INNOVATION IN THE PHARMACEUTICAL INDUSTRY

A Study of the Effects of Regulation on the U.K. Pharmaceutical industry

Carl William Peters

Presented in partial fulfilment
of the requirements for the degree
of Doctor of Philosophy

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A history of government drug regulation and the relationship between the pharmaceutical companies in the U.K. and the licensing authority is outlined. Phases of regulatory stringency are identified with the formation of the Committees on Safety of Drugs and Medicines viewed as watersheds. A study of the impact of government regulation on industrial R&D activities focuses on the effects on the rate and direction of new product innovation. A literature review examines the decline in new chemical entity innovation. Regulations are cited as a major but not singular cause of the decline. Previous research attempting to determine the causes of such a decline on an empirical basis is given and the methodological problems associated with such research are identified.

The U.K. owned sector of the British pharmaceutical industry is selected for a study employing a bottom-up approach allowing disaggregation of data. A historical background to the industry is provided, with each company analysed on a case study basis. Variations between companies regarding the policies adopted for R&D are emphasised. The process of drug innovation is described in order to determine possible indicators of the rate and direction of inventive and innovative activity. All possible indicators are considered and their suitability assessed. R&D expenditure data for the period 1960-1983 is subsequently presented as an input indicator. Intermediate output indicators are treated in a similar way and patent data are identified as a readily-available and useful source. The advantages and disadvantages of using such data are considered.

Using interview material, patenting policies for most of the U.K. companies are described providing a background for a patent-based study. Sources of patent data are examined with an emphasis on computerised systems. A number of searches using a variety of sources are presented. Patent family size is examined as a possible indicator of an invention's relative importance. The patenting activity of the companies over the period 1960-1983 is given and the variation between companies is noted. The relationship between patent data and other indicators used is analysed using statistical methods resulting in an apparent lack of correlation. An alternative approach taking into account variations in company policy and phases in research activity indicates a stronger relationship between patenting activity, R&D expenditure and NCE output over the period. The relationship is not apparent at an aggregated company level. Some evidence is presented for a relationship between phases of regulatory stringency, inventive and innovative activity but the importance of other factors is emphasised.

Keywords

Innovation: Regulation: Patents: Pharmaceuticals: Indicators.

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CHAPTER ONE: GOVERNMENT REGULATION OF INDUSTRIAL RESEARCH ACTIVITIES.

1.1 General introduction

Rapid technological change over recent decades has resulted in new hazards to society and the environment. To protect the interests of society Government has instituted a series of controls over many aspects of industrial activity. These include specific regulations which, although aiming to reduce the risks and dangers to society, have increased product costs and lengthened development times. This is an indirect effect of regulation and the general impact of regulations on the rate and direction of innovation is of particular importance. The chemicals industry and the pharmaceutical industry as a specific example are industries which have a history of regulation and are appropriate areas in which to examine any regulatory impacts.

Many studies have attempted to analyse the broad impacts of regulation whilst others adopt a case-study approach. Both methods have been troubled with complex methodological problems. If the drug industry is taken as an example, one major problem has been the limited in-depth knowledge of the process of drug innovation. This study will review the regulatory processes including the historical perspectives and, concentrating on the drug industry will trace the impacts of the regulatory system on the innovation capacity of the industry.

Before justifying a study of the drug industry, it is appropriate to review the growth of regulation in general.

1.1.1 The growth in regulation of industrial activities

As a focus for study regulation presents a unique position due to its widespread influence and the involvement of many different groups in such activities.

> "of all the factors which have influenced the pace and pattern of U.K. industrial growth in the last fifty years, probably none has been more significant than the widespread acceptance and application of the fruits of scientific discovery on the one hand, and the increased participation of the State on the other and the triangular relationship between science, industry and the State is often an all-pervading one." (1)

Taking the USA as an example, it is evident from figure 1.1 (2) that regulation by the State is not a recent phenomenon, what is significant is the increase in regulatory demand over the past few decades. A greater degree of control over industrial practices is now exercised by Governments, the pattern shown in the figure being equally applicable to the U.K. situation.

State regulation can be divided into policies that encourage industrial activities and those that seek to control or limit industry, though as will be demonstrated this distinction may be too simplistic. Generally however, regulation may be seen as a means of directing technology and the increase in such control may be attributed to an interaction of political, social and economic factors.(3)

The legal frameworks that had existed for controlling industry up to the mid 1960's were increasingly shown to be insufficient to deal with the new technological problems. The early measures were mainly economic based on market mechanisms designed to deal with economic sanctions and the demands for a more coherent regulation of scientific activities increased.

Worldwide political lobbying encouraged Governments to establish a series of ad-hoc institutional arrangements to protect society and the environment from undue risk or harm. The situation in the USA was typical and control measures proliferated to such an extent that many EEC countries are even today attempting to come into line with the requirements and regulations in force in the USA. The rationale behind the growth in regulation was that industrial activities were to be brought in line with the public interest. (4)

Figure 1.1

A Decade by Decade Comparison of Major Regulatory Legislation

Source: (2)

Nelkin (5) argues that three broad mechanisms exist for the control of technology:

1. A participatory system utilising pressure groups, trades unions and other professional bodies in a lobbying process.

2. A reactive control using regulatory agencies, often induced by an incident which the agency is too late to prevent.

3. An anticipatory control, a more recent development making use of the techniques of technology assessment and forecasting.

These three types of control can operate together or individually and may also represent the evolution of control mechanisms.

1.1.2 Types of regulation

Generally, regulations can be sub-divided into categories which include price control, control of market entry and specific workplace regulations, pollution controls and product regulation. These manufacturing regulations may be extended to encompass product safety before and after marketing, product efficacy, control of production, effluent, emission and waste and safe transport of hazardous material (6). In the case of the pharmaceutical industry, most of these will apply as well as the economic sanctions described.

Fundamental questions can be raised concerning the justification for regulations, this matter is not surprisingly fraught with political, moral, ethical and financial arguments and it seems more appropriate to concentrate, as Newburger would have it, on the type of regulation rather than argue over the question of intrusion of personal freedom (7). He finds justification for regulation, "if it induces conformity with some standard of conduct that through the democratic process we have come to prefer".

Whether the standards of conduct or type of regulation promulgated are preferred by society or industry is often of secondary importance compared with the conflict of interests that often arises following establishment of controls. It is this debate that will be the subject

of this study, the pharmaceutical industry being the focus. Firstly the regulation of the chemical industry in general will be reviewed followed by a study of regulation in the pharmaceutical industry.

1.1.3 Regulation of the chemical industry

The chemical industry has been one of the most stringently controlled due to the characteristics of the industry. A high rate of innovation and technological success based on a privately-funded,research intensive operation coupled to a history of managerial innovation are the important features (8).

The nature of the products is important to consider and the processes by which they are discovered and developed have become rigorously controlled. Incidents with DDT, 2,4,5-T,vinyl chloride and asbestos have ensured that the public are rapidly made aware of any technological hazards by the media.

The chemical industry has a history of control and the traditional control mechanisms were replaced with new approaches as an alternative to the allocation of any new regulatory body. The table below shows the 'traditional'and 'recent' approaches.

Table 1.1.

Regulation characteristics	'Traditional'	'New'
Jurisdictional boundaries	Fear of monopoly or destructive competition	Solve social or economic problems
Goals	Ensure health of industry	Not a goal
Evidence used	Financial or commercial	Scientific or technical
Instruments	Approval of prices, entry, exit mergers	Specific enforcements

Traditional and recent approaches to regulation

The new legislation of the 60's and 70's was seen as favouring the interests of society and having little to do with maintaining the security and profitability of the companies. Increasingly, scientific improvements in the ability to measure minute levels of pollutants led to stricter standards to prevent contamination. This approach was criticised by representatives of industry who argued that the demands were unreasonable and had little regard to the practical benefits of such high standards. Artificially high standards were thought to have been set by the government, a problem common to many industries.

The pharmaceutical industry has many characteristics common with those of the chemical industry in general, including the dependence on innovation based on privately funded R & D. This has led to a comparable level of regulation but with some distinct differences due to the type of product, their use and associated risks. The drug industry is perhaps more akin to the foods industry and the long historical relationship between the two would support this.

That the chemical industry is heavily regulated is impossible to deny and as a result, this has led to an examination of the impacts of regulation on the economic and technological activities of the chemical and more specifically the pharmaceutical industry. It is a useful starting point to examine the inter-relationship between industry, government and society and how regulation fits into this framework.

1.1.4 Industry, Government and Society

In the implementation of regulations, the government has an unenviable role to play. On the one hand industry creates wealth, jobs and services thereby contributing to the balance of payments (particularly the drug industry see chapter three) whilst on the other hand, industry has the capacity to cause undue harm to society as discussed earlier.

Government therefore has to perform a delicate balancing act between the desire to protect society and to stimulate industrial innovation and the latter predominates in times of recession. Pressure groups representing on one hand industry and on the other 'society' have argued at different times that the pendulum of regulation has swung too far in one direction or the other. Industry maintains that the cost of compliance is prohibitive and that society must pay for the level of protection offered. The critics of industry argue that excessive profits are obtained whilst hazardous workplace conditions are endured and potentially lethal products manufactured. Both viewpoints co-exist and it is the role of the government to balance the controls and ensure that a working compromise is reached. Whether this compromise favours one side or another is a point of debate. In this Industry-Government-Society relationship the role of each of the sides needs to be kept distinct with no obvious collusion if the regulatory system is to operate satisfactorily.

The drug industry represents an industry which is heavily regulated, interacts with society and Government and argues that regulation has had a serious impact on the rate and direction of innovation. The drug industry is therefore the focus of this study and prior to an examination of the impact of regulation on the industry it is necessary to outline the development of drug control in the U.K. Several distinct phases in terms of the severity of control will be shown to have existed.

1.2 Drug regulation in the United Kingdom

1.2.1 History of drug regulation

Drug control has a long history (9), an early move to standardise drug products in Britain occurred when the Select Committee on patent medicines published its recommendations in 1914. They amalgamated the plethora of laws concerned with drugs and instituted an early monitoring system under the control of the MRC which formed a framework for future legislation.

A number of Food and Drugs Acts were passed and until the 1950's drug control was the responsibility of a number of unco-ordinated authorities. This unconsolidated structure may be explained by a number of factors including the fact that many medicinal products of the time were ineffective but non-toxic and thus of little concern to the medical profession.

However the system began to receive criticism from a number of quarters as the field of toxicology had arisen and furthered knowledge regarding the effects of toxic substances on animals.

In 1949 the Advisory Council onScientific Policy established a sub-committee on toxic substances in consumer goods under the chairman Zuckerman (10). The committee was asked, 'To examine existing arrangements for regulating ingredients or processes potentially injurious to health used in the preparation of foods, beverages, drugs, cosmetics, insecticides and other substances intended for contact with the human body, and, if desirable, to make recommendations for the better control of these substances and processes'.

The following year, 1950, the committee reported and maintained that the level of knowledge of toxicology was low particularly in the case of chronic exposure. Acute toxicity, they argued, was relatively easy to detect. In order to further develop the field, the assistance of industry was sought mainly for co-operation in establishing a Central Toxicology Laboratory under the control of the MRC. The rapid growth of the consumer goods industry was instrumental in the formulation of more effective control and monitoring of toxic hazards. This development was again not linked to any other existing legislative instruments and merely added to the lengthening list of controls.

The medical profession was aware of the problem and made appeals for a more structured approach to the control of drug products. A suggestion was made by G. Discombe in 1951 (Central Middlesex Hospital) for the formation of a committee to collect evidence concerning drugs and to control any harmful ones (11). Within a decade an incident had occurred that had worldwide impact and repercussions throughout the drug industry and ensured that State control was rationalized, extended and strengthened. Thalidomide, as the drug was known in Britain, was a product of the Chemie Grunenthal Company of West Germany marketed in Britain by the Distillers Company for the first time in April 1958. Thalidomide was a sedative-hypnotic found to be effective and non-toxic in all animals used by the German company in testing.

After a few months of use in Britain, reports of congenital malformations in newly born children resulted in the products being withdrawn from world markets and failing to obtain marketing approval in others including the US. This incident with Thalidomide has been well-documented (12) and needs little further scrutiny except to recognise

the fact that this episode galvanised the governments of many of the countries affected into action regarding the type and effectiveness of domestic drug controls. In the US, the experience of other countries with the drug was a significant contributory factor in the formulation and subsequent enactment of the 1962 Kefauver-Harris Amendments to the 1938 Food Drug and Cosmetics Act. As Wade so succinctly put it, "The dawn of concern about adverse reactions had broken, its light has increased in the intervening years but even now it does not shine in every corner". (13) The complete history of drug regulation in the US has been researched by Temin (14) but the history of control in the UK is distinctly different from its American counterpart in terms of philosophy, organisation and administration.

The drugs produced by the Industry and marketed in the 1950's were powerful therapeutic tools compared with the products generally available in previous decades and were designed to treat conditions which until then had no effective drugs. These new drugs carried with them higher risks of iatrogenesis or drug-induced disease and the consumer was placed in a position of having inadequate knowledge concerning the products and was thus unable to make any rational decisions regarding choice of treatment.

In Britain, Thalidomide may have been an important stimulus to society to demand a more effective testing of drug products but this idea was already incorporated in the 1959 Report by the Poisons Board to the Home Office, expressing the need for legislation controlling the new generation of potent drugs which were not covered by the poisons regulations. The only regulation in force that covered non-addictive drugs being the 1956 Therapeutic Substances Act. This Act could be used to regulate sera, vaccines, injectable antibiotics and certain hormones and enzymes, clearly not broad enough to incorporate

the pre-marketing approval of most new drugs.

Significant political activity followed the reporting of the Thalidomide cases in Britain and a scrutiny of the Parliamentary proceedings of the time together with a review of the resulting reports, forms a useful point of reference to assess the attitude towards regulation that existed at the time.

As the Opposition Health Minister of the time Kenneth Robinson, was at pains to point out following Thalidomide, "The House and public suddenly woke up to the fact that any drug manufacturer could market any product, however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy or safety". (15)

The lack of any structured control of drug marketing was emphasized in May 1962 when Parliament was told that over half the drugs issued under the NHS had not been correctly tested (16). The responsibility for this testing, argued the Government, was that of the manufacturer and doctors had the ability to discriminate against unsatisfactory drugs by refusing to prescribe such products. Having raised the problems encountered with Thalidomide, Mr. Pavitt asked the Minister of Health Enoch Powell to establish a central body to ensure that all drugs used in the NHS were approved. The Minister replied that he had no powers to establish such a body.

The demand for some central control was a recurrent theme over the next month and in June 1962 a positive licensing system administered by the MRC was proposed (17). Opposition to this idea was based on the inability to guarantee the absolute safety of every new drug. No system of control, Parliament was assured, could have prevented the Thalidomide tragedy (a viewpoint still held by the anti-regulatory lobby). The authority of the doctor to choose appropriate drugs was once again used

as an argument against central control. The benefits and economic achievements of the drug industry and the professional integrity of its members were also underlined. This use of an economic argument for the justification of a freedom from control is not peculiar to the drug industry.

Although no decisions were publicly made during the 1962 Parliamentary session, the topic of drug control was raised again in 1963. A major debate on the NHS in May included a debate on the control and safety of drugs (18). It was during this debate that Kenneth Robinson stated his concern over the negative attitude of the Government Health Minister. Only after constant Opposition pressure was the matter referred to the Standing Medical Advisory Committee. They were asked to consider particularly the possibility of establishing a Statutory body for drug regulation. The Committee established a Joint Sub-committee of the English and Scottish Standing Medical Advisory Committees under the Chairmanship of Lord Cohen of Birkenhead(19)

The subsequent report of the Sub-committee was described by Robinson as "utterly unsatisfactory and disappointing" basically because they had proposed the formation of a non-statutory expert committee to deal with the review of evidence and advice regarding drug toxicity. The onus of responsibility was still on the manufacturer for the testing of any new product. The Cohen Committee did however also propose aspects of control dealing with labelling, quality control and regulation at the point of sale which they considered important.

The Cohen report also stated that "These arrangements themselves would obviously be more effective with legislative sanction than without and we are satisfied that legislation on the whole matter is urgently required"(20). The Committee agreed that mid-Victorian legislation

was unsatisfactory for modern drugs and that the subsequent "patching up operations" of the penicillin Act and the TSA were merely ad hoc and inappropriate. The review of all UK drug legislation was thought however by the committee to be a major undertaking and was necessary prior to the introduction of any significant new legislation.

Robinson was keen to point out that this review had been carried out by an interdepartment working party which had reported to the Minister in July 1962. This unpublished minority report saw no virtue in a non statutory system as a temporary expedient. The authors listed three major deficiencies, namely the non-cooperation of industry, the limited number of weak sanctions and the fear of providing a facade of safety without the reality. This opinion had however been ignored and the Opposition Health Minister noted with some regret that the Chairman and members of the suggested regulatory body had already been chosen. This, Robinson suggested, "...leads one to think that the Right Honourable Gentleman received the recommendation for which he had hoped" and accused the Minister of a dereliction of duty.

The opinions reported in the minority report hadthe support of the medical profession and the Pharmaceutical Society which held a press conference to air their fears over the temporary measures becoming permanent. The Cohen proposals had however the support of the ABPI (The Association of the British Pharmaceutical Industry) and the PAGB (Pharmaceutical Association of Great Britain) (21). Enoch Powell as Health Minister emphasised the "effective teeth" of the new system with the suggestion that doctors would only prescribe drugs that had obtained clearance from the regulatory body. This body would have the powers to

ensure the adequacy of clinical trials and that any subsequent legislation would be sounder, more practicable and better based as a result of experience under the voluntary arrangements. An important point was made by the Health Minister when he stated that absolute safety was impossible to guarantee and that relative safety was the limit of practical control. The prevention of Thalidomide type tragedies was difficult to ensure and reference was made to countries in which drug regulations existed but were unable to forecast or prevent congenital abnormalities induced by Thalidomide-containing drugs. Canada, Norway, Sweden and Denmark were cited as examples of such countries. Sections of Parliament remained unconvinced by the voluntary system. A further argument against the voluntary system stated that the public were acutely aware of the dangers of drugs and a delay of a year whilst legislation was drafted would be acceptable. Further, if legislation were demanded, a White Paper could have been produced by October 1963 and a Bill by Spring 1964.

The voluntary system proposed by the Cohen Committee was put into practice with the establishment of the Committee on Safety of Drugs (CSD) under the Chairmanship of Sir Derrick Dunlop. This Committee which became known as the 'Dunlop Committee'had no legal powers and was independent of the Ministers (22). The committee met for the first time on 6th June 1963 and came into full operation on the 1st January 1964, marking a turning point in the history of drug regulation in Britain.

The period prior to the debate over Thalidomide can be viewed as a period of relative freedom from regulation. Some anticipatory effect may have been felt in the drug industry prior to the setting up of the CSD, this being important if a temporal study of the rate and direction of innovation in the industry is to be conducted.

1.2.2 The Committee on Safety of Drugs

"There is a general consensus that the sole responsibility for the safety and efficacy of drugs cannot be left entirely to the manufacturer or prescriber" (23).

Philosophy

The terms of reference of the Committee were as follows:(24)

1. To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be made, and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted reports.

2. To obtain reports of clinical trials of drugs submitted thereto.

3. Taking into account the safety and efficacy of each drug and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports.

4. To give manufacturers and others concerned any general advice they may think fit on the matters referred to in paragraphs 1 - 3.

5 To assemble and assess reports about adverse effects of drugs in use and prepare information thereon which may be brought to the notice of doctors and others concerned.

6. To advise the appointing Ministers on any of the above matters.

Key points in the above duties included the explicit statement that the type of testing done by the manufacturers was to be left to industry to decide. At about the same time, an expert committee on drug toxicity established by the ABPI in August 1962 (The Hennessey Committee) and composed of industrialists, reported. The report was seen as a service to member companies of the ABPI regarding what in the committee's opinion were the best testing procedures and practices. These were recommended for guidance rather than as rigid rules. This represented a closing of

ranks within Industry at a time when concerted pressure on the newly formed CSD would have most impact. Copies of the Hennessey Report were circulated to the CSD for comments in July 1963 (25).

An interaction between Industry and Government was one of the fundamental aims of the drug regulatory system in Britain and was particularly vital in a situation where compliance with regulatory policy was not mandatory. However informal sanctions operated and as Wade put it, "...despite an absence of statutory powers the committee had powerful teeth" (26)

The functions of the regulatory body took place in three main areas, scrutiny of manufacturers information on a new drug before clinical trials began, scrutiny before marketing of the product and post marketing surveillance of the product. The relative importance of each of these functions fluctuated with time as will be seen. Agreement was obtained from the ABPI and the PAGB that no drug would be tested or marketed without the consent of the CSD.

From the outset, the CSD echoed the note of warning that no drug was absolutely safe and stated their aims as ensuring that drug products are as "...safe for their purposes as modern medical and scientific knowledge can determine" (27). This somewhat loose definition may have been responsible for extreme levels of accuracy being introduced as sophistication and technological improvement in measuring took place. A further important statement by the CSD was that the procedure of regulation, "... should not delay the emergence of drugs which could speed the recovery of patients or save lives", a point that is used by Industry to argue for the so-called "fast tracking" of drugs in Britain as adopted by the FDA in the US. The interpretation of this statement by industry and government is the centrepoint of much of the debate over the impact of

regulations on innovation. The administration of drug regulation and the contact with industry were to be as informal and flexible as possible and, "The committee encouraged the secretariat to make the necessary contacts with applicants as informal as possible and there is no doubt that manufacturers have appreciated this personal approach" wrote the CSD (28). This informality and flexibility has been widely reported and has engendered praise from regulators in other countries and industrialists alike. This attitude towards regulation may not be specific to the drug industry but may be an extension of the general attitude to State intervention. British drug regulation is often compared favourably with the far more bureaucratic and formal system operating in the US. The drug industry had been preparing for the introduction of controls and had to some extent already begun a major review of drug testing and this allowed a smooth passage to the new system.

1.2.3 Activities of the CSD

The CSD was originally composed of twelve physicians and scientists making up the part-time voluntary committee, they were backed up by a full-time secretariat that included six doctors and two pharmacists all of whom were civil servants. Four of the doctors were recruited from industry "on the principle of turning a poacher into a gamekeeper"(29). The CSD did no drug testing themselves leaving that responsibility to the companies.

The first year of operation of the CSD saw the introduction of a novel recording system for adverse drug reactions (ADR's). British regulatory committees have maintained that "there is ultimately no substitute for years of experience in the use of the drug in practice"(30). Adverse reaction monitoring by means of post marketing surveillance had been an important integral part of the British regulatory practice.

The novel system called the "Yellow Card" system invited physicians to report any adverse reactions to drugs in patients in their care. The cards were to be sent to the CSD and at the end of the first year 100 had been received (31).

At this stage in 1964 there was no retrospective review of products that were already on the market in relation to their safety. This important review was to take almost ten years to organize. The handling of the data from the companies concerning new products was expeditious due to the fact that informality, personal contact and the use of telephones avoided the accumulation of paperwork. This picture however was to change in later years. Another anomaly was that the premises of drug companies were notlicensed at this stage except for those under the auspices of the 1956 TSA (32).

The drug companies supplied a report of some 4000 pages in order to obtain clearance to market a drug (33), applications were dealt with at a rate of three months for a new drug substance and one month for a reformulation.

Efficacy was always considered in relation to safety as industry was opposed to the CSD demanding proof of efficacy per se, the terms of reference mentioning the purpose the drug is intended for. Any delay in the approval of a drug, industry argued,may be as serious as the approval of a dangerous drug and hence pressure was put on the CSD to accomplish its scrutiny as swiftly as possible at all times.

The threat of sanctions and the widespread cooperation of the companies ensured that in 1965 no drugs were marketed or put to clinical trial without the approval of the committee. In 1967, 68 and 69 products were marketed without approval (34), but due to pressure by physicians and the other companies, these products were soon withdrawn. Critics of

the CSD had argued that regulation would stifle research, data was produced by the CSD to try and refute this argument. The number of applications referred to the CSD annually was published in 1966 and showed an upward trend for the first three years of operation of the CSD. Data for later years revealed a decline in the number of applications referred to the CSD, product licence applications peaked in 1966 whilst clinical trial certificate applications peaked two years later.

