second half of the 1980s and early 1990s. These products gain market share very rapidly and are the first vaccines to enjoy full patent protection. US manufacturers also benefit from the NVICP act which has relieved them of any liability for vaccine injuries.

European manufacturers typically operate on a larger scale than their US counterparts and rely quite heavily on very price-sensitive export tenders. Although profitability data are not available, these manufacturers rely on scale effects which are very significant in vaccine production.

R&D investment in vaccines as a proportion of sales by US manufacturers declined for most of the 1970s, which appears to reflect poor patent protection, uncertainty over liability for vaccine injuries and exhausted technological opportunities during this period. Some crowding out by public sector research may also have occurred.

The early 1980s saw an increase in R&D intensity which may be attributable to biotechnology as a new technological paradigm with many new vaccines derived from genetically modified organisms. A 1980 US Supreme Court

ruling also granted patent protection to biological products for the very first time. In 1988 vaccine manufacturers were eventually relieved from vaccine injury liability with the establishment of the NVICP act.

From the above description the relative importance of these factors cannot be assessed with any certainty. Building on the theoretical concepts introduced in Chapter Four, the following empirical investigation aims to identify those of the above factors which significantly influence R&D spending in the vaccine industry.

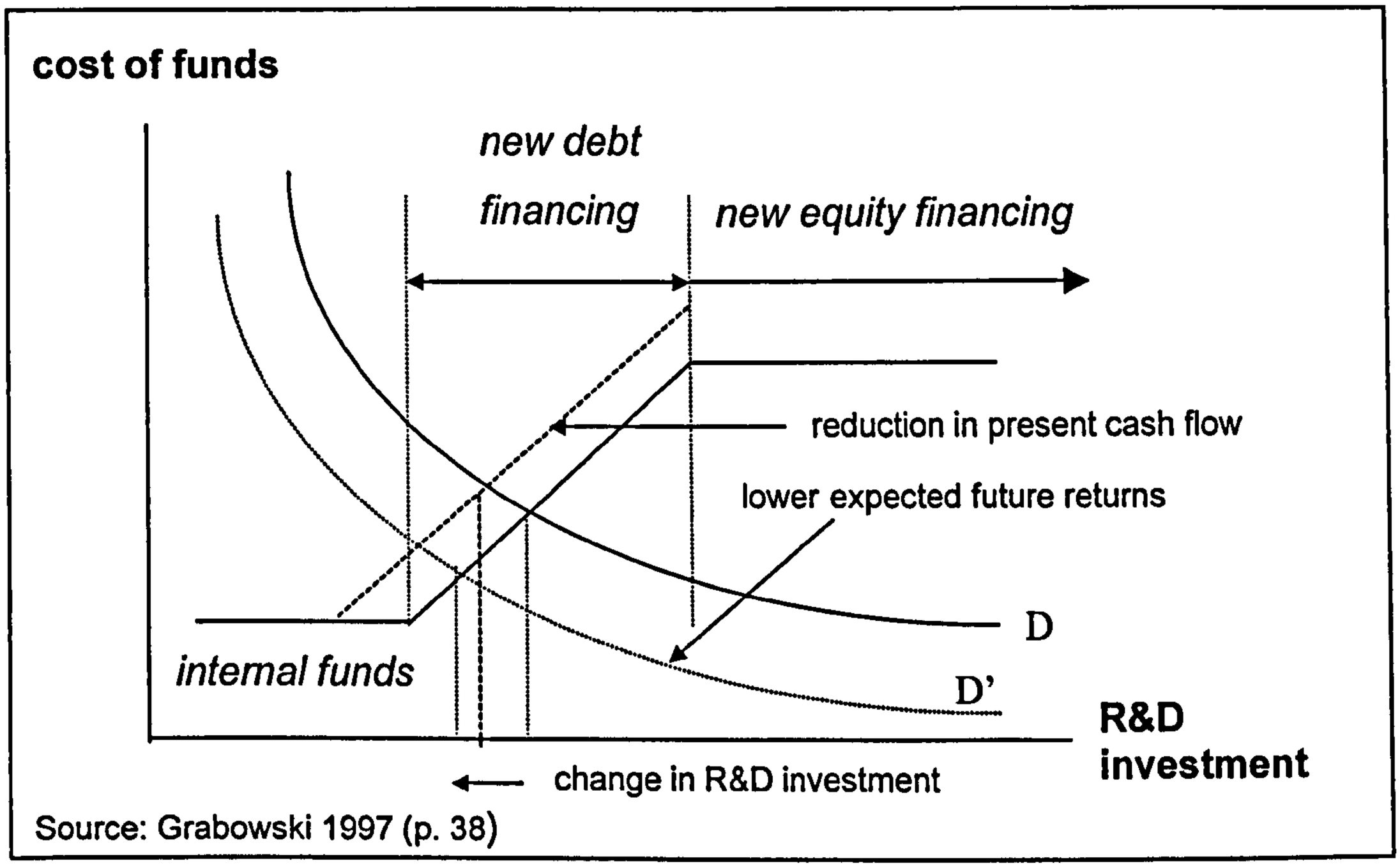
6 Modelling investment in vaccines

6.1 The model

Grabowski (1997, 2000) proposes an R&D investment model for the pharmaceutical industry which will be used here in a modified form. This model allows us to show not only the influence of differences in the costs of internal and external R&D funds, following work by Fazzari et al. (1988) and Hubbard (1998) in that area, but also the influence of technological opportunities, appropriability conditions and demand factors.

In a similar way to the models of Shepherd (1990) and Metcalfe (1997), a firm lines up its alternative investment projects and, starting with the projects offering the highest return, only takes on new projects when the cost of funds decline. The resulting demand for R&D funds (D) can be interpreted as a marginal return to investment curve and is here shown in fig 6.1.

Figure 6-1



Source: Grabowski 1997 (p. 38)

The supply of funds schedule depends on whether sufficient funds can be raised either internally, or in the form of debts, or on the capital markets as new equity financing. The supply of funds curve can be interpreted as a marginal cost of capital schedule and reflects the opportunity cost of alternative investments of the firm. As long as sufficient internal finance is available, the supply of funds curve is horizontal and reflects the user cost of capital. This segment of the supply of funds curve would be in line with conventional neo-classical investment theory. A rise in the user cost of capital would raise the opportunity cost of funds and shift the horizontal segment of the supply of funds curve upwards, thereby reducing R&D investment.

Once the firm needs to raise external finance, it faces a rising segment that represents the costs of debt financing. As outlined earlier internal and external finance are not perfect substitutes in practice. Equity finance can be more costly, especially for small offerings and initial public offerings. Fazzari et al. (1988) blame underwriting discounts, registration fees and taxes, selling and administrative expenses, and a higher tax rate on dividends than capital gains. Further to this, if a firm exhausts all internal funds and requires external finance, investors cannot distinguish between the quality of firms. Hence they require a premium to offset losses from investing in 'lemons'.

This rationale also applies to new debt financing. Agency costs and costs of financial distress, i.e. bankruptcy in the most extreme case, will increase with leverage, explaining the rising segment of the marginal cost of funds curve linking internal financing and new equity financing.

Equilibrium is established where the return from the last R&D project is equal to the marginal cost of funds. Grabowski (2000) believes that this view of the investment process is particularly relevant for the pharmaceutical industry, where the problems of great uncertainty about the outcome of R&D, the length of the R&D process (12-14 years) and asymmetric information combine to make the difference between internal and external funds especially important. In addition, unlike fixed investment in plant and

equipment, the outcome of drug R&D is simply new knowledge, which may or may not have new value.

The variable most likely to shift the supply of R&D funds schedule is cash flow of present products. The supply of R&D funds curve will shift to the left or right, determining when a firm would have to use the more costly debt or equity financing alternatives.

This model can also be used to show changes in the environment affecting the demand curve for R&D funds. Cash flow, for instance, is expected simultaneously to affect the cost of finance *and* expected future returns. An increase in cash flow should shift both the supply and demand curve for R&D funds. Grabowski (1997) suggests that in an empirical investigation the cash flow variable should appear twice, once as an indicator of cost of funds, but also as a proxy for expected return. How the two effects are distinguished in this study is discussed in the following section.

Other factors influencing expected returns and therefore shifting the demand for R&D funds curve are, for instance, an increase in the size of the market, changes in appropriability conditions (such as an extension in property rights), or any other changes in the regulatory environment. Any change in expected return to the project would affect the demand for R&D funds and the equilibrium level of investment changes accordingly.

6.2 Empirical implementation

This part will empirically evaluate the firm's R&D intensity as a function of the cost of funds and expected returns. The model concentrates on the three largest US vaccine manufacturers[1] over the period of 1976-1999.

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[1] As indicated in chapter five, the US vaccine industry is highly concentrated and dominated by domestic producers. The three largest US manufacturers will therefore represent a significant share of the US vaccine market.

Using a specific to general approach the following 1st order autoregressive process forms the starting point of the investigation:

Equation 6-1

$$\ln RD_t = \beta_0 + \beta_1 \ln PROFMARG_t + \ln RD_{t-1} + v_t$$

lnRD:	natural log of the ratio of aggregate R&D expenditure on biological products over sales of biological products in year t, i.e. ln (R&D spending/Sales)
lnPROFMARG:	natural log of aggregate company after tax profits plus depreciation plus R&D expenditure, deflated by sales, in year t, i.e. ln (profit/sales)

LnRD describes the natural log of aggregate R&D spending on biological products[2] deflated by aggregate sales of biological products, i.e. serves as an indicator of R&D intensity in the sample[3]. Since R&D spending over a longer time period is strongly trended, the use of a *ratio* such as R&D intensity addresses the problem of spurious regression arising from possible non-stationarity. Data on R&D spending are published by the US pharmaceutical manufacturers association PhRMA (Pharmaceutical Research and Manufacturers of America) in their annual surveys.

LnPROFMARG represents aggregate cash flow in the sample and, according to the original model, PROFMARG is expected to be positively related to R&D intensity through its influence on the cost of funds and expected return to R&D.

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[2] According to Grabowski (1997) R&D spending on biological products is a close approximation to R&D spending on vaccine products. The US Pharmaceutical Manufacturers Association's annual survey lists two subcategories of biological products: vaccines and blood/blood derivatives, but publishes data on *biological* R&D spending only.

[3] See figure 5.14 for a graphical representation and section 5.7. for a more detailed description of this variable

In order to compute lnPROFMARG, depreciation and R&D expenditure were added to company after tax profits, following Fazzari et al. (1988) and Grabowski (1997). Other authors[4] prefer to use the market value of the firm as an approximation of cash flow. The market value of the firm is however more likely to be determined by expected future cash flows which are unlikely to have an immediate impact on the cost of funds. Data on annual profits, depreciation and R&D expenditure were taken from Datastream.

Equation 6.1 also includes the log of the dependent variable RD_t lagged by one year which follows a partial adjustment specification common to most theories of investment at the industry level (Berndt 1991). The assumption is that firms aim for some target level of R&D investment intensity RD^*_t such that:

Equation 6-2

$$RD^*_t = \beta_0 + \beta_1 PROFMARG_t + u_t$$

Assume further that agents adjust towards this ideal using the following:

Equation 6-3

$$RD_t - RD_{t-1} = \delta (RD^*_t - RD_{t-1})$$

Where $0< \delta < 1$, $(RD_t - RD_{t-1})$ is the actual change and $(RD^*_t - RD_{t-1})$ is the desired change and δ the adjustment parameter. Rewrite equation 6.3 as:

Equation 6-4

$$RD_t = \delta RD^*_t - \delta RD_{t-1} + RD_{t-1}$$

From this follows that:

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[4] See for instance Grunfeld's (1960) original study.

Equation 6-5

$$RD_t = \delta RD^*_t + (1-\beta_0)RD_{t-1}$$

Substituting equation 6.2 into this gives:

Equation 6-6

$$RD_t = \delta\beta_0 + \delta\beta_1 PROFMARG_t + (1-\beta_0)RD_{t-1} + \delta u_t$$

The logarithmic form of this equation will lead back to the original equation 6.1 which can be estimated using OLS.

6.3 Estimation results

The following results have been obtained from the OLS estimation:

Table 6-1

Dependent Variable: LnRD
Method: Least Squares
Sample(adjusted): 1974 1999
Included observations: 26 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.113728	0.313250	-0.363058	0.7199
LnPROFMARG	0.451696	0.168190	2.685630	0.0132
LnRD(-1)	0.683964	0.119761	5.711050	0.0000

R-squared	0.717366	Mean dependent var.	-2.474906
Adjusted R-squared	0.692789	S.D. dependent var.	0.341081
S.E. of regression	0.189050	Akaike info criterion	-0.385445
Sum squared resid.	0.822017	Schwarz criterion	-0.240280
Log likelihood	8.010783	F-statistic	29.18860
Durbin-Watson stat.	1.914844	Prob(F-statistic)	0.000000

Both variables $lnPROFMARG_t$ and the lagged dependent variable $lnRD_{t-1}$ are significant at the five per cent level and have the expected sign. We can therefore reject the null hypothesis and support the view that an increase in aggregate cash flow will result in an increase in aggregate R&D intensity. This also supports the original hypothesis that firms' R&D intensity is responsive to

changes in the cost of funds. A one per cent increase in the ratio of cash flow over sales seems to result in just under half a per cent increase in R&D intensity. Likewise, an increase in the previous year's R&D intensity by 1% appears to be followed by a corresponding 0.7% increase in the current year's R&D intensity which also confirms the relevance of the underlying partial adjustment mechanism of allocating R&D resources, outlined above. The adjusted r^2 of almost 70% and the significance of the F statistic indicate a good fit of the model. The above estimation seems robust despite the relatively small number of observations[5].

The discussion of the economics of the vaccine industry in Chapter Five suggested a range of other factors that may influence the firm's investment decision. Hence, a range of other variables reflecting these possible influences were subsequently introduced into the original equation 6.2. one by one. None of these variables, however, proved to be significantly related to the variable lnRD. All variables were also tested for lagged influences but proved equally insignificant. These variables are listed in table 6.2:

[5] A number of statistical test have been performed on the above specification: The White heteroscedasticity test does not indicate heteroscedastic disturbances, the Breusch-Godfrey Serial Correlation LM Test does not show serially correlated errors, neither does Ramsey's reset test indicate a functional mis-specification. The Jarque-Bera normality test suggests normally distributed residuals.

Table 6-2

List of insignificant variables

$LnPATENT_t$	Natural log of public sector research effort in the vaccines area, expressed as patent grants for public sector research institutions as a proportion of the total number of granted patents in same area[6]. Product-oriented public sector research may have depleted the chances of appropriating patentable technology. Patent data are published on-line by the US patent office (www.uspto.org).
$LnSALES_t$	Natural log of US vaccine sales relative to total pharmaceutical sales. An increase in the market size for vaccines relative to pharmaceuticals may have improved expected returns in the former sector and as a result increase vaccine R&D intensity. Sales data by pharmaceutical subgroup are published in PhRMA annual surveys.
$LnPROFIT_t$	Following Grabowski (1997) lnPROFIT was created in an attempt to separate expected returns from cost of funds (variable PROFMARG). LnPROFIT is the natural log of the profit margin of the companies in the sample, calculated as pre-tax profits as a percentage of sales. A change in the profit margin changes expectations of future returns and may have increased R&D intensity.
PREG	Zero/one intercept dummy variable to distinguish the periods before and after the passing of the NVICP Act[7]. PREG is equal to one the year after the implementation of the Act in 1989. While the NVICP act has halted the price rise of most childhood vaccines which may have dampened expected returns, companies no longer had to calculate future compensatory payment into vaccine prices. The overall effect is therefore ambiguous.
PROPREG	Zero/one intercept dummy variable equal to one the year after a US supreme court ruling (1980) granted patent protection to biological products. The court ruling may have raised rate of return expectations on future vaccine developments.

Although lnPROFMARG reflects cost of funds effects, an increase in cash flow over sales will not only lower the cost of funds but simultaneously raise expectations of future returns. Ideally, the effect of a change in the relative cost of funds could be separated from the effect of a change in expected

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[6] See figure 5.12 in the previous chapter for a graphical representation of this variable

[7] See previous chapter for details on the National Vaccine Injury Compensation Plan (NVICP)

returns to R&D. Introducing lnPROFIT proved impractical, however, not only because the variable is insignificant; the correlation of the two variables, despite the differences in calculation, would also have presented problems of multicollinearity.

A change in cash flow over sales appears to be positively related to R&D intensity, because it simultaneously affects the cost of funds and induces firms to spend more on R&D in expectation of higher future returns.

6.4 Error correction model of R&D intensity

Despite the robustness of the above partial adjustment model and the fact that both explanatory and dependent variable are expressed as ratios, it cannot be ruled out that the variables are non-stationary and that the observed relationship between the variables is spurious.

A unit root test on lnRD, and lnPROFMARG reveals that they are integrated of order one, i.e. only become stationary after first differencing.

In the presence of non-stationary time series Engle and Granger (1987) have suggested the estimation of an error correction mechanism.

Following Thomas (1997, p. 383), the following equation 6.7 describes the long run *equilibrium* relationship between the two variables lnRD and lnPROFMARG:

Equation 6-7

$$lnRD_t = \beta_0 + \beta_1 lnPROFMARG_t$$

If the above equation is not in equilibrium, the equilibrium error can be expressed as:

Equation 6-8

$$\ln RD_t - \beta_0 - \beta_1 \ln PROFMARG_t$$

The *disequilibrium* relationship between lnRD and lnPROFMARG can then be expressed in the following general form:

Equation 6-9

$$\ln RD_t = b_0 + b_1 \ln PROFMARG_t + b_2 \ln PROFMARG_{t-1} + \mu \ln RD_{t-1} + \varepsilon_t$$

In equation 6.9 lnRD takes time to adjust to variations in lnPROFMARG which is consistent with the idea that lnRD is not always in equilibrium relative to PROFMARG. Note that if $b_2=0$ the equation will be a simple partial adjustment model such as 6.6 tested above, i.e. the partial adjustment model is nested within the general form 6.9.

As discussed previously, the main problem in estimating the above model is that both variables are non-stationary series and classical techniques may not be applicable because of spurious regression problems.

Following Thomas (1997), the above model can be converted into an error correction model which, given certain assumptions explained further below, contains only stationary series.

Subtracting $\ln RD_{t-1}$ from both sides of the equation, equation 6.10 is obtained:

Equation 6-10

$$\ln RD_t - \ln RD_{t-1} = b_0 + b_1 \ln PROFMARG_t + b_2 \ln PROFMARG_{t-1} - (1-\mu) \ln RD_{t-1} + \varepsilon_t$$

Adding and subtracting $b_1 \ln PROFMARG_{t-1}$ from the right hand side of 6.10 gives:

Equation 6-11

$$\ln RD_t - \ln RD_{t-1} = b_0 + b_1 \ln PROFMARG_t - b_1 \ln PROFMARG_{t-1} + b_1 \ln PROFMARG_{t-1} + b_2 \ln PROFMARG_{t-1} - (1-\mu)\ln RD_{t-1} + \varepsilon_t$$

or:

Equation 6-12

$$\Delta \ln RD_t = b_0 + b_1 \Delta \ln PROFMARG_t + (b_1 + b_2)\ln PROFMARG_{t-1} - \lambda \ln RD_{t-1} + \varepsilon_t$$

where $\lambda = 1-\mu$. Further reparameterisation yields:

Equation 6-13

$$\Delta \ln RD_t = b_0 + b_1 \Delta \ln PROFMARG_t - \lambda(\ln RD_{t-1} - \beta_1 \ln PROFMARG_{t-1}) + \varepsilon_t$$

having defined the new parameter $\beta_1 = (b_1 + b_2)/\lambda$. Finally $\beta_0 = b_0/\lambda$ is introduced as the second new parameter, which will give:

Equation 6-14

$$\Delta \ln RD_t = b_1 \Delta \ln PROFMARG_t - \lambda(\ln RD_{t-1} - \beta_0 - \beta_1 \ln PROFMARG_{t-1}) + \varepsilon_t$$

which is the error-correction model version of 6.9. Note that the term in parentheses can be regarded as the disequilibrium error from period t-1. Therefore the current change in lnRD depends on the change in PROFMARG and the extent of disequilibrium in the previous period. Since the value of lnRD is being corrected for any previous disequilibrium error this representation is called a first-order error-correction model (Thomas 1997).

This transformation could also be undertaken with second or higher order lags of the first differenced variables which leads to Granger's general formulation in 6.15 which shows the above error term simply as λu_{t-1}.

Equation 6-15

$$\Delta \ln RD_t = \text{lagged}(\Delta \ln RD, \Delta \ln PROFMARG) - \lambda u_{t-1} + \varepsilon_\tau$$

In order to ensure that all variables contained in this model are stationary, Engle and Granger (ibid.) suggest a two-step estimation procedure. In a first stage it is established that both variables are integrated of order one. As indicated above, lnRD and lnPROFMARG are both integrated of order one according to the Dickey-Fuller test for a unit root. After it is established that both variables are I(1), the long run parameters are estimated. OLS is used to estimate:

Equation 6-16

$$\ln RD_t = \alpha + \beta_1 \ln PROFMARG_t + u_t$$

Rearranging 6.16, equation 6.17 shows the residual, which is easily recognizable as the error correction term from equation 6.14, except the term below is not lagged by one period:

Equation 6-17

$$u_t = \ln RD_t - \alpha - \beta_1 \ln PROFMARG_t$$

Now the residual from the static regression 6.16 can be tested for stationarity using the Dickey-Fuller test for a unit root. Stationary results imply that lnRD and lnPROFMARG are co-integrated.

The null hypothesis of non-stationarity can be rejected at the 10% level[8]. It follows that the residual u_t is a stationary series which, in turn, implies that lnRD and lnPROFMARG are co-integrated.

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[8] In this case the series seems to be fluctuating around a zero mean, so both intercept and time trend were excluded from the test regression

Engle and Granger (1987) showed in their article that if two variables such as lnRD and lnPROFMARG are both integrated of order one *and* the two series are co-integrated, equation 6.16 can now be used to obtain an estimate of the long run parameters of the relationship between the two variables. The results of this estimation are presented in table 6.3.

Table 6-3

Dependent Variable: lnRD
Method: Least Squares
Sample(adjusted): 1974 1999
Included observations: 26 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-1.298879	0.357207	-3.636213	0.0013
lnPROFMARG	0.796692	0.238948	3.334169	0.0028

R-squared	0.316564	Mean dependent var.	-2.474906
Adjusted R-squared	0.288088	S.D. dependent var.	0.341081
S.E. of regression	0.287787	Akaike info criterion	0.420610
Sum squared resid.	1.987711	Schwarz criterion	0.517387
Log likelihood	-3.467936	F-statistic	11.11668
Durbin-Watson stat	0.574913	Prob(F-statistic)	0.002771

LnPROFMARG (depicting cash flow divided by sales) is, as in the previous partial-adjustment model, significantly related to R&D intensity and the coefficient has the expected positive sign. The relatively low r^2 can be expected since, by definition, only long run influences were looked at, thereby omitting information on dynamic or short run relationships between the variables.

Hence, in the second stage of the Engle-Granger two-step procedure the residuals from the co-integrating regression 6.16, can now be used as estimates of the disequilibrium error (the term in parentheses) in equation 6.14. Since all variables are now stationary, equation 6.14 can be estimated using OLS without the danger of producing spurious results.

Note from 6.14 that the disequilibrium error from period t-1 is expected to have a negative sign and needs to be lagged by one period. Further to that, lagged terms of the first level differences of all variables can be included in

the model and their inclusion will be determined by experimentation. Originally the first difference of both lnPROFMARG and the dependent variable lnRD lagged by one and two years respectively were included in the estimation but were subsequently omitted due to lack of significance.

This left the lagged residual from 6.16, which is the short run error correction term shown as ECMRESID(-1) in the output table, as the only significant variable. The short run parameters obtained from the regression are shown in table 6.4:

Table 6-4

Dependent Variable: ΔlnRD
Method: Least Squares
Sample(adjusted): 1975 1999
Included observations: 25 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
ECMRESID(-1)	-0.447861	0.136790	-3.274076	0.0032

R-squared	0.308726	Mean dependent var.	0.001204
Adjusted R-squared	0.308726	S.D. dependent var.	0.223031
S.E. of regression	0.185435	Akaike info criterion	-0.493052
Sum squared resid.	0.825263	Schwarz criterion	-0.444296
Log likelihood	7.163144	Durbin-Watson stat	1.571442

The error correction term has the expected negative sign. Current change in research intensity will, in the short term, depend on the disequilibrium error from period t-1. The coefficient of -0.45 indicates that only about half of the disequilibrium error of the previous period is made up in the current period.

Although the above specification seems robust[9], the goodness of fit as indicated by the adjusted r^2 is somewhat disappointing. Unlike in the estimation of the long run coefficient, the above specification does contain information on both long and short run parameters (the error term in 6.14 includes the lagged values of the level variables lnPROFMARG and lnRD).

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[9] Stability, coefficient, and residual tests indicate no problems of heteroscedasticity, no evidence of serially correlated errors and show normally distributed residuals.

More problematically, Monte Carlo studies have shown that estimates of the cointegrating regression in 6.16 can have small sample bias (Kennedy 1994, p. 254), and it is suggested that the separate estimation of the long run parameter be replaced by estimation of the full error correction equation, i.e. to estimate the long run relationship together with the short run parameters rather than separately. There is some evidence to suggest that the small sample properties of the estimates obtained in this way are superior to those of the two stage Engle-Granger procedure (Thomas 1997).

For the purpose of estimating the full error correction mechanism, 6.14 is multiplied out to obtain:

Equation 6-18

$$\Delta \ln RD_t = \lambda\beta_0 + b_1 \Delta \ln PROFMARG_t - \lambda \ln RD_{t-1} + \lambda\beta_1 \ln PROFMARG_{t-1} + \varepsilon_t$$

OLS can again be applied to 6.18. Further to lagged terms of lnPROFMARG and lnRD, differenced terms of other explanatory variables were also tested for short run influences on the change in research intensity (ΔlnRD). This, it was hoped, would improve the predictive power of the model. This is permissible as long as these variables are integrated of order one, again avoiding problems of possible spurious regression. Performing a unit root test on both lnPAT and lnSALE[10], both variables become stationary after first differencing and can therefore be included in the model.