Detailed statistics on applications will be given in chapter 5 when they are used as indicators of intermediate output of the R&D process. Rejections of drugs that would have otherwise reached the market was, in the opinion of the CSD, 'only a comparatively minor part of our function to provide checks on the safety of all new drugs'.(35)

1.2.4 Guidelines for drug testing

Initially, manufacturers had liberty over the testing schedules that they operated but this pattern was soon to change mainly due to the problems encountered by smaller firms in interpreting the CSD's requirements. These companies requested more specific guidance on the type of data required by the committee and in response the committee issued notes of guidance in 1965. The Hennessey Committee guidelines specifically noted that tests on reproduction would not be necessary unless it was intended that the action of the drug in pregnant women was to be studied. Drugs for the alleviation of illness in pregnant women must obviously be tested in this case. Tests for carcinogenicity would also normally, in their opinion, not be required. This was not the case for drugs already in use. Foetal toxicity was only determinable with any accuracy in man as the amount of data obtainable from animal models was limited (as in the case of Thalidomide). In 1966 the CSD decided to encourage manufacturers to undertake teratogenicity tests as these tests were thought to be, "...relatively inexpensive

and of short duration", criteria important to the companies. Why it took until 1965 for such tests to become a normal testing requirement is difficult to comprehend particularly in view of the teratogenic effects of Thalidomide. Lack of satisfactory animal models and a poor understanding of the link may have contributed.

Efficacy studies at this time were of little importance per se and the CSD made this point obvious by the clearance for marketing of a number of products which were relatively ineffective but innocuous. Multivitamin preparations are usually cited as examples of such products. The guidelines issued by the licensing authority are not technically a regulatory demand but are seen as a response to changing attitudes towards drug testing. They arise spontaneously as the environment for R&D alters. These guidance documents cannot become true demands until the EEC Directive relating to such regulations (EEC 75/318) is modified. (36)

1.2.5 The 1968 Medicines Act

The drug regulatory system based on the CSD was only a temporary framework prior to the introduction of specific legislation in preparation in 1965 and awaiting Parliamentary time. The need for statutory legislation was outlined in the White Paper of 1967 when it was stated " the provision of statutory backing for these safeguards would give greater reassurance and should not be further delayed" (37). Lack of cooperation was not a driving force behind implementation of the legislation (38) and the legislation was to be of a type that could include the flexibility and professional responsibility that had characterised the voluntary system although some difficulty was anticipated in the incorporation of such factors into an Act.

The Medicines Act 1968 incorporating the broad recommendations of the White Paper became law on 25th October 1968, "not to call the righteous but sinners to repentance" (39). It was an enabling Act allowing

further legislation as and when deemed necessary. As a comprehensive Act it replaced most of the previous drug regulations and was structured in such a way as to be compatible with EEC Directives, prior to Britain's entry to the Common Market and the Treaty of Rome.

Sections two and four of the Act (40) provided for the constitution of a Medicines Commission which has a broad brief and the formation of Expert committees respectively. The roles of the Medicines Commission were to advise Ministers on policies, expert committees and to consider representations from the drug companies regarding licenses or applications.

When the Medicines Commission was to be established the opportunity arose for it to be completely separate from the Ministry of Health and subsequently free of political pressure. A precedent existed in the shape of the MRC which was once a sub-committee of the Privy Council and therefore independent of other bodies. Ultimately the Commission became part of the Ministry of Health due to problems in the supply and promotion prospects of high quality staff in such a small department (41).

This plea for independence was incorporated into the terms of reference of the Commission and the expert committees. These have responsibility to the Health Ministers whom they advise and in return the Ministers may make suggestions to the committees. This relationship was however not without its problems, as Wade put it "...if the Minister turned around on us to do something and we didn't agree with it we would never do it. We would just walk. It doesn't cost me anything to walk out. I am not paid anyway for what I do for them" (42). If for any reason a mistake is made by a committee, Wade continues "...we can turn around and say 'OK in retrospect we have made a mistake, but on the data which we had, in our opinion, we made the right decision at that time'". Politicians were not bound to accept the advice of a committee but usually did,

"...there seems little chance that any judgment made by the committee would ever be reversed", wrote Gould in 1974 (43). This unwritten rule was broken in the case of Opren which will be mentioned later.

The scope of legislation was greater than that of the previous system and had provisions for quality control, powers over distribution, retail, supply, description, labelling and advertising of drug products for human or veterinary use. Lessons had been learned during the four years of operations of the CSD and many of the characteristics were directly transferred. Dunlop resigned as Chairman in May 1969 and was replaced by Eric Scowen. However, due to a delay, it was not until June 1970 that the CSM and its associated sub committees were appointed (44). With the cooperation of Industry, the changeover was smooth and for a while, both CSM and CSD worked concurrently,(25 June 1970-31 August 1971) the CSM working on policy and the CSD on routine matters. After 1 September 1971 the CSD tied up loose ends and the CSM operated alone. Administration was transferred almost en-bloc to the CSM. Therefore although the Medicines Act was passed in 1968 it was not fully implemented until 1971 a fact that must be taken into account in any temporal study. The formation of the CSM and other expert committees represents the first true regulatory stage although the earlier days of the CSD set the scene. Both periods are important phases in the history of drug regulation in the U.K.

1.2.6 The Committee on Safety of Medicines (CSM)

Under the Medicines (Committee on Safety of Medicines) Order 1970 (SI 1970/1257) the purposes and terms of reference were as follows: (45)

(a) giving advice with respect to safety, quality and efficacy, in relation to human use, of any substance or article (not being an instrument, apparatus or appliance) to which any provision of the Act is applicable: and

(b) promoting the collection and investigation of information relating to adverse reactions for the purpose of enabling such advice to be given.

A number of Expert Committees were established under Section 4 of the Act: British Pharmacopeia, CSM, Veterinary Products, Dental and Surgical Materials, and from 1975 the Committee on the Review of Medicines (CRM).

Under the CSM, licences were needed by the manufacturers before products could be tested in humans or marketed. These licences were designated the Clinical Trial Certificate (CTS) and Product Licence (PL) as before. Adverse reaction monitoring was maintained and extended, Licences of Right were issued for products already marketed and in clinical trials. All manufacturers were registered and issued with licences as were all wholesale dealers. Enforcement was handled by Inspectors who toured manufacturing locations to ensure compliance with quality control procedures.

One major difference from the old CSD system was that all products needed a licence and products already on the market were given the licences of right mentioned earlier. This was the first indication of a retrospective review of older products that was to develop over the next few years. The CSM policy regarding efficacy was reviewed and, "...it was agreed accordingly to adhere to the policy, originally stated by the CSD in 1965, that the Committee must consider efficacy in relation to safety" (46). This followed the statement in the earlier White paper regarding relative efficacy ie. "Efficacy in comparison with other drugs for the same indication will not be a determining factor in relation to the issue of the licence" (47). In 1972 the policy was reviewed again and a change of emphasis can be noted, "In future, the Committee will require the application (for such a product) to be supported by some evidence of efficacy before advising that a product licence should be granted" (48). This meant that harmless but useless products would no longer be allowed on the market. No specific efficacy guidelines can however be laid down(49).

All new prescription drugs had to be cleared by the CSM before clinical testing or marketing, minor modifications to already marketed products i.e. dosage change or minor ingredient variation would not need CSM approval and would be dealt with by the secretariat at another level. The Committee was still composed of voluntary part-time 'experts' and the informal flexible model was incorporated into the new structure. The CSM met twelve times in 1976 and under the new Committee, a series of guidance documents were issued. The leaflets called MALs (Medicines Act Leaflets) were aimed at ensuring adequate recognition of the type and standard of testing required by the Committee. Since MAL 1 was issued the series has been extended and revised and currently includes guidelines on all aspects of drug testing, marketing and labelling(50). An important 'gain' for industry was the acceptance by the CSM of data obtained from overseas testing: "The Committee would consider animal pharmacological and toxicological data in applications from any part of the world provided that there was evidence that the studies had been properly conducted and that the investigators had the necessary qualifications and experience to undertake them" (51).

This was an open invitation for manufacturers to carry out international testing and was of particular benefit to the multinational companies with limited research facilities in Britain. This was linked to the entry of Britain to the European Community in January 1973 and the subsequent implementation of EEC Directives including 65/65/EEC (licensing of medicinal products).

A joint ABPI/CSM working party was set up in 1975 to discuss the continuing theme of guidelines, in this case for carcinogenicity testing.

Also in 1975 the EEC Directives 75/318/EEC and 75/319/EEC came into force on the 20th May but apparently had little effect on UK licensing activity (52)

In 1977 the DHSS prepared a series of notes for guidance on carcinogenicity testing. The committee contained four representatives from industry (53), the CSM was later accused of producing guidelines of dubious value and adopting 'panic measures' (54). The ABPI R&D committee, in the meantime had prepared their own "Guidelines for pre-clinical testing" which updated the 1968 report. More attention was given to fertility and carcinogenicity studies (55).

This period of disagreement was due to confusion over the detail contained in the guidelines. Industry demanded more clarification of requirements, earlier warnings of any changes and more discussion whilst the DHSS preferred a more flexible non-definitive approach. Nevertheless in 1978 a document "Notes for guidance on carcinogenicity testing of medicinal products" (MLX 108) was issued by the DHSS (56). This document, the industry argued, would have a serious effect on the future of drug development in the UK and would force clinical work overseas due to the requirements.

1.3 Relations with Industry

In 1969 George Teeling-Smith wrote "...responsible pharmaceutical manufacturers welcome the type of controls to be applied under the 1968 Act, because they will help to prevent irresponsible competition from shady operators" (57). Since then many harsh and critical statements concerning drug regulation have been heard from the Industry.

As mentioned, the informal working relationship between the Industry and regulators was maintained during the transition from CSD to CSM. In the period 1973-4 discontent grew within industry over the delay in granting CT certificates. This lengthening delay said the CSM was attributable to, "...presentation initially of insufficient information by the applicant and slowness in remedying this later" (58). Industry emphasized the greater delay in Britain as compared with the similar process in other countries, a criticism which was countered by the CSM which considered that in these countries, "...effective controls on such trials" were not imposed.

Towards the end of 1974 a backlog of applications had built up due in part to a sharp increase in submissions coupled with a shortage of trained medical staff at the DHSS for processing applications. It was under this growing pressure that the CSM made regulations "...allowing the licensing authority to accept applications in less detail than provided for under the 1971 regulations" (S.I. 1975 No. 681) (59).

In 1977 a symposium was held on the subject of delays in CTC and PL applications and means of preventing such occurrences (60). This meeting was followed by a series of joint consultations concerned with the data requirements for CTC and PL applications. Eventually a working party was established under the direction of D. G. Grahame-Smith to

review requirements. This working party met regularly and had a target date of 1980 to complete their work.

In 1974 The Medicines Commission had indicated its intention to establish another section 4 committee, theCommittee on Review of Medicines or CRM to consider the 36,000 products already on the market holding full licences or licences of right. The CRM was established on 7th July 1975 and began its review activities with studies of anti-rheumatic, analgesic and psychotropic drugs. These products were chosen due to the widespread use and degree of abuse associated with these products as indicated by the level of adverse drug notification. 10,000 products were withdrawn almost immediately (voluntarily) by the companies, leaving some 26,000 products including dosage forms, many copies, toothpastes and shampoos. Under an EEC directive, the regulatory body had 12 years to complete the mammoth task of reviewing all products..

The review was considered by Industry to be a vast bureaucratic exercise, expensive and unnecessary as most of the products concerned were not serious risks and the majority had reached the end of their effective commercial life (61). Drugs withdrawn under the review procedure were normally withdrawn by the manufacturer following consultation with CRM if deemed necessary. In order to speed up the review, David Ennals announced in 1978 that it would be appropriate in certain cases to ban some products and eliminate the consultation stage of the 23,000 PLs of right in existence at that time (62). This put industry on the defensive and led to demands for a more resolute attitude to regulation coupled with a request for the CRM to explicitly state its reasons for the withdrawal of a product (63). Thus industry and regulators had polarised into an adversarial stance. (64).

The objectivity of the CRM was questioned along with their apparent lack of reasoned argument and prejudice of recommendation. Less secrecy on the part of the CRM and publication of the minutes of committee meetings was demanded (65). The difficulty of maintaining a regulatory balance was beginning to cause problems and was to lead to changes in the system. In February 1981 a conference to mark the 10th year of Medicines Act licensing was held at Sunningdale. The Regulators and Industry were represented, the former by Medicines Commission secretariat and the latter by representatives from the ABPI and PAGB. The conference was a "reappraisal of objectives and methods of controlling medicines for human use" and provided the opportunity for Industry to air its views. Once again, the need for effective informal and formal lines of communication was emphasized as well as a need to reduce the workload of the regulatory committees and secretariat. One proposal for a priority system for major new drugs was considered and likened to the US 'fast-track' system for the important new drugs. General conclusions from the conference were that the structure of the committees was on the whole satisfactory as was the balance between licensing, advertising control and enforcement activities. The review procedure of the CRM was thought to warrant investigation and simplification. Around this time the number of applications reaching the Authority declined and this, the Industry argued, was due to increasing regulatory demands placed on manufacturers. In reply the Medicines Commission felt that the standards were generally correct but recognised the need for flexibility.

The relationship between Industry and Regulators was in a rather delicate position due to the recent national reporting of adverse effects apparently linked to the use of benoxaprofen (trade name OPREN) a NSAID (66). Pressure from the press and consumer organizations as well

as the medical profession sought the removal of the products from the market. Delay of such withdrawals by the CSM in order to collect and analyse additional data was criticised and the Committee had to publicly justify its position. The delay in removing products was unfortunate in that a number of deaths were being linked to the use of the drug. This Opren incident, together with the Depo-provera case, highlighted the delicate nature of the Industry-Regulator relationship. In the latter case the decision to grant a product licence for the injectable contraceptive by the CSM was overruled by the Medicines Commission on the basis of undue risk to patients compared with the benefits. This was, the Medicines Commission argued, an exceptional case but remains one in which the focus of the media and public was brought to bear on the licensing authority.

In their 1982 Annual Report, the Medicines Commission and expert committees suggested that their public relations operation required uprating to counteract the adverse media publicity. The cooperation from industry was, however, reasonably good during this period. Fluctuations in the degree of regulatory stringency may arise due to the nature of the regulatory authority in the U.K. An important aspect is the nature of the industry-regulator relationship, this will be examined in more detail.

1.3.1 The regulatory balance

As many commentators have noted, the Government in Britain has two main levels of control over the drug industry resulting from two distinct governmental roles. Firstly as a regulator to ensure social welfare and secondly as a major purchaser of drugs for the NHS. This so-called 'double-edged sword' puts the State in an unique position. This can, as Dunlop argues, result in a clash of interests as industry attempts

to free itself from controls that may have an adverse effect on expansion, research and innovation due to the attempts to secure safety of drugs by rigid controls (67). The need for harmony is obvious but achieving this balance presents severe problems.

For many critics, the pendulum of regulatory control had, at this time, swung too far and was now having a damaging effect on industrial research. Dunlop agreed, "... it is possible that any increased safety of drugs achieved by the stringent regulations required nowadays is outweighed by the delay and expense of introducing, or even postponing altogether, valuable new remedies" (68). Interestingly, few industrialists would agree to a policy of deregulation, the regulations are a guarantee to the public that certain standards have been achieved. Teeling-Smith in 1969 (69) echoed this when he spoke of the common interest in sensibly applied regulations and "...as far as industrial legislation generally is concerned, the pharmaceutical industry is probably neither better nor worse off than industry as a whole".

His zealous campaigning of the Industry's cause since this time would, however, indicate that the drug industry has been selected out for increased regulatory pressure by successive governments.

Over-regulation is a theme that had been constantly used by industry to explain falling drug introduction rates, increasing drug development times and escalating costs. Many of the criticisms concentrate on the fact that regulations tend to extend rather than replace the existing controls. Increasing development times are of greater importance to the industry than costs and the plea for earlier clinical trials with more realistic preclinical testing requirements had been constant. Equally vociferous are the pressure groups that lobby parliament to extend the safety controls over new drugs. Major incidents with Eraldin and more recently Opren have increased this public awareness. The fact that drug

regulations failed to prevent such incidents forced the regulatory body into a further reappraisal of policy and approach (70). The rise of the pressure groups in the pharmaceutical arena is an important factor underlying the trends in regulatory pressure, the role of the groups representing the interests of industry is less well documented than the groups acting for victims of drug induced disease and needs to be outlined.

1.3.2. The drug industry's pressure groups

Traditionally the ABPI and its predecessors have put the industry's case in any debate over matters affecting member companies or the industry as a whole. This lobbying function was enhanced with the institution of the Office of Health Economics in 1962 which, as the 'think tank' of the ABPI has conducted numerous health studies particularly on the economic issues and is seen as a powerful lobbying group in the Industry/ Regulator relationship.

Recently however certain developments have taken place that consolidate industry's position and allow greater influence on external bodies. Drug regulation has become a 'science' and those persons in industry actively engaged in product licensing or drug registration activity have developed into a specialist managerial group. These activities have become so important that, as Greenwood puts it, "The future of the industry is clearly bound up with 'product registration'" (71). The need for a centralized registration unit within companies has resulted in all major companies forming such units from other pre-existing departments.

As toxicology itself has developed and is now recognised as a separate and distinct scientific discipline with academic courses, textbooks and professional qualifications, a similar thing has happened to regulatory affairs. Maturity of the 'field' of regulatory affairs can be demonstrated

with reference to the formation in 1977 of a professional Institute for those engaged in regulatory affairs. The British Institute of Regulatory Affairs (BIRA) met for the inaugural meeting in November 1977 and outlined its aims as, "...providing a professional identity for those engaged in regulatory affairs" (72) and to provide opportunity for educational advancement (73). BIRA was supposedly apolitical with no union affiliation but a more subtle role was envisaged by Teeling-Smith of the OHE when he proposed that BIRA should attempt to hold back British Regulatory activity as, "bureaucracy is the enemy of excellence and must be controlled"(74). Thus the industry has a professional institute with the knowledge, experience and political visibility necessary for effective lobbying of regulatory causes.

A second development was the formation of the Centre for Medicines Research (CMR) as an offshoot of the ABPI. The CMR was established in 1981 as a data generating and processing centre with specific project areas to investigate. These studies included trends in new drug development in collaboration with Dr. William Wardell, a keen drug industry commentator in the US and studies on data requirements for testing. In order to assist the CMR in the latter study it was decided to base the centre on the site of the British Industrial Biological Research Association (BIBRA) at Carshalton, Surrey, where expert knowledge and facilities were available. Patent life, post marketing surveillance and improved methods of assessing the 'quality of life' are also under study.

In a preliminary study on the duration of toxicity testing, a survey by the CMR showed that in most cases all effects have been studied in 3-6 months with little extra data being obtained from longer studies (75). Thus the CMR would push for a relaxation in the term of toxicity tests.

Finally, many private consultants and independent testing labs have come into operation which obtain work mainly from the smaller drug companies or those lacking research facilities. These private firms will have an

obvious vested interest in the regulatory activities of the companies and make up a quasi-industry pressure group. The result of persistent lobbying by the industry and the visible transfer of research activity overseas combined with apparently declining rates of innovation led to a reappraisal of regulatory policy, particularly concerning the timing of clinical trials. Industry had demanded earlier clinical trials with a flexible registration system, their influence was such that a novel scheme was formulated to alleviate some of the problems. The scheme was to be called the clinical trial exemption scheme and is an important stage in the history of drug regulation.

1.3.3 The Clinical Trial Exemption Scheme

Although the requirements for clinical trial certificates and product licences had been reviewed occasionally by the CSM and many changes had been made, some welcomed by the industry, much discontent over delays and requirements remained.

The ABPI had campaigned for many years for earlier clinical trials, thought to be a vital step towards preventing clinical work going overseas. An ABPI working party began a review of clinical requirements and the Medico-Pharmaceutical Forum, a group of industrial and academic pharmacologists chaired by Sir John Butterfield of the Medicines Commission, met on 5th December 1979 to discuss testing requirements for new drugs. The main theme was that of pre-clinical testing, arguing that UK requirements were excessive (four times higher than in Germany, Sweden, Holland and Denmark) forcing up to 80% of UK clinical work overseas. West Germany was cited as an example of a country where a system of guidelines and test summaries was used. This type of system was proposed as an acceptable alternative for the UK given that changes in the UK system were in the pipeline.

Two main proposals came out of this meeting; either a system using summaries of data lodged with the CSM and cleared rapidly or some exemption procedure allowing earlier CTs and thus reducing delays (76). The

recommendations were submitted in a twenty page summary to the CSM including provisions for starting clinical work if no objections were raised within 30 days of the committee receiving the summary data. Exempting certain trialists from clinical trials per se was thought to be unacceptable as this would probably lead to new bottlenecks.

In a statutory consultation letter under the Medicines Act, J.R. Long announced a proposed exemption scheme formally, the first announcement by the Secretary of State for Social Services having taken place on 16 April 1980 at the 50th Anniversary of the ABPI dinner. In the letter Long states that, "...changes could reasonably be made to existing methods of scrutiny of applications without endangering the safety of patients" (77).

Provisions existed within the Medicines Act under Section 35(8) for such a scheme to be incorporated within the same type of exemption scheme available to doctors, dentists and vets. This was a procedural change and meant that all existing requirements still had to be met. It was seen as a quick means of assessing the first reactions of a drug in humans and not carte-blanche for mass clinical trials to start (78).

The system was to be one of negative clearance as mentioned earlier, the companies having to wait a maximum of 35 days for notice of a failure to gain exemption. If notice was not forthcoming trials could begin. Refusal would normally be due to the prospect of unacceptable hazards in the proposed trials.

Exemption was subject to specific conditions, these included the approval of the trial by an ethics committee, formally recognising the role of the ethics committee which had previously been informal. All ADRs and changes in trial protocol were to be reported to the CSM. The use of ethics committees in this way was criticised by companies who argued that this would offset some of the time advantage gained (79). This however did not cause any problems in practice (80). The MLX 125 procedural proposals were laid before parliament in February 1981 as an Order of Council (81).

Running parallel with this development since late 1978 was a review of testing requirements being conducted by a working party under the chairmanship of D.G. Grahame-Smith. Delays in the review of recommendations by the DHSS concerned industry (82) and soon a second consultative letter, MLX 130 presented the new proposals for pharmaceutical and pre-clinical data requirements (83).

The CSM attempted to identify the requirements that placed most undue pressure on industry, their utility was reviewed and wherever possible changes were proposed. The CSM however insisted that any changes must be consistent with low levels of risk to patients or trialists currently in force.

The 'Grahame-Smith Proposals' were firstly, to facilitate early clinical trials with the amount of data linked to the extent of testing in a phased approach. The proposals were broadly in agreement with ABPI proposals. A minimum 'packet' of data from early limited dose studies on a restricted number of patients would be expanded as soon as the trial widened. Secondly it was proposed to divide the trials into two stages with flexible lines of demarcation:

> Stage One: early, searching, heavily monitored clinical pharmacology studies in a limited number of patients.
>
> Stage Two: develop studies further.

This would be appropriate in the case of full clinical trials as well as trials under the CTX scheme.

The licensing authority was broadly in agreement with the CSM over this change in requirements. Changes in data requirements were published in a MAIL (Medicines Act Information Letter) special No.32 and the CTX scheme came into operation in March 1981 and during the early period some

firms began to experience difficulties in preparing the summaries of data for exemption. The problems were those of poor presentation, inconsistent data and inadequately controlled trials (84). Generally, however, industry welcomed the moves made and suggested that time delays would be reduced and more drugs studied (85), other benefits including better relations and a decrease in the number of animals used were also mentioned (86). Some criticism of the scheme was expected and the administration of the applications was thought to have an ambitious time scale as well as being conducted on a somewhat ad hoc basis. Excessive laboratory animal data requirements and mutagenicity data caused concern (87).

It was not clear initially whether or not there would be procedural difficulties as the secretariat made most decisions without recourse to the expert committees. Theoretically at least, the CSM could demand extra data and again block or delay an application although in practice this would require exceptional circumstances (88).