Which of the lagged changes in explanatory and dependent variables have been included in the final specification of the model, has again been decided by experimentation. The following results have been obtained:

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[10] See table 6.2 for a description of lnSALE and lnPAT.

Table 6-5

Dependent Variable: ΔlnRD
Method: Least Squares
Sample(adjusted): 1977 1999
Included observations: 23 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.561119	0.323460	-1.734741	0.0999
ΔlnRD(-1)	0.584177	0.256118	2.280889	0.0350
lnRD(-1)	-0.601256	0.167442	-3.590839	0.0021
lnPROFMARG(-1)	0.661029	0.206410	3.202511	0.0049
ΔlnPAT	0.407197	0.155983	2.610526	0.0177

R-squared	0.497722	Mean dependent var.	0.020185
Adjusted R-squared	0.386104	S.D. dependent var.	0.214428
S.E. of regression	0.168008	Akaike info criterion	-0.539955
Sum squared resid.	0.508078	Schwarz criterion	-0.293109
Log likelihood	11.20949	F-statistic	4.459177
Durbin-Watson stat	2.073244	Prob(F-statistic)	0.011149

All variables are significant at the 5% level and the usual diagnostics[11] indicate a robust model. According to the regression output, short run changes in R&D intensity depend on the following short run parameters: changes in the log of R&D intensity lagged by one year, and changes in the ratio of vaccine related patents held by the public sector as a proxy for public sector research effort in this area.

These parameters indicate that almost 60% of the total change in R&D intensity is determined by previous year's changes while an increase in public sector research effort in the current year will result in a less than proportionate increase in R&D intensity, i.e. we would expect a 0.4% increase in R&D intensity as a response to a 1% increase in research effort led by the public sector. Although this result has to be interpreted very carefully[12], there

[11] The following statistical test have been performed: Ramsey's reset test, White's heteroscedasticity test, Jarque Bera normality test, serial correlation LM test, none of which indicate a specification problem. The covariance matrix does not indicate any multicollinearity problem.

[12] The reader will have to bear in mind that the proxy used here to measure public sector research effort is quite crude. We have simply taken the ratio of vaccine related US patents, which have seen some input by public sector institutions (e.g. universities), as a fraction of all patents issued in a year.

is no evidence from the analysis in this dissertation of public sector research effort 'crowding out' private R&D, which would have resulted in a negative coefficient for ΔlnPAT.

The negative sign of lnRD(-1) is expected because this is in effect the adjustment parameter λ (compare equation 6.18 and 6.14). The adjustment parameter indicates the extent to which any disequilibrium in the long run relationship between lnRD and lnPROFMARG is compensated for in the current period. The coefficient of 0.6 indicates that firms will adjust to the extent of 60% of the disequilibrium.

The long run coefficient of lnPROFMARG needs to be retrieved through a simple transformation. We have estimated $\gamma\beta_1$=0.66 and the adjustment parameter γ=0.60. That means that the long run parameter β_1 is equal to 0.66/0.60=1.1 This implies an almost proportionate increase in research intensity as a response to changes in cash flow divided by sales as a long run relationship. This is slightly higher than the long run relationship established through the Engle Granger procedure but, because of the small sample properties of the coefficient in this procedure, likely to be the more reliable estimate.

The value obtained for r^2 is also higher than in Engle-Granger specification but still somewhat low. There is little in the literature to indicate, however, whether higher values of r^2 can be expected from this kind of model.

6.5 Conclusions and policy implications

A number of conclusions may be tentatively drawn: in a simple partial adjustment model of firms' R&D spending behaviour, changes in cash flow (deflated by sales) and past values of R&D intensity appear to impact positively on the intensity of research and development (defined as R&D spending divided by sales) in the vaccine industry.

Other factors, such as the size of the vaccine market relative to pharmaceutical products (as a proxy for 'demand pull'), or the share of vaccine related patents held by public sector institutions (testing for evidence of 'crowding out'), were not significantly related to research intensity, at least in the partial adjustment specification. Neither was there any evidence of a structural break after the extension of patent protection for biological products in 1980 or the implementation of the NVICP act in 1988[13], two events which were expected to have a positive impact on firms' R&D spending behaviour.

Concerns over non-stationarity of the data series and a possible spurious regression led to the estimation of an error correction mechanism which, in the final form, confirmed the results of the partial adjustment model.

More specifically, the results emphasise the *long run* relationship between the cost of funds and the allocation of R&D resources. This has implications for a range of policies to promote industrial research and development. Any such measures designed to lower the cost of funds seem likely to yield the desired response in private R&D spending. Such support often comes in the form of R&D tax credits which increases the firm's cash flow and hence lowers the cost of finance. The above investigation suggests that such measures can be effective.

In the absence of government help, a capital market which is geared towards providing risk capital to innovators seems more likely to stimulate private R&D spending than a capital market which is risk-averse, and as a result makes the financing of 'risky' R&D activity prohibitively expensive. The extent to which the US venture capital market has contributed to the success of the national biotechnology industry is, of course, well documented.

The literature suggests that firms will also increase R&D spending as a response to an increase in expected returns to R&D. This cannot be ruled

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[13] See table 6.2 for a description of dummy variables PREG and PROP

out, since the variable used here as a proxy for the relative costs of funds[14] will not allow the researcher to distinguish fully between cost of funds and expected-return effects.

Further to that, the significant error-correction term indicates that firms will adjust to disequilibria in the long run relationship between the cost of funds and R&D intensity. The error-correction specification of the model has also revealed two factors influencing short term variations in R&D spending. Changes in R&D spending in the previous period is a good indicator of changes in current R&D spending. This pattern is expected since most R&D projects are longer term and require the firm to devote a continuous stream of resources over a longer time period.

The model also suggests a positive short run influence of year-on-year changes in public sector research effort on changes in the firm's R&D intensity. It is difficult to envisage the short term dynamics of this relationship given the rather crude nature of the variable used as a proxy for public R&D effort. What can be stated from this investigation, however, is that public sector research effort does not appear to 'crowd out' or replace private sector R&D spending in the short term.

The above investigation has obvious limitations. For example, the small number of observations has made it difficult to obtain significant coefficients. This is perhaps less of a problem since the researcher is less likely to commit a type one error, i.e. believe in the significance of a variable when in reality the influence is zero. On the other hand the influence of other variables may be neglected. What Gujarati (1995, p. 326) calls problems with 'micronumerosity' will also make the OLS estimators sensitive to small changes in the data. This is, potentially, the more serious problem because it

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[14] Depreciation and R&D expenditure were added to company after tax profits in an attempt to distinguish the cost of finance from the expected return to R&D effect. Expectation are more likely to be influenced by a company's pre-tax profits, a variable which was tested but showed no significant effect on R&D spending.

reduces the reliability of the estimates, and coefficients may change or become insignificant when more data become available.

There is little which can be done about the small number of observations as far as the above model is concerned, since at the time of writing all available data were included in the model and the number of relevant firms is very small. The exclusive focus on vaccine-producing manufacturers is probably justified in the context of this thesis. Given the more general relevance of the findings for science and technology policy, future research should perhaps be directed at the pharmaceutical industry as a whole.

In the remainder of the thesis the scope of the investigation will, however, be extended to include firms in the biotechnology industry, which has recently become very important for vaccine innovation. Although it is too new an industry to consider an investigation over a longer period of time, the availability of individual firm level data over a short period of time will allow the researcher to pool time series and cross-sectional data and thereby obtain a larger number of relevant observations.

Using research performance indicators of established biotechnology firms, the following section will look at another important aspect of the promotion of research and development, research co-operation and knowledge transfer between the public and private sectors.

PART TWO

RELATED ISSUES IN BIOTECHNOLOGICAL RESEARCH AND SCIENCE AND TECHNOLOGY POLICY

7 Public-private interaction and the impact on productivity of biotech research

7.1 Background

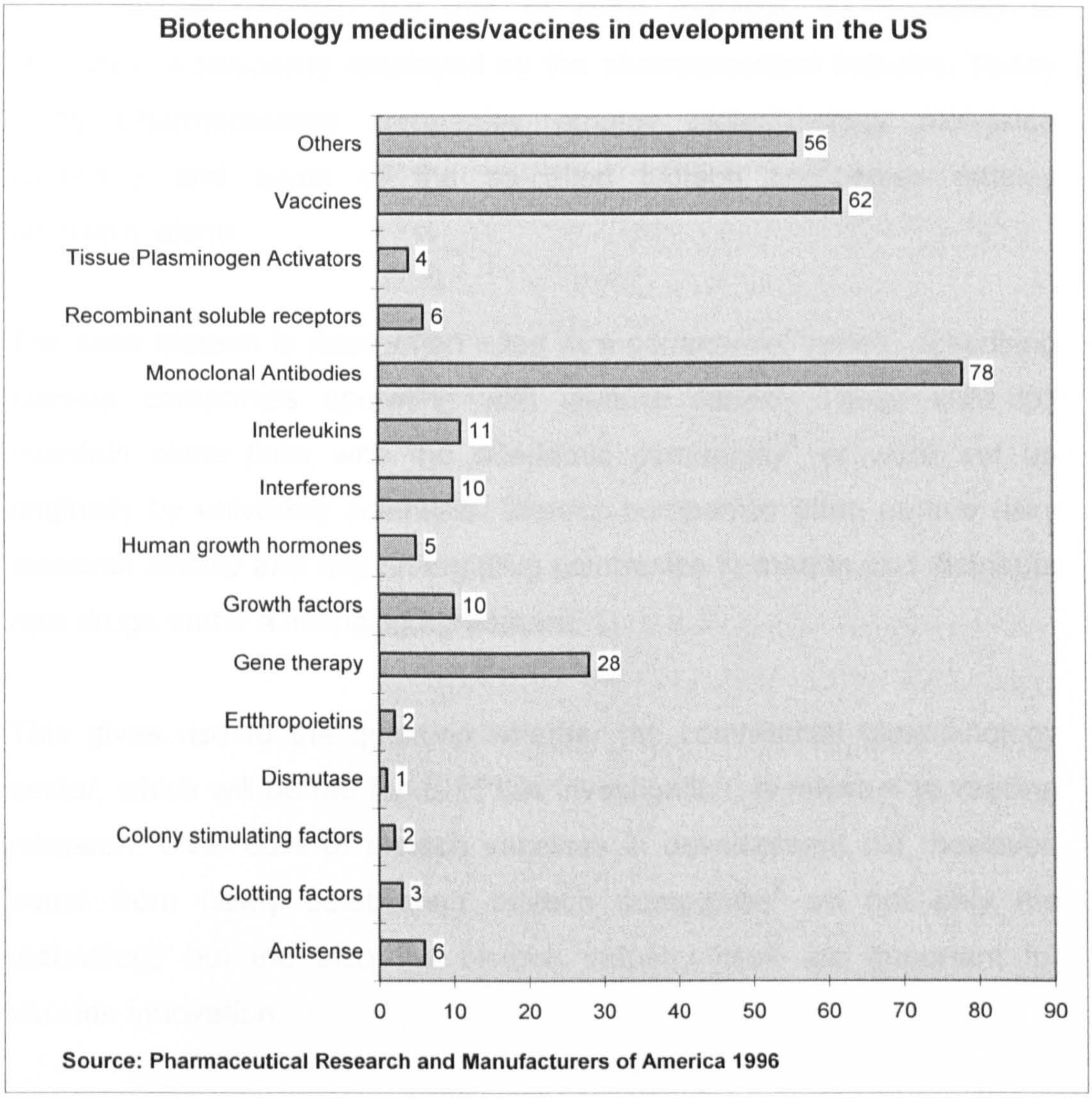
The previous Chapter sought to demonstrate that companies, when left to their own devices, respond primarily to changes in overall profit contributions when allocating funds to R&D, but there was no indication that firms responded to changes in demand ('demand pull') in the vaccine segment of the market. Neither was there any evidence that public sector research crowds out private sector R&D. On the contrary, organisations such as WHO (2000b), which are aiming to improve incentives for vaccine R&D, now take the view that joint public-private research is more likely to produce successful research than private sector research alone (the 'technology push' argument).

The Chapter will look for evidence in the literature that joint public- private research produces superior research outcomes. Chapter Eight will continue the argument, with an empirical investigation of the impact of public-private cooperation on the productivity of research in both the biotechnology and the traditional pharmaceutical industry.

7.2 The importance of biotech for vaccine innovation

The total number of biotechnology medicines in development in 1996 grew by 50% over the previous year (Pharmaceutical Research and Manufacturers of America 1996, p. 1). What makes biotechnology products so interesting in the context of this study is that vaccines are not only the second largest group of biotech products after monoclonal antibodies, vaccines also record the second fastest growth, up 44% over the previous year, after gene therapy (up 65%), but in total terms much smaller than vaccines as can be seen in figure 7-1.

Figure 7-1



The 62 vaccines in development include vaccines for cancer, AIDS, rheumatoid arthritis and multiple sclerosis. If vaccines are becoming such an important subgroup of biotechnology medicines, an understanding of biotech companies' R&D behaviour may help understand the rate of vaccine-related R&D in pharmaceutical companies.

Making a link between biotechnology employed and the biotech industry is, however, not as straightforward as it may seem (Financial Times, 26/11/96, p. 11). Pharmaceutical companies often claim that there is no biotech industry as such, because they feel they have used

biotechnology all along, while some of the so-called biotech companies do not. This is true, in a strictly technological sense of the terms involved. Biotechnology involves the use of living material, as opposed to chemistry -traditionally employed by the pharmaceutical industry. Today many pharmaceutical companies employ biotechnology alongside chemistry and some of the so-called biotech companies employ chemistry alone.

The term biotech is more often used in a commercial sense, describing start-up companies operating with venture capital. These start-ups maintain close links with the academic community[1] or were set up originally by university scientists. Biotech companies often pursue risky research activity and rely on big drug companies to market and distribute new drugs under a licensing agreement.

This gives rise to the question whether the commercial biotechnology sector, which will be the focus of this investigation, is relevant to vaccine research. Over 60% of biotech vaccines in development did, however, come from newly established biotech companies[2] so not only the technology but the also the biotech industry itself are important for vaccine innovation.

7.3 Joint research and networks of innovation

There is a large body of literature evaluating the motives for co-operation in biotech research. One area of research, mainly coming from the Strategic Management field, focuses on partnerships between large pharmaceutical companies and so-called new biotech companies.

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[1] More about the extent of these links follows in section 7.3.

[2] 44 out of 66 biotech vaccines under development are owned by firms associated with the biotechnology sector (Pharmaceutical Research and Manufacturers of America 1996).

Although not strictly related to interaction between the private and the public sector, which is the interest of this study, this body of literature has highlighted the role of networks of innovation and knowledge spillover. This is a good starting point for any further research and helps to understand part of the motivation to co-operate in the field of biotechnology.

From a theoretical perspective, collaboration in biotechnology lies between the 'extremes' of market exchange and the full vertical integration of all elements in the value chain within one company.

Exchange of knowledge, which is at the core of most, if not all collaborative relationships, does however involve transaction costs. Technical information cannot be exchanged in anonymous pure market transactions because of appropriability problems and the added need to develop complementary tacit knowledge, skills and assets (Barbanti et al. 1999).

Collaboration may also avoid the inefficiencies of complete integration, which in the context of the relatively young discipline of biotechnology means unaffordably high R&D expenditure, lack of responsiveness to rapid technical change, and a multidisciplinary character of the knowledge pool. By collaborating, firms can tap into that knowledge pool without the costs and risk of integration (ibid., p. 14).

On the downside, weak appropriability conditions make collaboration difficult and collaboration cannot be a substitute for building up strong technological capabilities in order to assess the value of information one is getting through collaboration (Arora and Gambardella 1994).

There is some empirical evidence that biotechnology firms collaborate more than other sectors of industry: Kleinknecht and Reijnen (1992) review the R&D co-operation literature using a sample of manufacturing

and service firms representative for an entire country, in this case the Netherlands. Kleinknecht and Reijnen discard the widely held belief that R&D co-operation occurs mainly in high-tech sectors and between large, oligopolistic firms which typically operate in global markets.

> "R&D collaboration appears to be a much more widespread phenomenon than is generally suggested in the literature, [...] there are only weak indications that the high costs and associated risks of new technologies are an incentive to co-operate on R&D [...], firm size has no influence on co-operation between firms, [...] and market concentration does not matter for cooperation with any type of partner." (Kleinknecht and Reijnen, 1992, p. 356).

The authors confirm, however, that biotechnology is the only sector with more-than-average R&D cooperation, while other high-tech sectors show little evidence that high-tech is conducive to R&D co-operation. The authors also seek to demonstrate that government innovation support facilities positively impact on co-operation and that the existence of a formal R&D department is conducive to co-operation with three or more partners, i.e. forming networks of innovation. This seems to suggest that formal R&D departments are more capable of exploiting external sources of knowledge.

Barbanti et al. (1999) suggest that collaborative relations could be considered a transient phenomenon, decreasing in scale and scope as the technology matures and the industry moves to higher degrees of vertical integration. On the other hand collaboration could also be seen as a new form of organisation of innovative activities reflecting the need to tap into to an increasingly complex knowledge base.

Evidence for either of these scenarios is inconclusive: Haagedorn (1990) researches the fact that R&D co-operation is becoming increasingly important in the biotech sector. The total number of biotechnology co-

operation agreements between firms has been increasing steadily from the early 1970s, when biotech was still in a state of 'infancy', until 1987 after which the rapid growth has slightly declined.

The most recent available figures (Mytelka 1999) show that prior to 1979 worldwide only 62 technological co-operation agreements were signed. In the period 1980-84 this figure rose to 222 agreements and between 1985-89 to 398. Towards the first years of the 1990s there was a steep drop in the numbers of agreements signed, falling to just 50 agreements in 1991. This decline seems only temporary and coincides with the economic downturn of the early 1990s, rather than reflecting a trend towards vertical integration. The number of new collaboration agreements picked up again in 1993, exceeding the 1989 figure by 34% but not quite reaching the 1985 figure of around 160 agreements.

Barley et al. (1992) investigate the structure of biotechnology co-operations in greater detail and find that the majority of organisations that form alliances with biotech companies are large diversified organisations such as drug companies. Geographically speaking, there is a tendency for European and Japanese corporations to become very heavily involved with US biotech companies, allowing them more autonomy than US corporations, while at the same time securing the funding of long-term research.

Haagedorn (1990) also investigates types of co-operation agreements in biotechnology. Among the modes of co-operation, joint R&D agreements represent the most important group with nearly 30% of all co-operative agreements followed by direct investment (19%), customer-supplier relations (15.3%), one-directional technology flows[3] (15.1%), joint ventures (13.5%) and technology exchange agreements (6.9%).

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[3] An example of one-directional technological flows would be licensing agreements.

This distribution is different from the Information technology sector where technology exchange (12.1%), joint ventures (16.9%) and one-directional technology flows (21.4%) are more important, whilst direct investment (13.1%) and customer supplier relations (9%) are markedly less so (Haagedorn 1990, p. 7). These differences confirm the special nature of biotech co-operations which are often between small biotech and large multinational companies, while the type of co-operations in the IT sector indicate partners of similar size and commercial strength. The more mature IT industry predictably shows a higher incidence of licensing agreements (which is here classified as one-directional technology flows).

Haagedorn (1990, p. 11) also investigates motives for undertaking the most important form of co-operation, joint research. Two motives clearly stand out: In the biotechnology sector, technological complementarity (38.1%) and the reduction of innovation time span (31%) are the two most significant reasons to undertake joint R&D, with the lack of financial resources coming a distant third (12.1%). As a motive for direct investment in biotech, technological competence of the partner comes top (36.7%).

Haagedorn's study is revealing, in that it shows the importance of technology transfer in joint research as a form and motive of co-operative research in the biotechnology industry. The study is however limited in its focus on inter-firm co-operation which at least in the case of biotech is just one form of co-operation besides co-operation with universities and other research institutions. Also, the motives are too broadly defined; technological complementarity seems more like a prerequisite for co-operation than an actual reason. Firms with complementary technology really are competitors in the first place; what makes firms in technologically-related fields co-operate rather than compete is the more interesting question to investigate.

A more detailed classification of possible forms of alliances is proposed by Forrest and Martin (1992) and presented here in table 7-1.

Table 7-1

Forms of alliances in the biotech industry

Operating joint venture	Independent third enterprise. Assets are contributed by both parties, who also share the risk
Equity investment	Investment by large established company in firm
Client sponsored research contract	Small company is paid to conduct research on particular products or processes
Marketing/ distribution agreement	Another company will market and distribute firm's product
Manufacturing agreement	Another company agrees to manufacture product
University agreement	Firm pays university to conduct research on its behalf
Research institute agreement	Firm pays institute to conduct research
Collaborative R&D	Agreement with another company to collaborate on development of specific product or process
Research and development limited partnership (RDLP)	Tax advantaged investment vehicle which provides funding for new product R&D at no cost to company
Technology licensing (inward)	Firm is granted access another company's patents or technology for a fee
Technology licensing (outward)	Reverse from above, firm receives fee

Source: Forrest and Martin (1992, p. 42)

The authors also show the incidence of alliances in this sector reported to them in a questionnaire survey, as shown here in Table 7.2.:

Table 7-2

Incidence of alliances reported by DBCs (Dedicated Biotech Companies)

	Rank	Number	Average number of alliances /firm
University agreement	1	219	5.21
Client sponsored R&D	2	179	4.26
Marketing/distribution	3	168	4
Technology licensing (inward)	4	133	3.17
Collaborative R&D	5	116	2.76
Technology licensing (outward)	6	86	2.05
Manufacturing	7	73	1.86
Equity investment	8	73	1.74
Joint ventures	9	50	1.19
Research institute	10=	22	0.52
RDLP	10=	22	0.52
Total (all types)		1146	

Source: Forrest and Martin (1992, p.44)

University agreements clearly come out top followed by client-sponsored R&D, Marketing/distribution and licensing agreements. This confirms the proximity to science of Biotech companies[4] and the nature of the relationship with large pharmaceutical companies which is characterised by either contractual R&D, licensing agreements or outsourcing of marketing and distribution functions, i.e., activities where the two partners complement each other rather than share the same expertise.

This complementary nature of the relationship then helps firms to realise their principal aims of forming alliances which Forrest and Martin (1992, p. 45) list as 'facilitating rapid exploitation of new technology', 'generating short term revenues', 'sharing the risk of new product development',

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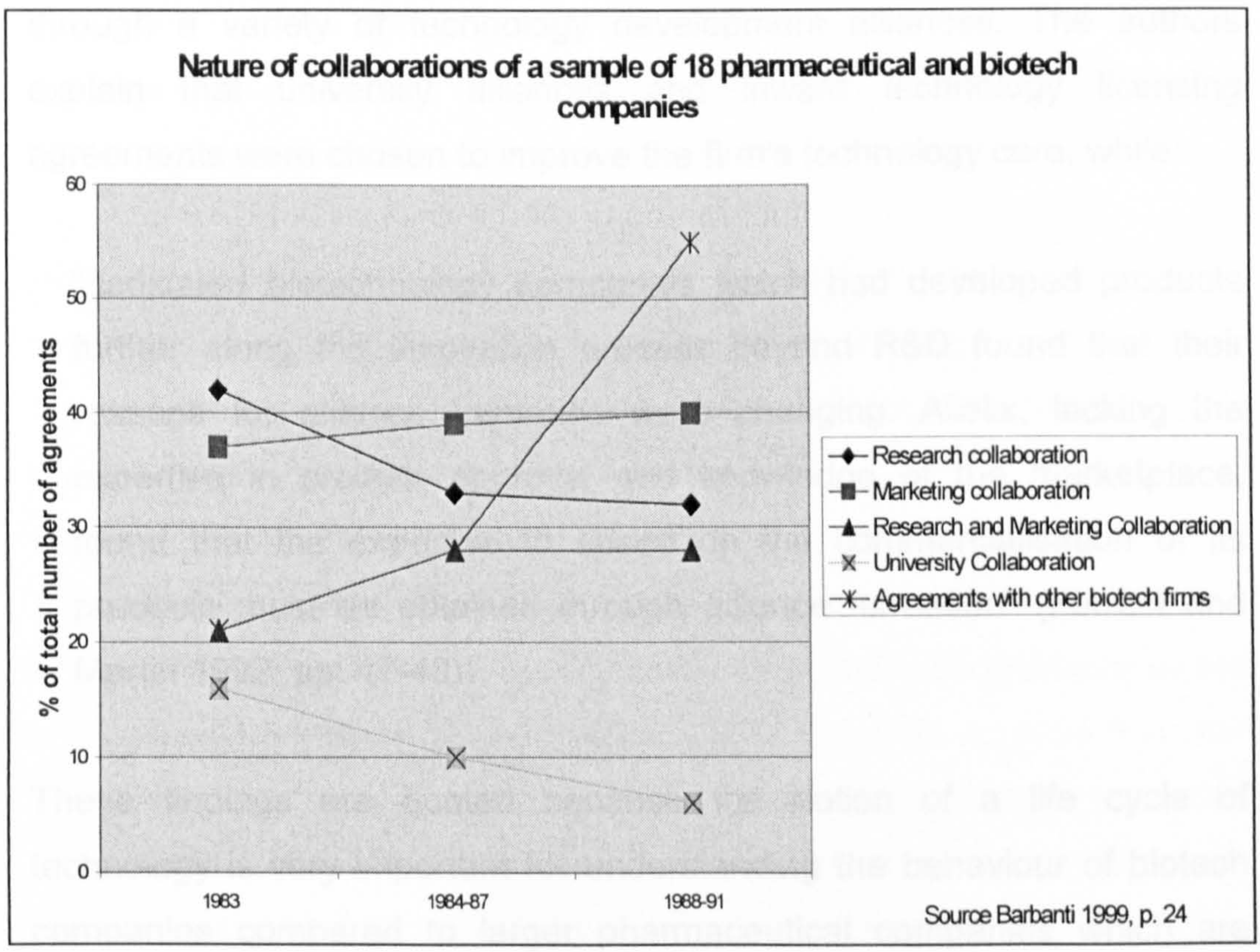
[4] Large pharmaceutical companies by comparison have so few links to the university sector that they were not reported in this survey.

'gaining access to financing', 'gaining credibility' and 'gaining access to a partner's R&D facility', listed here in order of importance.