The companies would also benefit in the long run from the fact that most overseas licensing authorities (with the exception of France and Japan) accept UK data and made repeat testing unnecessary (89).

From a DHSS point of view the scheme was working well and data produced by the Licensing authority seems to confirm this confidence.

1.4 Concluding remarks

The introduction of the clinical trial exemption scheme represents a move in the direction of deregulation albeit an intermediate one. This stage of the history of drug regulation is a distinct phase in the overall process which is outlined below.

Period	Regulatory Phase
Pre-1962	Period of unconsolidated regulation Lack of formal registration and testing
1962-1964	Transition period prior to non-statutory licensing by CSD, anticipated by industry
1964-1971	Regulation by the CSD, Medicines Act 1968 passed. Evidence of non-conformity.
1971-1981	Statutory licensing activity by the CSM, rise of industry's pressure groups, over-regulation claims
1981-	CTX scheme introduced, relaxation of regulatory burden

Theoretically, the turning points in the history of regulation should be those of 1964 with the establishment of the CSD and 1968 with the Medicines Act. It is however apparent that the early regulatory pressure may have been anticipated by industry and the Act did not come into operation until 1971 thus confusing the simple picture. These points are important, as in later sections the R&D activity of the U.K. drug industry will be reviewed and attempts will be made to correlate this with regulatory demand.

The impact of drug regulation on the U.K. industry is probably the best researched and least understood area of regulatory policy. The most important impact of drug regulation is said to be the debilitating effect on innovation, a subject that has received a great deal of attention from researchers in all countries. This impact will be reviewed in the next chapter in order to determine the feasibility of an impact study based on the U.K. pharmaceutical industry.

CHAPTER TWO: THE IMPACT OF GOVERNMENT REGULATIONS ON INDUSTRIAL ACTIVITIES.

2.1 Introduction and overview

It has been argued that regulations rarely have any direct role to play in the stimulation of innovation although instances of innovation to overcome compliance difficulties have been reported (1). Certain recent regulations have explicitly stated the need to prevent any unnecessary barriers to innovation arising from compliance. The U.S. Toxic Substances Control Act (TOSCA) has such a proviso as well as measures to control any unreasonable risks to society. It seems to be a generally held view that regulation has had an overall negative impact on industrial activity particularly research and development (2).

The impact of regulation on innovation and other business activities needs to be understood and quantified due to the implied relationship between innovation and economic growth. Regulation has a central role in science and technology in that it establishes an environment for R&D by shaping and directing technological change by means of legal controls (3). The regulatory impact can take place at many levels within industry, Ashford et al differentiate the effects into two main areas, those of main business innovation and compliance innovation. Changes in main business innovation have an influence on economic growth and thus on the standard of living. Changes in compliance innovation lead to changes in health, safety and environmental quality and thus changes in the quality of life (4). Ashford's model is based on the chemical industry and may be modified to suit the pharmaceutical industry where compliance changes may result in changes in main business, the two areas being closely related and more difficult to separate.

At an economic level regulations may increase product development time due to the extra time needed to ensure compliance, as well as increasing costs and overheads. These factors are often referred to as opportunity costs. Costs may be measured in development costs or in terms of lost revenue due to delays or product withdrawal. Regulations may increase the risk and uncertainty in product development which ultimately may lead to changes in research direction. Resources may be diverted away from 'offensive' or innovatory research in order to fund compliance costs (5). These extra costs may be passed on to the customer or result in fewer innovations reaching the market. The number of ways in which regulations may prove to be a barrier to innovation were outlined by the Environmental Protection Agency in the U.S. in a study of industries under its control(6). The effects in order of perceived importance were as follows:

Time pressures
Costs of compliance
Unclear implications of regulations
Delay in setting guidelines
Agency cannot or will not modify guidelines
Disagreement over regulations
Financial inability to comply
Inconsistent regulations
Lack of effective appeal procedure
Unwillingness of agency to explain regulations.

Many of the above criticisms have subsequently been cited as being of similar importance in the U.K. pharmaceutical industry in its experience with drug regulation (7).

Other impacts include the inability to calculate accurately the returns on investment (8) thus complicating the long-term planning of companies. This uncertainty and diversion of resources can result in a tendency towards concentration of firms in a sector or a domination by large firms who can spread the costs of regulation over a range of business interests.

This type of effect may alter the optimal organisation for R&D and a trend towards technologically 'safe' areas where compliance is more straightforward and where costings may be more accurate.

The deleterious effects of regulation do however need to be balanced against the benefits of regulation to industry and society. For example, industry may be stimulated into generating 'better' products or improved processes with productivity improvements (9). Saleable innovations may be induced and the overall level of creativity may be raised. At a more cynical level it can be argued that industry may use regulations as a scapegoat or blanket to hide any damage caused by a product or process that has been 'cleared'. Society on the other hand has a greater degree of protection from risks and hazards, has a channel for discussion and may, in some cases, be able to obtain compensation for any harm caused. Many of these costs and benefits are not easily quantifiable and are therefore difficult to introduce into any cost-benefit analysis of regulation. For this reason many of the studies of regulatory impact have tended to concentrate on economic criteria and tangible indicators. Before dealing with the studies that have attempted to analyse the impact of regulations on industrial activity it is necessary to examine the possible effects of regulation on the pharmaceutical industry. With this background it will then be possible to determine which characteristics to examine for regulatory impact.

2.2 The impact of government regulations on the pharmaceutical industry.

The British drug regulatory system has, as Wade puts it, "...made the firms do their own work better" (10). In doing so it has increased R&D costs and extended the time taken for drugs to reach the market. The regulatory body has been accused of unnecessarily delaying applications for clinical trials certificates and product licences. A failure rate of

8-10% has been common in applications although this may be attributed to applications from smaller firms with limited registration experience or resources. The number of refusals is also kept low as many companies will withdraw an application before the official refusal is notified to the Committee on Proprietary Medical Products and published in the J. Eur. Comm. in order to prevent competitors gaining an insight into the 'failure'.

Much of the delay in processing is undoubtedly due to the limited number of regulatory staff in the DHSS, poor communications within the Medicines Commission and also in no small way to incomplete or inadequate applications being submitted by companies (11). Both parties to the debate are responsible then for part of the delay and Griffin of the DHSS refers to the 'sins of the regulated and the regulator' (12)

Sins of the regulated	Sins of the regulator
Ignorance: Quality & inexperience	Complacency
Omission: How little can we get away with?	Aloofness: Failure to communicate
Commission: Failure to adhere to protocol	Rigidity of thought: no re-examination
Incompetence: Boredom	Pride and procrastination: Afraid to err causes delays.
Suppression of facts/distortion of truth	
Falsification: especially at the CT stage	
Misuse of statistics/interpretation.	

One of the main problems according to Griffin has been a breakdown in the lines of communication both within the firm and between companies and the DHSS. Establishing regulatory affairs departments separate from the R&D facility has, he considers, been to blame.

The CSM has been criticised within parliament by the Social Democratic Party who stated that the CSM would be dismissed if they were in power. Reasons given were that the CSM "...did not perceive their role correctly", and had a bad record on ADR monitoring. The Medicines Commission was criticised for spending too little on inspectorate activity (13).

Since the introduction of drug regulation, the pharmaceutical industry and its representatives have argued that over-regulation would have a serious and harmful effect on the innovation and future of the industry. Even the improvements under the CTX scheme have reduced regulatory pressure an insufficient amount for many industrialists. They point to other aspects of control including health and safety legislation as well as other commercial controls as illustration of the increasing regulatory regime. Eric Snell of the ABPI has described a 'jungle of regulations' facing the industry.

"Regulatory Jungle" (14)

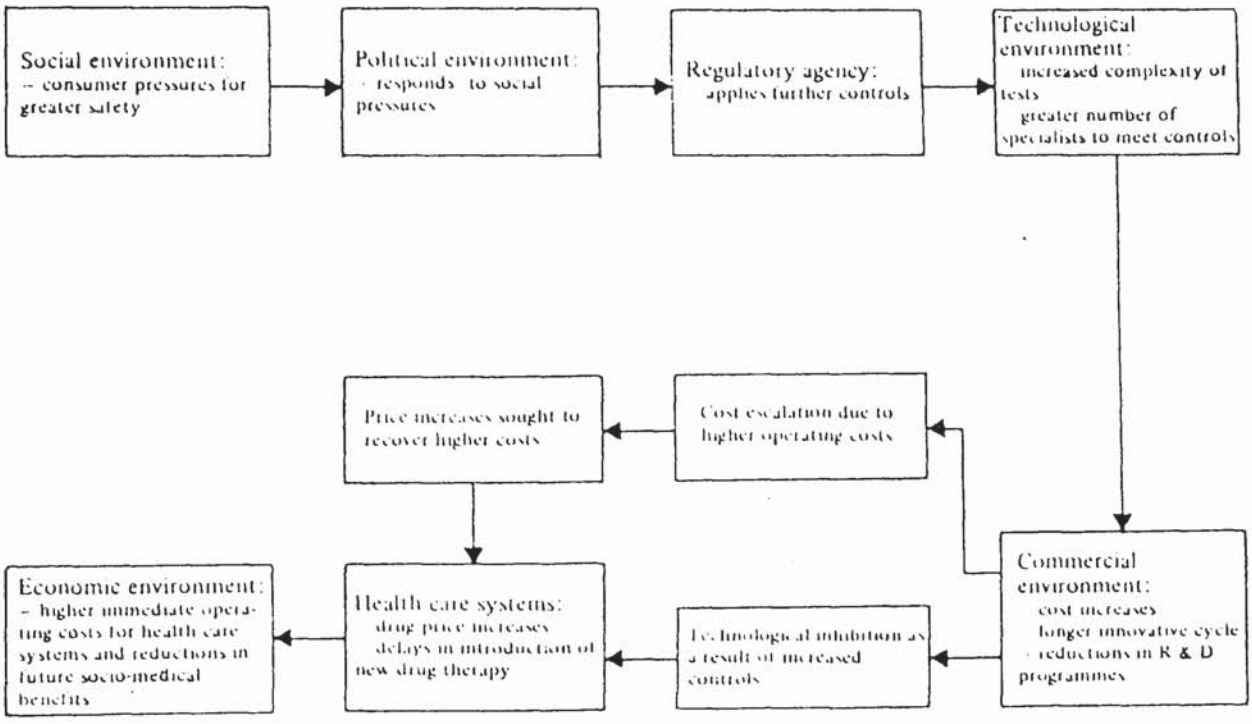
Chemistry and Pharmacy:	General provision for laboratories and factories; manufacturers' licence; Good Manufacturing Practices (GMP); permitted additives.
Toxicological, Pharmacological and Biological:	general provisions for laboratories and factories; Cruelty to Animals Act 1876; Good Laboratory Practices (for FDA compliance); safety guidelines (UK and EC); Dangerous Pathogens Advisory Group (DPAG); and Genetic Manipulation Advisory Group (GMAG).
Clinical Research:	DHSS authorization; medical ethics-ethics committee; patient confidentiality, patient consent and Declaration of Helsinki (1975); good clinical practice (for FDA compliance); guidelines-general (WHO), specific (EC, FDA); code of practive for general practitioner (GP) trials (ABPI); post-marketing surveillance.
Marketing and Promotion:	product licence; data sheet regulations; pharmaceutical prices regulation scheme (PPRS) (prices and promotion); ABPI code of practice; product review; labelling, and packaging regulations.
Others:	consumer group pressure; media pressure; government counter-promotion.

The International nature of the industry and market for drugs ensures that regulatory controls in major markets have worldwide repercussions on

the chief innovating companies. International harmonization of regulations under the EEC and WHO is thought to be more of a utopian ideal than a reality and regulatory departments in industry see international acceptability of testing data as a more reasonable and pragmatic step (15).

It seems unlikely that any further deregulation will occur in the near future given the recent pressure placed on politicians to ensure safety of drugs following the Opren incident. This will inevitably lead to a continuation of industry activity to promote the idea of risk acceptance and reduction of regulation stringency. The mechanism by which consumer pressure acts is shown by James (16).

Figure 2.1



Interactions of social pressures for increased drug safety on the operating environment of the pharmaceutical industry

The direct effect of regulatory control on costs etc. will be reviewed later but the indirect effect on innovation will be of primary concern. As will be demonstrated, the licensing statistics concerning the number of NCEs marketed per annum in Britain shows a levelling off following a decline. PL applications however have tended to rise. The NCEs produced have tended to be of a non-innovative type, adding to already oversubscribed therapeutic areas. Although industry justifies this by referring to the long lead times and the need for these products as sources of finance for more innovative research. Other commentators are more critical, T.B. Binns calls this a "deplorable performance on the part of the industry", particularly in view of the massive investment increases in real terms that the industry claims to have put into R&D. Binns continues, "...if present trends persist it seems inevitable that research will continue to become less innovative and less relevant to medical needs" (17). It is important then to distinguish between absolute rates of drug introduction and the type of product introduced.

2.3 Studies on regulation: methodological problems

Research into the problem of innovation and an analysis of factors affecting this process has been undermined by difficulties including a general lack of data due to the secrecy and industrial protection of information relating to drug products. Industry and press have traditionally been on opposing sides in many drug related incidents and very little objective data has filtered through the system. Due to patent protection, little information on R&D is released until late in the product's development cycle. Data on research is often unavailable due to accountancy procedures adopted within the companies. The information that is available tends to be found in very limited circulation publications or in expensive specialist economic surveys which are rarely publicly available.

As a result of the above, academic research has been limited and has often needed the cooperation of the industry and therefore introduces an element of bias or vested interest. Data from the licensing authority is sketchy as confidentiality to the industry is promised. As Lunde and Dukes observed, no data exists in many cases, on rejections, applications or efficiency. They also argue that the issues are obscured by propaganda and have decided to take a fresh look at the problem using sounder data. With cooperation from the WHO they have begun a 'European studies in drug regulation since 1979'. This study is still in progress and represents a shift from traditional studies' (18).

Other controls on drugs

Regulation of testing requirements is but one of a series of controls imposed on the industry as already mentioned. Economic control is an important factor determining the commercial environment and working practices, economic controls may include price, promotion and profit regulation and act to reduce funds available for innovative research.

However there is a conflict between economic constraint and social norms. If, as James argues, recession, unemployment and high levels of inflation result in economic control equally the desire for full employment, increased profits and rates of innovation will affect social norms reducing the importance of regulation in general. Therefore economic and technological controls must work in tandem and it is the resultant influence of these controls that is important. All regulatory factors, governmental, commercial and social interact to produce an 'environment' for innovation.

To this model must be added the pressures placed on research due to inadequate technical information and the limitations resulting from this. The complete system is therefore very complicated and separation of the individual components and quantification of their impacts is a daunting task. Most research has concentrated on the issues of product registration, price control and their impacts on the industry. Of these, drug regulation has received the most attention as it is seen to have identifiable and specific effects on the R&D activity of companies and in its present form, drug regulation is a recent phenomenon. The extent to which these assumptions can be substantiated will be examined later.

As a result of these problems traditional economic theory has proved to be of limited use in analysing regulatory impact (19, 20). Most studies have generated little empirical evidence and are often too general resulting in an inability to apply the findings to specific cases. One major problem is that of measurement of impact itself, in order to successfully measure impact a control is needed to eliminate regulation. This type of control has proved elusive, attempting to define a condition in which the regulatory influence is absent has resulted in a series of studies of an international nature (21).

Many studies have used a pre versus post regulation comparison and attributed any subsequent variation to regulation. The time lags between the stimulus and response often prevent the use of traditional econometric studies (22). A further difficulty has been to measure accurately the rate of innovation and hence any changes in that rate. In the case of the drug industry more meaningful indexes of innovative output have been developed and although not wholly accurate can give a clearer indication of any changes. A related difficulty is the lack of understanding of the mechanism of the relationship between regulation and innovation. An attempt will be made in the course of this study to clarify some of these areas.

Innovation has been the focus of attention in the majority of impact studies, both in terms of rate and direction of innovation. The measures of innovation adopted vary and the studies reviewed in the next section will demonstrate the variety of approaches. It is necessary in this section to extend the study to take account of world trends and international comparisons. The U.K. industry will be reviewed in greater detail whenever possible.

2.4 Examination of trends in drug innovation

The measurement of the level of innovative activity in the pharmaceutical industry poses interesting methodological and theoretical problems. Definitions of invention and innovation tend to concede that the rate of innovation can most suitably be measured by means of a count of inventions that are made available to some end user or marketed. The inference is, therefore, that innovation should be measured by a count of new products introduced onto the market. As new chemical entities (23) are deemed to represent the most significant therapeutic products they are generally used as an indicator of innovative output. The R&D activity of the industry is encouraged to develop products at regular intervals, a situation arising from the inability of manufacturers to compete in the ethical or prescription drug market on the basis of price alone. Innovation of important therapeutic products provides the competitive behaviour.

Most reviews of innovative output use a temporal study of drug introductions. Alternative measures of innovative activity have been proposed including counts of applications to licensing authorities for approval to market new products and counts of patents taken out by the companies. These are considered in greater detail in later sections. Each of these indicators measures the flow of inventions through the stages of the innovation process. To put the U.K. industry into perspective and to examine the methodologies adopted in earlier studies the next section will review the sources of data on the number of NCEs introduced onto various markets and the time periods of interest.

2.4.1 Counts of new product introductions.

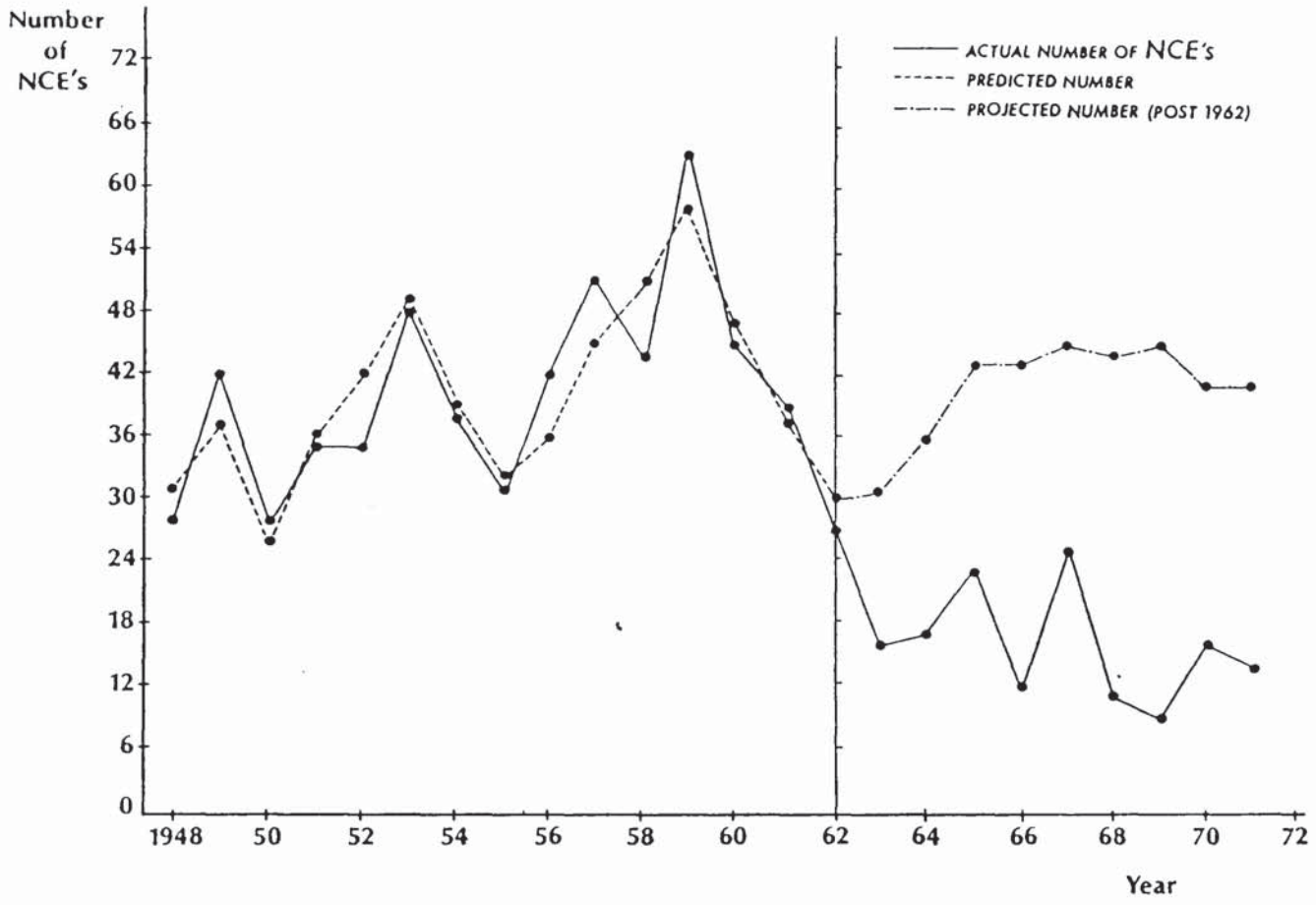
Many previous studies have examined drug innovation in the USA and have attempted to determine the social, political and economic factors that influence the innovation process. The data used in these studies can be traced to a limited number of primary sources.

Drug introduction data on an international basis is collected by Paul de Haen and it is this data that is used by Sam Peltzman in his study of new chemical entities actually introduced onto the USA market between 1948 and 1971 (24). The reduction in the number of annual introductions after 1962 from a projected level estimated by Peltzman is attributed to the impact of federal drug regulations. The Peltzman data is reproduced in Fig 2.2. The problems associated with this method will be discussed later, however a substantial decline is seen in the actual annual number of introductions which fell from a peak of around 43 per annum over the period 1959-1962, to around 17 per annum for the years 1963-1966. It is worth noting at this stage that the definition of an NCE adopted by de Haen differs from that of the U.K. DHSS mentioned earlier (25).

Schnee presents an updated compilation of the de Haen data together with a more detailed breakdown by type of product (26). It is noticeable from the table (2.1) that NCEs account for a small percentage of all drug introductions, the remainder being new formulations, combinations, dosages and duplicate products. Qualitatively however the NCEs are more significant. The figures are updated using more recent data. Schnee's data shows that the decline in total new products is steeper and begins earlier than the corresponding decline in single chemical introductions. This disparity between trends for various classes of drug products is important to note as it has led to much debate over the social benefits of the majority of drug products.

Much of the drug introduction data presented by Commissioner Alexander Schmidt in his evidence before the Senate Sub-committee on Health was compiled from de Haen sources. The data (Fig 2.3) was used to illustrate a worldwide decline in drug introduction rates since 1960 (27).

Figure 2.2



New Chemical Entities 1948-1971 (USA)

Table 2.1

Year	Total New Products	New Single Chemicals	Year	Total New Products	New Single Chemicals
1950	326	28	1966	80	12
1951	321	35	1967	82	25
1952	314	35	1968	87	11
1953	353	48	1969	62	9
1954	380	38	1970	105	16
1955	403	31	1971	83	14
1956	401	42	1972	64	11
1957	400	51	1973	74	19
1958	370	44	1974	83	18
1959	315	63	1975	91	16
1960	306	45	1976	62	15
1961	260	39	1977	72	18
1962	250	27	1978	85	23
1963	199	16	1979	113	15
1964	157	17	1980	162	13
1965	112	23	1981	120	18

New product introductions in the ethical pharmaceutical Industry 1950-1981

Sources: Schnee (1979)
Paul de Haen: Ten year new product survey 1950-1960, Non-proprietary name index vol VI (1967)
New products parade 1957-1977 (1978), New products survey 1972-1981 (1983) New York.

Figure 2.3

Annual marketing of NCEs in the U.S., England, France and Germany.

Source: (27,31)

Data on single entity drug introductions for the USA market over the period 1940- 1978 has been compiled by the US Pharmaceutical Manufacturers Association (PMA) (28). The decline in drug introduction rate is again apparent around 1960, there is some variation between the PMA data and that of de Haen due again to the definition of NCE used in each case (29). the PMA data is reproduced in Fig. 2.4.