Barbanti et al. (1999) use a mixed sample of pharmaceutical companies and biotechnology firms to investigate the structure of alliances over time. In their survey the number of agreements with universities has declined while collaborations with biotech firms have increased. These results are shown in the following figure:

Figure 7-2



The authors conclude from their findings that biotechnology is coming closer to commercialisation, which seems confirmed by the fact that research agreements have declined in importance. The sample is however heavily skewed towards the traditional pharmaceutical sector[5]

[5] Although all 20 corporations are active in biotechnology, only two firms in the sample (Genentech and Amgen) are dedicated new biotechnology firms.

and it is problematic to deduce a change in the lifecycle of the biotechnology industry from the above findings.

Forrest and Martin (1992) investigate changes in the life cycle of the biotechnology industry by analysing a number of case studies. The authors demonstrate that the reasons for alliance formation vary with the life cycle of the company. They quote the example of Applied BioTechnology, a small, young company in the R&D stage of its life cycle, which had already formed a variety of alliances at the pre-competitive stage of the process of innovation. The firm's founding scientists were the pioneers of the firm's technology and it aimed to augment this technology through a variety of technology development alliances. The authors explain that university alliances and inward technology licensing agreements were chosen to improve the firm's technology core, while:

> "dedicated biotechnology companies which had developed products further along the innovation process beyond R&D found that their reasons for alliance formation were changing. Allelix, lacking the expertise in product approval and knowledge of the marketplace, found that the expertise to speed up the commercialisation of its products must be obtained through alliance formation" (Forrest and Martin 1992, pp. 47-48).

These findings are quoted because the notion of a life cycle of technology is very important for understanding the behaviour of biotech companies compared to larger pharmaceutical companies which are arguably at a later stage of their technological development. Biotech companies are more likely to seek contacts with science, e.g. universities, in order to strengthen their technology core, than larger pharmaceutical companies which aim to exploit commercially a more established technology. More mature Biotech companies would also become increasingly concerned about second round financing and a

strategic alliance with a larger company might be formed for the purpose of bringing in much needed funds.

In a situation where a Biotech company tries simultaneously to develop a new technology from an early stage and commercially exploit another more mature technology, the company may enter a *network* of alliances, in this instance perhaps a science-oriented alliance with a university and a distribution alliance with a large drug company.

Earlier research into *network* relationships has either focused on ties between biotech firms, e.g. Powell (1996), or between pharmaceutical firms and biotech firms (Arora and Gambardella 1994). Oliver and Liebeskind (1998) have later added 'interpersonal ties' to the possible forms of network relationships.

Arora and Gambardella (1994) argue that the division of innovative labour, a necessary prerequisite to form networks of innovation, has been facilitated by the 'changing technology of technological change'. They point out that:

> "when innovations depended primarily on trial and error procedures based on physical experiments, much of the knowledge base of the firm was experience-based and tacit. The research process that was carried out based on such firm-specific knowledge produced information that was local and context dependent. Almost by definition, context-dependent information could not be used by an agent unfamiliar with the context within which the information was generated ...." (Arora and Gambardella 1994, p. 526).

As, for instance, the drug industry has been using computers to design new compounds and scientific understanding in molecular biology and the working of the human metabolism has grown:

> "concrete information comes to be related to more general classes of phenomena, it becomes less context dependent, and can be codified and in ways that are more meaningful and useful for other firms as well ... making the production process of new technologies more divisible" (Arora and Gambardella 1994, pp. 527-528).

The authors point out that although small firms were traditionally seen as more capable of innovating, largely because they could minimise problems of asymmetric information between innovators and resource allocators, they were in the past unable to delegate part of the innovation process to other entities for the reasons discussed above. With the division of innovative labour facilitated, the rate of innovation in small firms and networking activities between small and large firms can be expected to increase.

Whether networking has indeed generally paid off for Biotech companies has been investigated by Powell (1996). Powell argues that collaboration is connected to the growth of a biotech company. In his view networks of collaboration provide "entry into a field in which the relevant knowledge is widely distributed and not easily produced inside the boundaries of a firm or obtained through market transactions. We argue that biotech firms grow by being connected to benefit rich networks" (Powell 1996, p. 139).

Powell provides some empirical evidence for this view using a panel regression model on a sample of 225 Dedicated Biotech Firms (DBFs) over a five period, from 1990-1994. The authors found that experience gained through R&D or other alliances enables firms to enter further alliances, more diverse alliances and at the same time increases the degree of centrality within an alliance. It is this centrality coupled with network experiences which is statistically connected to internal growth of the company. In other words "R&D ties and other types of collaborations are the admission ticket, while diversity, experience, and centrality are the main drivers of a dynamic system in which disparate firms join

together in efforts to keep pace in high speed learning races." (Powell 1996, p. 138).

Oliver and Liebeskind (1998) categorise three different forms and associated functions of networks for sourcing intellectual capital in the biotech industry, *intra*organisational networks that operate at the individual or interpersonal level, *inter*organisational networks that operate at the individual or interpersonal level and interorganisational networks that operate at the *organisational* level.

As established above, Biotech firms would rely on a network of alliances with partners for different stages of the lifecycle of technology. In Oliver and Liebeskind's scheme, exchanges of new scientific knowledge, i.e. the earliest stage in the exploitation of knowledge, happens primarily in interpersonal networks, either inter- or intraorganisational. Interorganisational networks that operate at the organisational level are more likely to be used for the purpose of knowledge commercialisation and commercial development, i.e. at a later stage of the technology lifecycle.

Oliver and Liebeskind also point out that it is a notable feature of biotech firms that they maintain a "large number of individual level research collaborations with scientists at universities and other research institutions" (Oliver and Liebeskind 1998, p. 83). The authors illustrate the importance of these types of networks over the biotech product lifecycle in the following diagram:

Figure 7-3

The Product Development Cycle

Discovery R&D	Development R&D	Testing and Trials	Manufacturing and Distribution
Within University: Scientist – Scientist			
Within University: Scientist-Technology Transfer			
Within New Biotech Firms (NBF): Scientist-Scientist			
Between University and NBF: Scientist-Scientist			
Between Universities Scientist-Scientist			
Between University and NBF		Between NBF and Established Firm	

Type of Network Ties:	Individual: *Intra*organisational	Individual: *Inter*oganisational	Organisational: *Inter*organisational

Source: Oliver and Liebeskind 1998, p.93

Based on interviews and related literature the authors explain that knowledge is transferred to New Biotech Firms (NBF) or created within NBFs almost exclusively through interpersonal ties, either intra- or inter organisational; the number or interorganisational ties between NBFs and universities is, however, growing. At the same time, products flow out of NBFs via established firms and on to the market mainly through interorganisational ties.

What has been established in this section is that joint R&D between universities and biotech firms is important as a free-standing collaboration but more often as part of a network of alliances. Social networks, often based on individual ties between researchers, contribute greatly to the transfer of knowledge from one sector to the other. The following section will investigate further what is understood by research

undertaken at universities as opposed to development work in the private sector, how co-operation between the two sector can be measured and to what extent co-operation between these two sectors positively impacts on research outcome.

7.4 Interaction between firms and the public sector

This section aims to distinguish between different forms of research and discuss whether the terms research, development, science and technology are still accurate depictions of the work undertaken at universities, research institutions and the private sector.

'Basic research' or 'research' is seen as an attempt to advance the frontiers of human knowledge and it is not primarily directed towards any specific practical aim or application. It is carried out by universities, institutes, government establishments and sometimes the industry.

'Applied research' according to an OECD definition (OECD 1970) is "also an original investigation in order to gain new scientific or technical knowledge, it is however directed towards a specific practical aim or objective." In industry, this implies commercial objectives with respect to products or processes.

'Development' or 'experimental development' is the use of knowledge gained through research directed towards the production of materials and devices. Although it is primarily applied research and development which is carried out in a firm's R&D department, industry does depend on basic research with many of today's products derived from the ingenuity of individual researchers.

Since traditionally public sector research is concerned with the generation of fundamental knowledge which has no immediate commercial applicability, private sector funds are less likely to be invested in this

area. This may also help to explain why in the past pharmaceutical firms have undertaken little basic research. As outlined above the biotech sector seems to have changed this paradigm. Biotech firms are said to maintain closer links to the academic community and they are believed to rely to a greater extent on public-private interaction than traditional drug companies. Should intensive public-private interaction result in greater research productivity in the biotech sector then this has important implications on how to stimulate R&D and bring new products to the market.

Science policy has for many years tried to stimulate science in general and knowledge transfer from science to technology in particular, often justified on the grounds of the strategic importance and competitiveness of an industry such as Biotech. Surprisingly there is consensus across the political spectrum that central government's discretion is desirable when it comes to the allocation of funds for the advance of science. As Dasgupta notes (1994, p. 488):

"Perhaps because demands for closer management control over government funded science and engineering research to improve its social payoff do seem discordant when emanating from circles that, in other contexts, are instinctively doubtful of the public sector's capability to allocate scarce resources efficiently, the idea of bringing the work of academic researchers into closer connection with market-oriented industrial R&D projects has lately been gaining a remarkable degree of support."

Less consensus can be found over the question of how exactly this should be done. Should any nation choose to advance its own research into, for example, the human genome project or wait until the most advanced nation disseminates the results through the international scientific community? Does it make sense for a nation to catch up in biotechnology with the Americans or is a nation's competitiveness better

served if an alternative technology with a smaller knowledge gap is pursued[6]? And, of particular relevance for this study, what is to be gained from closer co-operation between science and technology and how do we measure or even define these gains?

The notion that something needs to be done to help science goes back to Arrow's (1962) idea of market failure in basic science and a systematic underinvestment in science[7]. Arrow was the first to make the important distinction between the production and the transmission of information, the latter being easier, less costly and less risky than the former. This gave information the character of a public good. Arrow also pointed out that purchasers of information could not assess its value prior to purchase without the information being revealed which no seller in his right mind would do. Any market trading commodities with the properties of information would be liable to breakdown because the benefits for the user cannot be appropriated by the producer of information. Arrow (1962, p. 623) follows that "for optimal allocation to invention it would be necessary for the government or some other agency not governed by profit or loss criteria to finance research and invention" and hence that the market would systematically underinvest into basic research.

Arrow's observations do not concern all types of R&D activity to the same degree. Dasgupta and David (1987 and 1994) argue that R&D activity differs in three aspects: First, the degree of uncertainty of research. The more applied the focus of research the greater the probability that some marketable product comes out at the end. Second, the difficulty of establishing property rights will determine the appropriability. The first and the second aspect will usually go hand in hand; the more applied the research the easier it is to gain property rights. Third, the attitude towards

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[6] The issue of how to identify the competitive advantage of nations in certain technological key areas will be addressed in more detail in chapter 9.

[7] Arrow's work and Demsetz's critique has been discussed in greater detail in chapter three

communicating the results of research: the more inclined researchers are to communicate their results, the less likely it is that returns on that research can be appropriated. All three aspects manifest the distinction between science and technology. While science is more likely to be subject to market failure, technology can be organised within the market framework because it is product-oriented hence patentable and often undertaken in the secrecy of corporate laboratories. For many years science policy was generally pursued on the premise that science needed state support and technology could well look after itself. Considerable attention was devoted to knowledge transfer to make sure that government-sponsored basic research findings would eventually inspire industry and hence growth.

Dasgupta and David (1987, p. 524), however, point out that:

> "an outside observer would be hard pressed to decide whether a research worker was a scientist or a technologist, merely by categorising the sequence of activities in which he or she was engaged, or examining the results obtained at any given point in the research programme."

Earlier Salomon (1973) had observed that modern scientific research can be treated as one continuous process which abolishes the gap between generalisation stages and application stages. Dasgupta and David (1994, p. 495) clarify that

> "what matters is the socio-economic rule structures under which the research takes place, and, most importantly, what the researchers do with their findings: research undertaken with the intention of selling the fruits into secrecy belongs unambiguously to the realm of technology."

Dasgupta (ibid.) also believes that researchers in the realm of science aim for priority, to be the first to have published a particular discovery,

while technologists reap the benefits of their effort in the form of financial rewards through increases in pay, share options, bonuses or rapid promotion.

This motivational divide is, however, not rigid. Many scientists see an initial employment in science and prolific publishing activity as signalling their qualifications to the potentially more rewarding technology sector of the economy. Dasgupta and David (1994, p. 514) believe that scientists could view their employment in academia as a preliminary step to a more rewarding employment in technology. Any change in the reward structure in favour of technology would explain scientists more actively seeking collaboration with, if not employment in, the technology sector[8]. This explains public private interaction in research as a scientist-driven phenomenon. There is however ample evidence that the technology sector is pushing into science as well.

Hicks (1995) analysed firms' motivation to publish across industry. She finds (p. 403) that in the US in 1991 companies produced 9% of science and engineering publications overall. In the biological sciences nine corporations had an average number of citations per paper that rank them among the top 25 US universities. Two companies -Cetus and Genentech- had average citations per paper that exceeded that of the top 25 universities. In other words some biotech companies' scientific publications are numerous and of a high quality.

Despite the importance of knowledge transfer, firms' propensity to publish stands in an apparent conflict with the need to appropriate information rather than share it with potential imitators. However, firms manage the public/private distinction very carefully. Hicks (ibid., p. 408) explains, "although patents appropriate knowledge, they also make it thoroughly public. Secrecy also appropriates but it is alternative to rather than

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[8] Chapter Nine will provide some statistics on the movements of scientific labour between sectors of the economy.

compatible with patenting. In choosing between secrecy and patenting, companies manage the release of their knowledge." Publication therefore depends on whether patenting is available; if information can be patented it can be published.

Rosenberg (1990, pp. 170-171) provides the most comprehensive list of reasons why firms would undertake long term research as opposed to short term applied research, and is quoted in full in table 7-3:

Table 7-3

<u>To produce research results:</u>

1. basic research results are often produced unintentionally.
2. In order to understand better how and where to conduct research of a more applied nature.
3. essential for evaluating the outcome of much applied research and for perceiving its possible implications.

Other reasons:

4. as a ticket to an information network.
5. to monitor and evaluate research being conducted elsewhere.

<u>Managers' reasons for performing basic research could be:</u>

1. because, who knows, we might come up with a fundamental breakthrough of proprietary value.
2. because it is not too expensive on a modest scale and the efforts of one or a few scientists can provide a big pay-off in terms of entry into new fields or even possibly a new product.
3. to improve basic understanding of the materials, processes, and phenomena with which we deal.

Other reasons:

4. to improve our image in the academic and scientific community.
5. to give us a window into new areas of technology before they become widely disseminated.
6. to help in recruiting high-grade technical people. Having some opportunity for doing 'their own work' helps to keep basic research-oriented scientists happy; it is a fringe benefit.

Source: Rosenberg (1990, pp. 170-171)

Maxwell and Eckhardt (1990) confirm some of the above for pharmaceutical firms. They could show that science made a significant contribution to bringing products to the market. In a historic review of 32 innovative drugs they conclude (1990, p. 395-396) that, "without these diverse non-industrial contributions, approximately 60% of the drugs would not have been discovered or would have had their discoveries markedly delayed." Firms will therefore benefit from undertaking scientific research or collaborating with science by identifying useful scientific

knowledge and in the process acquiring a first mover advantage over their competitors.

7.5 Public-private interaction and the impact on innovativeness

If firms' interaction with science helps them to acquire a first mover advantage, then firms' ability to transfer knowledge from science to technology should have a measurable impact on their innovativeness. This hypothesis has initiated a number of empirical investigations. Gambardella (1991) looked at the 14 largest US-based drug firms between 1973 and 1986, trying to establish whether firms which organise their internal research along the lines of academic departments are significantly better at exploiting science than firms which do not allow their scientists to publish or pursue research projects autonomously. Using the number of US patents as a proxy for innovation and the number of scientific papers as a proxy for in-house scientific capability[9] Gambardella (1992, p. 404) was able to show, that "innovation (patents) is correlated with measures of the in-house scientific capabilities (scientific publications) even after controlling for R&D."

Further than that, Merck, arguably the most successful US pharmaceutical firm, has introduced a quasi-academic system of peer review of internal research projects. Gambardella (1992, p. 393) finds that head scientists of particular research projects had to convince scientists on competing projects that an allocation of resources in their favour is justified. Cockburn and Henderson (1997) confirm that prior to about 1980 firms viewed publication as a distraction or a luxury but as the

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[9] The author points out that looking at the *number* of scientific papers only cannot account for differences in quality of these papers. Many company publications are indeed clinical papers concerned with patients' response to medication which is applied research rather than science. However, if one considers publishing as a measure of connectedness to the scientific community the number of papers still seems a reasonable proxy.

rate of scientific advance increased in the biomedical sector more and more firms started to encourage publishing and hire leading academic researchers. Publishing was also recognised as a cost-effective means of monitoring the quality of research and as tool for screening future recruits. This wasn't always good news for research productivity as Cockburn and Henderson (1997, p. 15) point out:

> "Firms that stressed publication and leading edge science 'too much' gradually developed research groups that were much more like universities than anything else - and that shared the universities' failure to be able to produce an actual, commercial product."

The subsequent emergence of peer-dominated committees to allocate resources across projects sought to ensure that there were good papers *and* commercial drugs as a result. Interestingly Arora and Gambardella (1990) have suggested that one of the reasons for the failure of established pharmaceutical companies to enter the biotech sector was that they were lacking the necessary access to networks of scientists.

A number of papers have empirically established the importance of scientific networks for the success of firms. Zucker et al. (1994) investigate how two Californian biotech firms source their scientific knowledge. The authors are particularly interested how social networks impact on learning and flexibility in the organisations. Social networks are defined as exchanges between legally distinct entities but without using competitive pricing or legal contracting. Firms could benefit from these networks "by sourcing scientific knowledge from a wide variety of external scientists and organisations" and by doing that "an NBF (New Biotech Firm) can increase the likelihood that it will be the first to gain access to, or knowledge about, new discoveries" (Liebeskind et al., 1995, p.10).

Sourcing information through social networks often manifests itself in collaborative research, which has the advantage that knowledge is

directly integrated into the R&D project of the collaborating firm. The authors measure the extent of social networking in terms of scholarly publications on which companies' scientists were named as authors. Using two Californian biotech firms the authors recorded the number, identity, and type of institutions at which collaborating scientists worked and at the same time the number of non-collaborative publications of the two firms. As a further variable, numbers of patents obtained by the two firms were gathered. Not only did scientists at both firms publish their research, a large number of publications were joint publications with authors from other institutions (Liebeskind et al. 1995, p.18). Most of the external exchanges were undertaken with universities and other non-profit institutions and were not governed by contracts or other market mechanisms but rather by informal scientific social networks. Perhaps surprisingly, only a small number of shared patents were recorded, which means that the collaboration was largely of a basic nature with little commercial relevance. The authors remind us, however, that in the case of biotechnology basic scientific discoveries can be as valuable as products. Liebeskind et al. conclude that it is the existence of these networks which is critical for a firm's success, although they do not attempt to establish a causality between research collaboration and the number of patents.

As a next step, the influence of 'star scientists' on a number of aspects of firm's success was investigated, most notably by Zucker, Darby and Armstrong (1994), Zucker and Darby (1995a, 1995b), Zucker, Darby and Brewer (1998) and Zucker and Darby (1999).

The authors showed that proximity of star scientists would generate knowledge spill-overs into the sector of new biotechnology firms and could explain the initial location as well as subsequent performance measures such as the number of products in development, products on the market and changes in employment.

The initial hypothesis postulates that information, rather than being a nonrivalrous good, should be analysed as excludable knowledge, held by the group of discoverers of that knowledge. After the 1973 discovery of the basic technique for recombinant DNA by Stanley Cohen and Herbert Boyer, it took 10 to 15 years for this knowledge to spread sufficiently widely and to become scientifically routine. These discoverers subsequently become scientist-entrepreneurs who often remained professor at a university faculty and ran businesses on the side. If this is the case, then the existence of 'star' scientists, defined as researchers discovering more than 40 genetic sequences until the early 1990s, will have an impact on where new biotechnology enterprises are created. That is, in close proximity to university sites. Zucker, Darby and Brewer (1998) show that beside the proximity of star scientist, the number of top universities in the region, the number of faculty with federal support, the number of venture capital firms in the region, total employment and average wages all positively influence the stock of biotech using firms at the beginning of 1990 by region. As far as causation is concerned, the number of star scientists most likely impacts on the availability of federal funding, venture capital and the academic reputation of the faculty itself.

For the purpose of this study, the aspect of interaction must be explored in greater detail. The works cited above have explored proximity of science to the firm or scientific activity within a firm but not specifically interaction between firms and the scientific community, although interaction is clearly assumed to take place in all of the above approaches.

In a non-biotechnology context Cockburn and Henderson (1997) have explored the traditional pharmaceutical industry and the extent to which public-private interaction, measured as co-authorship of scientific papers, has had a positive impact on research productivity, measured as important patents per research dollar spent. Cockburn and Henderson

confirm Gambardella's (1992) findings that pharmaceutical companies publish heavily.

To compute the interaction variable, Cockburn and Henderson searched the Science Citation Index for a sample of 20 pharmaceutical companies over an eight year period. For each published paper they counted the number of addresses listed in the index. Where more than one address is listed, this is interpreted as a collaboration between institutions. Each authorship has then be classified into separate categories: No co-authorship, a co-authorship with a university, another private sector company, the National Institute of Health, other public sector institutions, not-for-profit organisations and hospitals. Counting the total number of authorships, no co-authorship (43%) was followed by university co-authorships (34%), hospital (10%), private sector (5%), not-for-profit, public sector (both 3%) and National Institute of Health co-authorships (1%).

Over time co-authoring rose sharply, with the fraction of university coauthorships rising from 24% in 1980 to 38% of the total in 1994 largely at the expense of no co-authorships which declines from 62% to 35% in the same time period. Coauthorships in other categories did not follow an apparent trend although hospital and private sector co-authorships have seen an increase, although from a small base.

These figures are quoted in detail because they lead to the core question whether an increase in co-authorships has led to an increase in research productivity. Since there are significant variations in co-authorships between the twenty firms the hypothesis can be tested whether research performance differences can be attributed to differences in firms' linkages to the scientific community. Cockburn and Henderson were using a subset of 10 firms for which data on research performance were available. Research performance is measured as patents per research dollar. The fraction of co-authorships with universities is used as a proxy

for the degree to which the firm is interacting with the scientific community. As a second explanatory variable Cockburn and Henderson use publications per research dollar as a proxy for investment into capacity to absorb basic research results.

Their OLS regression shows that the fraction of co-authorships with universities and papers per research dollar are both significant in a specification including a time trend and firm dummies.

Despite the small sample these results may be carefully interpreted as showing a positive influence of a firm's interaction with the public sector (co-authorships with universities) and proximity to science (papers per research dollar) on research productivity (patents per research dollar spent).

In other words, Cockburn and Henderson have shown that a firm benefits from undertaking joint research into science despite issues of appropriability and the public good aspect of basic research discussed above.

7.6 Concluding remarks

This chapter has investigated the extent and motives of collaborative research in the biotechnology industry, an industry instrumental to future vaccine innovation.

Collaborative research has grown in importance since the first biotechnology companies were established in the 1970s. Depending on the stage of the life cycle of the individual firm, a biotechnology company will either seek to strengthen its scientific base by collaborating with a public sector institution such as a university, or at a later stage collaborate with a larger pharmaceutical company in order to distribute or

market its products. Having products at different stages of development requires firms to enter networks of alliances.

There is evidence that firms which maintain close links with the scientific community are more successful in terms of patents obtained. Cockburn and Henderson (1997) showed in an extensive bibliometric analysis of the traditional pharmaceutical industry that those firms which publish more overall, and in collaboration with universities, are more productive researchers in terms of patents obtained per research dollar spent.

The following Chapter will expand Cockburn and Henderson's analysis to the biotechnology sector. If collaboration with science has a strong impact on the productivity of biotech research then it will have an impact on one of the most important subgroups of biotech research, vaccines.

The results of this investigation could be of interest for the biotechnology industry, with the less productive firms aiming to improve the way they spend their R&D resources.

This research also addresses issues in science and technology policy. A strong link between public-private interaction and research success could indicate that public money is typically effectively being spent on collaborative public-private projects, perhaps more so than on R&D subsidies for corporate research alone.

8 Modelling Research productivity

8.1 Background

As the previous chapter has shown, basic science is no longer the exclusive domain of public sector research institutions. Pharmaceutical and biotechnology companies undertake more and more scientific activities, which manifest themselves in the rising number of research papers published under the company's name. Private sector companies also tie themselves to the scientific community through networks of collaboration, which can take different forms depending on the stage of the life cycle the product or company is at.

Scientific activity and interaction with the university sector were shown in Cockburn and Henderson (1997) to be positively related to research success in the pharmaceutical industry. The contribution of this part of the thesis lies in investigating whether this is also the case for the biotechnology industry. This analysis will also allow comparisons between the two industries: the extent to which the two different sectors are exposed to the scientific community and whether the research productivity of the two sectors differs.

The results of this investigation may be of interest to R&D managers within a firm and could have some wider implications for Science and Technology policy. If higher research productivity turns out to be associated with closer R&D collaboration between firms and the scientific community, one could argue that closer collaboration ought to be encouraged. Proximity to science does, however, not necessarily *cause* research success. Causality could run the other way round: successful companies may hire good people, who happen to publish more than their peers and keep closer links with universities. The policy lesson is then reversed: rather than pursuing basic scientific activity, firms ought to hire

good people and 'tolerate' their publishing and collaborating with university scientists.

The issue of causality is therefore important for the understanding of research success. Hence, in the concluding part of this chapter, a Granger causality test will be performed using a data set which observes a selection of three pharmaceutical companies from the original cross-sectional data set over a longer time period.

8.2 Method

The methodology is broadly in line with Cockburn and Henderson (1997) which will also allow comparisons with their results: The Science Citation Index is searched for publications of a sample of 10 Biotech firms and 5 pharmaceutical firms over a three year period (1996-1998). Each publication is classified into SELF (no co-author), UNIVERSITY (university co-author), NIH (National Institute of Health as co-author), PUBLIC (public sector research institutions), PRIVATE (for profit organisation, mostly other pharmaceutical companies) NONPROFIT (not for profit, non government institutions, e.g. Wellcome Trust), HOSPITAL[1] and UNCLASSIFIED. It must be noted that a paper co-authored by a pharmaceutical company and two different universities would in the above scheme be recorded as two coauthorships, one with each university.

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[1] Unlike Cockburn and Henderson (1997), this Chapter categorises teaching hospitals as hospitals rather than universities. This distinction is somewhat arbitrary. For the purpose if this study, however, the type of research undertaken at any of these institutions is relevant. Teaching hospitals are more likely to publish clinical studies, while university departments are more likely to publish basic science. Since this study aims to model interaction with the science base, teaching hospitals should probably be included in the hospital rather than the university category.

In the pooled OLS estimation the dependent variable 'Research Productivity' is measured as patents granted per research dollar spent in a particular year. Predictors include the fraction of coauthorships with universities as a proxy for the degree of interaction with the public sector. The regression equation also includes the variable total papers per research dollar spent, depicting whether a firm is generally publication-friendly or not. One zero/one dummy variable distinguishes between biotechnology companies and the traditional small molecule sector. The following equation has been estimated:

Equation 8-1

$$REPRODit = \beta1 + \beta2PUBFRIENit + \beta3PUBINTERit + \beta4BIOCOMPit + ut$$

where:

REPRODit = patents per research dollar (in real terms) of firm i in year t
PUBFRIENit = papers per research dollar (in real terms)
PUBINTERit = fraction of co-authorships with universities
BIOCOMP = dummy variable, equal to 0 for a pharmaceutical company, equal to 1 for a biotech company.

8.3 The data

Data on R&D spending were taken from company reports, where available, or from the compulsory company filings with the US Security and Exchange Commission accessible on the World Wide Web. Included in the sample are ten US members of the organisation of biotechnology companies ('Bio') with an R&D expenditure in 1998 in excess of $50 million. Five of the largest US pharmaceutical companies were also included in the sample. Research expenditure has then been deflated in order to calculate REPROD and PUBFRIEN.

Individual patents granted per company can be accessed via the US Patent Office's database, searchable on the World Wide Web (http://www.uspto.gov).

Authors of scientific publications can be identified either by searching the author field of the Science Citation Index or in this case by searching the address field for the organisation a particular author is affiliated with. A typical reference would list more than one organisation in the address field. If for instance the biotech company Genentech was listed alongside the National Institute of Health, University Hospital Munich and the University of Manchester this would count as one paper and three co-authorships, one with the NIH, one with a hospital and one with a university.

8.4 The extent of interaction in the sample

Table 8.1 gives an overview of the sample and indicates the degree to which companies in the sample interact with other institutions:

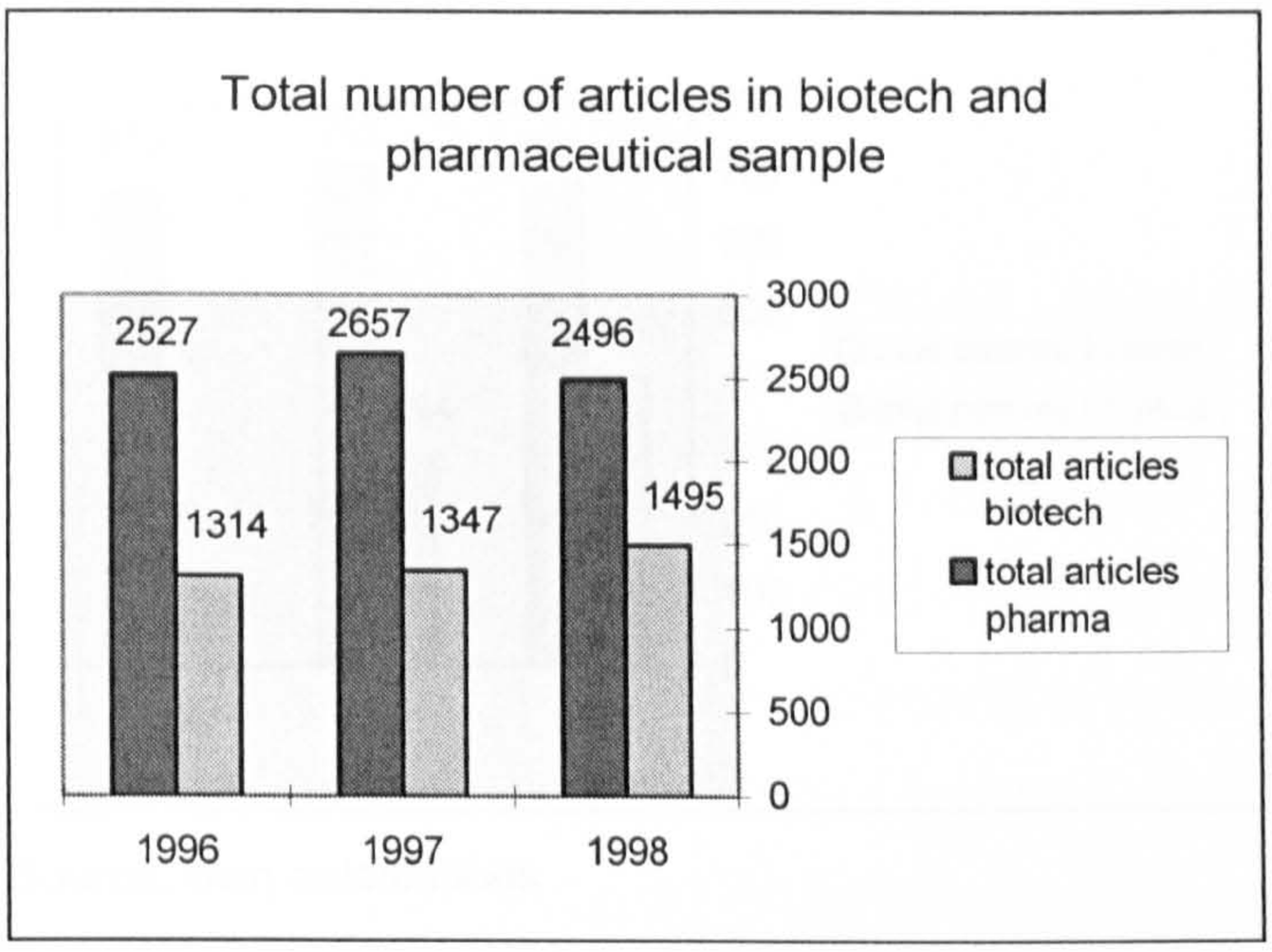
Table 8-1 – The extent of Coauthorships in the sample

Companies in the sample 1996-1998	total number of:		fraction of coauthorships with:					
Firm	**articles**	**coauthorships**	**Universities**	**Self**	**hospitals**	**private**	**public/ non-profit**	**Unclassi-fied**
Alliance Pharmaceuticals	58	89	0.51	0.36	0.04	0.07	0.01	0.01
Amgen	1211	2258	0.47	0.14	0.16	0.06	0.14	0.03
Biogen	199	372	0.51	0.12	0.13	0.05	0.19	0.00
Centocor	150	336	0.41	0.08	0.24	0.06	0.18	0.03
Chiron	761	1487	0.39	0.14	0.21	0.10	0.15	0.01
Genentech	1167	1969	0.36	0.23	0.21	0.09	0.09	0.02
Geron	71	204	0.51	0.09	0.09	0.02	0.22	0.07
Genzyme	261	474	0.35	0.18	0.25	0.12	0.05	0.02
Gilead Sciences	171	279	0.36	0.33	0.14	0.06	0.09	0.02
Millennium Pharmaceuticals	107	242	0.46	0.06	0.25	0.10	0.17	0.00
Lilly	2208	3495	0.34	0.28	0.20	0.09	0.08	0.01
Bristol Myers Squibb	1547	2748	0.35	0.22	0.23	0.09	0.10	0.01
Warner Lambert	877	1277	0.35	0.37	0.13	0.07	0.06	0.02
Pfizer	1468	2437	0.36	0.26	0.19	0.10	0.07	0.02
Abbott	1580	2571	0.30	0.30	0.23	0.07	0.08	0.02

fractions may not add up to 1 due to rounding

The total number of articles published in the two subsections of the sample is almost constant for pharmaceutical companies and slightly on the increase in the biotech subsample over the three years.

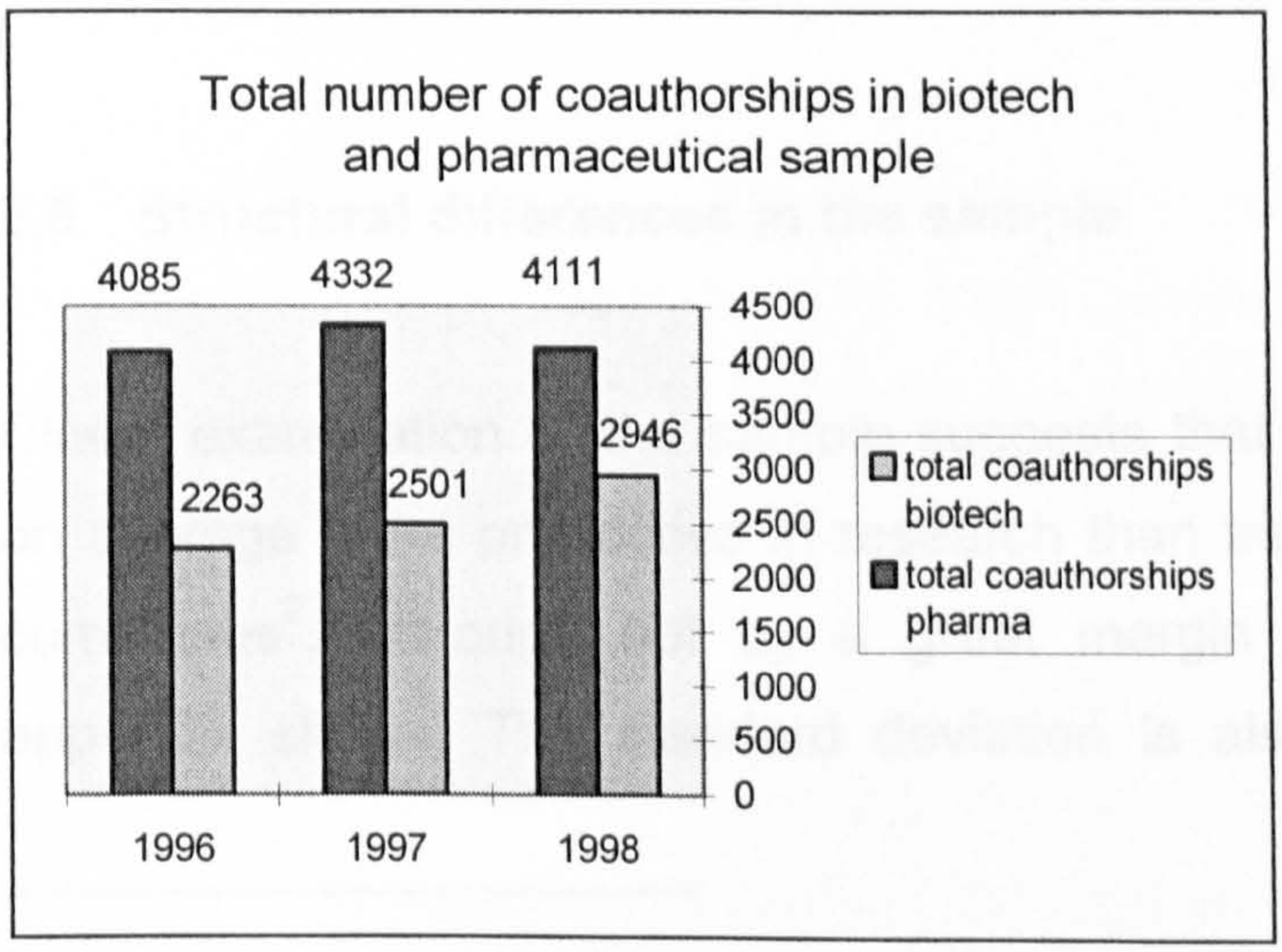
Figure 8-1



Source: own calculations

The number of coauthorships in the pharmaceutical subsample is almost constant over time while the biotech sector experiences a 30% increase in co-authorships over the three year period. This suggests that the sector intensified contacts with the science base over the period.

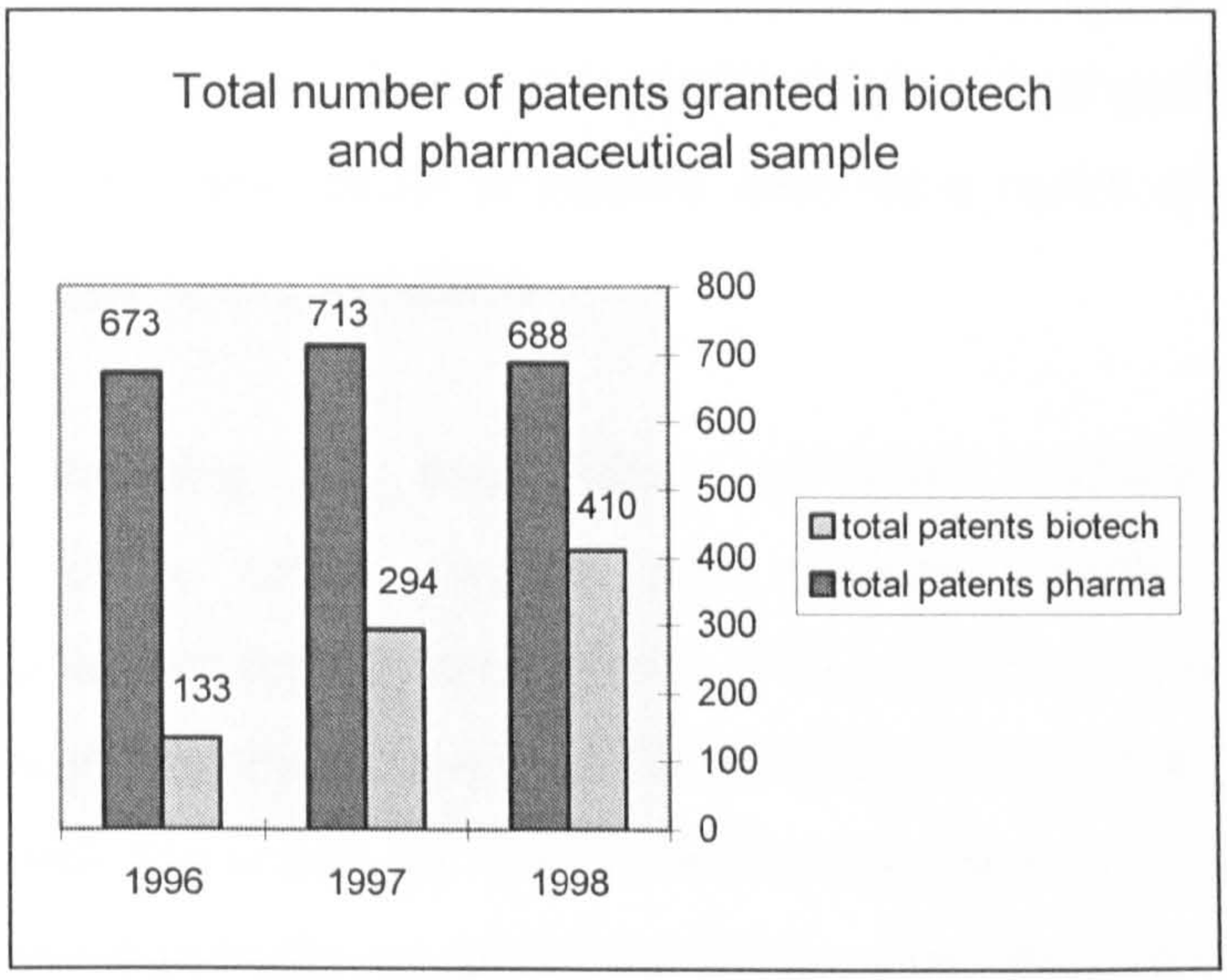
Figure 8-2



Source: own calculations

The number of patents granted to the biotech subsample shows the most dramatic increase over the three year time period.

Figure 8-3



Source: own calculations

The total number of patents granted in this sector has increased more than threefold from 1996 to 1998 underlining the biotech sector's growing importance in the race to find new cures for diseases. Given the fact that the companies in the sample are well established biotech firms this increase in patents obtained indicates that the industry has not reached the maturity of the pharmaceutical sector, where the number of new patents granted appears to stagnate.

8.5 Structural differences in the sample

Closer examination of the sample suggests that biotech companies are on average more productive in research than traditional pharmaceutical companies[2], although not by a great margin as the boxplot in the appendix shows. The standard deviation is also much greater in the

---

[2] See Appendix to this chapter for two sample, two tail t-Tests on each of the three variables by subgroups biotech and pharmaceuticals.

biotech subsample. The sample mean is however statistically significantly different. This gives rise to the question whether the greater research productivity in the biotech sector is a reflection of the life-cycle of the industry, with research productivity eventually declining to the level of the more mature pharmaceutical industry. The greater variation in research productivity could of course also be a result of greater variations in the explanatory variables.

Analysing the explanatory variables, biotech companies appear to publish more papers per research dollar spent than traditional pharmaceutical companies. The mean of the variable PUBFRIEN is significantly different (95% confidence interval) in the two subsamples with the mean for the biotech subsample (also shown in the box plot in the appendix as group 0) higher than the mean for the pharmaceutical sector (shown as group 1). In other words, the sample indicates that the proximity to science is greater in the biotech sector than in the traditional pharmaceutical sector.

The sample mean of PUBINTER of the biotech subsample (group 0), is statistically different (at the 95% level) from the sample mean of the pharmaceutical subsample (group 1). This indicates that biotech companies in the sample have more coauthorships with universities as a percentage of total coauthorships than pharmaceutical companies.

Summarising the above findings, biotechnology companies are on average closer to science and more productive researchers than pharmaceutical companies, although the variation among biotechnology firms is much greater in terms of research performance and proximity to science.

Whether the variation in the explanatory variables is a meaningful predictor of research productivity of the individual firm will be explored in the following section.

8.6 Regression results

Results from the pooled OLS regression[3] are shown in the following table:

Table 8-2

Dependent Variable: REPROD
Method: Least Squares
Included observations: 44

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-2.29E-07	7.83E-08	-2.931477	0.0056
PUBFRIEN	0.391642	0.046143	8.487654	0.0000
PUBINTER	5.33E-07	1.96E-07	2.718628	0.0096
BIOCOMP	-1.39E-07	4.09E-08	-3.386268	0.0016

R-squared	0.668408	Mean dependent var.	1.68E-07
Adjusted R-squared	0.643538	S.D. dependent var.	1.50E-07
S.E. of regression	8.95E-08	Akaike info criterion	-29.53393
Sum squared resid	3.20E-13	Schwarz criterion	-29.37173
Log likelihood	653.7464	F-statistic	26.87671
Durbin-Watson stat	1.570264	Prob(F-statistic)	0.000000

These results indicate that both publication friendliness and interaction with the university sector are positively related to research productivity of the firms in the sample. PUBFRIEN, or publications per real research dollar spent, is significant at the 5% level. PUBINTER, the fraction of coauthorships with universities is also significant at 5%. Both variables have the expected sign. The sector dummy BIOCOMP[4], significant at the 5% level, supports the above descriptive statistics: biotech firms publish and interact more with universities and achieve on average a higher

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[3] Note that one outlier has been removed, reducing the total number of observations from 45 down to 44. The company in question has in the year concerned produced an implausible number of patents when compared to the previous and following year and the rest of the firms of comparable size.

[4] BIOCOMP is an intercept dummy variable. In a separate specification two multiplicative dummies for PUBRIEN and PUBINTER were introduced, which take the value of the respective variables for all biotechnology companies. These did, however, prove insignificant.

research productivity. The above estimation has a reasonably high r^2, a highly significant F statistic and seems robust overall[5]. There is no evidence of multicollinearity due to a negligible correlation between the two explanatory variables[6].

8.7 Preliminary conclusions and policy implications

From the above the following conclusions can be drawn: Biotech companies undertake more scientific activities and interact more closely with science than traditional pharmaceutical companies. While showing a greater variance, the average research productivity of the biotech companies in the sample is also greater than that of the traditional pharmaceutical industry.

Within each of the two sectors, companies which undertake more science or co-operate more closely with universities than their competitors are more likely to show a higher level of research productivity. This indicates, that Cockburn and Henderson's (1997) findings for the pharmaceutical industry also hold in the biotechnology industry .

What is however not clear from the above specification of the model is whether greater proximity to science does indeed *cause* greater research productivity. It may well be that, as is often suggested, the proximity of star scientists *causes* the firm to churn out more patents which would be in line with Zucker et al's (1999) point of view.

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[5] The following statistical tests have been performed: White heteroscedasticity test, Serial correlation LM test, and Ramsey's reset test for specification error, all of which were satisfactory. The Jarque Bera normality test suggests normally distributed residuals.

[6] The correlation coefficient of PUBINTER and PUBFRIEN is 0.05

On the other hand, a successful firm may attract star scientists, who happen to publish a lot. Registering a patent will then allow the firm to publish results, otherwise the publication would give away the findings.

Publication will also alert other firms to the patent and could act as a deterrent to undertake research in a similar area, although this may also invite other firms to invent around the patent.

Hence, good scientists could follow research success rather than cause it. The implications for science policy and research strategy at the firm level would be somewhat different, since publications in this scenario turn out to be a necessary evil rather than a warrant for research success. Therefore, the issue of causality requires a closer investigation. This will be subject of the following section.

8.8 Do biotech firms learn from universities or is it the other way round?

Most of the literature reviewed in Chapter Seven argues the case of a knowledge spillover in order to explain differences in firm's research performance. Zucker et al. (1999) for example claim that proximity of star scientists or top university departments causes a spillover of knowledge into the biotech sector which as a result becomes better at researching new products. This view seems entirely plausible particularly for the early founding years of the biotechnology industry when many companies were effectively spun off successful university departments.

It is, however, not clear whether this causality still holds. One could argue that the wealth of talent is now located in the biotech sector and that the more productive of these companies also attract the more gifted scientists from the university sector. This would be more in line with Dasgupta's (1994) and Rosenberg's (1990) view. Once talented scientists are being attracted to join the most reputable companies they

will push for publications which in turn shows up as proximity to science. In this interpretation it is the already productive biotech sector which causes interaction with the scientific community rather than the other way round. These days universities may well learn from biotech firms. Once the possibility of this reverse causality is taken into consideration the implications for science policy and research strategy do become more ambiguous. Should interaction with the scientific community be actively encouraged or is this interaction a necessary price successful firms have to pay if they want to get good scientists?

8.9 Testing for causality

This section will address this causality issue with a relatively simple test of causality, the Granger test[7]. Thomas (1997, p. 461) defines Granger causality as follows: "X is said to be a Granger cause of Y if present Y can be predicted with greater accuracy by using past values of X rather than not using such past values, all other information being identical."

More precisely, the Granger approach first investigates how much of the current Y can be explained by past values of Y and then examines whether adding lagged values of X offers a better explanation. Lagging explanatory variables by three years, the equation estimated would take the following general form:

Equation 8-2

$$Yt = \alpha_0 + \alpha_1 y_{t-1} + \alpha_2 y_{t-2} + \alpha_3 y_{t-3} + \beta_1 X_{t-1} + \beta_2 X_{t-2} + \beta_3 X_{t-3} + \varepsilon t$$

---

[7] See for example Gujarati (1995, p. 620) for a more detailed explanation of this technique or the help function of Econometric Views (Eviews version 3.1) for a non-technical description.

Equation 8.2. is estimated first, followed by a restricted form not including X. The null hypothesis is that $\beta_1 = \beta_2 = \beta_3 = 0$, that the lagged X does not belong into the equation. i.e. X does not 'Granger cause' Y. If the β coefficients in equation 8.2. are significantly different from zero then X does Granger cause Y. To test this hypothesis the F-test is used calculated from the residual sums of squares obtained from the two equations.

Strictly speaking, Granger causality is not based on an acceptable definition of cause and effect (Judge et al 1985, p. 667), and "does not imply that Y is the effect or the result of X. Granger causality measures precedence and information content but does not by itself indicate causality in the more common use of the term" (Econometric Views, Version 3.1). Should Granger causality occur, i.e. the equation contains more information after the inclusion of a lagged regressor, changes in X effectively precede changes in Y so the likelihood of having found a meaningless correlation are somewhat reduced.

Equation 8.2. uses a three-period lag, although a longer lag might have been used -depending on the assumption about the longest time over which one variable could reasonably predict the other. This is, of course, a problematic decision since the lag length can influence the outcome of the test or, as Gujarati (1995, p. 622) puts it, "the direction of causality may depend critically on the number of lagged terms included".

Econometric Views (Version 3.1) suggests that more rather than fewer lags should be used since the theory is based on the relevance of all past information. Practically the number of lags will also depend on the number of observations, variables and resulting degrees of freedom.

8.10 Is there causality between research productivity and proximity to science?

In the analysis above, the variable publication friendliness proved to be significantly related to research success and the question was raised whether proximity to science causes research success or whether successful firms attract successful scientists and later tolerate their propensity to publish.

The Granger test could offer some insight into which of the two variables precedes or (Granger) 'causes' the other. No matter which way the causality runs, the relationship between patents and publications is likely to be lagged by a number of years. Critical data are available on a yearly base and for the time period between 1976 and 1999 which does not allow for much experimentation with the length of lags. Hence, three different time lags, three, four and five years, will be chosen here.

Since there is theoretical underpinning for causality running from publication friendliness to research success and vice versa, two equations will be estimated for each of the three different lag specifications. These two equations will then be estimated for three different pharmaceutical companies which were also part of the original sample, over the period 1976-1999[8], first in a reduced form and then including REPROD and PUBFRIEN respectively. Starting with the following two equations the length of the lags will be increased to four and five years respectively.