Alternative data is provided by the US Food and Drug Administration (FDA), the regulatory body responsible for the administration of the Food Drug and Cosmetics Act. They give data showing the number of new drug approvals, ie. the products that have been licensed for marketing in the USA. Their definition of a novel chemical product is again different (30). The dates are of approval and not marketing, a further complication. Some products may conceivably be licensed but not marketed. This data was used by Schmidt and has subsequently been used by other commentators (31) A decline in NCE output is again illustrated. (Tables 2.2 and 2.3).

The yearly approvals of new drugs by the FDA have also been used in a disaggregated form to illustrate the trends that exist within the overall decline. The categorisation of products in terms of their therapeutic gain is considered again later.

This considerable array of data from a number of sources tells us much about the USA situation but little about the British situation, a certain amount of information was provided by Schmidt and showed a less severe reduction for the UK. The nationality of the innovating firm is an important factor, the relative introduction rates for products developed in various national industries show that the USA has suffered a far greater reduction that the UK. The data presented by Grabowski, Vernon and Thomas is shown in Fig 2.5 to illustrate this.

Figure 2.4

New single entity drug introductions to US market 1940-78

Source: (28).

Table 2.2

Year	Total NCEs	NCEs Excluding Salts	Year	Total NCEs	NCEs Excluding Salts
1950	44	33	1963	13	12
1951	55	47	1964	25	19
1952	40	37	1965	23	18
1953	73	55	1966	18	16
1954	60	36	1967	23	18
1955	57	44	1968	7	7
1956	52	44	1969	12	10
1957	73	53	1970	17	17
1958	45	32	1971	17	13
1959	76	56	1972	11	9
1960	55	47	1973	18	17
1961	43	36	1974	16	16
1962	30	26	1975	12	12

Annual FDA approvals of new chemical entities 1950-1975

Source: (31)

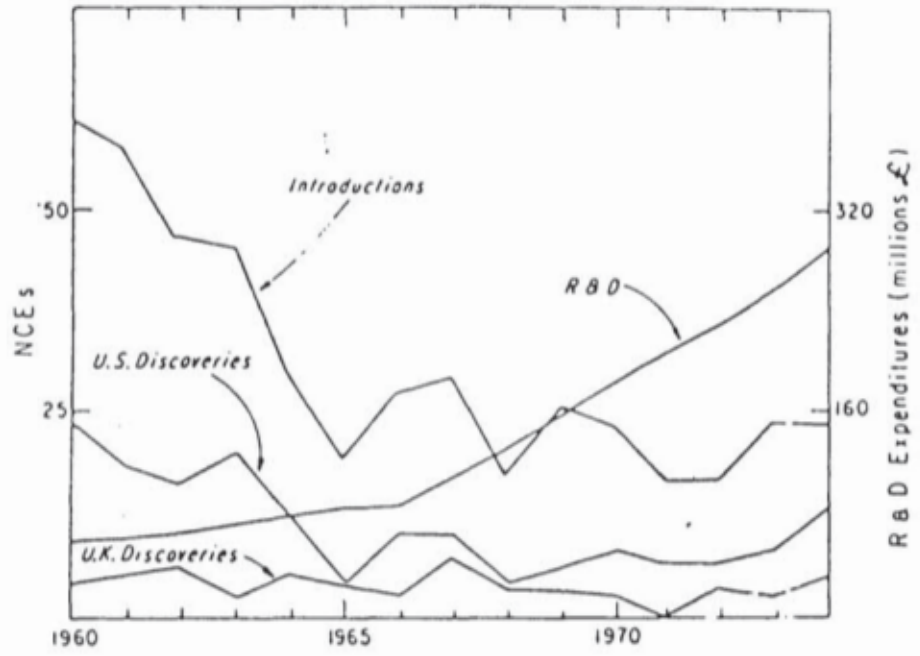
Table 2.3

Year	Original INDs Submitted	INDs Discontinued by Sponsor	Original NDAs Submitted	NDAs Approved	New Molecular Entities
1963	1066	6	192	71	16
1964	875	215	160	70	20
1965	761	306	221	50	13
1966	715	580	216	50	17
1967	671	627	128	74	16
1968	859	564	108	56	11
1969	956	482	60	39	11
1970	1127	n.a.	87	53	18
1971	923	1167	256	68	14
1972	902	452	272	42	10
1973	822	311	149	77	14
1974	802	399	129	95	23
1975	876	472	137	68	15
1976	855	524	127	101	23
1977	925	802	124	63	21
1978	925	588	121	86	22

New drug filings with Food and Drug Administration 1963-1978

Source (28)

Figure 2.5



Introduction of NCEs in the U.K. 1960-74, R&D expenditure at constant 1958 prices

Figure 2.7

Great Britain-Pharmaceutical products introduced 1956-76

Considerable international data has been collected by Erika Reis-Arndt of Boehringer Ingelheim for NCE introductions since 1961. The contributions of the USA and the UK drug industries to the total world introduction rates are given in Fig 2.6 . The USA has maintained its position as the source of the highest percentage of NCEs over the period. The decline in innovation is apparent as well as the steeper USA decline compared to the UK.

The UK industry was responsible for around five percent of all introductions over the period 1961-1977. The introduction of drugs onto various markets by the country of first introduction reveals that the USA has suffered a sharp decline compared with the UK, the USA was ranked fifth in terms of world introduction rates with France, Germany, Japan and the UK taking the first four positions. Tables 2.4 and 2.5 contain the relevant data.

The most comprehensive information on the UK industry and the rate of drug introductions has been presented by Steward (32). Information was given for the period 1958-1978 based initially on the database of introductions generated by the Centre for the Study of Industrial Innovation (CSII) for the NEDO report,'Innovation in the Pharmaceutical Industry' (33). This data was analysed and extended to give a clearer picture of innovation rates in the UK using a number of sources. This research will be considered in more detail shortly as it forms a framework for the introduction data used in subsequent sections of the present study.

From the Steward data (Figs 2.7 and 2.8) a decline in the total number of new products including combinations and dosage forms is seen. The decline in NCE introductions is apparent but not as severe thus mirroring the USA situation. The decline in NCE output although smaller represents an important trend as any decline in such potentially important products may have significant social and commercial implications.

A final source of introduction data is the licensing authority, they provide statistics on the number of product licences granted for novel products as well as the number of new chemical entities marketed annually (see table 2.6). It is noticeable that the data from the U.K. authority is less detailed than that provided by the U.S. counterpart.

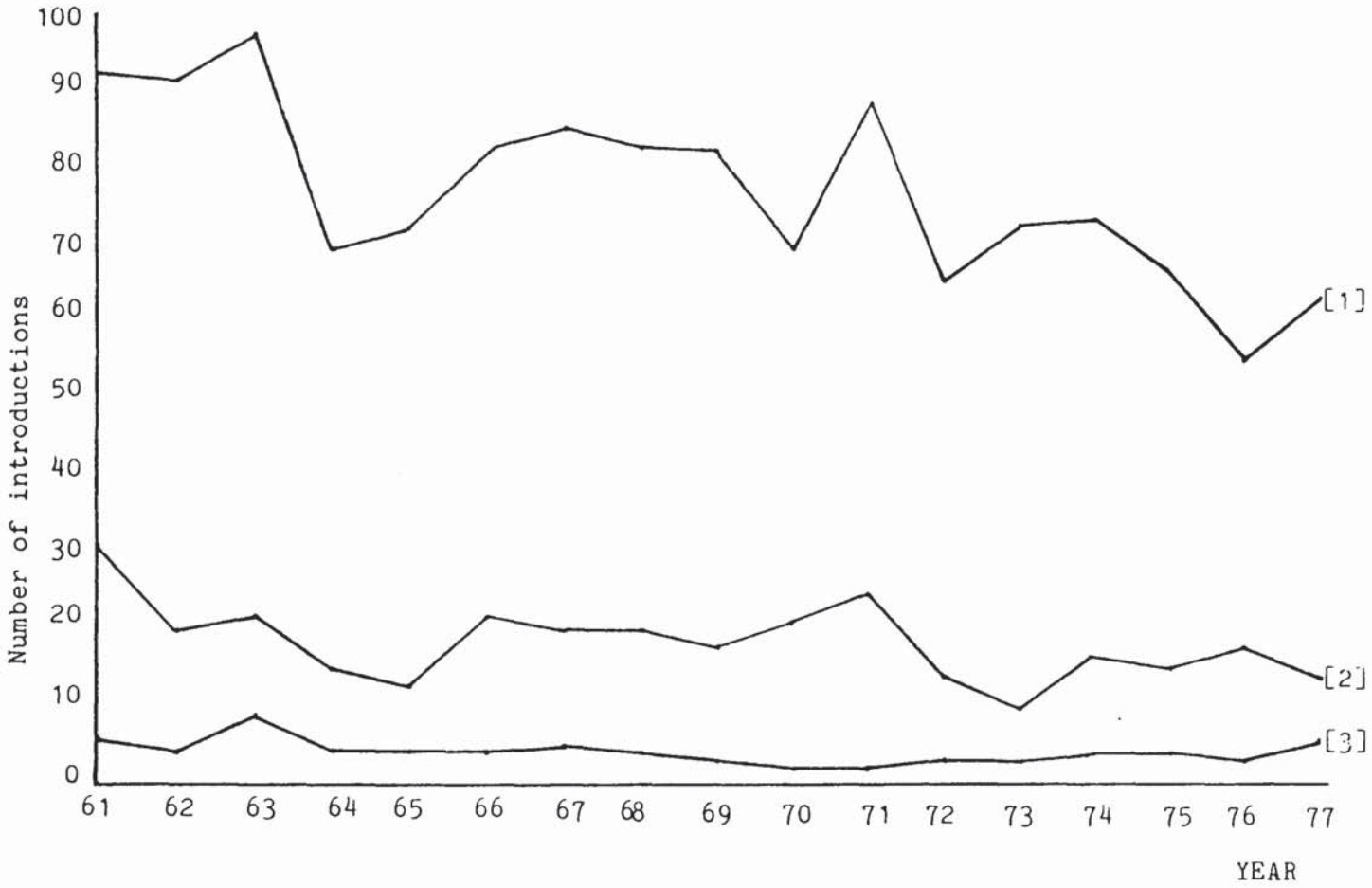
Table 2.6

Year	Number Marketed
1971	37
1972	-
1973	25
1974	19
1975	19
1976	19
1977	19
1978	20
1979	14
1980	23
1981	9

NCEs Marketed 1971-1981 in the U.K.

Source: (65)

Figure 2.6



World NCE introductions by nationality of innovating firm

Source: (67).

[1] Total world introductions

[2] U.S. firm's introductions

[3] U.K. firm's introductions

Table 2.4

Year of First Introduction	USA	UK	Total
1961	31(1)	6(1)	93
1962	20	4	92
1963	22(1)	9	98
1964	15	4	70
1965	13	4	73
1966	22	4	83
1967	20(1)	5(1)	86
1968	20(2)	4	84
1969	18(1)	3(1)	84
1970	21(1)	2	71
1971	25	2	90
1972	14	3	67
1973	10	3	74
1974	17(1)	4	75
1975	15	4	68
1976	18(1)	3	57
1977	14	6	65
Total	319(9)	70(3)	1330
%	23.4	5.1	100

Number of introductions 1961-1977 by the country of origin of the developing firm or institution

The numbers in brackets indicate that one drug was introduced simultaneously in two countries either independently or from two firms jointly.

Source: (67)

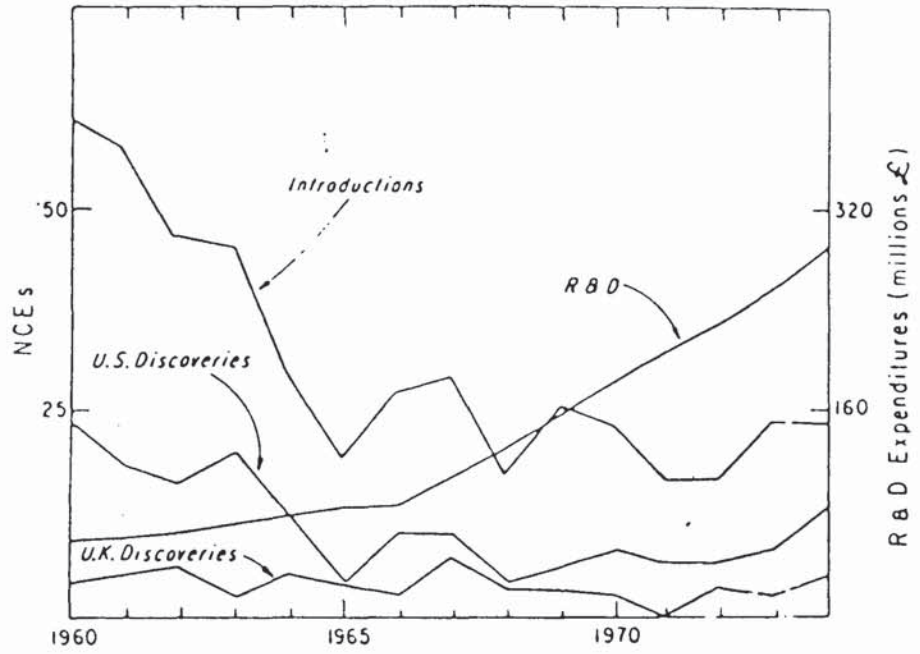
Table 2.5

Year of First Introduction	USA	UK	Total
1961	27	9	93
1962	12	6	92
1963	7	17	98
1964	7	7	70
1965	4	4	73
1966	6	8	83
1967	5	10	86
1968	2	11	84
1969	3	7	84
1970	6	4	71
1971	6	8	90
1972	4	7	67
1973	6	6	74
1974	4	11	75
1975	3	5	68
1976	2	6	57
1977	3	6	65
Total	107	132	1330
%	8.0	9.9	100

Number of introductions by country of first introduction

Source: (67)

Figure 2.5



Introduction of NCEs in the U.K. 1960-74, R&D expenditure at constant 1958 prices

Figure 2.7

Great Britain-Pharmaceutical products introduced 1956-76

2.4.2 New product introductions for U.K. owned companies.

In later chapters science and technology indicators measuring inputs to and intermediate outputs from the innovation process are developed for use in a study of the U.K. owned companies. Terminal output of NCEs for these firms needed to be ascertained for completeness. The justification for selecting these firms as a focus for research is given later but it is pertinent to include an analysis of their drug output at this stage.

From the list of U.K. drug introductions produced by the CSII and subsequently used by Steward, all introductions made by U.K. owned firms were extracted. The Firms of interest are outlined in Chapter three. The introduction data was updated to include all introductions made until 1982 using Drug and Therapeutics Bulletin and The Pharmaceutical Journal. A final list of drug introductions was drawn up but required further analysis and cross-checking for accuracy. Additionally, a number of extra pieces of information could be added to the list of drugs.

The year of U.K. introduction was noted as well as the company responsible, the proprietary and non-proprietary names. It was assumed that some drugs had been licenced from other firms and were not a result of innovative activity in the firms of interest. In order to determine the number of such products, cross-checking was undertaken in two main source references namely The Merck Index and Marshall Sittig's Pharmaceutical Manufacturing Encyclopaedia (Noyes Data Corporation 1979).

As a check on the source of the drug, patents relating to each product were determined. Patent information was obtained from Sittig and Merck as well as the name of company responsible for the first introduction of the drug.

Patents were examined and checked to see if the patentee was the same as the introducing firm, some patents were found to belong to other firms and these instances were noted. Some patents listed in

the sources were evidently not directly related to the drug product per se as a basic patent and this was also noted. To check the accuracy of the sources each firm was contacted and asked to check that the patents listed were the key patents for the products in question. Some firms were willing to undertake this task whilst others failed to respond. For those firms that did respond it was evident that some patents listed in the sources were process improvements or minor innovations. This must be noted if raw data is used in any future studies.

A final list of drugs with their associated patents for introductions made by U.K. owned firms is given in Appendix A. Those products with sources other than the introducing firm are highlighted. From the results it is evident that the innovative output of the U.K. owned firms showed little or no decline since 1960. This result differs from that of the U.K. industry as a whole and the world pattern. The U.K. owned sector appears to have maintained its innovative activity despite any regulatory pressure. This may be due to the strength of a limited number of highly innovative firms in a relatively small sample.

The implications of this activity in relation to regulatory factors will be analysed in later sections. Given the decline in NCE output in the industry in general and the fact that the U.K. industry has suffered less dramatic declines the interpretation of the reasons behind a decline in innovation rates must be reviewed and the reasons for the difference assessed.

2.5 Review of studies dealing with the decline in drug innovation rates

2.5.1 Introduction

There are a number of possible factors that may lead to a decline in drug innovation rates and ideally each should receive attention. However, some of the factors are difficult to quantify and have been unamenable to standard economic analyses. The majority of studies concerned with drug innovation have linked the decline to one factor in particular, namely the effect of federal or governmental regulations since the early 1960s. Most studies give scant notice to any alternative factors behind the decline. It is worth bearing in mind that causation of the decline is not proved by the mere coincidence of regulation and a decline in innovation rate as measured by product introduction rates.

In reference to the UK situation little attempt has been made to document the decline in introductions except in comparison with the USA. Many studies have been of an impact analysis type where the influence of **regulations on the product output** of the industry has been analysed. In doing this they make the assumption that regulations are the most important factor behind the decline, where account has been made of alternatives this has resulted in the incorporation of subjective estimates into rigorous econometric models of regulation.

Early studies illustrate the two main opposing views which may be thought of as the views of the 'regulators' and those of the 'industry'. The debate between the two has been long and complicated with many side issues involved, in many instances it will not be necessary to include these aspects unless they are directly relevant. In the following review of studies their applicability to the present study and their importance will be noted. It is worthwhile to set the context for many of the studies as they arise from a common theme, that of USA drug regulation since 1962.

The 1962 Kefauver-Harris amendments to the 1938 Food Drug and Cosmetics Act are viewed as a watershed in drug regulation in the USA, the role of the Thalidomide tragedy in encouraging the adoption of the Amendments has been well documented but it may have only provided a final impetus to allow the passage of the Amendments through Senate. Silverman and Lee (34) give a thorough account of the rough passage afforded to the Amendments in the US political arena by the industrial pressure groups and, interestingly, by the FDA itself.

In August 1962 the Kefauver Bill was passed by Senate and in September of the same year the Harris companion Bill was also passed, both were eventually joined to form the Kefauver-Harris Amendments. The result was that a proof of efficacy clause was added to the existing proof of safety clause in the 1938 Act. A further major change was the removal of a procedure that allowed automatic clearance of marketing applications for new products within a set period unless opposition was encountered within the FDA. In the Amendment a process of positive vetting was included with established testing procedures and requirements, the regulating authority having total responsibility for the type, duration and extent of testing necessary to satisfy the safety and efficacy requirements.

2.5.2 Studies

Martin Baily (35) attempted to incorporate the effects of the 1962 Amendments in a production-function model of new product development for the US drug industry. He demonstrated that a simple correlation between expenditure on R&D and the rate of new drug development between 1954-1969 was negative. There seemed a need to account for the disturbance in this relationship. Shifting the R&D function of the model improved the statistical relationship between R&D input and the rate of product development. However, another proxy variable was needed to account for a factor called the 'depletion of research opportunities' which Baily assumed had an impact on the rate of drug development. This variable was derived

from a seven year moving average of past total introductions. Baily thus recognised the two main factors which have had an influence on drug development post 1960. Although he was conscious of the assumptions that he made and was critical of any spurious correlations that may arise, this does represent one of the first accounts of research that recognises the importance of non-regulatory factors.

A continuation of the production-function approach is seen in the work of Sam Peltzman(36), he explicitly attempted to quantify the effects of the 1962 Amendments on the drug industry in the United States. The methodology used was of the cost-benefit analysis type and investigated whether more valuable drugs resulted from the new regulations. The post 1960 decline in product introductions was seen to begin in this period and not represent part of a longer term trend with earlier roots. A similar model to that of Baily was used for the unregulated introduction of drugs by testing the model in relation to the available actual data for the pre 1962 period. Extrapolating post 1962 using the model showed a divergence between the projected and actual rate of drug introduction (see Fig.2.2) The variation between the two rates was said to give an estimate of the effects of legislation. Peltzman summarised the study by noting that the Amendments were responsible for a significant reduction in the flow of NCE's and that all of the observed difference between pre and post Amendment rates could be attributed to the legislation. Balancing costs and benefits of the Amendments, he concluded that the regulations failed in that effective drugs were prevented from reaching the market and also that prices of drugs had increased as a result. One benefit of the regulations was noted, that of reducing consumer waste on ineffective drugs.

Peltzman's study has been criticised by Temin amongst others who argues (37) that Peltzman is wrong in assuming that the Amendments had immediate impact in 1962, he argues that the Amendments did not represent any radical modification in the processing of drug applications and that the data presented would tend to overestimate the effect of any regulation.

It may be more relevant to criticise Peltzman's demand-pull model and its applicability in studies of the drug industry. The potential for innovation on a technical basis tends to be downgraded using this model and it may be more useful to examine the supply side factors including the effect of regulation and other criteria on the R&D process. The approach fails to take into account such factors as depletion of research opportunities due to effects on the level of basic research. Furthermore, the linking of the post-1962 drug output to the market and useage of products may be unfounded. This type of approach which argues that regulations may be responsible for all the decline in innovation rates is a common one which is due in part to the difficulty in applying economic models to such a complex issue. The view of the 'regulators', the FDA on this matter was given by Alexander Schmidt in evidence before the Senate subcommittee on health in August 1974. These hearings which later became known as the Kennedy drug lag hearings were cited by the FDA as evidence to support their claim that the impact of regulations on the development and marketing of drugs was overestimated by industry and was only one of many factors involved (38). After conceding that there was indeed evidence to show a decline in the output of drugs in the USA, Schmidt made the following observations:

1 The decline in introduction rates began prior to the enactment of the 1962 Amendments.

2 The decline was greater in those drug products that represented little or no therapeutic gain than for those products that represented modest or major therapeutic advances. The latter products had been developed at a constant rate since the mid 1950s.

3 The 1960s decline was a worldwide phenomenon and could not therefore be due to a single cause eg the US Amendments.

4 The increase in gaps in biomedical knowledge caused a decrease in opportunity for drug developments, this being one of the features of a technologically mature industry.

In the case of the first point, the observation is correct, as shown by the data (See fig.2.9). Critics of the FDA, however, argue that the Kefauver-Harris Hearings which began in December 1959, led to an anticipatory effect on the industry prior to the actual enactment of the Bills.

In the case of the therapeutic gain that each product represents, this is the next level of analysis and will be dealt with in more detail later.

The fact that a worldwide decline in introduction rates took place in the early 1960s is insufficient proof for many commentators who argue that the decline in the US took place earlier and was more marked than in any other country. The additional arguments used to illustrate the alternative view include the "echo effects" that result from the influences placed on a multinational industry that are seen all over the world. The size and complexity of the US drug industry together with the importance of the US as adrug market would have serious impacts on all national drug industries.

The "depletion of research opportunities" argument proposed by Schmidt is often raised as another major impact on drug innovation over the period. The concept however has caused problems for many critics who find it difficult to put into quantitative or qualitative terms. As a

result the notion of research depletion is often presented with no empirical evidence to support it. Other studies that attempt to deal with this matter are reviewed later.

In the same evidence, Schmidt, after failing to give much credence to the impact of regulations on the rate of innovation proceeded to emphasise the moves made within the FDA to streamline the regulation process and to ensure that the US was not at a disadvantage compared to the rest of the world. The Drug Lag appears in many of the studies of innovation in the drug industry and will be mentioned whenever relevant. The drug lag is however a slightly different problem to that of a reduced innovation rate and is the consequence of a reduced marketing rate compared with the other countries of interest.

Barry Bloom of Pfizer, examined the rate of drug discovery in an analysis of the US NCE introductions from 1940 (39). He adopted a somewhat cautious approach to the reasons behind the decline and concluded that the causes of the slowdown in drug discovery were multiple and complex and although he later conceded that in his opinion, regulatory constraint appeared to be the most significant factor. Bloom cited other reasons including a lack of basic biological knowledge and the increase in standards in drug research leading to a difficulty in meeting them. Bloom analysed the drug output in some detail by means of therapeutic categories and found a greater decline in products where drugs were already in existence on the market for treatment of a particular disease. This could account for over 50% of the total decline. See Table 2.7.