---

[8] Because the Granger causality test requires time series data, the number of periods had to be in increased significantly compared to the previous sample

Equation 8-3

$$REPROD_{it} = \sum_{i=1}^{3} \alpha_i PUBFRIEN_{t-i} + \sum_{j=1}^{3} \beta_j REPROD_{t-j} + \varepsilon_{1t}$$

Equation 8-4

$$PUBFRIEN = \sum_{i=1}^{3} \lambda_i PUBFRIEN_{t-i} + \sum_{j=1}^{3} \delta_j REPROD_{t-j} + \varepsilon_{2t}$$

where:

REPRODit = patents per research dollar (in real terms) of firm i in year t

PUBFRIENit = papers per research dollar (in real terms) of firm i in year t

The sample is restricted to three pharmaceutical companies (Pfizer, Warner Lambert, and Bristol Myers Squibb) since these were the only companies to release historic R&D spending figures. Biotechnology companies have not been around long enough to be included in the sample.

For the calculation of REPROD, R&D spending has been deflated by the US GDP deflator. The variable PUBFRIEN is the same as in the previous section, also based on deflated R&D figures.

The reduced form of equation 8.3. would exclude PUBFRIEN, while the reduced form of equation 8.4. excludes REPROD. Should the sets of PUBFRIEN and REPROD coefficients in 8.3. and 8.4. respectively be significant, then feedback, or bilateral causality is suggested. If the two sets of coefficients are insignificant then both variables are independent.

8.11 Granger test – empirical results

Plotting the variables (see figures A 8-5, A 8-6 and A 8-7 in the appendix to this chapter) it becomes clear that research productivity has declined across all three companies in the sample over the 24 year period from

1976 to 1999, which means that pharmaceutical companies at the end of the 1990s get fewer patents out of every research dollar spent than in the previous two decades.

The number of articles per research dollar spent has remained almost constant over the same period although there appears to be a distinctive surge in publishing activity in the first half of the 1990s followed by a decline since 1995. Two of the companies (Pfizer and Warner Lambert) reached an all time peak in publishing activity in the early to mid 1980s.

Going back to what was said previously, the declining research productivity suggests that traditional pharmaceutical companies may have reached the end of a technological paradigm and new patentable innovations are now increasingly generated in biotechnology companies.

The cyclical movements of publishing intensity may reflect the companies' desire to catch up with the new technologies, the all time high in the 1980s certainly coincides with a surge in scientific activity in biotechnology long before the first biotechnology drugs came to the market.

Two problems present themselves when trying to establish whether Granger causality runs from REPROD to PUBFRIEN or vice versa. First of all, in two out of three cases (Warner Lambert and Bristol Myers) the relationship between REPROD and PUBFRIEN breaks down in the long run and only in one of the three companies (Pfizer) the variable PUBFRIEN is significantly related to REPROD. This makes the Granger test somehow meaningless for the other two companies, since in the absence of a long run relationship between the two variables causality should not occur by definition.

The Granger causality test results are presented in table 8.3 for all three companies, for each of the three lag specifications. As outlined above,

the test works with the null hypothesis that REPROD does not Granger-cause PUBFRIEN in the first regression and that PUBFRIEN does not Granger-cause REPROD in the second regression.

Table 8-3

Pairwise Granger Causality Test **PFIZER**

Sample: 1976 1999

Lags: 3

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	21	1.72864	0.20695
PUBFRIEN does not Granger Cause REPROD		1.43678	0.27414

Lags: 4

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	20	1.60939	0.24044
PUBFRIEN does not Granger Cause REPROD		0.53015	0.71636

Lags: 5

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	19	3.44002	0.05916
PUBFRIEN does not Granger Cause REPROD		0.57330	0.72014

Table 8-4

Pairwise Granger Causality Tests **Warner Lambert**

Sample: 1976 1999

Lags: 3

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	21	1.53598	0.24897
PUBFRIEN does not Granger Cause REPROD		0.99926	0.42202

Lags: 4

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	20	1.80504	0.19815
PUBFRIEN does not Granger Cause REPROD		3.62076	0.04063

Lags: 5

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	19	1.25541	0.36823
PUBFRIEN does not Granger Cause REPROD		1.12177	0.42043

Table 8-5

Pairwise Granger Causality Tests **Bristol Myers**

Sample: 1976 1999

Lags: 3

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	21	0.33636	0.79932
PUBFRIEN does not Granger Cause REPROD		0.06111	0.97943

Lags: 4

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	20	2.30875	0.12286
PUBFRIEN does not Granger Cause REPROD		0.25651	0.89967

Lags: 5

Null Hypothesis:	Obs	F-Statistic	Probability
REPROD does not Granger Cause PUBFRIEN	19	3.16143	0.07208
PUBFRIEN does not Granger Cause REPROD		0.36400	0.85969

The results for Pfizer lead us to *reject* the null hypothesis that REPROD *does not* Granger cause PUBFRIEN, but only in the five year lag specification. This corresponds with the results for Bristol Myers Squibb in the five year lag specification but contradicts the results for Warner Lambert in the four year lag specification which would lead us to reject the null hypothesis that PUBRIEN does not Granger cause REPROD. The results for Pfizer should carry far more weight since it is this company which shows a significant long run relationship between the two variables.

Although the Granger causality test does not prove causality, these results indicate that at least in the case of Pfizer, values of REPROD have greater predictive power of PUBFRIEN than past values of the variable itself, i.e. it cannot be ruled out that companies' proximity to science is a scientist-driven phenomenon, an idea more in line with Dasgupta's (1994) and Rosenberg's (1990) view.

These authors postulate that successful scientists are attracted to successful (i.e. productive) companies and they will keep publishing to

signal their scientific excellence. This view would be at odds with Zucker's (1999) spillover theory, which postulates that the proximity to science *causes* the research success of the company.

8.12 Concluding remarks

Although evidence from the Granger causality test is quite weak, it cannot be ruled out that research productivity precedes the number of publications and the consequences of this for research strategy and science policy are quite important:

It is far from clear that proximity to science will cause superior research outcomes. There are some indications that successful companies attract scientists and generate publications almost as a by-product.

The preceding analysis suggests that companies which employ good scientists are still the more productive researchers, not necessarily because they interact with science or publish papers, but because they have good people which are also more likely to produce good medicines.

This makes the promotion of scientific talent and the movement of scientist between the public and the private sectors an important issue to investigate in particular when it comes to designing an effective national system of innovation. This is the subject of the following Chapter of this thesis.

8.13 Appendix to chapter 8

Figure A 8-1 Testing for differences in sample means

Two-Sample T-Test and Confidence Interval: reprod pharma, reprod biotech

```
Two-sample T for reprod p vs reprod b

                N      Mean        StDev       SE Mean
reprod ph       15   1.1310E-07  5.0993E-08  1.3166E-08
reprod bio      30   2.0138E-07  1.7468E-07  3.1892E-08

Difference = mu reprod p - mu reprod b
Estimate for difference:  -0.000000
95% CI for difference: (-0.000000, -0.000000)
T-Test of difference = 0 (vs not =): T-Value = -2.56  P-Value =
0.015  DF = 37
```

Two-Sample T-Test and Confidence Interval: pubfrien pharma, pubfrien biotech

```
Two-sample T for pubfrien ph vs pubfrien bio

                N      Mean        StDev       SE Mean
pubfrien ph     15   4.0900E-07  1.0914E-07  2.8179E-08
pubfrien bio    30   8.4813E-07  3.8920E-07  7.1059E-08

Difference = mu pubfrien p - mu pubfrien b
Estimate for difference:  -0.000000
95% CI for difference: (-0.000001, -0.000000)
T-Test of difference = 0 (vs not =): T-Value = -5.74  P-Value =
0.000  DF = 36
```

Two-Sample T-Test and Confidence Interval: pubinter pharma, pubinter biotech

```
Two-sample T for pubinter ph vs pubinter bio

                N      Mean      StDev    SE Mean
pubinter ph     15    0.3420    0.0351     0.0091
pubinter bio    30    0.4173    0.0853      0.016

Difference = mu pubinter ph - mu pubinter bio
Estimate for difference:  -0.0754
95% CI for difference: (-0.1118, -0.0390)
T-Test of difference = 0 (vs not =): T-Value = -4.18  P-Value =
0.000  DF = 41
```

Figure A 8-2

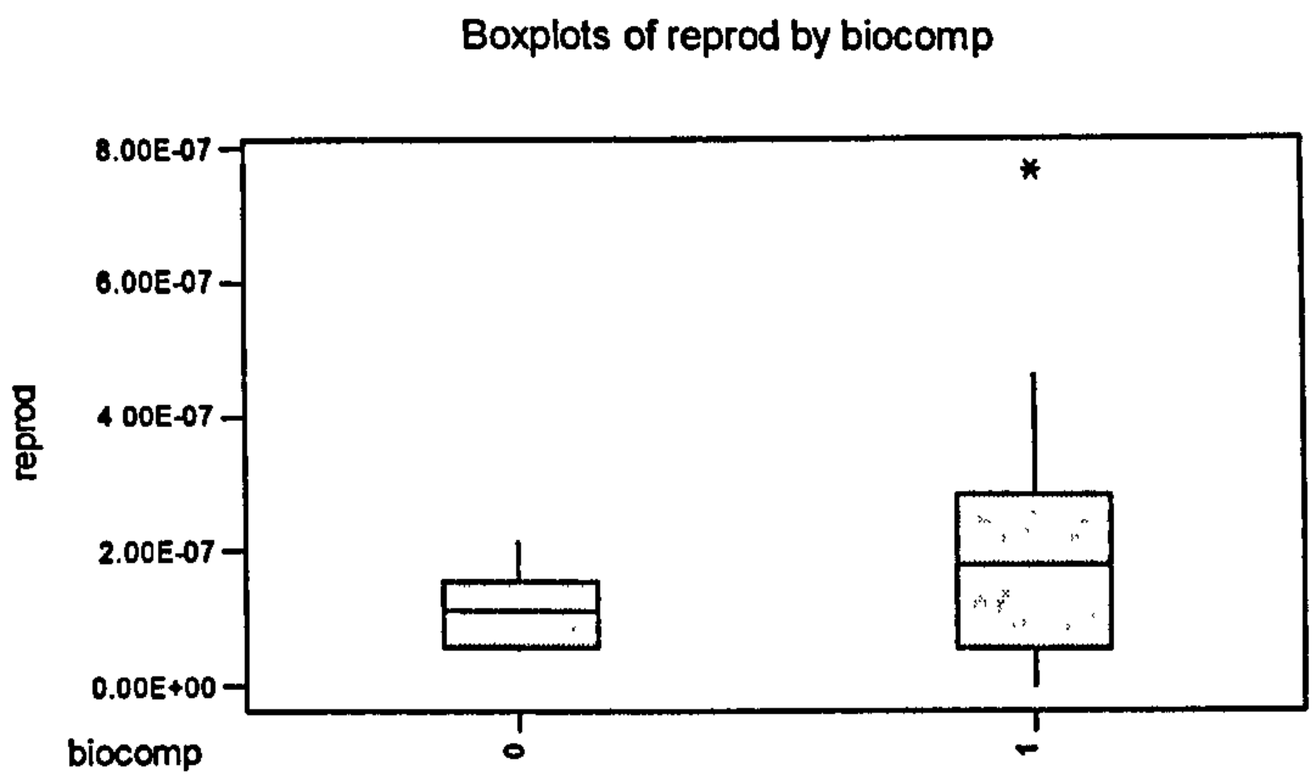


Figure A 8-3

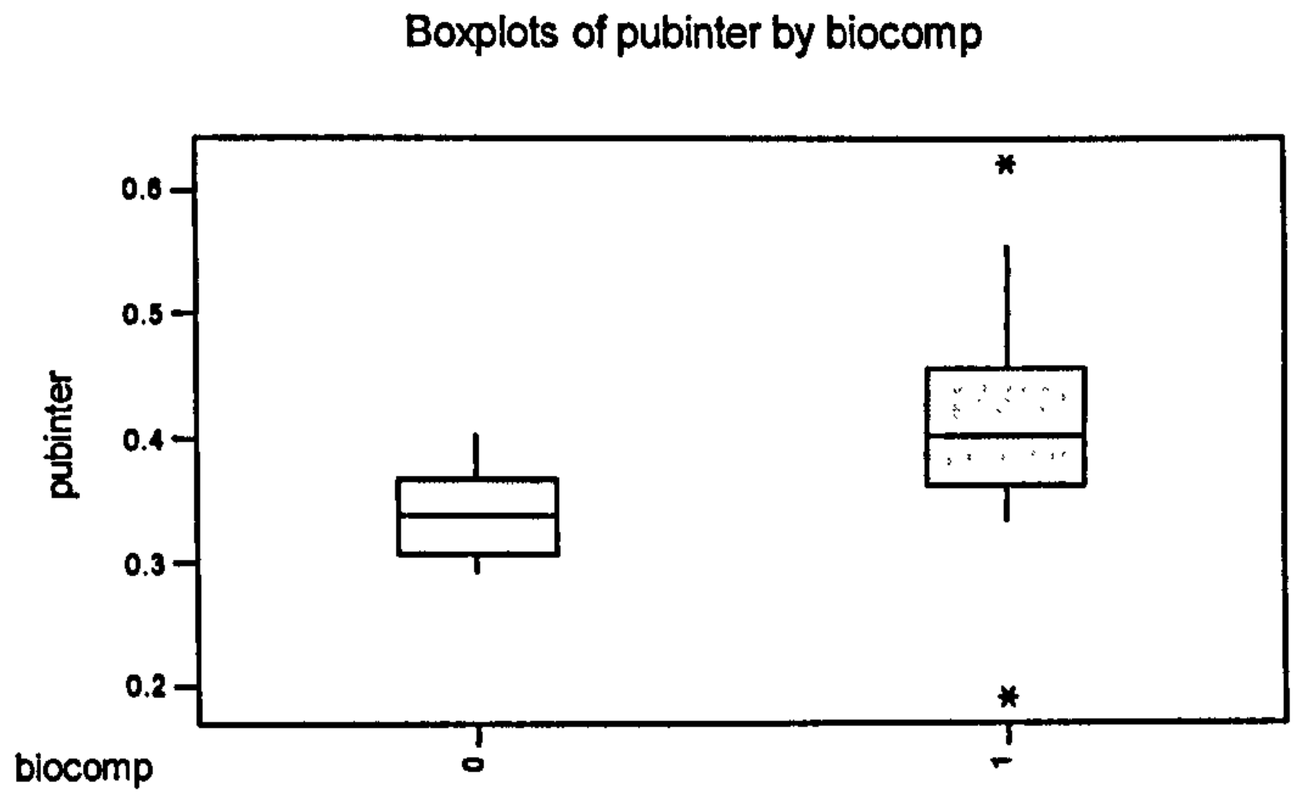


Figure A 8-4

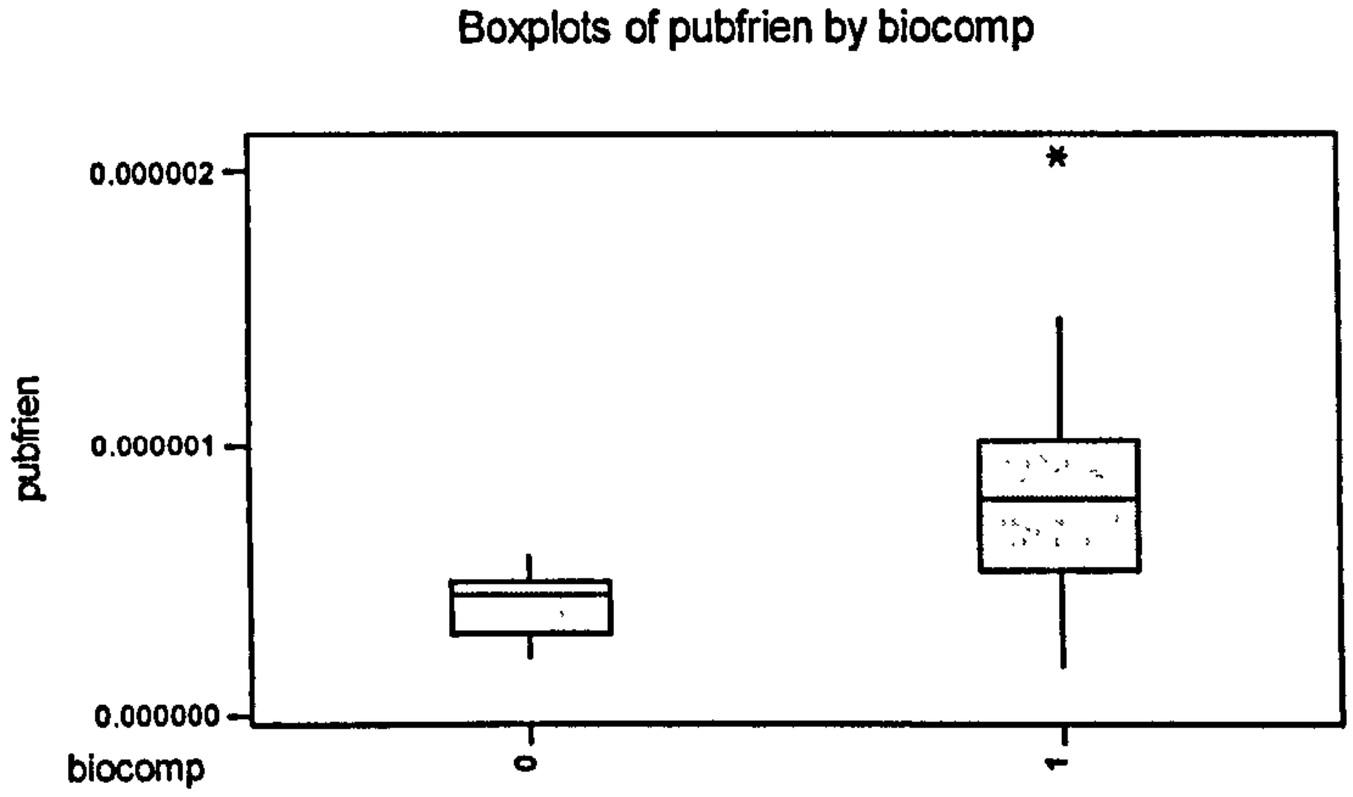
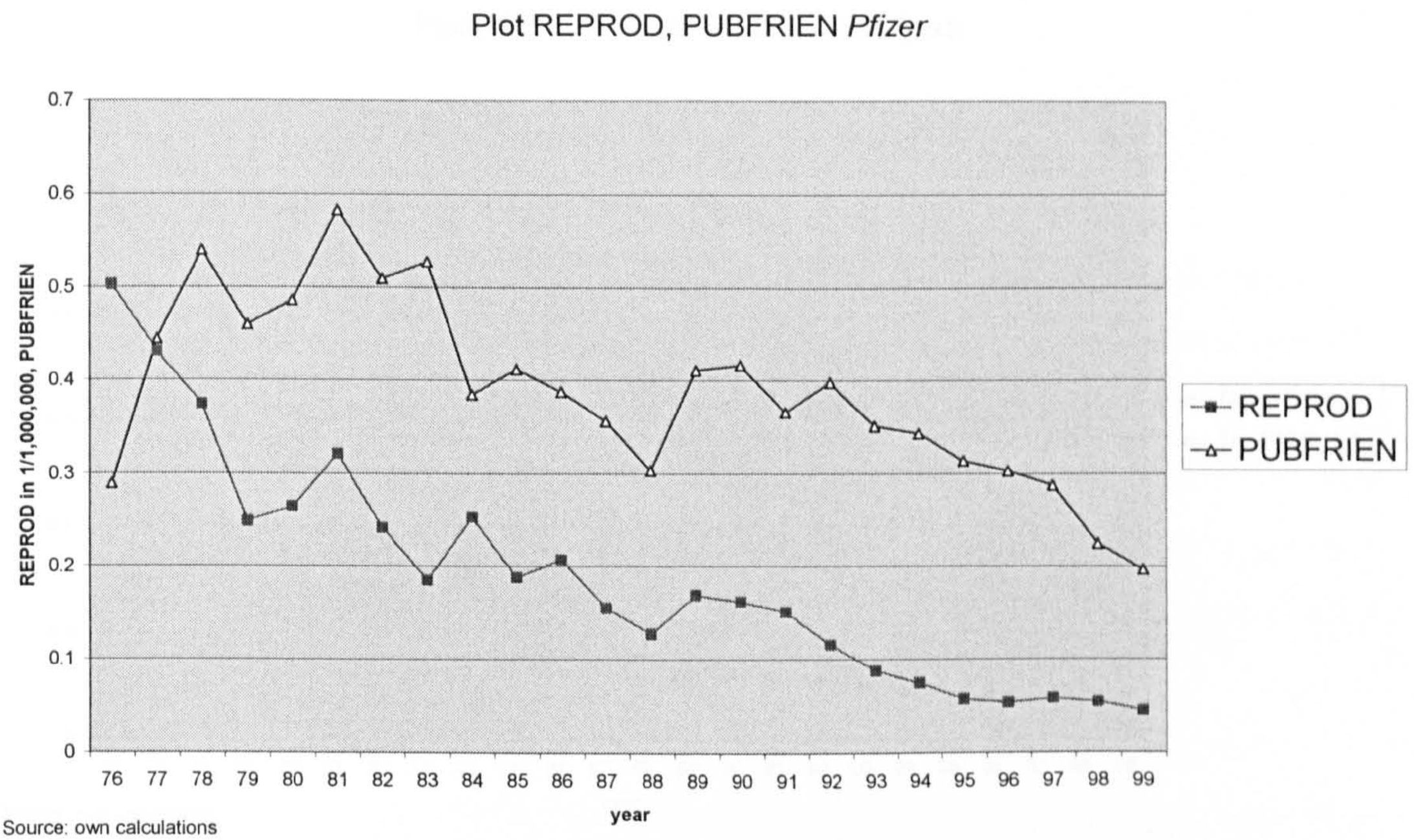
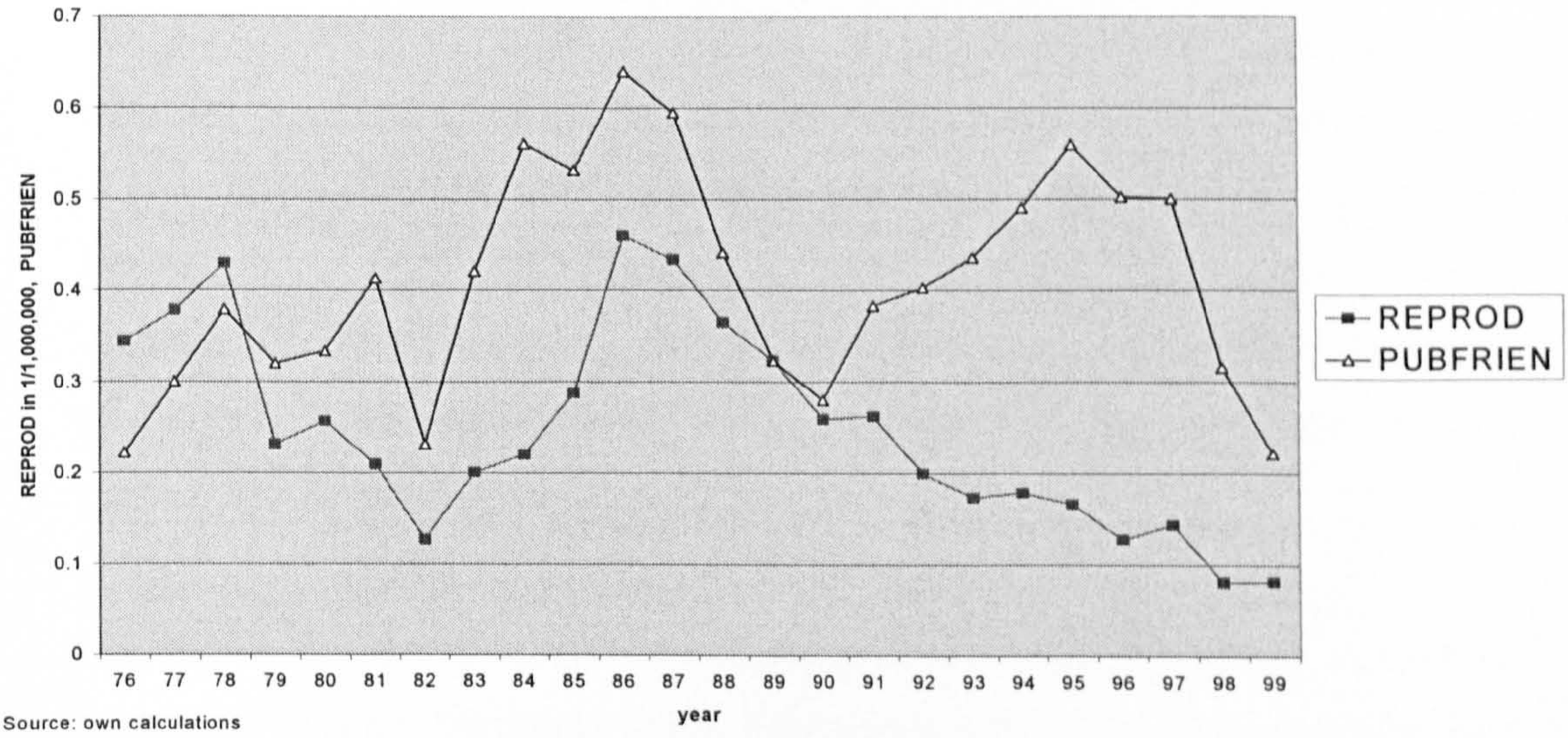


Figure A 8-5



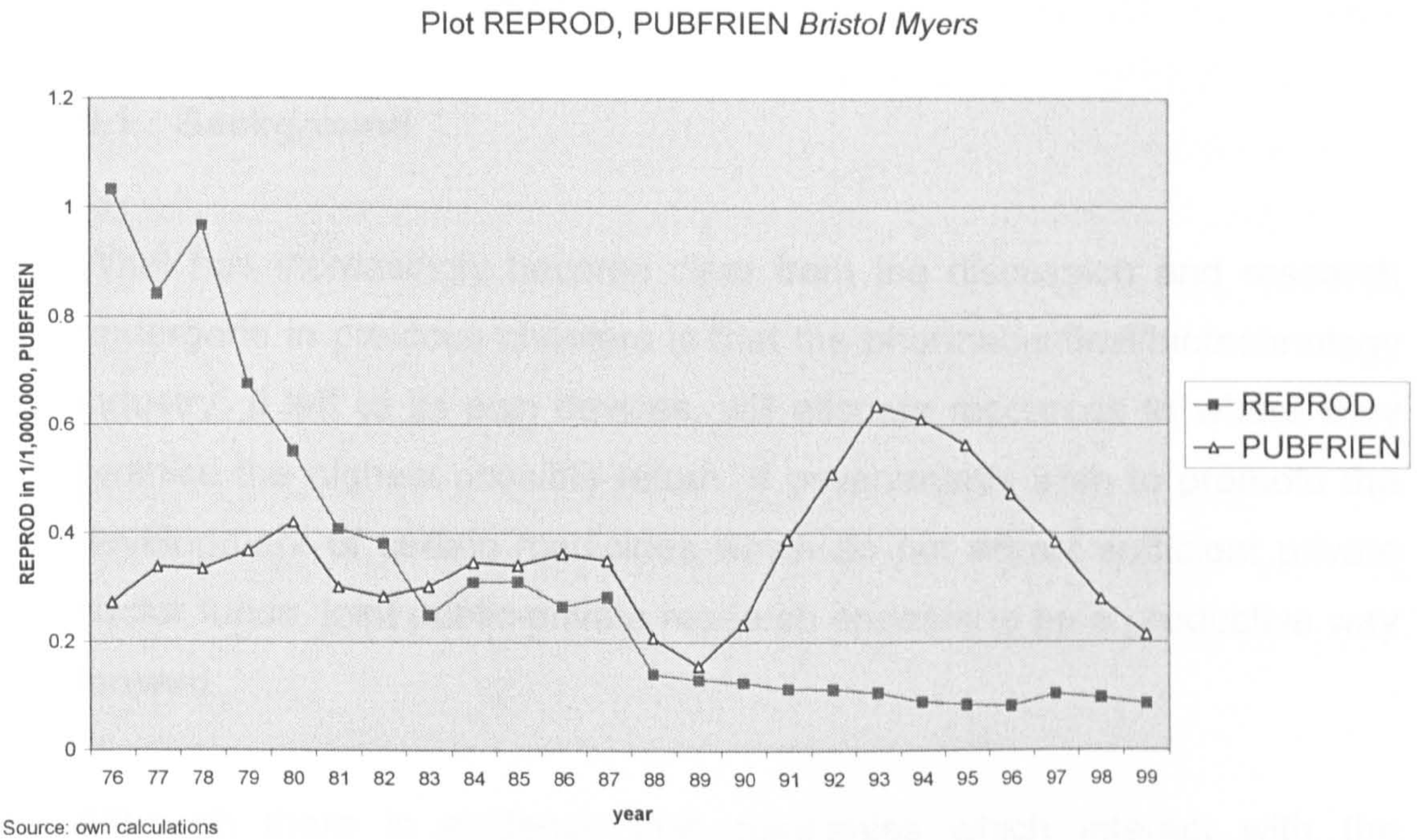
Source: own calculations

Figure A 8-6



Source: own calculations

Figure A 8-7



Source: own calculations

9 Research policy, centres of scientific excellence and movement of scientific personnel[1]

9.1 Background

What has increasingly become clear from the discussion and research undergone in previous chapters is that the pharmaceutical/biotechnology industry, if left to its own devices, will allocate resources to where they promise the highest possible return. If governments wish to promote the development of certain medicines which do not attract sufficient private sector funds, joint public-private research appears to be a productive way forward.