Table 2.7

Category	Number of products introduced	
	1958-1962	1963-1967
Antihistamines	9	0
Antitussives	4	0
Antispasmodics	7	2
Muscle relaxants	8	0
Antinauseants	3	1
Thiazide diuretics	10	2
Sulphonamides	5	0
Antiobesity	4	1
Corticosteroids	14	3
Tranquilizers	16	7
Psychostimulants	9	4
Antibacterial/antifungal	13	10

Therapeutic categories of products introduced 1958-1967

Bloom therefore introduces another dimension into the debate, that of the direction of innovation and the impact of various constraints on the targeting of products.

The proposal that a lack of basic knowledge is hindering research is discounted by Bloom in another paper (40) when he states that, "If anything, today's therapeutic research should be able to produce more important new drugs than emerged in the 'golden age' of the 1950s". The incentive structure available to industry is thought by Bloom to have altered to the detriment of society in that the regulations geared to prevent the marketing of products with no significant advantage over already existing products, also prevent research in socially favourable areas such as chronic degenerative disease, contraception etc. (41).

Weatherall, a drug industry executive, cites reasons for the slowdown in the rate of drug discovery and classifies them into four types, namely: technical, legal, emotional and financial (42). This recognition of the complexity of the problem expands the debate into even more difficult areas but fails to provide any framework to allow for the separation and quantification of the individual factors.

Gross (43) goes further than Weatherall and, although agreeing with the latter, puts forward additional reasons namely the undue burdens of routine testing with little emphasis on innovative research, inefficient management (an argument also favoured by a DHSS official), the lack of imagination in research coupled with constraints on innovative thinking and finally the continuous time pressures. He does however concede that these problems are not peculiar to the drug industry but are encountered by academic researchers.

Henry Grabowski of the American Enterprise Institute has been a leading researcher in this field for many years and in a comprehensive series of reviews (44) makes a number of points concerning the decline in innovation. He recognises the problem of separating the non-regulatory factors from the regulatory influence and using the methodology developed by Baily and Peltzman, describes an attempt at separation.

The study by Grabowski, Vernon and Thomas, uses a production-function model and compares the US and UK rates of drug introduction. This is therefore a pioneering step in the study of drug innovation and, if effective, would enable public policy decisions to be made with more accuracy. Five hypotheses are listed to explain the decline in the rate of innovation:

1) Tighter regulations.
2) The decline is illusory, no decline in effective drugs.
3) Depletion of research opportunities.
4) Post-Thalidomide caution by Industry and physicians.
5) Advances in pharmacological science leading to increased testing and costs.

In this study, the UK is used as a control to attempt to eliminate the regulatory effects. The R&D productivity of the UK and the US industries are calculated, ie. the number of NCE's discovered per effective R&D $. Non-regulatory influences are assumed to affect both of the industries in a similar way. In order to exclude the impact of UK drug regulations on the model, only data for the period prior to 1971, the date of introduction of official regulations in the UK under the 1968 Medicines Act is used. Grabowski shows that the impact of the 1962 US Amendments on the UK industry was not statistically significant. In order to exclude any "echo effect" due to the presence of US firms in the UK market, the introductions from UK domestic research are identified and used in the analysis. All assumptions made by Grabowski were thought to be conservative and underestimate the effect of regulations in the US.

The results show a significant decline in R&D productivity on both sides, with the United States showing a stronger relative decline over the period of six times as compared with three times in the UK. In the latter part of the period studied, the influence of UK regulations are apparent. The difference in productivity rates is considered by Grabowski to be due to the 1962 Amendments, with non-regulatory factors being important. Complete separation of the factors proved impossible.

A critique of the methodology adopted by Grabowski is given by Parker (45), who again criticises the vague way in which research depletion is accounted for by means of a variable calculated from a count of NCE's over time or by means of research expenditure. Neither could be considered as a direct measure of this factor. Another criticism concerned the use of a GNP deflator in the calculation of R&D expenditures, the use of a more specific R&D deflator being preferred. This criticism could be made of most studies but the use of such specific deflators is

in its infancy at this time, a factor that will be discussed in a later chapter.

Grabowski's research, although it attempts a separation of factors, fails to deal with the whole problem and therefore is open to criticism. Many studies use a 'black box' approach to R&D and suffer accordingly.

William Wardell, working from a medical viewpoint has been one of the most consistent commentators studying technological change in the drug industry. In 1975 Wardell and Lasagna (46) suggested three ways in which to design a study in which the impact of regulations on the drug industry could be assessed.

1) The analysis of one country over time, covering periods previous to and following the introduction of regulations. This approach would remove most of the international effects, but would not account for time-variable non-regulatory factors.

2) A horizontal study using a set time and comparing various countries. This removes the time-variables but introduces the international problem.

3) A combination of both the above approaches; although time-variables would exist, Wardell uses this method in long term studies.

The relative importance of non-regulatory factors is difficult to assess using the latter approach and they recognise this, "it must be kept in mind that the differences to be described are not solely the result of differences in legislative and regulatory policies working in isolation. In many cases, however, it is possible to discern that differences in regulatory philosophy are a prime cause of differences in drug development and usage".

They then assume that regulatory variation is the most important factor in studies comparing international drug innovation rates.

By means of a comparison of the rates and direction of introduction of drugs in the UK and US, Wardell and Lasagna attempt to separate the effects of US regulations from other factors. This approach is very similar to that of Grabowski, but is conducted from a medical standpoint rather than a purely economic one. The availability of drugs is viewed by Wardell as being due to a set of determinants which can vary between countries. These determinants include regulatory influence and the current level of knowledge or 'state of the art' in sciences. Again the UK is used as a control as the standard of health care and the presence of a large and innovative drug industry roughly parallels the US case.

Over the period 1962 to 1971, Wardell and Lasagna show that the US lagged behind the UK in the rate of drug introduction. particularly in certain therapeutic areas. This phenomenon has become known as the drug lag and has been subsequently studied by Wardell over an extended period and has also received the attention of industry's critics and academic researchers. Such importance was placed on the findings of Wardell that the Schmidt Hearings before the Senate provided a forum for discussion of the problem.

The variation between the US and UK is accounted for in this study purely in terms of regulatory stringency. Temin (47) has criticised this study for its lack of quantitative content and the use of many subjective statements. He argues that Wardell has compared the US in a state of change with the UK prior to the introduction of regulations. The final criticism by Temin concerns the fact that this approach cannot answer the question of whether a tighter or more flexible regulatory policy is preferable.

In a later study Wardell shows that by 1976 the wide discrepancies in certain therapeutic areas had closed, particularly in the cardiovascular diuretic, respiratory and gastrointestinal fields. This was attributed to the introduction of drug regulations in the post 1971 period in the UK, and an increased capacity for foreign firms to enter the US market and satisfy US federal regulations (48). Wardell continues his studies using data obtained from the drug companies via a questionnaire. The number of NCE's that are taken into man in clinical trials by each company surveyed in the US were noted (49). A decline is seen for the post 1963 period, see Fig.2.10.No data for the earlier years is given and therefore Wardell is unable to comment on whether the decline was part of a longer trend or was a new phenomenon. The role of regulation in causing the decline is then difficult to determine.

The move towards foreign clinical trials for products originating in the US is also shown. Particularly in the case of foreign companies with established international research facilities. This trend is noticed in many innovation studies in the US and is one of the reasons behind the review of regulatory activity that took place.

In an update of the drug lag data to 1979 Wardell continues his attack on the regulatory system, "it is my judgement that the drug lag and the unhealthy state of pharmaceutical innovation in the United States...stem largely from an underlying malaise in new drug regulation" (50). This he considers to be due to the fact that regulations act in a direct and powerful way on research and development activity. The FDA 'knowledge depletion' hypothesis is dismissed as being 'transparently specious' and any suggestion that,as that FDA argues, knowledge acquisition occurs on a cyclical basis, is considered "preposterous".

Figure 2.10

Number of NCEs first given to man abroad or in the US by US companies

Source: (49)

Therefore although the aim of Wardell's work was to assess the non-regulatory impacts as well as the regulatory impact, little evidence is given and Wardell returns to the traditional view. No improvement in the methodology necessary to separate these effects was forthcoming.

David Schwartzman, in his economic study of innovation in the US pharmaceutical industry takes the overall view of the range of constraints on the industry and argues that the decline in innovation is due to a reduced rate of return on investment, this itself being due to a number of reasons including the 1962 Amendments. The pressures put on the industry's incentive structure with the proposed changes in patent law, Maximum Allowable Cost (MAC) legislation as well as the diversion of resources to satisfy regulatory testing requirements are cited by Schwartzman as other reasons. The funding of research is a topic that is given special attention because of the often misplaced belief that directing funds into basic research will lead to applied research breakthroughs. Schwartzman shows that the drug industry is far removed from the traditional model of research as exemplified by pure physics. The flow of knowledge in the drug industry is not uni-directional from basic to applied research and the use of traditional models is not satisfactory. The linear 'black box' model of drug research with input and output as the most important variables needs improvement for studies of drug innovation to have any accuracy and policy value (51).

The unresolved problem of separating regulatory and non-regulatory factors is re-emphasised by Steward and Steward and Wibberley (52). Steward presents data for UK drug introductions based on the earlier NEDO commissioned lists of drugs. An important aspect of the debate concerns the therapeutic significance of the innovations, which Steward considers to be more important than the actual rate.

Steward agrees that regulations have had an impact on introduction rates and that for the UK introductions, fewer products have been withdrawn since the regulations came into force. This would indicate that a number of products that would have been subsequently withdrawn from the market for reasons of toxicity, efficacy or market performance have been prevented from entering the market in the first place.

Recently, few studies have generated any new empirical data concerning the decline in innovation rates probably because the rates over recent years have been fairly constant and have reached an equilibrium position. Commentators continue to make statements and cite probable reasons but fail to back the comments up with any data. One of the most popular approaches is to state rather nebulously that there has been a change in the environment for R&D in the industry (53). The US PMA (54) uses introduction data to show the decline but continues by stating that:

"Even without the tougher regulatory requirements for approvals a decline in new product introductions might have occurred as researchers developed more sophisticated instruments and techniques for measuring safety and effectiveness and addressed more complex problems such as the development of therapeutic agents for the more intractable diseases".

This concept of sophistication is an important matter and was cited by a UK regulatory affairs manager as of concern to his company (55). The extent to which companies would test products in the absence of official regulation is another area of contention. Some argue that most of the testing done under the Medicines Act would be done anyway as a precaution by the industry.

The PMA apparently recognise the complexity of the situation and the possibly less important contribution made by regulation. They continue, "the weight of evidence seems to point to changes in the regulatory process as a major, although not the sole cause."

In a similar capacity, David Taylor of the Office of Health Economics (OHE), London, the 'think tank' of the ABPI, agrees with the argument that regulations are not the sole cause and he argues that the Thalidomide incident triggered an inevitable response to the unhindered growth of the industry. Taylor and other industry commentators recognise the fact that some balance needs to be established between the interests of industry and those of society wherever there are points of conflict.

Other commentators argue that the influences on the process of drug innovation are so complex that current analyses using measures of NCEs, R&D expenditure and sales offer valid approaches but fail to achieve any fundamental understanding of the innovation process per se. This failure to understand the complexity of the innovation process and to view the output of pharmaceutical R&D as a homogeneous flow has stimulated research that aims at a fuller understanding of the nature and direction of innovation. Such studies are commendable but make use of the NCE output of the industry as a starting point and make no comment on the innovation process.

Ashford in a study prepared for the National Science Foundation in the U.S. presents an introductory discussion which reviews current innovation theory and goes on to apply this theory in a critical way ot drug innovation. Ashford identifies three main variables in drug innovation namely, regulatory policy, the R&D process itself and the therapeutic significance and direction of drug output. The relationships that exist between all three are said to be dependent on the specific drug produced.

In order to evaluate these variables, the major regulatory, non-regulatory and public sector events influencing drug innovation need

to be identified. The process of innovation is characterised by means of a time series of therapeutic types, together with the use of a category for benefits of the drug. Using specific examples, derived from three therapeutic categories, general hypotheses can be developed and tested. Further details of this analysis will be considered later (56).

A more recent study commissioned by the OHE and undertaken by Hartley and Maynard of the Department of Economics and Related Studies at York examined the costs and benefits of UK drug regulation. This study is of particular interest as it contains data relating to the seven UK owned companies of interest and deals with the impact of the 1968 Medecines Act on the UK industry. By means of a questionnaire survey conducted between March and September 1980 which received 16 replies, data on costs and, to a lesser extent, benefits of the Act were obtained (57).

The use of this type of approach in dealing with health issues results in unconvincing methodologies and a lack of objective data on the benefits of drug regulation. The costs of drug regulation were shown to outweigh the benefits although little time and effort was devoted to the latter. The impact of other influences on drug innovation is considered in passing but as little attention is given to other factors, the questions dealing specifically with the Act, few conclusions are given.

The decline in innovation is not correlated directly with regulatory influence and causation is not conclusive. Regulations are assumed to be only one variable impinging on a complex innovation model. Results of the questionnaire indicated that only one respondant out of ten who replied to a question concerning the major effects of drug regulation considered that a reduction in the number of new drugs was the most important effect. The lengthening development time was ranked first with a reduction of innovation rate being third placed.

The above study shows the difficulty in obtaining any consensus regarding the effect of regulations and a number of studies have attempted to examine the effect of regulations on more closely defined criteria. One such group of studies attempted to analyse the effect of regulations on the output of drugs of varying therapeutic significance in order to determine any trends. These studies and their conclusions will be discussed next.

2.6 Analysis of drug output by therapeutic significance.

A decline in output of all pharmaceutical products particularly new chemical entities would be expected if, prior to the introduction of safety and efficacy regulations, products lacking these basic qualities were marketed. Regulations, if operating satisfactorily, would result in a reduction of these products. Underlying this point are many questions including whether unsafe or ineffective drugs were marketed prior to the introduction of regulations. Were regulations able to prevent such drugs being marketed subsequently ? The empirical evidence generated by a number of researchers can be used to illustrate these points.

It is generally agreed that market forces alone were insufficient to prevent the marketing of products with undesirable side-effects. Reference is usually made to the Sulphanilamide tragedy of 1937-8 in the U.S. which led to the 1938 drug legislation and the Thalidomide cases of the 1950s which stimulated the adoption of the 1962 drug Amendments.

The measurement of the safety and efficacy of any drug is subjective, based on expert assessment. Many attempts have been made to to evaluate the NCE output of the drug industry using rating systems for therapeutic significance. Any decline in drug output may be acceptable if confined to products of limited effectiveness or safety. The studies that have attempted to use such assessments are outlined below.

Alexander Schmidt in the 'drug lag' hearings used the argument of therapeutic significance to explain the decline in innovative output. Products offering little or no gain over existing products were shown to have declined significantly since the introduction of efficacy requirements in the U.S. The FDA data used has since been criticised by Grabowski who argued that FDA ratings of important therapeutic advances, of which he described four, had all shown different therapeutic ranges. This, argued Grabowski, rendered the data ineffective. Table 2.8 gives the studies.

Table 2.8

Year Drug Introduced	Number of drugs deemed important			
	1971	1972	1973	1974
1950	6	3	3	6
1951	6	5	6	11
1952	14	12	13	12
1953	10	6	7	9
1954	8	5	10	8
1955	14	6	5	3
1956	10	4	4	4
1957	13	9	10	6
1958	12	5	6	4
1959	21	8	9	4
1960	15	6	8	6
1961	15	4	4	2
1962	16	7	7	6
1963	10	4	6	5
1964	10	7	8	5
1965	12	5	7	4
1966	8	4	5	4
1967	12	8	9	6
1968	9	5	4	3
1969	4	2	2	1
1970	8	4	6	6
1971	-	5	5	5
1972	-	-	-	0
1973	-	-	-	2

Four FDA assessments of important therapeutic advances 1950-1973

Source. (66)

The number of 'important therapeutic advances' have generally dropped with successive assessments.

The FDA classify drug applications by means of chemical type and therapeutic potential. Chemical types can be broken down into six main categories (59):

TYPE 1) New Molecular Entity
2) New Salt
3) New Formulation
4) New Combination
5) Already Marketed Drug Product
6) Already Marketed Drug Product (same firm)

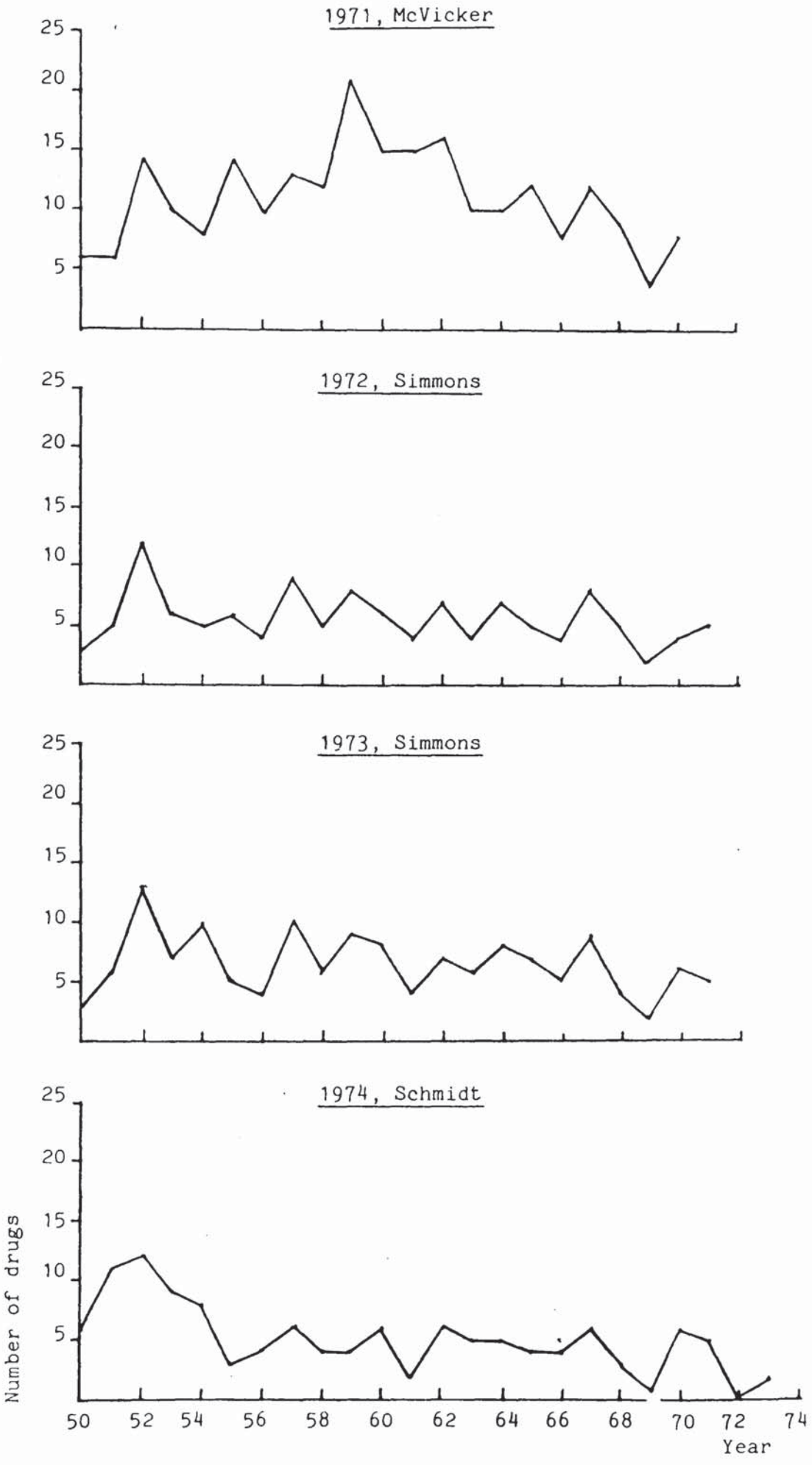
In terms of therapeutic potential, five categories are used:

TYPE A) Important Therapeutic Gain
B) Modest Therapeutic Gain
C) Little or No Therapeutic Gain
D) Special Situation
E) DESI/OTC Claim.

Categories A, B and C are of most interest to this particular type of analysis. If the FDA assessments are closely examined (see Fig. 2.11) then it is apparent that the McVicker assessment is the only one that shows a steep decline in the number of important gains marketed since 1962. All the others show a very much shallower decline or an undulating constant output over the period 1962 on.

Peltzman, in his cost-benefit analysis of the impact of the 1962 Amendments (60) argues an alternative view to that of the FDA. He assumes in his study that a reduction in waste on ineffective drugs would result from the regulations and uses a set of 'expert' drug evaluations to illustrate the point. The 'cost' of inefficacy, he proposes, should have declined since 1962 in the three scenarios that he uses, ie hospitals State public assistance formularies and the American Medical Association Council on Drugs and Drug Evaluations. In each of the examples chosen

Figure 2.11



Four FDA assessments of important new therapeutic advances

attempts are made to draw up lists of effective drugs (therapeutically and interms of cost) and the impact of regulations on the structure of these lists is examined. Peltzman argues that little evidence for a reduction in saving on ineffective drugs is seen. Market forces are, in the opinion of Peltzman, sufficient to ensure that ineffective drugs remain off the market. Regulations, he argues, have had little impact on the qualitative nature of drug output. The use of subjective listings of drugs as a point of analysis in this study would appear to reduce the accuracy of the results obtained. The use of limited drug lists such as adopted by the WHO and, more recently, the DHSS is often criticised by industrialists for their incomplete nature.

Data on the U.K. is not as comprehensive, only one major study, that of Steward has produced any comparable data. In their study of innovative activity in the pharmaceutical industry in 1970, NEDO's pharmaceutical sector working party commissioned Alan Angilley and George Teeling-Smith of the Centre for the Study of Industrial Innovation (CSII) to produce a list of all world NCE introductions 1958 to 1970. This resulted in a final list of 466 drugs which was subsequently analysed on the basis of the performance of each drug in the total drug market, in its market sub-group and for therapeutic significance at the time of introduction. For some drugs additional data on chemical novelty was obtained. The therapeutic assessment was achieved using a panel of U.K. medical experts, each drug was assigned a rank number from one to five. The categories used were as follows;

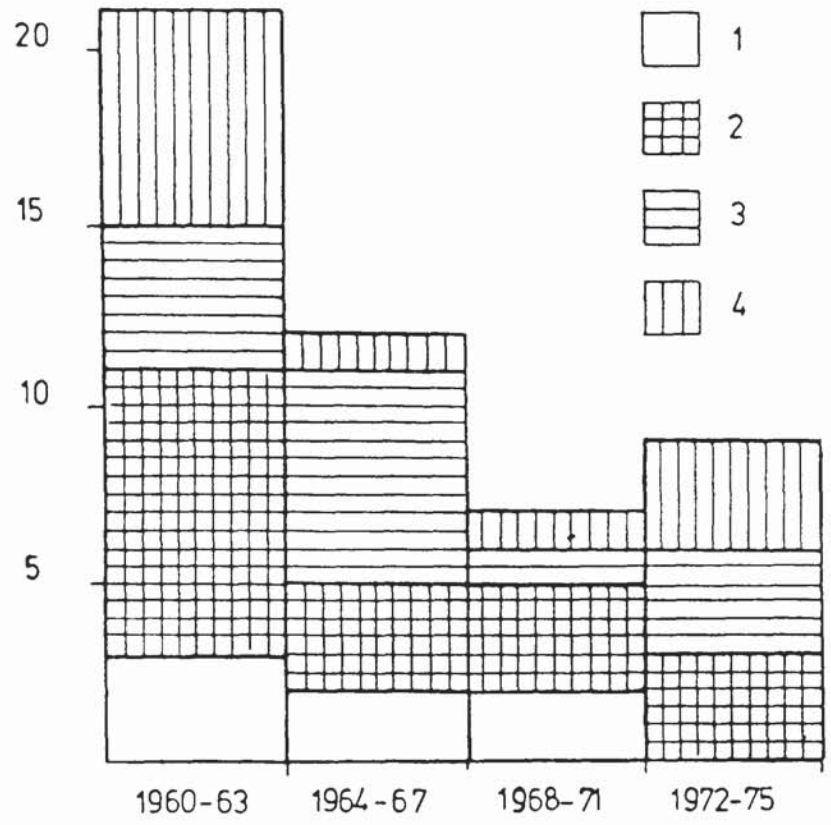
1. Fundamental new medicine of major clinical significance
2. Important new medicine offering substantial advantages for a majority of patients.
3. Useful new medicine offering advantages for a minority of patients.
4. New medicine offering marginal advantages over previously existing therapies.
5. New medicine offering little or no advantage over previously available therapies (61).

NEDO, however, did not release the data in the form of a table of annual introductions; this analysis was done by Steward who produced a breakdown of drugs marketed in the UK by the therapeutic significance and year of introduction. See fig.2.12This data to 1970 was updated by Steward for the period 1971 to 1976 using the introduction data in Drug and Therapeutics Bulletin and Medical Letter. Qualitative assessments were achieved using the statements made in these journals concerning the therapeutic significance (See fig 2.12) Also, for the Steward analysis, the NEDO categories 2 and 3 are combined in one (62).

A decline in total output of drug introductions is seen, with the 'least significant' showing the greatest overall reduction. All categories decreased in output over the period including the most 'fundamental' drugs. The percentage of drugs of little or no therapeutic/marginal significance remained high over the period, with increases in these categories coinciding with the periods just prior to the introduction of regulatory controls in the UK. If the products originating from the UK owned companies are analysed in the same way, the reduction in fundamental or useful products is notable. This is of concern as the results were thought to be biased in favour of UK domestic products due to the use of UK 'experts' See fig.2.13.

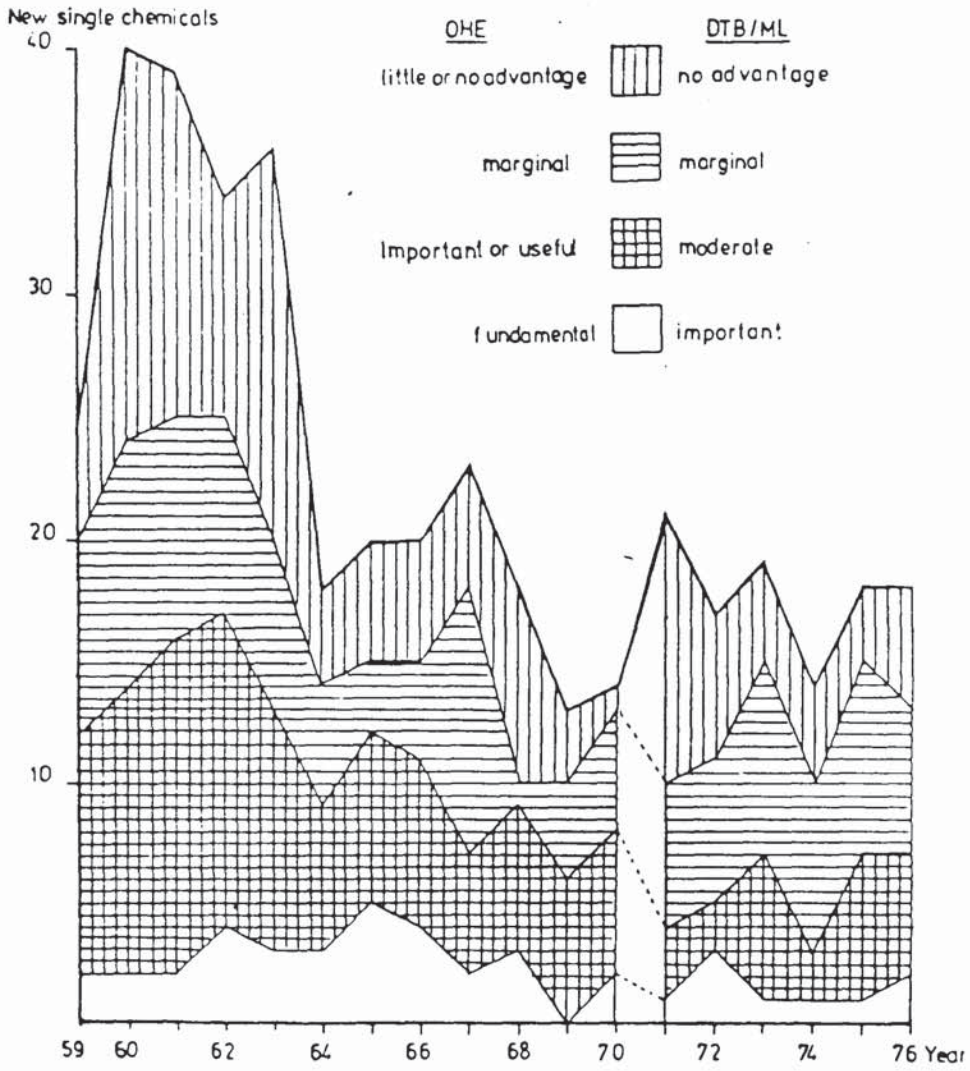
It would seem from the evidence that regulations have resulted in a reduction in the number of less significant products reaching the market but the number of more important products has also declined together with the products of 'fundamental' significance. This is important to policy-makers who have to balance the benefits of drug regulations with their costs. Steward illustrates one of the benefits of drug regulation with reference to the rate of withdrawal of NCE over the 1960-1975 period. This data shows that a sharp decrease in the number of withdrawals took place following the establishment of regulatory practices in the UK in 1964. (See fig.2.14)

Figure 2.12



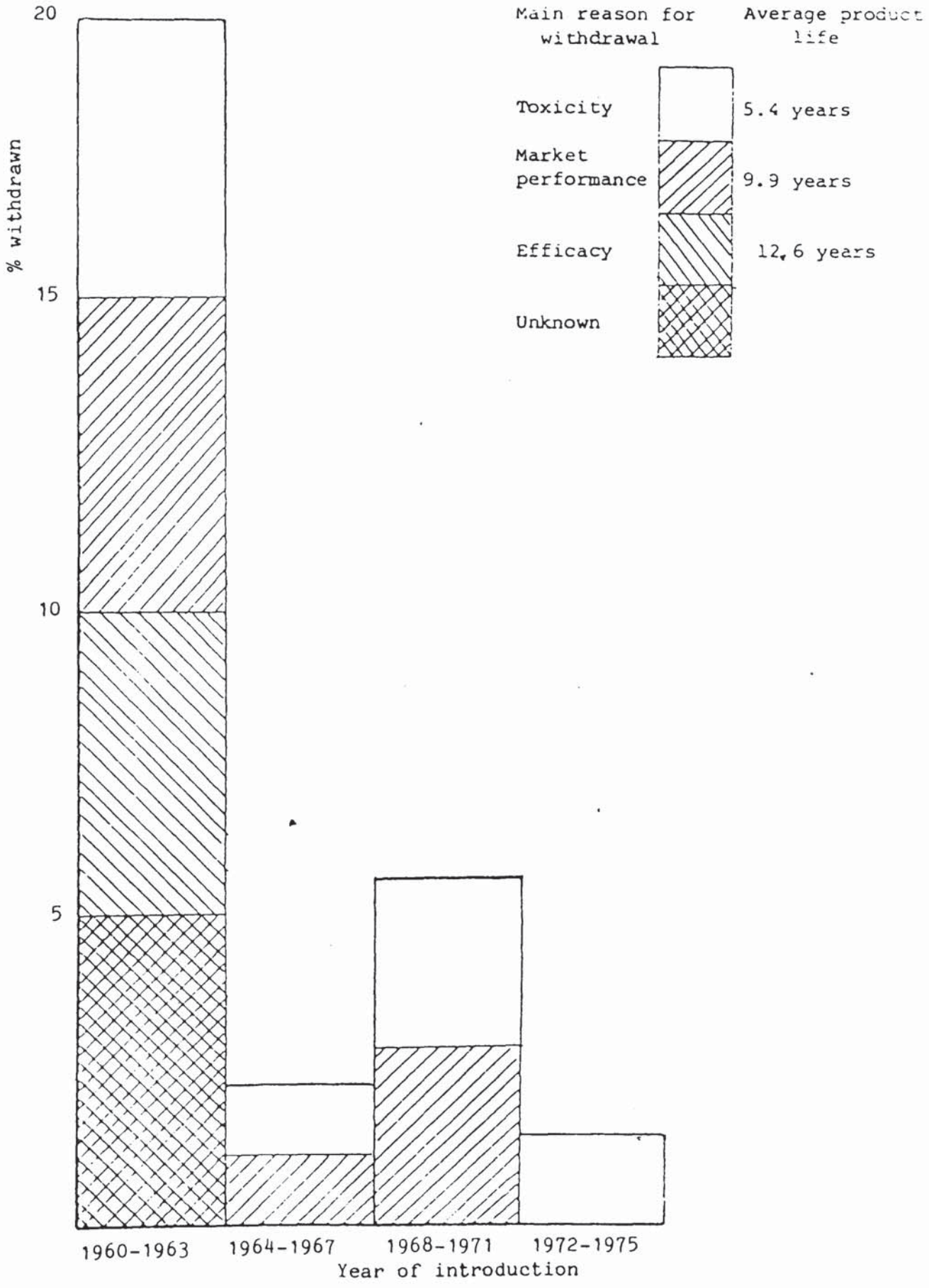
New drugs discovered by British-owned firms and marketed in the U.K. 1960-1975 by therapeutic significance

Figure 2.13



New drugs marketed per year according to therapeutic significance 1959-76

Figure 2.14



Great Britain: Withdrawal of NCEs introduced 1960-75

Withdrawals for reasons of efficacy (or lack of) were eliminated towards the latter part of the period, a goal of public policy apparently then fulfilled.

A related issue was examined by Ashford et al in a NSF sponsored study of the relationship between aspects of regulation, innovation and therapeutic benefits (63). Ashford states the need for more disaggregated data concerning the output of the innovation process. The study aims at detecting variation in innovation, regulation and therapeutic benefits in a selection of therapeutic areas. The chosen drugs were divided into prototype or non-prototype, prototype drugs being the first members of a drug family to come to market and would therefore represent novel chemicals. With the exception of antibacterials, Ashford found an increase in the proportion of prototype drugs in the post regulatory period as compared with the pre-regulatory period. The exceptions were explained by the assumption that antibacterial products had less stringent testing regimes than other products and were more likely to be marketed regardless of relative significance.

Since the prototype status was regarded by Ashford to be roughly comparable to the therapeutically significant category of drugs described earlier, this result would tend to contradict the findings of earlier research by indicating a shift in the post regulatory period to products of greater therapeutic significance. Similarly Ashford argues that a trend towards the development of products for the treatment of acute (less than 6 month) diseases is taking place. This would appear to contradict earlier findings which intimate that the trend was towards products for the treatment of chronic diseases such as hypertension in order to secure a more lucrative market. Ashford also notes the reduction

in adverse reactions following the 1962 Drug Amendments.

Evidence to support the Peltzman findings is produced by Wiggins (64) using data for a more recent period. The approach is that of a production-function model as used by Baily but in this case reducing the constant returns to scale factor and allowing for some variation in regulatory stringency between therapeutic classes. Wiggins shows that for the period 1970-1976 'regulation has reduced the rate of new drug introductions and that this effect has not been smaller for the more important new drugs'. A significantly larger reduction in the percentage of therapeutically important new drugs as compared with those of modest or little or no therapeutic significance is demonstrated which, he argues, fails to support the FDA position.

2.7 Conclusions

The general statement that regulations must have an overall negative impact on the innovative activities of industry has led to a series of studies that seek to examine the the specific effects of regulations on the pharmaceutical industry. This interest derives from the apparently identifiable impacts of regulation on such a research-based industry. A number of possible effects of drug regulation on the industry have been outlined but the benefits of regulations to industry and society prove to be more difficult to ascertain with any accuracy.

Industry points to a jungle of regulations preventing traditional levels of innovation whilst critics note the output of less innovative products. A lack of data pertinent to the issues has resulted in a number of studies attempting to directly measure the effects of regulatory controls. Some studies attempt to construct non-regulatory scenarios as controls, others determine methods for measuring the rate of innovation using counts of NCEs, licencing activity or patent application rates.

Analysis of NCE output in the USA has led to the conclusion that the rate of introductions has declined since 1962, the period of increasing drug regulation. This decline is mirrored in world NCE introduction rates and in the U.K. where the decline is shallower.

Given this decline the factors responsible and the implications of such a trend have been analysed. Non-regulatory factors such as a decline in research opportunities, technical sophistication and diseases of complex aetiology have been cited as reasons for the decline but their identification and quantification have proved difficult.

Most researchers argue that the decline in NCE activity can be attributed wholly or mainly to increasing regulatory activity. Many studies have been hindered by a lack of objective data and full understanding of the pharmaceutical R&D process.

Some commentators have discussed the effect of regulations on the therapeutic significance of the NCEs developed. Evidence has been presented to support the view that regulations have reduced the output of less innovative and potentially harmful drugs.

In order to reduce the need for a 'black box' attitude towards R&D and to gain a fuller understanding of the changes in the R&D environment, the next chapter will describe the innovation process in more detail. The U.K. owned companies in the domestic industry will be examines as there is little research dealing with these firms specifically.

The points at which regulations act need to be identified as well as locating any possible indicators of the rate and direction of innovative activity. This analysis will then develop into a discussion of the use of science and technology indicators in the pharmaceutical industry and the problems associated with their use. Two main elements are selected for discussion, firstly whether the decline in NCE output is mirrored in the U.K. owned drug firms, including any inter-firm variation and secondly, whether it is possible to correlate any trends with changes in the U.K. regulatory system.

CHAPTER THREE: THE U.K. PHARMACEUTICAL INDUSTRY

3.1 Introduction

The pharmaceutical industry maintains a unique position in manufacturing industry, a study for the OECD in 1969 (1) recognised the key characteristics as the type of product manufactured, the unprecedented research and development input, the social impact of the product and the general nature of the industry in terms of the type, size and number of companies involved. These features will be clarified in later sections. A further important feature of the industry is its continuing economic strength even in a period of general economic decline. Many reports of the strength of the industry have been recorded (2). The contribution of the industry to the balance of trade (over £523 million 1980) (3), its importance as an employer and its record of innovation must also be recognised.

Given the economic importance of the industry, any constraint on its economic and scientific activities would, it is argued, be detrimental not only to the industry but to the UK economy and society as a whole. Britain is seen as a favourable location for international pharmaceutical companies as well as indigenous firms and is therefore a representative focus of attention. With the National Health Service being a major purchaser of drugs, the Government has a vested interest in an efficient drug industry.

3.2 Structure of the industry

The UK pharmaceutical industry is composed of transnational or multinational companies, the names of which have become commonplace throughout the world, as well as a group of smaller indigenous companies, thus forming a two tier structure (4). Relatively few companies are of a multinational nature due to the enormous resources necessary to maintain a company whose

success depends on innovative products with long development times and large development costs. Only a few indigenous companies have sufficient resources and expertise to operate in such a manner. A strong foreign orientation to the industry is due to the economic advantages of operating in the UK including the availability of a relatively cheap skilled scientific workforce (5).

The multinational companies show a high degree of concentration, the top 25 companies in the world are responsible for half the world pharmaceutical output, a tendency that is increasing (6). The A.B.P.I. produces a list of member companies (7) which contains most of the companies operating in the UK (8). A total of 146 companies are listed some being subsidiaries, five registers are included, the most relevant for this study being the medical specialities register which lists firms producing drugs not advertised to the public. These drugs are ethical or prescription only medicines (POM), other types of products may also be produced by these firms but on a separate register, the names of the other registers are given below (9).

The medical specialities register lists 88 companies, the nationalities of which were traced using 'Who Owns Whom' and were found to comprise:

USA	34	Sweden	3
UK	19	Denmark	2
West Germany	8	Austria	1
Switzerland	5	Ireland	1
France	4	Italy	1
Netherlands	3	Others	7

Of the 19 UK-owned companies, most are subsidiaries of major companies and produce generic standard formulary medicines, depending on the parent company for R&D facilities. The above breakdown mirrors the world picture in that the USA, UK, West German and Swiss firms are prominent. An interesting point to note is the absence of the developing Japanese industry.

The names of the 19 UK companies and their parent company are given in the table below. (table 3.1)

Table 3.1

Company	Parent
Allen and Hanburys Ltd.	Glaxo
Beecham Research Laboratories	Beecham
Bencard	Beecham
The Boots Co. Ltd	Boots
Duncan Flockhart & Co. Ltd	Glaxo
Fisons Ltd.	Fisons
Howard Lloyd & Co. Ltd	R & C
Immuno Ltd.	nf
ICI plc	ICI
Lloyd Pharmaceuticals Ltd	R & C
Norgine Ltd	nf
Paines and Byrne Ltd	nf
Pharmax Ltd.	nf
Reckitt & Colman	R & C
Smith and Nephew Pharmaceuticals Ltd	nf
Stuart Pharmaceuticals Ltd	ICI
WB Pharmaceuticals Ltd	nf
Wellcome Foundation Ltd.	Wellcome
Westminster Laboratories Ltd.	R & C

Note: nf means that no parent company was listed in 'Who Owns Whom'

Medical Specialities Register: U.K. Companies

3.3 The Pharmaceutical Industry's Products

The industry produces a range of items which not only contains medicines but foods and other medical and surgical supplies. If drug products alone are considered, it is usual to group them according to the following convention:

Ethical pharmaceuticals:	Prescription drugs (POM) available only on the production of a prescription (FP10) form signed by an authorised medical professional.
Over the counter (OTC) drugs:	Drugs generally available from pharmacists and more recently from supermarkets, etc.
Veterinary products:	For animal use only.
Bulk Chemicals:	For further processing.

The category that will be considered in this work will be ethical products as these usually result from long and expensive periods of research and development in company laboratories and are of great importance due to their potential therapeutic effectiveness and profit generation.

These products are marketed worldwide hence the multinational nature of the industry and the preponderence with licensing of products to other companies. The main markets for UK firms are EEC countries and Africa (10). UK firms have captured approximately 2.7% of the world drug market as compared with 17.3% for US firms and 32% for W. European firms as a whole (11). In terms of the British market, about 73% is held by foreign firms.

Products are diverse, the market is fragmented with a marked tendency to oligopoly due to the presence of many sub-markets. A drug manufacturer may hold a very small percentage of the total drug market but monopolise a sub-market. Aspects of the above characteristics will be expanded upon in the following accounts in which the activities of the UK owned companies are reviewed in more detail. An initial general history of the UK industry will be followed by individual case histories of the seven main UK owned firms.

3.4 History of the UK Pharmaceuticals Industry

The drug industry in the U K is a comparatively recent phenomenon, particularly in its present form. Thomas, in his history of the industry, complains of a lack of early data (12). Although most British firms were already in existence in the 19th Century, it was only after two world wars that an international reputation was developed. Reorganization of British industry during the 1914-1918 war provided a stimulus to many firms, which continued in the inter-war period and was further enhanced by the demand for drugs due to the second world war (13).

The development of the antibacterial 'sulpha' drugs in the 1930's particularly 'M&B 693' was a first indication of a trend towards a new type of drug R&D as compared with the earlier type of natural product development. The demand for penicillin antibiotics and well established drugs in the UK was stimulated by the blockage of basic material supply routes by the German forces from the late 1930's, and the lack of products from the powerful German drug industry of the time. Several UK firms were involved in the development of penicillins in the 1940's including Boots, Burroughs Wellcome, Glaxo, ICI and May & Baker, many of whom pooled resources with US industry to develop surface culture fermentation methods and later, the more efficient deep culture (14).

Those companies that had some experience of dyestuffs manufacture had a distinct advantage up to this time as the type of technology involved and the nature of the chemicals had many similarities with the type of drugs being produced. By the end of the second world war many UK firms had developed or consolidated an interest in drugs and by 1947 the UK industry was the second largest in the world (15). The formation of the National Health Service in 1948 was another incentive to the UK firms, providing a large and expanding captive market.

By the late 1950's Thomas estimated that there were about 260 firms making up the drug industry, 160 producing prescription drugs only, 80 producing proprietary drugs only and 20 producing both types of product. However, he noted that, 'it is probable that not more than a dozen firms engage in innovation research on an appreciable scale' (16). Moreover, he found little cooperation between British firms in research, there being more international collaboration as existed during the war. Since this time the UK industry has been responsible for a large number of important breakthroughs in drug therapy, the output of drugs from the UK firms will be considered in more detail in later sections.

Any academic study of the industry from its early days is hindered by the international nature of many of the firms involved and their tendency towards acquisitions and mergers. Difficulties are also experienced due to changes in classification of the industry over time, the drug industry has been included in the dyestuffs, food, and chemical industry at different times. The classification adopted in this study is that of the Standard International Classification (SIC), 2720 being the class for 'Pharmaceutical chemicals and preparations'. (17).

A further complication arises from the fact that many of the drug firms of interest have business interests outside the pharmaceutical field. This makes extraction of information relating to pharmaceuticals specifically very difficult. Even within those firms that have few interests outside drugs it is difficult to obtain data relating to ethical products in isolation. Given the nature of the drug industry as described and the inherent problems of studying such a complex and nebulous industry it was decided to concentrate on one sector of the drug industry, that of the UK owned firms. If any level of analysis was to be attempted it was thought that a more comprehensive and balanced study would develop from a study of a number of companies making up an identifiable unit. Since this study intended to develop the use of science indicators, the

use of a limited number of firms would make the empirical work manageable. One aim was to avoid aggregated data as much as possible and assess the availability of data that would be essential if a satisfactory study using indicators was to develop.

The rest of this chapter and subsequent ones will develop the analysis of the UK firms, their activities and outputs. Initially a review of their respective histories and areas of interest will be used to set the scene for more detailed analysis. Each firm will be dealt with in turn and its history outlined, most of the information was obtained from business histories, annual reports, specialist surveys and journals such as Scrip and IMS Pharmaceutical Marketletter . All firms were contacted and requested to provide company history most were able to provide some information.

3.5 Case Histories of UK owned pharmaceutical companies.

3.5.1 Beecham Research Laboratories (18)

BRL was established by H. G. Lazell, then director of Macleans toothpaste, between 1945-47 at Brockham Park, Surrey. A budget of £100,000 per annum allowed research to take place into amino acids, antitubercular drugs, penicillin pastilles, penicillin G and to market Prodexin an antacid, Paynocil an analgesic and Nacton an antiulcer drug (19). The discovery of Penicillin V elsewhere halted Beecham's development of penicillin G but with the assistance of Ernest B. Chain, Beecham entered antibiotic research with new found enthusiasm with the synthesis of p. aminobenzyl penicillin which was an easily modified stable molecule. The fortuitous discovery of 6-aminopenicillanic acid (6-APA) in a fermentation broth in 1957 provided the company with the penicillin core which was found to be relatively easy to convert to penicillin G. Pure 6-APA was extracted in January 1958 with the possibility of almost unlimited side chain modification.

Beecham were from this point, having a distinct advantage over the technology available to competitors, committed to the development of semi-synthetic penicillins. A consultant, Sir Ian Heilbron, suggested that BRL synthesise 6-APA instead of using the normal fermentation production and engaged Bristol Myers, a US company, for technical assistance. Eventually over 200 new penicillin molecules were produced, two of which were notable; one was a costly molecule with a broad spectrum anti-bacterial action and the other was resistant to penicillinase but not acid stable and had to be administered by injection. Both of these discoveries underwent further testing and development in the laboratories.

Bencard, a Beecham subsidiary, had previously been marketing drug products and in 1959 BRL assumed responsibility for all ethical products and Bencard merged with the former. Almost immediately a range of new

products were launched; in November 1959 a Bristol Myers compound Phenethicillin, was launched by Beecham as 'Broxil', the first of the semi-synthetic penicillins. In September 1960, methicillin, 'Celbenin' the penicil linase resistant penicillin was marketed followed by ampicillin, 'Penbritin' which was seen as an advance on Parke Davis' chloramphenicol or Pfizer's tetracycline. October 1962 saw the launch of cloxacillin, 'Orbenin' and a combination product of 'Orbenin' and 'Penbritin' called ' Ampliclox'. In 1967 carbenicillin, 'Pyopen' was marketed maintaining Beecham's dominance of the antibacterial market.