Although there is evidence that companies which interact with the scientific community are also the more productive researchers, the causality is far from clear. The previous chapter has raised some doubt that proximity to science itself is responsible for research success.

Causality tests suggest that scientists may be drawn to successful companies and continue to publish in order to signal their scientific excellence. What becomes the focus of attention in such an environment is the movement of scientists and the knowledge they carry, or, as Bartholomew (1997, p. 7) puts it, "biotechnology innovation may be conceptualised as the product of the accumulation of scientific knowledge in research institutions and firms (stocks) and the diffusion of that knowledge between them (flows)".

These insights gives further rise to the question how a national system of innovation should be designed to effectively further the accumulation and diffusion of knowledge, specifically in biotechnology, which is of great importance for new vaccine development.

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[1] This chapter is a modified and updated version of Kramer and Shackleton (2001)

Bartholomew (1997) has identified several features of the national institutional context which can affect the stock and flow of scientific knowledge: the tradition of scientific education, patterns of basic research funding, linkages with foreign research institutions, degree of commercial orientation of academia, the venture capital system, national technology policy, technological accumulation in related industrial sectors, and the mobility of scientific labour.

Some of these factors have been discussed in previous chapters, most notably the role of basic research, the patenting system, and the interaction between universities and biotechnology and pharmaceutical corporations.

Sharp (1989) stresses the importance of the mobility of scientists in the process of technology creation and diffusion. She believes that the US competitive model, for instance, is fed by very substantial expenditures on basic research, which provides the life-blood of the system and so:

> "the failure to sufficiently support the basic scientific infrastructure remains a real concern in the UK, where the nation's strongest advantage –its superior pool of creative scientists- is increasingly drawn to other countries where scientific research is rewarded with financial support in addition to social respect" (Bartholomew 1997, p. 19).

Porter (1990) has recently revived the view that nations which produce a greater number of scientists per capita will also produce more leading-edge research which in turn positively impacts on the nation's competitive advantage.

This chapter will focus on the tradition of scientific education, basic research funding and labour mobility and aims to investigate the relationships between these factors. As the following analysis will show,

the relationship between educating scientists and research success is far from clear when individual countries' research performances are compared.

Using the example of the British and German Higher education system, it can be shown that international scientific labour mobility can to some extent overcome shortages of domestic scientists. Further to that, maintaining low entry barriers into the academic community may produce better research than investing in home-grown talent and then sheltering academics through high entry barriers.

The emphasis will often be on the science and technology sector as a whole which has to do with the limited availability of data. Where possible, implications for biotechnological research and the promotion of medical knowledge in vaccine products will be discussed in greater detail.

9.2 Research Productivity: talent and technological capabilities

The current paradigm of science and technology policy draws intellectual inspiration from endogenous growth theory. It holds that investment in higher education implies investment in technological capabilities with a multitude of positive growth effects on the economy. An increase in higher education funding is believed to improve the quantity and quality of research undertaken. Publicly-funded basic research will then create more knowledge, which is made available to others to exploit. A recent review of the literature (Salter et al. 2000) suggests that the social rate of return for public investment in research could indeed be upwards of 25 per cent per annum.

Another aspect of public investment in research and development is to build on the knowledge of academics working *together* with industry (Dasgupta and David 1994, Hicks 1995, Rosenberg 1990). A recent report suggests that public funding and investment by the private sector

are strongly correlated, in particular "UK industrial funding per member of staff returned to the RAE (the higher education funding body's Research Assessment Exercise) increases as total R&D funding increases" (HEFCE 2000a, p. 8).

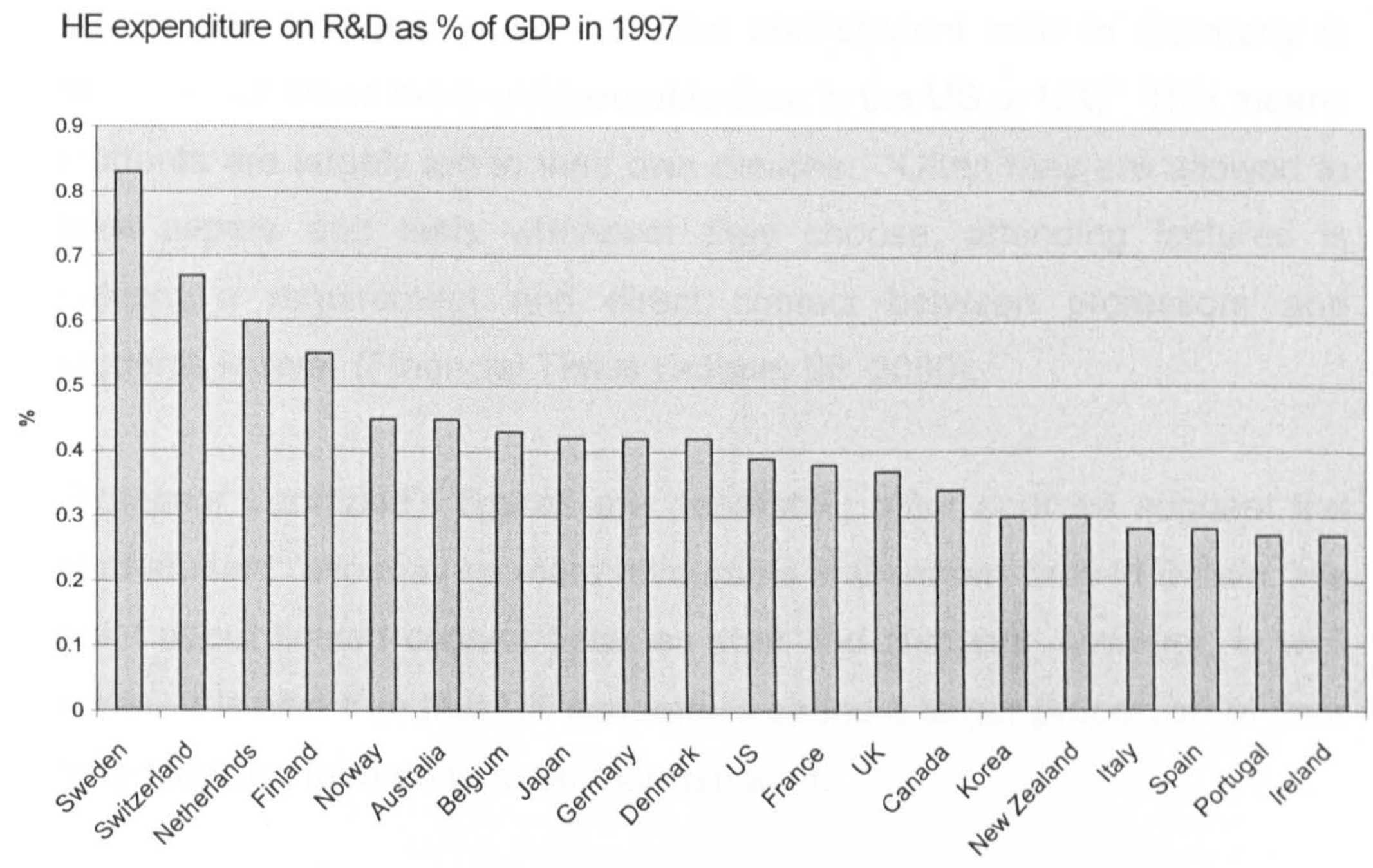
This knowledge spillover refers to the belief that a firm can benefit from the proximity of an academic research institution through joint research projects or the less tangible informal exchange of information (Hicks 1996). This is turn creates jobs in key industries such as biotechnology, where centres of scientific excellence explain the geographic location of firms in America and Europe (Zucker, Darby and Armstrong 1994, Zucker and Darby 1995a, 1995b, Zucker, Darby and Brewer 1998, and Zucker and Darby 1999).

Besides direct funding of research, investing more in the production of graduates is also believed to offer considerable benefit to society. Graduates "bring enthusiasm and a critical approach that stimulates others and raises standards. Moreover, the skills acquired during education are often a necessary precursor to the development of more industry-specific skills and knowledge" (Salter et al. 2000, p. 62).

The existence of these spillovers is held to justify the nurturing of national talent as a key objective of science and technology policy. In light of these arguments, alleged underinvestment in higher education in the UK compared to other countries in mainland Europe has become a matter of political concern.

A recent report commissioned by the Higher Education Funding Council for England has offered a characteristically gloomy assessment of Britain's future innovative strength. The authors claim that Britain has over the last two decades chronically underinvested in research and development in the higher education sector compared to other leading nations in Europe (ibid.).

Figure 9-1



Source: Main Science and Technology Indicators OECD 1999

However to assume Britain's below-average investment in higher education research and development has necessarily reduced competitiveness in disciplines vital to the economy is to confuse inputs with outputs. The belief that greatly increased government investment is desirable also implies considerable confidence in the ability of governments to "pick winners" in their funding policy: we know that in other areas of industrial policy the record has been very far from impressive (Burton 1983).

Britain manages to attract a relatively larger number of young people into Science and Technology disciplines than many of its competitors. Germany, for instance, has less than half the number of IT graduates per 100,000 employees as the UK (OECD 2000). The Financial Times reports that the situation is exacerbated by German study times, which are among the longest in the world. On average Germans stay in higher education for more than six years, compared with 4 in the United States

and 3.5 in the UK. The same source quotes Professor Klaus Landfried, President of the Association of Universities and Higher Education Institutions, who points out that "the staff-student ratio in Germany is three to four times more unfavourable than in the US or UK," This means students are largely left to their own devices: "Often they are allowed to take papers and tests whenever they choose, attending lectures is seldom a requirement and direct contact between professors and students is rare" (Financial Times October 26, 2000).

Professor Landfried's figures are debatable; other sources suggest the staff-student ratio may be more favourable in Germany than in Britain. His point about limited contact between staff and students, however, is well made. It is also true that UK academics spend a larger proportion of their time teaching than do tenured German staff.

Yet despite the apparent lack of investment in R&D compared to other European countries, research productivity remains high in the British higher education sector. Salter et al. (2000) concede that the productivity of its higher education system (expressed in both number of papers over total public investment in higher education, and citations per paper), puts Britain among the most productive nations, as illustrated in Table 9-1.

Table 9-1

Research Productivity in the Higher Education Sector

	Papers per $ million*	Rank	Citations per $ million**	Rank	Papers per researcher***	Rank
UK	**16.0**	**1**	**70.5**	**1**	**11.2**	**4**
Canada	14.7	2	61.0	3	10.9	5
Australia	13.9	3	48.3	7	10.2	6
Ireland	12.9	4	38.2	10	7.0	11
Spain	12.1	5	36.3	11	5.2	13
Sweden	11.3	6	52.3	4	15.7	1
Switzerland	10.9	7	65.7	2	13.3	2
Netherlands	10.3	8	48.7	6	11.3	3
France	9.8	9	38.3	9	8.4	9
Belgium	9.5	10	41.3	8	9.9	7
US	9.2	11	49.0	5	9.2	8
Italy	9.0	12	34.0	12	5.6	12
Germany	**7.9**	**13**	**31.9**	**13**	**7.2**	**15**
Portugal	7.2	14	17.9	15	1.8	16
Austria	7.1	15	25.9	14	7.3	10
Japan	3.6	16	11.7	16	4.5	14

* Million of R&D expenditure in 1997 in $ PPP

** from ISI National Science Indicators

*** OECD sources

Source: Katz 2000, taken from OECD, Main Science and Technology Indicators, OECD Statistics, 1999 and ISI National Science Indicators

In absolute terms, Britain's total number of publications in all scientific fields is second only to that of the USA. British scientists are also the second most cited in the world, again after the Americans. In terms of citations per paper, Britain occupies sixth position. British papers receive on average 4.5 citations compared to Germany's and France's 2.7. The top two countries are Switzerland (5.9 citations per paper) and the US

(5.4) (Salter *et al* 2000 quoting National Science Indicators, Institute for Scientific Information).

How does a higher education sector allegedly deprived of sufficient finance and talent produce such impressive results? The answer may again lie in flows of skilled labour, not only across borders but also from other sectors of domestic industry. Students and scientific personnel may be attracted to British centres of scientific excellence, by study opportunities and the convenience of English as a language of tuition and international scientific exchange.

9.3 Labour mobility and clusters of research and development activity

Technological clusters can be observed in many "high-tech" areas, for example biotechnology and information technology. In the corporate sector the more a firm is internationalised, the more likely it is that other inventors working in the same technological area are located in the same region, as Mariani (1999) suggests. This is also true for centres of research excellence at universities which attract clusters of firms operating in related technologies, both in Europe and in the United States (Zucker et al 1998 and 1999).

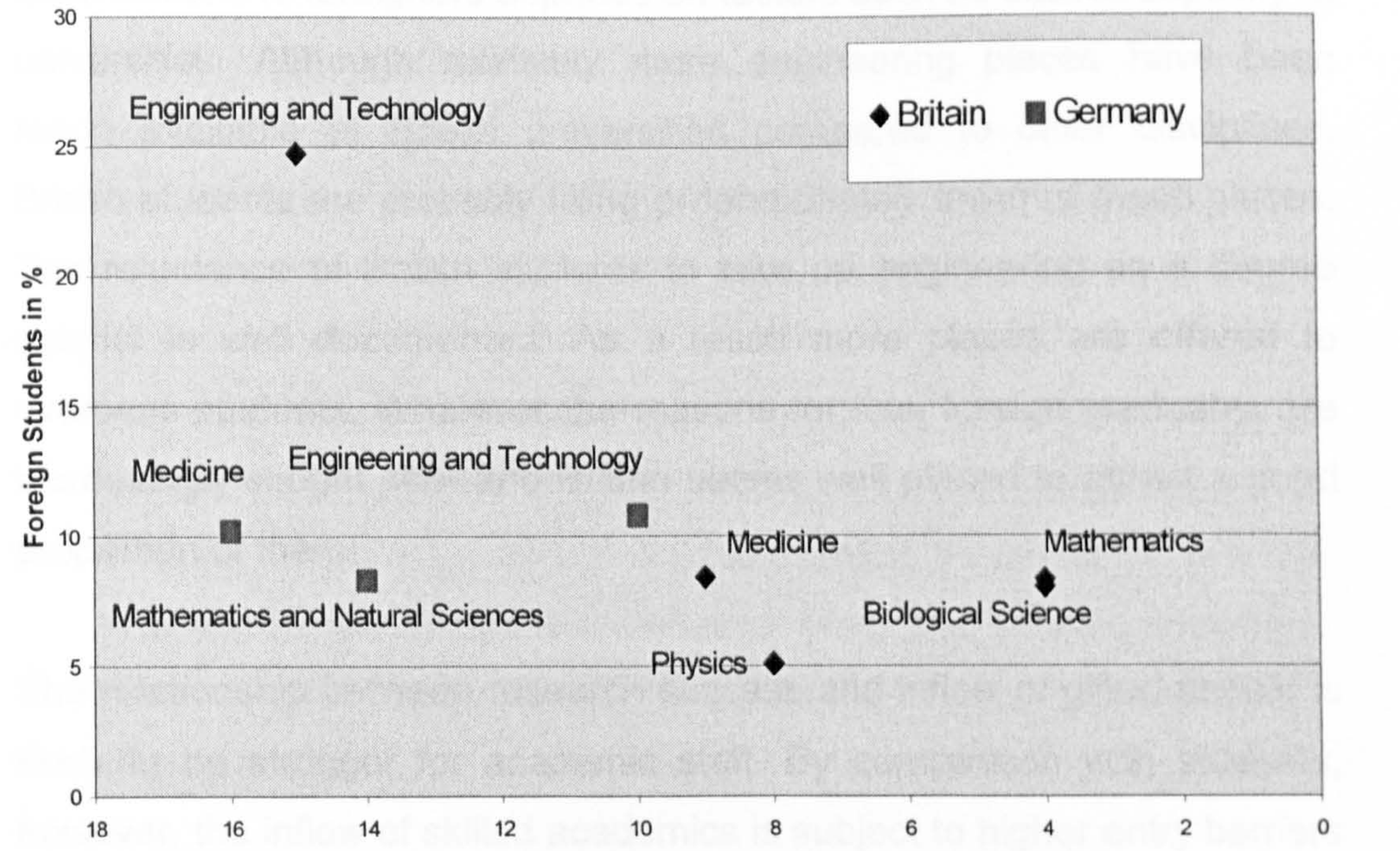
If research and development investment concentrates on centres of excellence, it is a plausible assumption that R&D personnel in both science and technology move along with it. A country with a disproportionate number of such clusters is likely therefore to attract an influx of human as well as physical and financial capital. A country experiencing a net inflow of skilled scientists and technologists might,

even in the long term, be able to compensate for limited investment in research and the training of graduates[2].

As far as a student's motivation to study in another country is concerned, it could be argued that their choice of subject area will be guided by the strength of a country in an academic discipline. After all, agglomeration theory suggests that good university departments attract employers[3], which in turn create jobs for new graduates.

Figure 9-2

Research excellence and foreign student numbers in the UK and Germany 1994-1998



Source: UCAS, National Science Indicators, ISI, Statistisches Bundesamt

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2 Britain has already in the past managed to compensate labour shortages of, for instance, doctors and nurses by attracting such skilled labour from other countries.

[3] Companies may for example sponsor Professorships to have access to the best graduates, set up research facilities close to universities or co-operate in other ways with the local university.

There is however little evidence for this line of argument, as Figure 9.2. shows. When comparing the UK's and Germany's international citation impact[4] with the ratio of foreign students in subject disciplines for which comparable figures are available, there appears to be no relationship between the two. Germany's share of foreign students is just about constant, between 8 and 11%, while Britain's share of foreign students appears to be slightly lower in most key disciplines except Engineering with 24% - surprisingly, an area where research output is ranked poorly. Britain's good research record in Maths and Biological Sciences, by contrast, attracts relatively few foreign students.

The concentration of overseas students in particular fields is not the result of demand factors alone. The supply of higher education qualifications to foreigners depends on factors such as excess capacity at universities. Although relatively more engineering places have been made available at British universities compared to other disciplines, British students are probably filling proportionately fewer of these places. The reluctance of British students to take up engineering as a degree subject is well documented. As a result more places are offered to overseas students. Whatever the reasons for this, foreign graduates are increasingly sought after and Britain seems well placed to attract a good proportion of them.

The relationship between research success and inflow of gifted people is likely to be stronger for academic staff. By comparison with students, however, the inflow of skilled academics is subject to higher entry barriers as a result of different qualification requirements. To illustrate flows in and out of a research environment Gravensen (2000, p. 3) uses a 'Tower' and a 'Pyramid' model.

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[4] Number of citations per paper published, a widely used measure of the quality of published research

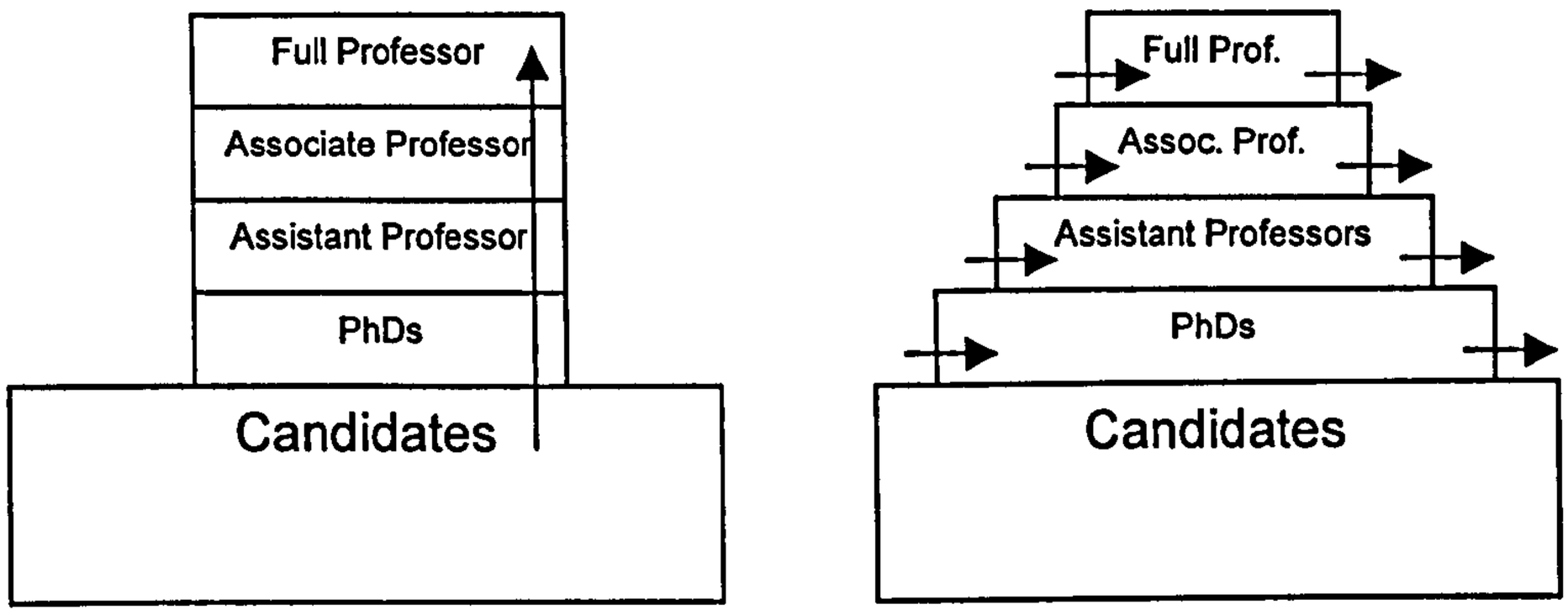

Figure 9-3 : Tower and Pyramid research environments

Source: Gravensen 2000, p. 3

In the Tower model all candidates for higher research positions are educated at lower level and all "non-usable" candidates are sent back into the surrounding economy. In other words there is an outflow, but in the most extreme case no inflow into the system from outside - except at the entry level. Economists would see this as an extreme case of an internal labour market, with the usual strengths and weaknesses of such an arrangement. Compared to the Pyramid model, a 'Tower' environment helps create highly specialist knowledge as a result of the long time which higher level researchers spend in the system. A research Pyramid environment, however, is believed to create the greater innovation potential, with plenty of opportunity for knowledge transfer to and from the surrounding economy.

The Tower model most closely resembles the German higher education research set-up. Entry barriers, except perhaps at PhD level, are high, partly due to the requirement of a 'Habilitation', the higher education teaching and research qualification which is still necessary to become a full professor at a German university[5]. Few academics outside Germany

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[5] In June 2001 the German Secretary of State for Education initiated a reform of the German Higher Education Framework Law which will introduce the successful

or practitioners from outside the university sector can therefore become full professors. To complete both PhD and Habilitation typically takes ten years after obtaining a masters level qualification. An academic post at Habilitation level tends to be a five-year fixed-term assistant teaching or research contract, and few academics will want to delay progression to a tenured professorial position by working long spells outside the university sector. Unsurprisingly, in- and outflow in the German research environment is very limited.

The situation is different in the UK research environment. Although career academics are the norm, considerable mobility between the research sector and other sectors of the economy is facilitated by the lack of entry barriers into higher education. Although the PhD qualification is becoming an entry requirement in most academic disciplines, more experienced members of staff still find it easy to move in and out of the university sector as long as they keep an active interest in research or other scholarly activities. Professors without a PhD are nothing unusual in the UK, while in Germany almost all Professors are Doctors[6].

Ideally, mobility rates in the British and German higher education sector should be compared. This does however present problems of aggregation and comparability of data. As a first step Labour Force

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completion of 'Junior Professorships' as a pathway to a tenured position at German universities. Junior Professors are no longer expected to write an habilitation but embark on other research activities such as journal publications instead. The Junior Professorship is, however, still on a (six-year) fixed term base and does not allow for an automatic progression to a tenured position. Although research autonomy seems to have improved when compared to the previous regime, job security hasn't. The aim of the Junior Professorship to attract young scientists who would otherwise have left the country may well be compromised by this uncertainty.

[6] In order to cope with the rapid expansion of the German Higher Education Sector in the 1960s and 70s some Professorships were awarded to teaching staff without Habilitation or PhD qualification. Thirty years later, the German convention remains that of addressing professionals by their full title: it still allows people to distinguish the 'proper' *Professor Doktor* Meyer from the mere *Professor* Schulze.

Survey data have been used to identify mobility rates in the British education sector as a whole and compared with other sectors of economic activity, most notably the Information and Communication Technology sector, notorious for skills shortages and high levels of staff fluctuation. This is based on the methodology employed by the OECD to measure mobility rates in Scandinavian countries (Akerblom 2000). Further to that, international mobility rates are shown for these sectors of activity. For this purpose industrial classification categories (SIC 92) have been recoded to identify three distinct ICT sectors and a further four broad industry sectors including education[7]. In order to identify mobility of skilled personnel, the selected population includes only those members of the working age population in Great Britain who have achieved an educational qualification of at least first degree level.

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[7] The following two- and three-digit industry codes have been isolated to represent the Information and Communication Technology sector: Manufacture of Office Machinery and Computers (SIC 30), Manufacture of Radio, Television and Communication Equipment (SIC 32), Telecommunications (SIC 642), Computer and Related Activities (SIC 72). The other sectors follow standard two-digit SIC classification, excluding the ICT sectors. A further breakdown into individual ICT sectors is possible although problematic because of the small number of respondents in these categories in the LFS.

Table 9-2- Cross industry higher level labour mobility rates in the UK

	Currently employed in: ICT	Agriculture, mining, manu-facturing, utilities, construction	Services	Education	Health and Community Services	Total
Employment situation 12 months ago						TOTAL
Working in paid job or business	250171	532214	1046693	827044	847940	3504062
1 for same organisation	207607	466180	909878	759604	760321	3103590
2 for different organisation	42563	66033	136297	67439	87618	399950
3 **narrow mobility rate (2/1+2) in %**	17.01	12.41	13.02	8.15	10.33	11.41
4 Sectoral breakdown of 2:						
ICT	22023	3121	6086	924	2474	34628
Agriculture, mining, manufacturing, utilities, construction	5597	39521	21413	5919	6423	78873
Services	10790	16620	83950	7613	21838	140811
Education	1408	2693	6420	40992	8782	60295
Health and Community Services	2747	4077	16812	9774	46281	79691
5 total of cross industry movers (included in 4)	20542	*26511*	*50731*	*24230*	*39517*	*161531.00*
cross industry mobility rate (5/2)	48.26	56.77	37.22	35.93	45.10	40.39
6 lived abroad 12 months ago (included in 4)	*2839*	*2235*	*2839*	*4504*	*2420*	*14837*
international mobility rate (6/2)	6.67	3.38	2.08	6.68	2.76	3.71

Source: Labour Force Survey 1999/1, own calculations

It is worth noting that mobility in the ICT sector is far higher than in other sectors, a larger fraction of people having worked for a different organisation one year ago (this is termed the *narrow mobility rate*). The fraction of people having worked for a different organisation one year ago is among the lowest in the education sector, with around 8%. Interestingly the ICT sector does not attract disproportionately more people from other sectors of industry by comparison with other sectors.

The cross-industry mobility rate, although above average, does not indicate that the ICT sector is 'poaching' talent from other sectors of industry. Again, the education sector has one of the lowest cross-industry mobility rates, which means that fewer people than in any other sector move across disciplines.

Where the education sector is clearly on a par with ICT is international mobility. A disproportionately larger fraction of highly-skilled workers comes from abroad in comparison to other sectors. Almost 7% of all workers in education and ICT who were working for a different organisation one year ago came from a country outside the UK. This is up to *three times* as high as other sectors of industry. This suggests that education and ICT personnel are relatively highly mobile internationally, and that lowering and that measures to liberalise admissions are likely, in the UK at least, to pay dividends.

A further breakdown of the education sector reveals that the more research intensive divisions of higher education and research institutes show far higher mobility rates that other educational institutes such as primary and secondary schools. Staff fluctuation in particular at research institutes is high, with around 17% of staff with a higher education level[8] having worked for a different organisation.

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[8] Defined as holding at least a first degree

Calculating international mobility rates and cross-industry mobility rates (the latter being reported here) is, however, problematic because of the small size of the sample. Although it is not surprising that the cross-industry mobility rate is comparatively lower in schools when compared to universities (around 19% and 54%, respectively, having worked outside the education sector the year before), the number of observed cases in the Labour Force Survey is very low at this level of aggregation and these results have thus to be treated with caution.

Table 9-3 – Cross-industry higher level labour mobility rates in education in the UK

		Currently employed in:		
		Education		
	Employment situation 12 months ago:	Universities	Other educational institutions	Research institutes
	Working in paid job or business	201908	578119	47017
1	for same organisation	181430	538079	40095
2	for different organisation	20478	40040	6921
	narrow mobility rate (2/1+2) in %	11.29	7.44	17.26
4	Sectoral breakdown of 2:			
	Office accounting and computing machinery			
	Telecommunications	558	366	
	Computer and related activities			
	Agriculture, forestry, fishing			
	Mining, quarrying			
	Consumer goods			402
	Wood, pulp and paper, printing, oil refining	475	356	1573
	Metals, machinery (not ICT)		841	
	Other manufacturing	834		509
	Energy and water			593
	Construction	336		
	Wholesale and retail trade, hotels, restaurants	560	1916	403
	Transport, storage, post, communications	459		
	Financial intermediation	880	455	
	other services	2093	847	
	Universities	5448	789	1285
	other educational institutions	2046	30511	
	research institutes	470	443	
	Health activities	2049	368	982
	other community services	2881	2320	1174
5	Total of cross industry movers (included in 4)	11125	7469	5636
	Cross industry mobility rate (5/2)	54.32	18.65	81.43

Source: Labour force Survey 1999/1, own calculations

Another set of data has been used to compare the effects of entry barriers in the German and British higher education sectors. Comparing the number of foreign academics completing a Habilitation in Germany in 1999 with the number of foreign academics at lecturer/researcher level in the UK, two classifications broadly equivalent in seniority and age, the difference between Germany and the UK is remarkable.

Of 1926 academics in Germany graduating at that level, 1822 are German, 104 or 5.3 % are from other countries (see Table 3). By contrast, in Britain as many as 18.2% of junior research staff (lecturers and teachers) are of foreign origin – 10.4% from outside the European Union (Table 4). China, Germany, the USA, the Irish Republic and France are the main countries of origin for foreign junior academic staff. Britain is a popular destination among young academics as a result of low entry barriers and the use of English as the language of international scientific exchange.

Table 9-4

Number of habilitations awarded by nationality in 1999

Country	Total number
Germany	1822
Austria	14
Netherlands	9
UK	7
Greece	7
Russia	6
Italy	5
Switzerland	5
Turkey	5
France	4
Poland	3
Argentina	3
Canada	3
Vietnam	3
Bosnia Herzegovina	2
Others	28
TOTAL	1926

Total foreigners	104 (5.4%)
European	84 (4.4%)
Non-European	20 (1%)

Source: Statistisches Bundesamt

Table 9-5

Number of full-time junior academic staff (lecturer/ researcher) in the UK by nationality

Country	Total number of staff
China	1510
Germany	1420
US	1270
France	1090
Irish Republic	1090
Italy	740
Greece	700
Australia	680
India	610
Canada	510
Spain	500
Netherlands	430
Russia	300
New Zealand	240
Iran	190
EU	6600 (7.8%)
Non EU	8820 (10.4%)
Total number junior academic staff	85050

Source: HESA staff record 1999

And finally, using Higher Education Statistics Agency data, inflows and outflows of full-time wholly institutionally-financed British academic staff can be compared for selected "cost centres" (disciplines), as shown in summary form in Table 9-3.

Table 9-6

Net flow of full-time academic staff for UK Higher Education Institutions (HEI) and selected cost centre groupings

	net gain/loss UK HE Sector (% of labour force)	net gain/loss UK Private Sector (% of labour force)	net gain/loss overseas HEI (% of labour force)	net movers (% of labour force)
Medicine (non-clinical)	3.38	0.60	mv	7.85
Anatomy, Physiology and Biosciences	2.82	0.20	0.80	3.21
Chemistry	2.76	-0.92	mv	0.02
Physics	0.65	mv	mv	-1.31
Earth, Marine and Environmental Sciences	1.14	0.00	mv	0.57
Mechanical and Civil Engineering	2.51	0.97	mv	1.16
Mineral, Metallurgy and Materials Engineering	1.85	0.00	mv	1.85
IT and Computer Engineering	2.35	0.00	0.67	0.51
Humanities, Languages, Design and Architecture	2.18	0.82	0.61	2.46
Mathematics	1.79	mv	mv	0.45
Business and Management	2.40	0.80	0.13	3.74
Media, Social Studies and Geography	2.76	0.79	0.59	4.13
Education	3.67	0.43	mv	7.97
TOTAL HE sector	2.51	0.63	0.49	3.57

source: HESA staff record 1999

mv: missing value, suppressed due to small numbers

With the exception of Physics, it appears that all cost centres shown gained staff over the 1998-99 period. Medicine and education receive the largest net gain of almost 8%[9], Anatomy, Physiology and Biosciences, the areas of particular interest in the context of this thesis, still experience a net gain of more than three per cent of the labour force. Columns 2 to 4 in the Table indicate the proportion of net movers (as a percentage of the

[9] Calculated as (total movers in minus total movers out) as a percentage of total staff.

labour force) coming from within higher education, from the private sector or from overseas higher education institutions. As one would expect, most British academics move within the HE sector. However most academic disciplines are net gainers from the private sector. Amongst the disciplines experiencing the biggest "brain gain" from private industry is mechanical and civil engineering. Even IT and computer sciences, however, shows no net loss even though private sector rewards are high.

Of course net movement between higher education and other sectors does not reveal the quality of skills exchanged. Biotechnology specialists might be entering the Higher Education sector at a low level but exiting at a higher level, taking the skills they have acquired with them: this would constitute a "brain drain". On the other hand, older and more experienced staff might be leaving the private sector and moving into higher education towards the end of their career. The direction of changes in the quality of the stock of skills in higher education may therefore be ambiguous.

Interestingly, all the key disciplines for which data are available show a significant gain from overseas higher education. Biosciences and information technology lead the way, with net gains of 0.8% and 0.67% of the labour force respectively.

These results show a possible explanation why Britain has high research productivity despite relatively low investment in higher education research capacity. Britain has, as in other areas of its economy, benefited from its position as a prime destination for higher-skilled personnel.

Judging by the considerable net inflow of scientists, particularly in those subject areas where British science is doing well (such as biosciences and computer science), concerns about losing technological capabilities seem unfounded. Compared to Germany which, because of barriers to entry, attracts comparably few young academics from abroad, Britain is well placed to attract talent in key areas of technology.

Furthermore, if the number of university places is led by demand for graduate labour in a certain subject area, Britain is able to attract a significant number of foreign students where the number of domestic students falls short of capacity. Foreign engineering and technology graduates, for example, are likely to find it relatively easy to take up their first employment in the UK, especially if the government is making visas easier to obtain. This can also help alleviate skills shortages in the domestic labour force.

From a science policy viewpoint, "brain gain" and "brain drain" data may help to identify academic disciplines where a country has a comparative advantage. A successful subject area experiencing a net inflow of scientists (and this could include an inflow from other sectors of the economy as well), is more likely to generate a knowledge-cluster-creating innovation and economic growth. The number of graduates needed is likely to increase in those areas where technological capabilities are strong and the higher education sector would be well advised to allocate funds and university places accordingly.

9.4 Conclusion

In this Chapter a number of aspects of the movement of highly-skilled labour between sectors and between countries were surveyed. A number of tentative conclusions can be drawn from this analysis.

Discussions of the need for investment in higher education research and development ignore the considerable variations in research productivity associated with different levels of investment. Britain's strong performance in published research suggests that the institutional structures of higher education have a much more important effect than was previously thought. More open 'Pyramid' systems may have greater

potential for innovation and research productivity than 'Tower' systems where there is little inflow or outflow of personnel at higher levels of the hierarchy. This is certainly true for areas such as British biosciences which has experienced a net inflow from other sectors of the economy and abroad.

A related observation is that inflows of students from the rest of the world may be an important factor in building research potential. A liberalised system of visas for students may allow many to be semi-permanent additions to the domestic stock of highly-skilled labour on graduation, offsetting the reluctance of domestic students to enter certain scientific and technological fields.

More generally, a country which imports highly-skilled personnel may be enabled to maintain or improve its technological capabilities by this means as well as by domestic investment in research, development and the training of domestic skilled labour. European countries more generally now recognise the importance of attracting foreign financial and physical capital flows, bringing in new resources and the opportunity for transfers of technology and best practice. Recognition that attracting flows of human capital can pay similar dividends is beginning to dawn on policymakers.

10 The relevance of the thesis' findings for Science and Technology Policy

10.1 Background

Prior to concluding the thesis this chapter will put the findings so far in the wider context of Science and Technology Policy. Here, other relevant aspects of Science and Technology Policy which lay beyond the scope of this thesis will also be discussed.

From a macroeconomic perspective Science and Technology Policy takes inspiration from Neoclassical Growth Theory and Endogenous Growth Theory which sees the advancement of technology in production as an important factor underlying economic growth. Chapter four of this thesis introduced the reader to Solow's (1957) neoclassical growth theory and the notion of a long run steady state equilibrium, at which point the economy grows at a growth path at a rate equal to the sum of population growth and the rate of (labour augmenting) technological progress. Without a constant rate of technological progress, growth would cease because of decreasing marginal returns to the accumulated factor capital (Freeman 1997).

The positive growth impact of R&D investment does not in itself provide a rationale for government intervention. If markets for the production of knowledge do fail, however, government would have a strong reason to reallocate resources in favour of R&D. As outlined in Chapter Three, Nelson (1959) and Arrow (1962) have argued that scientific and technical knowledge possesses a public goods dimension. Knowledge being a non-rival good from which consumers can only be partially excluded will not allow producers of that knowledge to fully appropriate the potential revenues, because other individuals can benefit from knowledge at no cost to them.

In this case not enough knowledge will be produced in the market economy. The difference between what consumers would be prepared to pay had knowledge been fully appropriable by the producer and what consumers actually pay is called spill-over. (Department of Finance Canada,1997).

This implies that there is a significant gap between social returns and private returns to R&D and a large empirical literature has attempted to estimate the extent of that gap. If social returns to R&D can be found to be substantially above private returns then that indicates that returns to R&D cannot be fully appropriated and hence there is underinvestment in R&D.

Griffith (2000) explains, that the most common way to estimate private rates of return to R&D is using production functions of the kind:

Equation 10-1

$$Y_{it} = A_{it} F(K_{it}, L_{it})$$

Where output Y of firm i in period t is produced using factors of production capital K and labour L and A defines total factor productivity. Total factor productivity will be endogenously determined[1] by the stock of knowledge G and other factors. This can be written as:

Equation 10-2

$$A_{it} = \eta \ln G_{it} + b \ln X_{it}$$

Where X stands for all other factors. The parameter:

[1] This method is obviously closely related to 'endogenous' growth theory which attributes changes in total factor productivity to the amount of resources devoted to the creation of knowledge. See also Chapter Four for a brief discussion of exogenous and endogenous growth theories.

Equation 10-3

$\eta = (\delta Y_{it} / \delta G_{it}) \times (G_{it}/Y_{it})$

is then the elasticity of output with respect to knowledge stock and:

Equation 10-4

$r = \delta Y_{it} / \delta G_{it}$

is the rate of return to the accumulation of knowledge. Accumulation of knowledge is in empirical studies often proxied by R&D expenditure.

Griliches (1992) estimates η (the elasticity of output with respect to knowledge stock) to be 0.07. Further to that, Griliches calculated G_{it}/Y_{it} (knowledge stock divided by total value added) to be 0.26 so r must be 0.07/0.26 = 0.27 which implies that the private rate of return to R&D is around 27%.

When this result is compared with estimated social rates of return it becomes apparent that knowledge spills over from the original inventor to other firms. Measurement of social rates of return follows this logic by estimating the growth of one firm as a result of R&D undertaken by other firms. These can of course be in the same industry, an upstream industry, and the scope can be broadened to include industries in other countries as well, which could significantly raise the social returns to R&D. Hence social rate of return estimates need to interpreted with the scope of measurement in mind.

In a review of the literature Griffith (2000) finds that narrow measures (rate of return to industry from R&D conducted in same industry) range from 17-34% while broad measures (including for example R&D carried out in upstream industries) add another 41-82% to the narrow rate, which indicates that the total social rate of return to R&D is often in excess of 100%.

Regardless of whether some of these measures under- or overestimate the true social rate of return, the consensus is that R&D spillovers are significant, and government therefore has a mandate to bring the private incentives to R&D back in line with the social rate of return and hence correct the outcome of the market with regard to the production of knowledge. The policy designed to achieve this correction is referred to as Science and Technology Policy.

10.2 Science and Technology Policy

Bringing private and social rates of returns more in line[2] can be achieved by a variety of means which can be broadly distinguished into regulatory and fiscal support[3].

Table 10-1

Regulatory support	Fiscal support
• patent system and other measures to support intellectual property rights	• government-sponsored R&D • government procurement of new technologies • direct subsidies to universities or companies undertaking R&D • tax incentives (such as R&D tax credits)

Source: Canada Department of Finance 1997

Other authors such as Griffith (2000) take a broader view and would, for instance, include competition policy as regulatory measure[4], which raises

[2] This does not imply that policy makers have accurate knowledge of socially optimal levels of R&D.

[3] Following the Canadian Department of Finance's interpretation of the scope of science and technology policy (Department of Finance Canada 1997)

the question whether other government policies which may indirectly influence a firm's innovative behaviour, such as education and training, monetary and trade policies, should also be considered under the rubric 'science and technology policy' (Ruttan 2001).

Mowery (1995) defines the boundaries of science and technology policy to include only policies that are "*intended* to influence the decisions of firms to develop, commercialise or adopt new technologies" (ibid, p. 514). The issue of intent is important here because according to Mowery indirect policies such as the above have rarely been designed or implemented to affect innovative performance. This may, however, exclude important explanatory factors from the analysis of science and technology policy.

Mowery himself concedes that the policies that are intended to influence innovative performance may not exert the greatest influence on such performance when compared with, for example, indirect policies such as competition, monetary, fiscal or trade policy which will affect the level of investment in R&D in an economy.

Griffith (2000) suggests the inclusion of human capital formation; likewise Ruttan (2001) considers education and training an issue of science and technology policy.

Here direct measures included in table 10.1 will be discussed, plus some issues in education and training policy, while other indirect policies predominantly affecting the macro-environment of the firm lie well beyond the scope of this thesis.

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[4] Not least since Schumpeter claimed that large firms and concentrated markets are more likely to innovate, competition policy could indirectly influence a firm's innovative behaviour through its influence on market structure.

It is necessary to discuss the effectiveness of the above measures and the findings of this thesis in the wider context of national systems of innovation; different countries or groups of countries (such as the European Union) employ different means to influence the decisions of firms to develop, adopt or commercialise new technologies. The effectiveness of science and technology policy measures will also depend on the country-specific institutional context, part of which is set up and controlled by government, part of which outside the boundaries of science and technology policy but nevertheless exerts a strong influence on companies' innovative behaviour, such as for example the existence of a strong venture capital market.

10.3 National Systems of Innovation

Beije (1998) defines a national system of innovation as a group of private firms, public research institutions, and several of the facilitators of innovation (such as patent offices, government organisations for technology policy, chambers of commerce, innovation centres, venture capital organisations), which interact to promote technological innovations.

Within these groups Bartholomew (1997) has identified a total of eight features of the national institutional context which can affect the stock and flow of scientific knowledge: the tradition of scientific education, patterns of basic research funding, linkages with foreign research institutions, degree of commercial orientation of academia, the venture capital system, national technology policy, technological accumulation in related industrial sectors, and the mobility of scientific labour.

A national system of innovation is then, according to Metcalfe (1995, p. 464), "a system of interconnected institutions to create, store, and transfer knowledge, skills and artefacts which define new technologies".

Ergas (1987) distinguishes two fundamental types of national innovation systems, those which are *mission-oriented* and those which are *diffusion-oriented.*

Mission-oriented systems, such as the UK and the US, are according to Beije (1998), distinguished by university research which is geared towards the commercial exploitation of scientific findings. As a prerequisite to the effective knowledge transfer scientific labour tends to be highly mobile between universities and also universities and the private sector. A further feature of mission-oriented systems is an efficient market for corporate control and a well developed venture capital market which further aids the diffusion of scientific knowledge by selecting and promoting those R&D projects which are the commercially most promising. In such an environment government involvement is modest, and the diffusion of scientific knowledge is left to the market place.

The pre-eminent shareholder value orientation in mission-oriented systems tends to create short-term R&D investment decisions[5], however, so that long term research programmes with highly uncertain outcomes, in selected sectors such as defence, aerospace, and medicine, are (often exclusively) financed by government.

Diffusion-oriented countries such as, for instance Sweden, Switzerland, and Germany maintain permanent and close links between government, banks and industries. These links are often of a financial nature: Banks are often creditors *and* shareholders in R&D-intensive industries, and would in many cases have a representative on the company's supervisory board. Such close scrutiny will at the same time allow a more long-term orientation of investment projects and perhaps present greater incentives to invest in projects with an uncertain outcome.

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[5] Demsetz might ask whether we are not unduly comparing this kind of decision making to some elusive 'ideal' state of affairs.

At the same time, diffusion-oriented countries maintain a bond between industry and government in keeping up high levels of training and education. A good example for this is the German dual system of vocational training and the responsiveness of the German government in initiating a Green card scheme to alleviate skills shortages in the Information Technology sector of the economy.

In such a system, technology diffusion and the broad-based capacity to innovate becomes an explicit part of the government mandate.

In practice, most national systems of innovation would lean towards either of the two systems but show features of both mission and diffusion oriented systems. What lies beyond contention is that firms and entrepreneurs are the primary actors in the generation of technological artefacts, and that their activities are *supported* by the accumulation and dissemination of knowledge (Metcalfe 1995).

As far as regulatory support is concerned almost all national systems of innovation rely on a functioning patent system to protect innovation. The optimal patent length is still subject to debate (Carlton and Perloff 2000, pp. 522-528) and the current patent length of 20 years has been chosen rather arbitrarily[6]. It can be shown (ibid.), at least theoretically, that either infinite patent protection or no patent protection will result in too little investment. The reason for this is quite clear: in the absence of any property rights, immediate imitation will lead to the innovator not being able to appropriate a return on R&D. Infinite patent protection will result in excessive duplication of research because too many firms will be racing

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[6] Carlton and Perloff (2000) explain that prior to the patent law change of 1995, patents in the United States lasted for 17 years. The length of patent protection, part of the first piece of legislation passed after the Constitution was signed into law by George Washington in 1790, was apparently related to the length of an apprenticeship, which lasted for 7 years. Some in Congress wanted a patent length of two apprenticeships, others preferred a patent renewal after 14 years for another 7 years. Congress simply split the difference and offered a term of 17 years.

to obtain the patent which offers large potential rewards. The literature on patent races and patent length, and most recent game-theoretical contributions have been touched upon in Chapter Four and will not be discussed here any further. As far as the contribution of this thesis is concerned, the empirical investigation in Chapter Six did not show any evidence of a structural break in R&D intensity when firms could for the very first time obtain patent protection for biological products.

As far as fiscal support measures are concerned, the starting point of any investigation should lie in a clearer understanding of the accumulation of R&D resources at the firm level. The empirical investigation in Chapter Six models R&D intensity in the specific case of the vaccine industry as a response to market and non-market forces. Although the predictive power of the model is somehow compromised by the small number of observations, at least one clear result seems to have emerged from both the partial-adjustment and error-correction specifications of the model: cash flow matters as a determinant of R&D intensity, either through its influence on the cost of finance of R&D projects or as a proxy for expected future returns.

This is relevant inasmuch as it indicates that the emphasis on venture capital markets and the market for corporate control in mission-oriented systems is not misguided. For the majority of R&D projects and specifically those which have not been earmarked by government as strategically important will be able to attract private sector funding as long as the cost of finance is not prohibitively high or finance is not available at all.

Most mission-oriented countries would rely on a mix of fiscal support measures to target specific technologies for further development or commercialisation. The share of government support of the total R&D budget is often greater in mission-oriented countries than in diffusion-oriented countries. Metcalfe (1995) would call these policies 'supply

policies' as opposed to 'adoption policies' which are more widely used in diffusion oriented countries.

Fiscal support would either take the form of direct subsidies, government procurement of new technologies or various forms of tax incentives. The principal difference is that direct subsidies or government procurement target specific projects and therefore involve governmental discretion, while tax incentives still leave it to the market to allocate resources.

Targeted basic research funding would often cover the entire costs of projects undertaken at universities or public research institutions and new projects are often accompanied by a shift in priorities. Ruttan (2001) describes how in the United States the success of science in advancing military technology during the war, most notably the 'Manhattan project' created the belief that advances in scientific knowledge could become a major source of economic growth and human welfare. The author notes that different US administrations have each emphasised different social objectives. While in the 1960s military objectives have been expanded to include the conquest of space, during the Johnson and Nixon period an effort was made to shift resources to areas more relevant to President Johnson's 'war on poverty'. Nixon moved the basic research agenda to energy, control of natural disasters, transportation, drug control and most famously the 'war on cancer' to "demonstrate that the same focusing of scientific capacity that led to man's landing on the moon could also result in a cure for cancer" (ibid. p. 556).