A manufacturing licence was granted to Bayer at this time in exchange for a penicillin G splitting enzyme, an example of the cooperation that has continued up to the present. In 1970 flucloxacillin, 'Floxapen', a major new product was launched followed by another, amoxycillin, 'Amoxil' in 1972. At this time a positive policy of diversification of product areas was initiated and the expenditure on antibiotics R&D was reduced to less than half of the total. Anti-allergy products, for example, 'Pollinex' and 'Migen' were launched in 1973, these being slow release desensitising vaccines. Other specific interests were in cardiovascular, gastrointestinal, CNS disease, arthritis and metabolic diseases including obesity and diabetes. Mianserin, 'Norval', a tetracylic antidepressant was launched by Bencard in 1976.

During the period 1976-77 Beecham had a new molecule, Clavulanic acid or 'Clavulanate' under trial, developed an injectable amoxycillin, had a diabetes treatment in clinical trials and were developing another anti-asthmatic and antirheumatic. 1979 saw the clinical trials of several more 6-APA derivatives and the launch of the oral antibiotic ticarcillin, 'Ticar', a semi-synthetic penicillin for serious gram negative infections.

Outside antibiotics limited clinical trials of a novel antiinflammatory continued as did those for a new antidepressant and lipid-lowering agent of W. German origin.

Potassium clavulanate had by now been combined with amoxycillin to form a product that finished clinical trials in 1980 for launch in 1981. 'Clavulanate' was an important discovery in that it inactivated penicillinase and allowed the combined antibiotic to act more efficiently. By 1980 the benzodiazepine tranquilizer ketazolam,'Anxon' had been marketed and in the following year Beecham had more products in research than ever before. 'Nabumetone' a non-steroidal anti-inflammatory drug was in the final stages of clinical trials and anti-acne, deep vein antithrombic and anti-angina drugs were being tested. In all, 26 products were listed as being in development in 1981 (20).

Early advances in antibiotic research were rapid and successful, however Beecham anticipated difficulty in producing continually improved products and their limited amount of product diversification can be seen as a response to forecasts of future likely product areas. 'Amoxil' has consistently proved to be a major contributor to the growth of the company over the years since 1972 and by 1980 had become the world's most frequently launched patented drug. Licensing allowed 51 launches in 1980 as compared with 31 for Wellcome's 'Septrin' (21).

3.5.2 The Boots Company Ltd. (22)

Boots has one of the earliest origins for a British drug firm, the Boot family had a pharmacists shop in Nottingham in the 1850's, one of the earliest published indications of pharmaceutical products being an 1877 advertisement for Jesse Boot's 'Woodhouses Rheumatic Elixir' (Boot himself being arthritic). During the first Great War, Boot built a factory for the manufacture of fine chemicals including aspirin and began to employ specialist scientists. During the 1920's the manufacture of insulin was undertaken, furthering the size of the R&D team, a further extension took place in the 1930's under the research director Dr. F.L. Pymen who took Boots into steroid hormone research (particularly adrenal and sex steroids).

The Second World War caused a shift in emphasis, as for many manufacturers, into the area of penicillins. Boots was one of the first producers of penicillins by deep fermentation techniques as developed by American scientists at Upjohn. Their cooperation with Upjohn was to continue after the war.

In the 1940's Boots were involved in research on the use of desoxycorticosterone acetate for Addison's disease and thus continued the steroid work. Merck scientists had been working on synthetic adrenal steroids and had found some activity in a compound, Kendall's E later to be called cortisone, discovered by Sarett. Another product Kendall's F was more potent. These discoveries were initiated by the rumour that Luftwaffe pilots given steroids were able to resist high altitude oxygen deprivation, a claim that was subsequently not proven.

Hobday and Thompson of Boots were at a conference in 1949 when the antiarthritic properties of cortisone were outlined by Hench and Kendall of Merck. The Boots representatives, on their return, recommended that

Boots' research efforts be directed at these advances. Boots signed an agreement with Upjohn in 1952 in a wide area including corticosteroid synthesis. They began the manufacture of cortisone and hydrocortisone in the same year but were dependant on US progesterone as a starting material. Both products had side effects (contra-indications) which limited their use and this led Boots into a search for a synthetic non-steroidal product. A limiting factor was the lack of an animal model of inflammation, the cotton wool granuloma test failed to show any evidence of activity in a number of compounds in tests. Aspirin was thought to be a useful antiarthritic due to its analgesic properties but another anti-arthritic, phenylbutazone, had no analgesic activity leading Adams of Boots to suggest that the aspirin effect was the true required antiinflammatory action. Adams and Burrows developed the erythma test for antiinflammatory action in 1955 and the following year introduced an extensive screening programme for molecules based on the salicylate structure and other carboxylic acids, eg. phenoxyacetic and phenoxy propionic acids from Boots' other main interest in herbicides. They found that the best compounds had antiinflammatory, antipyretic and antirheumatic properties.

Three promising compounds were isolated, however two were withdrawn from clinical trials because of side effects, the third later called dytransin, 'Ibufenac' was marketed in April 1966 following CSD approval even though some instances of drug induced jaundice were found in use. Following more notifications of jaundice, the drug was withdrawn from the UK in 1968 but later found a market in Japan where genetic differences eliminated the jaundice effect.

Propionic acids showed no serious side effects and of several synthesised, one, Ibuprofen, was selected and following approval was marketed in February 1969 as 'Brufen'. The product now sells at a rate of 880,000 million tablets per annum worldwide.

The biphenyl type of compound had been shown to have a high anti-inflammatory activity and a number of such compounds were screened, one later given the name Flurbiprofen emerged as the most promising with interesting ability to inhibit prostaglandin synthetase. The product, 'Froben' was marketed by Boots in 1977. Boots' most recent introduction, the antiulcer product pirenzepine, 'Gastrozepin' was launched in 1982.

3.5.3 Fisons Ltd. Pharmaceutical Division. (23)

Fisons is one of the world's smaller pharmaceutical companies with any research capability and they entered the field rather later than most companies, indeed, '...it claims to be one of the last research-based pharmaceutical operations in the world to establish itself from scratch' (24) Fisons was an established manufacturer of agricultural and horticultural products including fertilizers and later with interests in scientific equipment.

In 1966, Sir George Burton, the chief executive at Fisons wanted to expand the company into strong growth areas one of which was identified as drugs because of the relatively low capital investment necessary to start up as compared, for example, with fertilizers. The company had a research facility and expertise in the synthesis and testing of chemical products and could therefore start operating fairly rapidly. £12 million was raised by selling off some of its subsidiaries the amount was thought sufficient to establish Fisons in one small sub market, the only feasible operation (25).

The research centred on anti-asthmatic products and Fisons were fortunate to develop a novel compound, disodium cromoglycate, later given the trade name 'Intal' which was introduced in 1968. This product was to be the mainstay of the pharmaceutical division, later being made available in a number of presentation forms for a variety of uses under the trade names 'Nalcrom', 'Rynacrom', 'Lomusol' and 'Opticrom' as well as 'Intal'

and 'Intal compound'. Innovation took place in drug delivery systems with the development of the spinhaler, nebuliser and more recently the aerosol, advances that helped Fisons retain some credibility as a pharmaceutical manufacturer.

Since the patent for 'Intal' was due to run out in 1982 with prospects for competition increasing, the company had to market another product fairly rapidly. For some time the company was considered to be a 'flamingo' in that its one product supported all its pharmaceutical operations and provided over three quarters of all company profits at one stage. A compound related to 'Intal' namely Proxichromil was developed and due for launch in 1981 with a substantial market. Proxichromil failed to satisfy certain drug safety requirements and was withdrawn by Fisons only a few months before its launch date. Since Fisons claimed to have invested over £12 million in developing the drug this loss of finance resulted in financial difficulties for the company. The pharmaceutical division was to some extent saved by selling the fertilizer business, followed by major reorganisation of the division in 1982-1983. This episode is used by some industrialists as an example of the risks taken by drug firms in researching and developing new products. Fisons research interests in 1981 included an anti-ulcer product, a vasodilator, antihypertensives and a number of antiasthmatics. (26).

3.5.4 Glaxo Laboratories Ltd. (27)

Glaxo is the antithesis of Fisons in that it has a long history and a multitude of products in a variety of therapeutic areas. There are two main strands to the Glaxo group, one originating in Silvanus Bell's Plough Court pharmacy in the City of London in 1715, later to be home to the philanthropist William Allen. Allen later founded Allen and Hanburys which moved to Bethnal Green.

The second strand began in 1873 when Joseph Nathan established a New Zealand import-export business and in 1903 Maurice Nathan whilst on a visit to Debenhams in London was introduced to the roller drying of milk, an invention that Nathan put to use to capitalise on excess skimmed milk production from the family's butter factories. Their product given the name 'Glaxo' was used as a baby food.

Harry Jephcott, a member of the company whilst on a visit to Washington to a dairy conference in 1923 became interested in the newly discovered 'vitamines' and the following year Glaxo were marketing 'Ostelin' a vitamin D concentrate. The interest in medicinal products was extended into vaccines and hormones. Crystalline Vitamin D was extracted in the 1930's and in 1935 Glaxo Laboratories Ltd. was set up in Greenford.

The Second World War took Glaxo into antibacterial research and the firm were soon manufacturing penicillin by surface culture. The far-seeing Jephcott encouraged the firm into deep fermentation production, gaining a head start on competitors and allowing rapid commercial growth. By 1948 their fermentation expertise allowed the production of streptomycin for the treatment of tuberculosis. Isolation of crystalline vitamin B12 for the treatment of pernicious anaemia and the synthesis of thyroxine hormone in 1948 ensured continued growth. The 1950's saw a further diversification of activity with the multi-stage synthesis of cortisone (1954), a development that was to lead to a number of successful products

as did research on semi-synthetic antibiotics based on the Cephalosporin C molecule. The active moeity of thyroxine, liothyronine, was identified in 1952, the freeze drying of the BCG vaccine was accomplished in 1957. In 1958 Allen & Hanburys became part of the Glaxo Group and brought expertise in a number of areas including research into bis-quaternary ammonium salts used as muscle relaxants.

The marketing of griseofulvin by Glaxo in 1959 as an oral antifungal product extended the range with a very successful and effective drug. Research into cephalosporins at Greenford was rewarded by the NRDC who licenced Glaxo to produce and develop a range of products based on academic research leads. Products were launched in 1964 as cephaloridine, 'Ceporin', 1969 as cephalexin, 'Ceporex' and 1978 as cefuroxime, 'Zinacef', all cephalosporins (28). A number of acquisitions took place in the early 1960's with Evans Medical (1961), for their manufacturing and packaging functions, Duncan Flockhart a firm first established in Edinburgh in the 1800's was absorbed in 1963 as was Macfarlane Smith with their analgesic expertise. The Group were at this time interested in respiratory diseases including allergies and immunological problems, cardiovascular and CNS disorders.

Betamethasone, 'Betnovate', an anti-inflammatory corticosteroid was launched in 1963 from Greenford with related products launched in 1972, clobetasol propitionate, 'Dermovate' and 1976 clobetasone butyrate, 'Eumovate'. The late 1960's saw the acquisition of British Drug Houses (BDH) and Farleys, 1968, a year in which research at Ware resulted in the marketing of salbutamol, 'Ventolin' an adrenergic beta stimulator for the treatment of bronchospasm. This launch was followed in 1972 with 'Beconide' for asthma and 1975 by 'Beconase' for hay fever both based on beclomethasone dipropionate research at Ware. An intravenous anaesthetic was launched in 1972 under the name of 'Althesin' and in 1973 BDH was sold to Merck.

Between 1972 and 1978 sixteen products were launched (29) including an influenza vaccine 'Fluvirin' by Evans Medical, fazidinium bromide, 'Fazadon' a muscle relaxant, eight extensions to the steroid range and one major discovery, labetalol, 'Trandate' an alpha and beta blocker for the treatment of hypertension.

A proposed merger of Glaxo with either Boots or Beecham was blocked by the Monopolies Commission in 1972 (30), a promising antiasthmatic (AH7255) failed toxicity tests in 1978 (31) and stockbrokers feared a lack of promising developments since corticosteroids were seen as a mature area with future prospects unlikely and there was a global overcapacity of penicillins.

Research had continued for ten years on an anti-ulcer product based on H2-antagonism and a product, ranitidine, 'Zantac' emerged in October 1981 at a cost of over £30 million but with enormous market potential. A recent development has been in a third generation cephalosporin ceftazidime, 'Fortam'.

Despite a traditional poor marketing performance and a tag of 'the quoted university', Glaxo remains in the top twenty of world companies and research continues at Ware and Greenford into a number of areas including biotechnology.

3.5.5 ICI plc Pharmaceutical Division (32)

Imperial Chemical Industries is a highly diversified company with a number of divisions apart from pharmaceuticals, these are: agricultural, fibres, Mond, explosives, organics, paints, petrochemicals, plant protection and plastics. The pharmaceutical division is small in comparison with other multinational pharmaceutical firms and only 6% of ICI's gross sales is provided by pharmaceuticals (33). However, over a quarter of ICI's profits comes from drugs and the importance of the pharmaceuticals division has increased as recession has hit the other divisions (34).

ICI's interest in drugs began in the 1930's with the dyestuffs division as it then was, the relationship between drugs and dyestuffs had been established in Germany and a small group of ICI chemists began research in 1936 to be joined by a number of biologists in 1938. The second world war provided a stimulus for a number of developments and two discoveries made in 1940, sulphamidine,'Sulphamezathine' an antibacterial and proguanil,'Paludrine' were produced in 1943 and 1947 respectively. The discoveries were closely related to herbicidal chemicals and the diversity of ICI's research interests was an advantage over many years.

ICI chose not to use foreign technology and subsequently their penicillin manufacturing operation was not competitive with Glaxo and others using US techniques. In the early period the problem was that products often fell between the two stools of pharmaceuticals and dyestuffs, dyestuffs claimed general rights over any discoveries. The separation of the divisions, although initiated in 1942 was slow, probably because tax reasons favoured their amalgamation.

The setting up of Imperial Chemicals (Pharmaceuticals) Ltd. in 1942 was followed by the formation of the embryonic pharmaceuticals division in 1944 but until 1952 this was an ill-defined division dependant

on dyestuffs and a "losing business" (35). At this time then, ICI was essentially a producer of heavy rather than fine chemicals.

The Pharmaceuticals division as a distinct entity was made possible by a move in 1957 to Alderley Edge in Cheshire, a year when the inhalation anaesthetic halothane,'Fluothane' was marketed. The traditional ICI emphasis on infectious disease was transferred to new areas including cancer chemotherapy, analgesics and anticonvulsants as well as an area that was later to prove the most successful, cardiovascular disease. A treatment for atherosclerosis was introduced in 1963, clofibrate,'Atromid-S' which was a blood serum lipid-lowering agent indicating the interest in a very profitable new market. The most important ICI discoveries were made in the 1960's with the beta-adrenoceptor blocking drugs, which are used in the treatment of hypertension, angina, supraventricular arrhythmias and thyrotoxicosis (36).

Propranolol 'Inderal' was introduced in 1965 followed by practolol, 'Eraldin' in 1970 and atenolol,'Tenormin' in 1981. Beta blocker research proved most productive for ICI who took a world lead in cardiovascular drugs. Other products included an antiinflammatory fluocinolone,'Synalar' in 1961, tamoxifen,'Nolvadex', a paliative for breast cancer 1973, viloxazide,'Vivalan' an antidepressant in 1974 and an antineoplastic razoxane,'Razoxin' in 1977. Griseofulvin,'Fulcin' was also marketed by ICI.

ICI retains a preoccupation with in-house products and 80% of all drug sales arise from their own products. They remain one of the 30 most successful world drug firms and have a wide research portfolio outside the cardiovascular field. Work has been done on interferons and prostaglandins as well as on an antiulcer drug called 'Tiotidine', work on which had to be abandoned following carcinogenicity indicated in rodent studies.(37)

3.5.6 Reckitt and Colman Pharmaceutical Division (38)

Reckitt and Colman is amongst the smallest of the UK owned drug firms, better known for its household and toiletry products although its medicinal product history dates back to the 1930's. Founded in 1814 as a Hull grocery company, Reckitt remained outside the medicinal area until 1929 when a laboratory began work on antiseptics and disinfectants. The discovery of the safe and effective 'Dettol' antiseptic in 1930 took Reckitt into the pseudo-pharmaceutical field and when marketed in 1932 formed the basis for a pharmaceutical reputation. A decline in child-birth mortality rates at this time has been attributed in part to the preventative action of 'Dettol' on puerperal sepsis when used in hospitals.

In 1948 Reckitt introduced a soluble calcium aspirin 'Disprin'and followed this up in 1952 with 'Codis', a combination of aspirin and codein. Colman, the mustard manufacturer, merged with Reckitt in 1953. A joint research association was set up with J.F. Macfarlan of Edinburgh in 1957-8 who were pioneers of morphine production in the nineteenth century and had considerable expertise in the field of analgesics. Research on alkaloids based on morphine was extended by K.W. Bentley who headed the medicinal chemistry investigation in 1960. His aim was to find a potent morphine type analgesic without the associated serious side effects of morphine.

The discovery of the 'M' series of oripavines (Phenolic bases of thebain-a morphine alkaloid) gave a number of promising leads. One, Etorphine was later developed for veterinary uses, whilst another, Buprenorphine was to become a later success as a powerful human analgesic. In 1960 Westminster, a firm famous for senna products, was acquired providing the opportunity to expand the pharmaceutical group. Since a research facility was now available at Kingston on Hull and Macfarlan were to be acquired by Glaxo, the joint association research was transferred

to Hull in 1963.

Outside analgesics, an antacid product,'Alcin' was launched in 1962 and in the latter part of the decade an interest in cardiovascular drugs led to the marketing of a novel sulphoxide vasodilator, Tolmesoxide. The second main strand of research was however anti-rheumatic products and a number of products were investigated. By 1969 R&C announced the further development of their pharmaceutical activities and consolidation of the R&D facilities led to a new pharmaceutical division in 1971 although sales were still controlled through the household and toiletries divisions.

A joint venture with Labaz S.A. in 1973 resulted in Reckitt and Colman marketing Labaz products in the UK. Sodium valproate,'Epilim' was introduced in 1974 by Reckitt and Colman for the treatment of epilepsy. In 1973 Lloyd pharmaceuticals was acquired. After nearly fifteen years in R&D the buprenorphine now called 'Temgesic' was made available nationally in February 1978. An antiasthmatic product fenclofenac,'Flenac' was launched in September of the same year.(39)

Problems of compliance with government regulations and the need to restructure the pharmaceuticals division were constant themes throughout the 1970's, some research programmes were dropped to allow efforts to be concentrated on the traditional Reckitt and Colman research areas (40). The pharmaceutical activities were fully restructured in 1980, effectively abandoning further innovative research and development.

3.5.7 The Wellcome Foundation Ltd. (41)

The Wellcome Foundation is unique amongst pharmaceutical manufacturers in that, since 1936, all shares in the company are owned by the charitable Wellcome Trust which uses all profits generated to support medical research in hospitals and universities. Wellcome since its inception as Burroughs Wellcome & Co. in 1880 in London by two American pharmacists (later to become British citizens) has maintained its position as an innovative company with a range of products for human and animal use.

Wellcome Physiological Research Laboratories (1894) produced the first diphtheria antitoxin whilst Wellcome Chemical Research Laboratories (1896) was engaged in plant alkaloid research. Early work by Henry Dale at WPRL was concerned with ergot alkaloids, adrenaline, histamine and acetylcholine, for which achievements he shared a Nobel prize.
WCRL, during the pre-world war one period was producing essential medicines such as 'Kharsivan' the Wellcome equivalent of 'Salvarsan',aspirin and bismuth salicylate in anticipation of the blockage of supplies from Germany.

During the period 1946-1951 a massive expansion of WCRL resulted in the discovery of the novel compounds: procyclidine,'Kemadrin', an anti-parkinsonism drug, triprolidine,'Actidil, Actifed',an antihistamine, methoxamine,'Vasoxyl' a vasoconstrictor and cyclizine,'Marzine' an antinauseant.

In 1952 WCRL and WPRL combined to form Wellcome Research Laboratories and stepped up research into tropical diseases (a key area of Wellcome research up to the present) resulting in the discovery of pyrimethamine, 'Daraprim' for malaria prophylaxis, piperazine,'Antepar' for threadworm and roundworm infection and bephenium,'Alcopar' for hookworm. During this time collaboration with American researchers was a fundamental element of Wellcome's continuing success and many discoveries have resulted from joint research with Wellcome scientists in the USA. The fact that

Wellcome has research facilities in the USA and UK makes the identification of the original research for any product difficult. The use of patent material does allow a certain degree of elucidation.

Discoveries in the late 1950's and 1960's were numerous but most notable were bretylium tosylate,'Bretylate' the first adrenergic neurone blocking drug, azathioprine,'Imuran' for the prevention of transplant rejection, the antihypertensive bethanidine sulphate,'Esbatal and allopurinol for gout and associated uric acid disorders. Another USA/UK collaborative product, trimethoprim, an antibacterial identified in the 1950's was combined with suphamethoxazole in a combination called 'Co-trimoxazole' or 'Septrin' to provide a synergistically acting formulation for the treatment of bacterial infections. This product was launced in 1968.

Research into prostaglandins under John Vane led to the discovery of Prostacyclin in 1976, this chemical inhibits platelet aggregation and is a useful treatment for thrombosis. Vane was to receive a Nobel prize and a knighthood for his efforts in prostaglandin research. The most recent Wellcome discovery was acyclovir,'Zovirax' for the treatment of herpes virus, it was launched initially in 1981. Other areas of interest include malaria, interferons and biotechnology in general to which end Wellcome Biotechnology was formed in 1982.

3.6 General conclusions

The pharmaceutical industry can claim a unique position in manufacturing industry, its economic strength and structure based on research and development necessitates constant product innovation. U.K. firms are significant in the world market for pharmaceuticals, holding second place behind the US in terms of important products (see table 3.2).

Table 3.2

Country of origin	Number of products in top 100	% of world market 1980
U.S.A.	35	9.5
U.K.	14	4.2
W. Germany	14	3.3
Switzerland	12	2.5
Japan	8	1.7

Top 100 world drug products: British contribution

Source: (42)

However, in terms of ranking by sales the British firms have apparently declined since 1970 (see table 3.4). The seven firms of interest have widely differing research portfolios and histories and have shown alternative approaches towards drug development in changing economic and social climates. This provides an interesting focus for study as it may be possible to determine differences in regulatory impact between the firms of interest. The direction of innovatory activity is summarised in Table 3.3 and the trends in drug output will be examined later.

Having gained an overview of the nature and activities of the U.K. owned firms of interest, the next stage is to examine the drug R&D process in more detail in order to identify indicators of innovative activity and construct some model of the R&D process.

Table 3.3

	Beecham	Boots	Fisons	Glaxo	ICI	R&C	Wellcome
Antibacterials	X			X		X	
Beta-blockers					X		
Antihypertensives				X	X		
Respiratory			X			X	
Rheumatic disease		X				X	
CNS	X	X			X	X	
Antiviral							X
Antifungal				X			
Anti-ulcer		X		X			
Corticosteroids				X			

Summary of Major Drug Areas of British-Owned Companies.

Table 3.4

	1970		1980	
	Sales US $ millions	World Rank	Sales US $ millions	World Rank
Glaxo	261	16	1214	15
Wellcome	136	25	1064	18
ICI	67	35	829	24
Beecham	132	26	819	25
Boots	na	na	591	33

Economic Summary (43)

CHAPTER FOUR: RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY

4.1 Introduction

It is necessary to understand something of the process of research and development in the pharmaceutical industry in order to identify the stages at which regulations act, to identify the probable indicators of inventive and innovative activity and to appreciate the determinants of the rate and direction of these activities.

As indicated earlier the reasons for studying the R&D process lie in the nature of competition in the industry and the importance of research in that competitive behaviour. Cooper considered that, 'research is the very life blood of the industry. A firm's innovational success determines its probability - its profitability its research. Being first with each research discovery determines whether a firm is a success or a failure' (1). Innovation has provided the industry with a basis for growth and profitability and continues to do so.