Many governments would view their funding of basic research activities as a sufficient means to support technological advance. Hindsight tells us that the faith in targeted government funding of basic research is perhaps exaggerated and more recently governments, not only in the US, have reduced their support for basic research and led them to contemplate restrictions on the dissemination of the result of publicly-funded basic research (Mowery and Rosenberg 1989).

A possible reason for the lack of success of targeted basic research programmes is that public investment in R&D tends to 'crowd out' private investment, so that the total net increase in R&D is sometimes negligible. Hence, a subsidy-based incentive policy can be judged effective if it increases *total* R&D spending as a result of the subsidy. Any policy which simply replaces private R&D which would have been carried out on the same timescale has little justification (Metcalfe1995). This is also referred to as the 'additionality' problem.

Evidence of crowding out is inconclusive. In a review of the literature Mowery (1995) finds that federal funding of industry basic research produced offsetting decreases in private funding of basic research, while government basic research spending led to higher levels of private R&D expenditure in process development, i.e. during the later stages of the R&D process. This thesis has also investigated the possibility that some crowding out through targeted government financing occurs in research and development of vaccine products. In this study publicly held patents in the area of vaccines were used as a proxy for R&D undertaken or financed by government. In the error correction specification of the model, the changes in the number of publicly held patents over a 23 year period were positively associated with short term changes in R&D intensity in this area of research. While the interpretation of these short term dynamics is somewhat difficult, there appears to be no evidence of public investment crowding out private investment in vaccine research.

A form of government support which leaves the private sector more discretion as to where it directs R&D investment are tax incentives in favour of R&D expenditure, or R&D tax credits as they are often called. R&D tax credits are used in the US, Australia, Sweden, and have been recently introduced in the UK for small and medium-sized enterprises.

R&D tax credits allow firms to offset a certain percentage of R&D expenses against their tax bill. As a minimum provision in all G7 countries, R&D expenses are treated like any other current and capital

expenditure and can be offset in their entirety against the tax bill. Expenses on R&D capital expenditure are often depreciated over a certain period, some tax systems allowing an accelerated depreciation.

The R&D tax credit will allow companies to offset a certain percentage of their R&D expenses in excess of 100%. The base for this extra allowance is often an incremental increase in companies' R&D expenditure, i.e. extra R&D rather than total R&D will be rewarded through a reduction in cost of the increase in R&D. The United States, for example, provides a 20 per cent R&D tax credit to all research expenditures that exceed a company's predicted R&D expenditures for a taxable year. This credit was enacted in 1981 and has been continuously extended ten times. Congress has recently approved a five-year continuous extension of the so called research and experimentation (R&D) tax credit, from June 30, 1999 to June 30, 2004.

The reason for the temporary nature of the R&D tax credit is that tax credits come at a considerable cost to the tax payer. One should also bear in mind that the reason for government support is the existence of R&D spillovers. Should these spillovers accrue in a country other than the country granting the tax credit, the rationale for the tax credit is somehow weakened. Hall and Wosinka (1999, p. 4) concedes that the specifically Californian R&D tax credit may not have the desirable effect, since:

> "it would seem that encouraging firms to locate their R&D facilities in the state of California might not yield benefits that are easily confined to the state; in fact, most of the spillovers might flow to those outside the state.

However, there appear to be reasons that high technology firms in the same industry like to locate next to each other so that:

> "encouraging firms to move to your state early in the development of a new industry will probably mean that other firms will be attracted in the

future, and that other firms in the state are more likely to benefit from knowledge spillovers from the industry because of their geographical proximity" (ibid., p.4)

This reasoning is, of course, also relevant for R&D tax credits in other closely-integrated economies such as the EU, where countries attempt to be among the first to attract high-tech clusters through preferential tax treatment or otherwise.

Bloom et al. (1999) use a panel of data on tax changes and R&D spending in nine OECD countries over the period 1979-1997. They find that tax incentives are effective in increasing R&D intensity. A 10 per cent fall in the cost of R&D stimulates just over a 1 per cent rise in the level of R&D in the short-run, and just under a 10 per cent rise in R&D in the long-run.

In the short run, however, the total revenue lost from the granting of R&D tax credits appears to outweigh R&D expenditure induced by the tax relief, a result confirmed by Mansfield (1986b) who finds a ratio of between 0.3 and 0.4 of incremental R&D spending as a proportion of tax revenue forgone.

These results do indicate, however, that an R&D tax credit can in the long run be effective in raising R&D expenditure. The results of this thesis, although not specifically measuring the effects of tax credits, can also be interpreted in favour of the effectiveness of R&D tax credits. R&D tax credits lower the cost of R&D finance through an increase in the company's cash flow. This effect was previously shown to be positively related to a firm's R&D spending.

Griffith (2000) points out that this does not necessarily make R&D tax credits desirable. In her view, the rise in R&D expenditure may also be due to a re-labelling of activities, or a rise in scientists' salaries, rather than a genuine increase in knowledge output.

Hence, R&D tax credits raise serious cost-benefit questions, which are common to most forms of government subsidies. For reasons outlined above[7], overall benefit of R&D tax credits are notoriously difficult to measure and increases in industrial R&D often fall short of the revenue forgone, which has led Metcalfe (1995, p. 441) to dismiss R&D tax allowances in general, and find them "a blunt instrument with small effects".

There are of course a number of policy instruments which are less target-oriented but take inspiration from the idea that faster knowledge diffusion and easier access to new information for those undertaking R&D will positively impact on economic growth and productivity. This fits reasonably well into the notion of a *diffusion-oriented* science and technology policy.

Introducing a different terminology, Justman and Teubal (1986) would call the measures discussed so far 'tactical' measures, since they are often aimed at the development of specific technologies, and consider policies aimed at the innovation infrastructure in an economy 'strategic' measures.

When the emphasis is laid on diffusion of knowledge or knowledge/technology transfer from one institution to another, networks of innovation and the connectedness of the institutions with one another become important subjects of investigation.

Of course many different institutions are involved in this process of knowledge diffusion: not only firms, and universities but also government research institutions, banks, professional bodies and many more. Chapter Seven has in some detail reviewed the literature on research collaboration and networks of innovation, specifically in the biotechnology area, and this will not be repeated here. Metcalfe (1995) puts forward a

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[7] in particular the difficulty in estimating social returns to R&D.

number of key research questions which cover knowledge diffusion issues and which have been partly, although not exhaustively, addressed in this thesis:

The first question is concerned with the general direction of science and whether it should be directed more to supporting innovation. This is closely related to the question whether closer links with technology and research sponsorship from industry undermine the openness of science and its capacity to stimulate competitive development. This set of questions has been partly addressed with respect to biotechnology and pharmaceutical products in Chapter Eight. There is evidence that firms which show a greater proximity to science and which collaborate more closely with the scientific community show higher research productivity in the particular area of medical and specifically biotechnology research. What could also be shown is that the biotechnology companies in the sample were on average just as productive in research as the more traditional pharmaceutical companies, but showed a significantly higher exposure to the scientific community when compared to their pharmaceutical counterparts.

These results can be interpreted as follows: while there cannot be a target level of collaboration, the extent of which seems to be determined by tradition and the development of the specific industry, those firms within a given industry which seek to explore the science base either through collaboration or own basic research are likely to be more successful researchers.

Should 'connectivity' specifically between firms and universities therefore be promoted? This is a question more difficult to answer since in practice 'connectivity' is achieved via a variety of mechanisms (Metcalfe 1995). Beside collaboration agreements, mobility of scientists in the labour market in particular between universities and firms are important connecting mechanisms. The empirical investigation in Chapter Eight could not establish whether scientific success preceded or 'Granger

caused' technological success or vice versa. The former would have indicated that it is the scientific activity of the firm itself which makes it more successful in research. A reverse 'causality' would have led to the conclusion that successful firms attract scientists which happen to publish extensively without this proximity to science being a contributing factor to research success.

Whichever way causality runs in this case, the current trend in science policy to promote closer links between firms and the scientific community does not seem to be misguided.

The mobility of scientists leads to the second central question of 'strategic' science and technology policy according to Metcalfe (1995, p. 465):

> "Since science and technology compete for many of the same skills how should policy influence the distribution of creative talent between the two worlds? What should be the appropriate balance between research and skill formation in higher education institutions?"

The common view that a nation needs to educate and look after its own scientists has been recently popularised by Porter's (1990) 'competitive advantage of nations'. In Porter's view nations which produce a greater number of scientists per capita and will produce more leading edge research which in turn positively impacts on the nation's competitive advantage.

Sharp (1989) and Yuan (1987), to quote another example of this view, praise the sheltered environment of German academics, through the provision of a well-financed research budget and facilities, social prestige, and the security of being a public servant.

Bartholomew (1997) points out that a nation which does not look after its scientists may lose them to another nation, suffering from so called 'brain

drain'. In her view, the US competitive model is fed by very substantial expenditures on basic research, which provides the life blood of the system and so:

> "the failure to sufficiently support the basic scientific infrastructure remains a real concern in the UK, where the nation's strongest advantage – its superior pool of creative scientists - is increasingly drawn to other countries where scientific research is rewarded with financial support in addition to social respect" (ibid., p. 19).

Chapter Nine has addressed a number of these issues, in particular the question whether the alleged underinvestment in scientific infrastructure in the UK causes brain drain which should manifest itself in a flow of scientists out of the university sector and an underperformance of UK science compared to other industrialised countries. This study has found no evidence for either of these two possible effects. UK scientists are among the most productive researchers in absolute and relative terms, i.e. not only publish a lot of papers, but churn out the highest number of research papers per dollar of research funding.

More importantly, the British higher education sector experiences a considerably larger inflow of educated scientists from abroad (brain gain) when compared to, for instance, Germany, where entry barriers into the scientific labour market are much higher. Furthermore there is no evidence in any subject area that 'underpaid' scientist leave the scientific community in droves to benefit from the more lucrative terms in the private sector. On the contrary, strategically important disciplines such as biological sciences or Information technology experience a net inflow of scientists from the private sector.

What cannot be concluded with any certainty is what kind of skills are crossing the boundaries between science and technology. Scientist 'head counts' cannot distinguish between the Nobel price winner's exodus to the private sector and the failed technologist seeking refuge in the less

pressurised world of higher education. We have learned from the previous deliberations, however, that good scientists working more closely with the private sector can hardly be considered bad news.

10.4 Concluding remarks

A number of conclusions can be drawn in the context of two very different national systems of innovation, the US and Germany, and referring to the biotechnology industry as an illustrative example.

The success of the US biotechnology industry is probably due to two factors. Firstly, the commercial orientation of the university system and the close co-operation of biotechnology firms with universities allows both sides to recognise commercial opportunities of findings and gain a first mover advantage. Secondly, biopharmaceutical research appears to be sensitive to the cost of finance of projects and start-up companies have proliferated thanks largely to entrepreneurial academics and a functioning venture capital market.

Bartholomew (1997) points out that there is a downside to this focus on biopharmaceutical applications, which have the highest commercial value in the form of new drugs. The USA has not been able to develop a great breadth of expertise as for example in agriculture or environmental application of biotech, where other countries such as Germany are taking the lead.

German universities and the state financed Max Planck Institutes are devoted to pure scientific research and operate very distantly from industry. While they are slow in translating scientific advances into commercial opportunity they do not necessarily *lack*, but *lag* (ibid.) to link the science base with the industrial base. In the long run German firms may be able to recreate the American success in areas which are slower to reveal commercial opportunity.

In a diffusion-oriented system such as the German, innovators are further supported by extensive cooperation between industry and banks to secure finance, government, firms and education institutions to secure the right number of skilled personnel[8].

A cause for concern is, however, that such a rigid system may not be sufficiently flexible or responsive to support the kind of academic entrepreneur which has emerged from US universities: The venture capital market is underdeveloped; the academic labour market is not open enough to attract scientific talent from abroad or compensate for any outflow of scientists to universities abroad.

The 'sheltered environment' (i.e. a professorial position) may or may not be offered to a German academic at the end of a period of temporary employment (recently limited to a total of twelve years). Most scientists in other countries will have already obtained tenured positions (or be on a 'tenure track') by then or recognised their lack of scientific potential and secured more suitable positions in the private sector instead.

Under these circumstances foreign universities or high tech companies will continue to tap into the pool of expertise, which is not good news in a system which does not allow much entry from other sectors of the economy or countries.

Alternatively, scientific talent could be drawn out of the higher education sector into the private sector. Although evidence from Britain indicates that mobility between the two sectors works both ways, entry barriers in German higher education could make it more of a one way street.

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[8] The German 'dual system' of vocational qualification is considered very important for the competitiveness of German firms and requires a considerable planning effort. Each

This study indicates, however, that unless talent leaves the country for good, scientists crossing the Rubicon between science and technology is perhaps not such a great cause for concern.

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trainee will not only work in a firm but attend the local specialist secondary school for two days a week.

11 Conclusions

This thesis was motivated by concern regarding an apparent lack of investment in the research and development of vaccine products which could offer a dramatic net benefit to societies, particularly those affected by diseases such as Malaria and Aids, which are yet incurable and particularly prevalent in the developing world. The important contribution vaccines products can make to world health was briefly outlined in Chapter Two.

The aim of this thesis is, therefore, to provide decision support for science and technology policy which attempts to promote the research and development into new vaccine products.

The starting point of this investigation has been to establish that markets fail to allocate sufficient resources to the development of new vaccine products. In Chapter Three it was shown that reason for this is twofold. Not only are vaccine markets imperfect due to the existence of positive externalities and the impure public good aspect of vaccine products. There is also evidence of systematic underinvestment in research and development in general, because firms cannot fully appropriate the social returns to their investment.

Social returns to investment in excess of private returns to investment indicate the existence of R&D spillovers which justify government policy to increase the total volume of investment, either through direct or indirect science policy measures. Science policy can attempt to directly influence the direction of research through government subsidies or targeted fiscal support, or implement regulatory measures such as for example a patent system or policies designed to influence human capital formation.

In order to assess the effectiveness of individual science policy measures industry's response to a range of market and regulatory forces will have to be understood more clearly.

The microeconomic branch of the innovation economics literature was introduced in Chapter Four. Three determinants of R&D spending are often cited: technological opportunities, appropriability conditions and demand conditions. Much of the debate in the literature is related to the relative importance of these factors.

Some authors attribute technical change to the supply of innovation (technology push), others argue that demand induces industry to innovate (demand pull) while at least some empirical evidence suggests that both factors are equally important.

Most empirical studies will however be compromised by the unclear distinction between need and demand which reflects the lack of consideration of the role of the entrepreneur to foresee potential demand.

Pharmaceutical economists attribute great importance to regulatory factors, which can influence a firm's R&D spending decision negatively through, for instance, a more stringent drug approval regulation, or positively through improved patent protection, both affecting what is referred to as appropriability conditions.

Evidence from case studies suggests that drug companies are facing diminishing returns to R&D. The finance literature suggest rising cost of finance depending on whether new projects are financed through cash flow, new debts, or whether new equity finance will have to be raised. The combination of diminishing returns and rising cost of finance makes an R&D resource allocation model plausible which sees firms equate the return on the last R&D project (marginal return) with rising marginal cost of funds (due to differences in the cost of internal and external finance). The optimal level of R&D spending is where marginal return to R&D equals marginal cost of R&D and factors influencing the expected returns to R&D or cost of funds schedule are likely to influence the firm's R&D spending decision.

These factors were discussed in Chapter Five in the specific context of the global vaccine industry. The industry can be broadly divided into European and American manufacturers, which are pursuing two very different strategies with regard to scale and international exposure.

American vaccine manufacturers supply almost exclusively to their domestic market which allows a return on investment similar to pharmaceutical products. This is partly due to a new generation of genetically engineered paediatric vaccines launched in the second half of the 1980s and early 1990s. These products gain market share very rapidly and are the first vaccines to enjoy full patent protection.

European manufacturers operate on a much larger scale than their US counterparts and rely quite heavily on price-sensitive export tenders. These firms' return on investment depends to a large extent on economies of scale effects which are very significant in vaccine production.

R&D investment into vaccines as a proportion of sales by US manufacturers declined for most of the 1970s which appears to have reflected poor patent protection, uncertainty over liability for vaccine injuries and exhausted technological opportunities during this period. Some crowding out by public sector research may also have occurred.

The early 1980s have seen a reverse in R&D intensity which may be attributable to biotechnology as a new technological paradigm with many new vaccines derived from genetically modified organisms. A 1980 US Supreme Court ruling has also granted patent protection to biological products for the first time. Since 1988 US manufacturers also benefit from the National Vaccine Injury Compensation Plan (NVICP) which has relieved them, at least domestically, of any liability for vaccine injuries.

Chapter Six models R&D spending in the US vaccine industry over a 25 year period. In a simple partial adjustment model, changes in cash flow (deflated by sales) and past values of R&D intensity appear to positively impact on the

intensity of research and development (defined as R&D spending divided by sales) in the vaccine industry.

Other factors, such as the size of the vaccine market relative to pharmaceutical products (as a proxy for 'demand pull'), or the share of vaccine related patents held by public sector institutions (testing for evidence of 'crowding out'), were not significantly related to research intensity, at least in the partial adjustment specification. Neither was there any evidence of a structural break after the extension of patent protection for biological products in 1980 or the implementation of the NVICP act in 1988, two events which were expected to have a positive impact on firms' R&D spending behaviour.

Concerns over non-stationarity of the data series and a possible spurious regression led to the estimation of an error correction mechanism which, in the final form, confirmed the results of the partial adjustment model.

More specifically, the results emphasise the long run relationship between the cost of funds and the allocation of R&D resources. This has implications for a range of policies to promote industrial research and development. Any such measures designed to lower the cost of funds seem likely to yield the desired response in private R&D spending. Such support often comes in the form of R&D tax credits which increases the firm's cash flow and hence lowers the cost of finance. The above investigation suggests that such measures can be effective.

In the absence of government help, a capital market which is geared towards providing risk capital to innovators seems more likely to stimulate private R&D spending than a capital market which is risk averse, and as a result makes the financing of 'risky' R&D activity prohibitively expensive. The extent to which the US venture capital market has contributed to the success of the national biotechnology industry is, of course, well documented.

The literature suggests that firms will also increase R&D spending as a response to an increase in expected returns to R&D. This cannot be ruled out,

since the variable used here as a proxy for the relative costs of funds will not allow the researcher to fully distinguish between cost of funds and expected return effects.

Further to that, the significant error correction term indicates that firms will adjust to disequilibria in the long run relationship between the cost of funds and R&D intensity. The error correction specification of the model has also revealed two factors influencing short term variations in R&D spending. Changes in R&D spending in the previous period is a good indicator of changes in current R&D spending. This pattern is expected, since most R&D projects are longer-term and require the firm to devote a continuous stream of resources over a longer time period.

The model also suggests positive short run influence of year-on-year changes in public sector research effort on changes in the firm's R&D intensity. It is difficult to envisage the short term dynamics of this relationship given the rather crude nature of the variable used as a proxy for public R&D effort. What can be stated, however, is that public sector research effort does not appear to 'crowd out' or replace private sector R&D spending in the short term.

The exclusive focus on vaccine-producing manufacturers will not allow for a large number of observations and given the more general relevance of the findings for science and technology policy, future research could be directed at the pharmaceutical industry as a whole. This would allow the collection of data on an individual firm level over a longer period of time. This pooling of data will increase the number of observations considerably and will result in a model with greater predictive power.

In the remainder of this thesis the scope has been extended to include firms in the biotechnology industry. The reason for the shift in emphasis is that biotechnology is becoming increasingly important for vaccine innovation, with almost a quarter of new biotechnology products in development being vaccines.

The focus of research in Chapters Seven and Eight is on collaborative research in the biotechnology industry, since joint research between the private and public sectors is believed to be a particularly productive way to bring new medicines to the market.

Collaborative research has grown in importance since the first biotechnology companies were established in the 1970s. Depending on the stage of the life cycle of the individual firm, a biotechnology company will either seek to strengthen its scientific base by collaborating with a public sector institution such as a university, or at a later stage collaborate with a larger pharmaceutical company in order to distribute or market its products. Having products at different stages of development requires firms to enter networks of alliances.

There is evidence in the literature that firms which maintain close links with the scientific community are more successful researchers in terms of patents obtained. This thesis has empirically investigated the research productivity of a sample of large biotechnology and pharmaceutical companies in the United States. Using the number of papers published per research dollar spent as a proxy for basic research and the number of co-authorships as a proxy for public-private interaction, Biotech companies undertake on average more basic research and interact more closely with the university sector than traditional pharmaceutical companies. While showing a much greater variance, the average research productivity of the biotech companies in the sample is also greater than that of the traditional pharmaceutical industry.

Within each of the two sectors, companies which undertake more science or co-operate more closely with universities than their competitors are likely to show a higher level of research productivity. This confirms earlier findings for the pharmaceutical industry.

What did not become clear from the original specification of the model is whether greater proximity to science does indeed *cause* greater research productivity. Some authors suggest that the interaction with scientists makes

the firm more productive in research, while others believe that a firm which is successful in research attracts those scientists, who tend to publish more than their peers. In other words, good scientists may follow research success rather than cause it.

The implications of the latter scenario for science and technology policy would be very different indeed, since publications can be seen as a necessary evil rather than a warrant for research success. Hence, the issue of causality required a closer investigation.

Although evidence from a Granger causality test proved to be quite weak, it cannot be ruled out that research productivity precedes the number of publications. The consequences of this, not only for science and technology policy but also the firm's research strategy, are twofold: Proximity to science may not *cause* superior research outcomes and there are some indications that successful companies attract scientists and generate publications almost as a by-product. The analysis also suggests, however, that companies which employ good scientists are the more productive researchers, not necessarily because they interact with science or publish papers, but because they have talented employees which are more likely to produce good medicines.

This makes the promotion of scientific talent and the movement of scientist between the public and the private sectors an important issue to investigate, in particular when it comes to designing an effective national system of innovation.

Chapter Nine has addressed a number of these issues, in particular the question whether the alleged underinvestment in scientific infrastructure in the UK causes an outflow of scientists from the university sector possibly to other countries (brain drain) and an underperformance of UK science compared to other industrialised countries.

It was found that discussions of the need for investment in higher education research and development ignore the considerable variations in research

productivity associated with different levels of investment. UK scientists are among the most productive researchers in absolute and relative terms, i.e. not only publish a lot of papers, but churn out the highest number of research papers per dollar of research funding. Britain's strong performance in published research suggests that the institutional structures of higher education have a much more important effect than was previously thought. More open 'Pyramid' systems may have greater potential for innovation and research productivity than 'Tower' systems where there is little inflow or outflow of personnel at higher levels of the hierarchy.

More generally, a country which imports highly-skilled personnel may be enabled to maintain or improve its technological capabilities by this means as well as by domestic investment in research, development and the training of domestic skilled labour.

The British higher education sector experiences a considerably larger inflow of educated scientists from abroad (brain gain) when compared to, for instance, Germany, where entry barriers into the scientific labour market are much higher. Using data from the Higher Education Statistics Agency (HESA), there is no evidence that scientist leave the scientific community to benefit from the more lucrative terms in the private sector in any of the subject areas investigated. On the contrary: disciplines believed to contribute more than others to current and future growth of an economy such as biological sciences or information technology experience a moderate net inflow of scientists from the private sector.

What cannot be concluded with any certainty is what kind of skills are crossing the boundaries between science and technology. The scientist 'head counts' used here could not distinguish between star scientists and junior researcher and future research into the movements of scientists might want to look at the specific type of skill associated with these movements.

This thesis concludes with Chapter Ten which aims to put the findings of the thesis in the wider context of science and technology policy.

National systems of innovation differ considerably and can be broadly distinguished into mission- and diffusion-oriented systems. In practice, national system of innovation would lean towards either of the two systems, and rely on a mix of policies to promote research and development.

Mission-oriented systems such as the United States generally rely on functioning venture capital markets to select promising R&D projects and promote academic entrepreneurs. As a prerequisite to an effective knowledge transfer and rapid commercialisation of innovations, scientific labour tends to be highly mobile between universities and also universities and the private sector.

Mission-oriented systems tend to create short-term R&D investment decisions. Long term research programmes with highly uncertain outcomes, such as the important 'war against cancer' or the more controversial 'missile defence shield' are then (often exclusively) financed by government.

This thesis' findings support the effectiveness of the principal design of mission-oriented systems. What could be shown is that firms' R&D decisions are sensitive to the cost and availability of finance. A good example for this is the proliferation of the US biotechnology industry which has proliferated thanks largely to entrepreneurial academics and a functioning venture capital market.

Diffusion-oriented systems emphasise the transfer of knowledge from universities to the private sector because, traditionally, basic scientific research operates more distantly from industry.

While these systems are slow in translating scientific advances into commercial opportunity, they may be able to recreate commercial success stories such as biotechnology in areas which are slower to reveal commercial opportunity. Innovators are further supported by co-operation between industry and government to secure the right number of skilled personnel.

Some national innovation systems may, however, not be sufficiently flexible or responsive to support the kind of academic entrepreneur which has emerged from US universities: Venture capital markets, particularly in continental Europe, are underdeveloped; and the academic labour market is not open enough to attract scientific talent or compensate for any outflow of scientists to universities or companies abroad.

What is beyond doubt, is that vaccine research and development offers considerable social gains which cannot be fully appropriated by private enterprise. Expected private return on vaccine products is further compromised by uncertainty over the future market size and scientific feasibility of new vaccines. If this is the case, any innovation system will have to resort to targeted government or donor financing for projects deemed too risky and long term by academic entrepreneurs.

This does not mean that institutions entrusted with the task of developing vaccines should derive exclusively from the public sector. Collaborative research between biotechnology firms and universities has been shown to work effectively and more successfully than institutions operating on their own.

Since entrepreneurs have a role to play in the development of future vaccines, any national system of innovation cannot ignore the importance of the cost and availability of funds on the R&D spending decisions of these firms. The marginal R&D project, which could after all be the future malaria vaccine, is more likely to be developed if the cost of R&D funds are low enough to compensate for the considerable risk of vaccine projects.

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