Since research is deemed so important, it is not surprising that compared with other industrial activities, little detailed information is provided by companies concerning their activities and indeed there seems to be little consensus regarding the definition of the terms 'research' and 'development'. Cooper continues, 'It is paradoxical that the industry's central justification for price and profit premiums is research, and yet few are sure what the word actually means, how much of it there is, and who undertakes it'. (2). Variation in interpretation of these terms means that comparison of the activities is hindered and data produced by companies or national agencies is not

directly comparable. The degree to which this problem has been alleviated and definitions accepted as standard will be discussed later.

This lack of objective and standardized information has led to the adoption of a "Black Box" approach to the R&D process where only readily identifiable inputs to and outputs from the R&D process are considered. This approach leaves much to be desired as the flow of discoveries through the process can, if studied, reveal fluctuations, trends and decision points which are of importance to policy makers and analysts. One intention of this study was to explore the R&D process in more depth and identify specific 'indicator points'.

Much of the published work on R&D is based on the US industry and although the US companies are engaged in production of similar types of products as the UK industry, the variation in business environment and historical precedents prevents direct comparison being made. This chapter will begin to outline the process of drug R&D from its organizational roots to product launch so as to provide a framework for a model which will incorporate indicators of R&D activity.

4.2 The Research and Development Process.

4.2.1 General Comments

An oft-mentioned criticism of studies of R&D is that they tend to consider the physics or engineering type of model with a simple flow through from basic research to applied research and development. The case for drugs is somewhat different in that , 'New drugs cannot be designed by logical deductions from valid general principles, chemical theory alone is not enough and biological theory is woefully inadequate' (3). The linear relationship between research and development does not apply because, 'there is a great deal of research in development' (4), and feedback occurs, with advances in applied research allowing further elucidation of basic

scientific principles. Basic research, argues Schwartzman, cannot be separated from applied research, a tendency that exists in other studies of the industry (5). These relationships have policy implications in that the effect of curtailment of basic research would be difficult to estimate and reduction of expenditure on applied research could affect basic research indirectly.

It is evident that the difficulty in defining R&D is due in no small way to the interpretation of what activities are contained in 'research' and 'development', definitions used in empirical studies will be outlined later but those adopted by NEDO in their 1972 study 'Focus on pharmaceuticals' were as follows: (6)

> Research: 'Covers scientific and medical investigations relevant to the discovery of new drugs or of new applications of existing drugs, for human or animal health purposes'.

Even this definition may be too broad for the purpose of the present study the new application of existing drugs could be construed as non-innovative and the inclusion of animal purposes may extend the remit beyond the required limits.

> Development: 'All other activities subsequent to or overlapping the research phase leading to the production of new pharmaceutical products in saleable form....covers new or existing drugs'.

This does not take into account the non-linear nature of R&D and a certain amount of overlap will occur.

Since the differentiation of stages of R&D is, in theory, difficult to rigidly enforce, the most appropriate means of distinguishing between stages is to study the drug R&D process in the industry and note the activities that may be defined as research or development in each stage. The process does differ between companies due to differing ethos and structure as well as area of interest. The first logical step is to consider the setting up of a research project portfolio.

4.2.2 Establishing a research function

Statistics such as '88% of all NCE s introduced between 1950 and 1969 originated in industrial laboratories' (7) , are used to emphasise the concentration of drug research activities in industrial laboratories but the fact that only industry has the available resources necessary to conduct such research is not often added (8). Drug R&D is an extremely expensive business in terms of capital expenditure and the need for a highly qualified scientific and engineering staff. Any company wishing to engage in drug research must base any judgement on an acceptance of the need for such resources and the statistical risk of failure which is high. Even if products are developed, a return on investment may take many years but on a positive note a successful product could allow the company to monopolise a lucrative market.

The environment for the conduct of R&D has changed over the past few decades, a transition that is difficult to quantify but has resulted in smaller companies finding it difficult to divert resources to innovative drug research. Factors that have varied include costs, regulatory demand, public attitude and scientific and technological advances. Along with these are a number of criteria that influence decision making and may be thought of as rules or guidelines that are used to assess the likelihood of success of any project.

A company would hope to develop a research programme which is a number of selected projects each with an associated proportion of overall resources devoted to it. The number of projects established by each company will depend on the availability of resources, relative project sizes and area of interest, the NEDO study found that the minimum critical size would be three projects (costing about £1.5 million in 1970).

The selection of projects and the allocation of resources between them is a logistical problem of great magnitude, the industry has developed selection procedures that begin with simple check lists as exemplified by that of Mottley and Newman in which five factors are given values between one and three and a total for each project obtained by multiplication,allowing competing projects to compete for funds (9). More sophisticated planning methods involve a detailed consideration of the market potential based on the prevalence and type of disease to be treated, general rules state that the market should be such as to allow a seven fold increase, in real terms,of the development costs (10).

The comparative efficacy of the proposed drug and number of existing treatments defines the degree of competition, these criteria are used to define the type of product required. Technical feasibility is important, the assessment of which involves the number of 'leads' available, past effort by the company in the area, patenting profile of the area and other background information. Management policy, availability of facilities, staff and expertise are also considered along with more technical factors (11).

The difficulties with gaps in knowledge ensure that planning cannot be as logical and premeditated as would be desired, the non-scientific constraints including resource mean that a company would need to spend a minimum of about 7-12% of turnover on R&D and be prepared to fund failures on the way. Cross-subsidy of projects does occur enabling the least financially rewarding projects to continue (drugs for low incidence disease and drugs for third world infectious diseases are examples) (12). For a new research programme, it has been estimated that approximately twenty years is a not unreasonable time to consolidate a project portfolio whilst a ten year wait for candidate products to arise is acceptable (13).

Psychological problems can arise within a company if product launches are infrequent; fluctuations in confidence, feelings of stability, ability to take risks, trust and personal relationships can occur. For a R&D facility to remain effective good communications and leadership are necessary and the maintenance of such conditions are as much the desire of planners as is the physical organization (14).

4.2.3 Organization for R&D

Since R&D in the drug industry involves a range of areas of interest and disciplines, there needs to be some way of organising staff to facilitate and optimize innovatory activity. It is difficult to distinguish between a multi- or interdisciplinary approach since both operate often at the same time within a company. All companies have to somehow coordinate projects that are complex involving expertise in a number of fields and a range of possible approaches have been defined. Generally, industrial research laboratories have a tendency to a 'horizontal' as opposed to the academic 'vertical' structure. Within this, five possible organisational structures exist (15).

* Subject/Discipline-permanent departments reporting to a head.
* Stage/Phase-split by basic, applied research, development etc.
* Product/Type-)
  Process/Type-) - Multidisciplinary teams.
* Project/Problem-Short term, multidisciplinary, 'brainstorming'.

All of these approaches may be used in combinations in the same company.

Before expansion in 1952, Beecham research was organized along subject/discipline lines with seven department heads reporting to the research director. By 1964 a move to project lines had taken place and by 1968 the company was using an area of research/end product structure decided by a research policy committee of senior management. Development

of drugs was still in subject/discipline lines. This structure was seen to facilitate planning, evaluation and control and the use of dynamic projects involving 6-60 people helped to motivate staff.

ICI retained a subject/discipline approach with research and development as distinct functions, fifteen multidisciplinary teams worked within the separate departments. Wellcome had a similar structure. Fisons, up to 1968, had a series of specialist teams overseen by steering committees but from this date began to use a matrix system involving multi/ interdisciplinary teams (16).

Changes in organisational structure have arisen because of constraints including regulatory pressure and a much more structured approach to R&D has developed. The use of critical path management (CPM) and PERT control techniques as management tools has been necessary to ensure the most efficient use of resources and time and may represent one beneficial aspect of drug regulation ensuring that companies conduct R&D in a more rigorous and efficient way.

4.2.4 The discovery of candidate drugs

Drug candidates are substances with identifiable biological and pharmacological activity that, with further testing and development, may result in safe and effective drugs. The first practical aim of drug research is to produce a number of such candidates that can be exploited. The research department should, 'Gather all information having a bearing on the project then analyse all relevant factors to translate scientific advances into practical aims' (17). However, as indicated earlier, gaps in knowledge prevent such a methodical approach and the means of identifying candidates are diverse. These means can be broadly divided into two, one scientific and medical and the other a marketing approach. The latter attempts to target research into economically attractive areas that are also technically feasible. The scientific approach is better documented and will be discussed in more depth.

Discovery is preceeded by fundamental biological research which seeks to gain an insight of the mechanism of a disease process and thus define a biological target, eg. an enzyme, hormone, mediator chemical etc. This type of work will result in a pool of published knowledge which can be exploited by all companies. From this early research the desired properties of a drug can be surmised along with suggested chemical structures. Substances then have to be prepared that have the required elements of structure and hopefully, the desired properties. This is however a simplified account and the actual process of candidate generation may be much more random, a number of approaches are used in the industry to produce candidates (18):

A Natural products - from microorganisms, plants, animals.
B Synthetic molecules - artificial, to fit the hypothesis of activity.
C Modified molecules - by whole or partial synthesis.

Products of early research can be tested and further developed by using the following approaches:

1. Screening: Large numbers of chemicals are tested in a series of pharmacological test stytems. Costly and risky.

2. Molecular modification: The required general structure is modified to optimize the properties of the precursor.

3. Rational approach: Takes account of known or postulated modes of drug action but is limited by knowledge.

It is possible to incorporate all the above methods into a grid and describe the type of drugs that have been produced using the various methods. See table 4.1 overleaf.

Table 4.1

	NATURAL PRODUCTS	DERIVATIVES/ANALOGUES	SYNTHETICS
SCREENING	antibiotics, eg penicillins. alkaloids and antitumour drugs	Lysergic acid and derivatives	Benzodiazepine tranquilizers. Antiinflammatory (Indomethacin)
MOLECULAR MODIFICATION	Tetracyclines Penicillins Ergot alkaloids	Sex hormones Semisynthetic penicillins, Tetracyclines and cephalosporins	Tricyclic neuroleptics antidepressants antidiabetics, antithyroid.
RATIONAL APPROACH	L. Dopa Insulin	Antimetabolites for bacterial, cancer chemotherapy. -methyl dopa	Pralidoxime Propranolol and other beta blockers.

After Berde (19)

Drugs resulting from a variety of research methods

Screening involves subjecting molecules to a range of tests to reveal, for example, chemotherapeutic, pharmacological, biochemical and immunological activity. Screening is an expensive, time consuming and risky business but has let to significant therapeutic advances.

Molecular modification is the most frequently used approach in the industry (20), but has been criticised for resulting in a number of similar drugs with minor variations in activities and properties (so-called 'me too' drugs). The non-steroidal antiinflammatory drugs are often cited as examples of drugs produced by molecular modification. The position of the industry, accused of 'molecular roulette' has been vigorously defended (21). The 'rational approach' is more dependent on the state of the art and relies on breakthroughs in basic levels of biological understanding. The number of serendipitous discoveries are said to be significant although trends to a logical approach to drug development may hinder fortuitous discovery. New therapeutic uses may be discovered during screens of existing molecules and these are a bonus to the industry.

Once biological activity has been discovered in tests, whether *in vitro* or *vivo*, eight to ten thousand potential substances may have been identified, depending on the approach used, over a minimum period of one to two years (22). These molecules, having some activity, must next undergo rigorous testing to specify the properties and behaviour of the molecule in animals prior to testing in humans. The next stage, the preclinical phase will be outlined below.

4.2.5. Preclinical testing of drugs

Schwartzman argues that a drug is not 'discovered' until the molecule has demonstrated a degree of safety and efficacy in clinical trials and therefore preclinical testing can be considered as an extension of the discovery phase rather than development (23). The aim of such testing is to elucidate the activity of the drug before testing in man, the activities included under the heading must take into account the requirements of the drug regulatory authority and prior to clinical trials the DHSS must be assured that all preclinical work has been completed (for recent amendments, see the CTX scheme in Chapter One). The guidance document MAL 4 describes the necessary testing requirements (24).

The information required by the Medicines Division of the DHSS for a new product is outlined below. A further series of screens will have resulted in a 90-95% rate of attrition of compounds leaving 20 or so compounds which may be patented.

Table 4.2

A. 1. Product particulars
   2. Clinical trial protocol
   3. Supplementary details

B. Pharmaceutical data: Finished product, manufacture of dosage form, quality control, development pharmaceutics and biological availability, stability, containers, identity of materials, manufacture, development chemistry, impurities, specification, batch analysis, stability, metabolism.

C. Experimental and biological studies:
   1. Pharmacology
   2. Pharmacokinetics
   3. Animal toxicity: Single, repeated. Subacute, intermediate, chronic
   4. Reproduction studies: Fertility and teratogenicity included.

CTC Requirements (25)

As well as new drugs, any products administered by a new route and new mixtures of drugs must also fulfil the above requirements. This may also be the case for new dosages and for less common ingredients, a point of consternation for the industry. The species of animal used varies but may include mouse, rat, hamster, guinea pig, rabbit, cat, dog, pig and monkey depending on the suitability of the species as a model for the human situation.

Since preclinical research uses animals as models of the human there are always difficulties in ensuring that the drug will actually behave in the animal as expected in man. The direct approach to testing attempts to mirror the effect in man in the animal, sometimes the pathological state is induced in the animal before testing, eg tumours, inflammation, hormone deficiency etc. The indirect approach examines the effect of the chemical on biophysical or biochemical parameters in the animal model used. If no model is available or no recognisable parameters exist, the activity of the drug on test may be compared with that of a known active drug. A profile of the compound on test may be built up in a battery of tests.

All the approaches mentioned have weaknesses particularly in modelling the human condition, for this reason a number of animal species may be used in the tests. A large number of animals are used to allow statistical significance of the results to be determined, but recent pressure from anti-vivisection groups and also from within industry has led to the investigation of alternative testing procedures. The use of in vitro techniques such as cell and tissue culture is seen in companies but has limited use in many cases.

Preclinical trials are split into phases but these overlap due to the length of some of the long term toxicological and fertility studies. Pharmacodynamic studies attempt to describe the effect of the molecule in animals and man, the main and side effects, duration of action and acute toxicity. Pharmacokinetic studies are to assess the absorption, distribution of the drug, metabolism and excretion. Toxicology studies continue with subchronic (less than six months) trials in various species, chronic toxicology studies are of particular importance for those drugs that will be used for chronic diseases such as arthritis, hypertension and hormone deficiency. Reproduction studies are important if the drug is to be given to women, since the Thalidomide incidents, fertility, teratogenicity, peri and post natal toxicity studies have assumed a greater importance. Mutagenicity studies may involve in vitro testing eg. Ames test in microorganisms as well as in vivo testing.

Alongside the animal studies are tests on the chemical itself to determine purity, stability, and finished product formulation as well as the feasibility of scale-up of manufacturing processes. Regulatory demands may affect the number, type and duration of studies, the animal species used and the acceptability of formulations. Eventually a reduction of about 50% of molecules on test will result because of failures resulting from unacceptable ratios of therapeutic use to risk.

After a minimum of two to three years from identification of a candidate only a few compounds may be worthy of testing in humans in clinical trials (26).

4.2.6. Clinical trials

A clinical trial may be defined as,

> "an investigation or series of investigations consisting of the administration of one or more medicinal products where there is evidence that they may be beneficial, to a patient or patients, by one or more doctors or dentists for the purpose of ascertaining what effects, beneficial or harmful, the products have." (27)

The pharmaceutical industry differs from many other manufacturing industries in that at the clinical trial stage the product is taken out of the company's hands and placed under the responsibility of experienced clinicians in hospitals and clinics either within or outside the UK. The company must have obtained a clinical trial certificate or have exemption under the CTX scheme before proceeding to this stage.

The trials are again split into phases, based on the number and type of patients involved. The first phase uses a small number of healthy volunteers to determine tolerance, type of effect, dose effect relationship, duration, side effects, absorption and metabolism.

The second phase involves a selected number of actual patients to determine optimum dosage, absolute efficacy, tolerance and side effects when compared with other medicaments. Although comparative efficacy is not a regulatory demand, the company would be keen to emphasise any advantages of the new drug over competitors. Phase three involves larger numbers of patients to ensure statistical significance and is the most expensive and personnel intensive phase of R&D. Therapeutic profiles are drawn up for the drug and any possible drug interactions considered.

Animal studies run in parallel, chronic toxicity up to several years, carcinogenicity and other long term trials overlap with the clinical trials. This work may be done within the company or by one of the contract research firms that have arisen. Clinical trial protocol is severe and evaluation of the trials, writing of reports and assimilation of data may take a further two years after the end of the trials. Trials have to be structured so as to allow a thorough and objective study, for this reason cross over, comparative and single series may all be used, and may be double or single blind involving the use of placebos.

An attrition rate of over 50% due to problems with safety or efficacy reduces the number of drugs to reach the end of clinical trials successfully to one or two and takes a minimum of three to four years. Once clinical trials have been conducted the company must send all relevant information including patient files to the regulatory authority for approval to market the drug and gain a product licence (28). A product licence is necessary for all new drugs, new uses of existing drugs and new mixtures and sometimes for a new route of administration, new dosage or formulation or the use of little-known ingredients. Only after the grant of a licence can a company market a drug in the UK.

4.2.7 Launching a drug on to the market.

Launching a drug involves planning the marketing approach, recruiting or training the salesforce of medical representatives (detailmen) and producing sales literature for distribution to the medical profession and data sheets for reference. Packaging, quality control of manufacturing, labelling and pricing are all regulated and inspectors ensure compliance. The product may be launched to become an economic success or

failure, the scientific rate of success may be 10,000 to 1 but the rate of economic success much lower, as not all products are successes. The company will also plan the overseas launches whether by subsidiaries or by licencing the drug to other overseas companies.

Once a product is marketed, the company and regulatory authority keep a check on the drug by post-marketing surveillance to detect any incidences of serious side effects or iatrogenesis. Further research will also take place to improve the product, its formulation, means of administration and other technical features.

The above account gives an indication of the length and complexity of the drug R&D process, to determine changes in the rate and direction of innovation necessitates the use of science indicators. The following sections will describe a model of the R&D process and identify the points at which indications of the rate and direction of the R&D effort occur and assess the availability of data for the UK companies.

4.3 A model of the pharmaceutical R&D process.

Figure 4.1 shows the stages of the R&D process described earlier, the content of each stage is not exhaustive but contains the main elements. Certain factors are common throughout the process including the technical, statistical, information and management backup. These operations may be carried out within interdisciplinary teams or by central resource units. Drug regulation considerations are usually dealt with by a specialist department as is patent and trade mark work.

Decisions have to be made at regular intervals but at certain points there are major decisions and appraisals of progress and these are indicated on the model. At these points all interested staff would be involved including marketing, scientific and technical staff. As the drug proceeds through the various stages and more resources are invested, the momentum of the project increases and decisions to abandon or shelve the product become increasingly difficult. Motivation of staff will

Figure 4.1

	Discovery Phase		Activity and Preclinical Safety Phase		
Inputs: R&S expenditure, manpower (QSEs), information, technical assistance, statistics, planning and support. Continues >>>>>>>>					
Outputs: Trade marks, CTC/CTX applications, Scientific papers, Business reports, Patent application					
Activities:					
Market research Medical needs Research ideas Finance ? Policy ? Literature search Patent search	Research programme Research projects Selection of structures Synthesis planning Basic research to define a biological target	Compounds Screens Activity observed Develop screens Primary and secondary screens Acute toxicity Prepare compounds Identity, Purity Formulation Gen. Pharmacol.	Selection of candidates File prov. patents Detailed technical & economic appraisal	Formulations Stability tests Process dev. Mutagenicity Animal pharmacol. Synthesis of radioactive compounds Acute/6 month tox. 2spp Reproduction studies Pharmacokinetics Clin. Trial protocol	Clinical samples Further selection of candidates Chronic/long term tox. & carcinogenicity studies in 2 spp.
Attrition:		10,000 compounds	20-30 compounds	18 compounds	less than 10 compounds
Time: Estimates; 3 years (ICI), 0.5-5 years (Berde), 1-2 years (Bartling), 5-7 years (Loveday)					4-6½ years (Glaxo)
				2-4 years (ICI), 2-3 years (Bartling), 2 years (Berde)	

A Model of the Pharmaceutical R&D Process

Fig 4.1. continued

Clinical Safety and Efficacy Phase			Marketing Phase	
Inputs: > > > > > > > continue.				
Outputs: Product licence applications, Granted patents, Publication in medical journals, New products, Overseas Regulatory applications				
Activities:				
Volunteer studies Safety Activity Dose Absorption Side-effects Pharmacokinetics Sub-chronic toxicity Supplementary animal pharmacology	Limited trials Efficacy Detailed absorption, excretion and metabolism in man Manufacturing processes Plant design/building Sales formulation and packaging Bioavailability Stability International clinical trials Overseas pharmacy, pharmacology and toxicology when needed	Extended trials in several centres	Data sheets Packaging Promotional literature Sales force Samples Quality control U.K. launch Continued product and process development New indications Post marketing surveillance	Overseas launches New formulations
Attrition:			1 compound	Derivatives, salts etc.
Time: 2-3 years (Bartling), 6-10 years (Glaxo)				

increase around product launch date and will spill over into the post launch phase.

Although the model, as outlined, is essentially a linear one, feedback does occur along the process as information is uncovered perhaps proving useful for elucidation of earlier stages for other products. Process research will run in parallel with product development, the need for cost effective manufacturing processes is fundamental to the industry. Patents will be filed for the manufacturing processes as well as for the drug and any derivatives or analogues.

Since the R&D process is either conducted within the company or delegated to consultancy companies in confidence up to the clinical trial stage which is again conducted in a confidential manner until publication, there is little information publicly known about the work until the latter stages. Generally the first indication the the public has of any R&D taking place is the marketing of a new product. In order to conduct a study of the rate and direction of innovative activity and the effects of constraints on this process then a study of the end products only will tell little of the effects on the preceeding stages. Products are marketed relatively infrequently and the development lead times are long enough to jusify the use of intermediate indicators. They may be used to monitor the process of drugs through research and development, estimate the number of potential products and the times taken to progress through each stage with the attrition rates . These points will be considered later preceeded by a review of possible science and technology indicators. This will be followed by a presentation of data relevant to the U.K. pharmaceutical industry.

4.4 Indicators of industrial research and development

R&D is a major element of the innovation process, innovation in pharmaceuticals has been defined as, 'the sequence of activities directed towards the successful introduction of original pharmaceutical preparations', or, 'the development of improved manufacturing processes for existing preparations' (29). A more general definition states that,

> 'Scientific and technological innovation may be considered as the transformation of an idea into a new or improved saleable product or operational process in industry and commerce...it thus consists of all those scientific, technical, commercial and financial steps necessary for successful development and marketing of new or improved manufacturing products, the commercial use of new or improved processes and equipment' (30)

A thorough understanding of the R&D process is therefore a useful step towards understanding the complex and often ill-defined innovation process, a desire to understand the innovation process arising from the importance placed on technological change and its implications for economic growth.

Any means of enhancing the innovative capacity of a country or sector receives attention from policy analysts and for the reasons given science and technology indicators have been developed since the early 1960's by a variety of national and international organizations. They envisaged the roles for indicators to include: (31)

* Improving allocation of resources for science
* Setting priorities in science and technology
* As a guide to new opportunities
* To enhance the productivity and competitive position
* To achieve a higher return on investment
* To allow a greater international trading strength
* To achieve a higher per capita level of income
* To indicate the rate and direction of technological change
* To reduce uncertainty

Indicators may be used by those engaged in science, industrial, economic and social policy research and now form an important part of many governments assessments. They may be used to compare national

criteria and can be used to show up temporal change. They may be quantitative or qualitative using gross or fine measures; the tendency is towards quantifying the innovation process (32).

The main organizations lobbying for the widespread use and collection of R&D indicators are the OECD, UNESCO and the National Science Board of the United States,National Science Foundation. Since the 1960's these agencies have sought to harmonize the concepts and definitions used in the surveys of national R&D efforts, a process that is not yet complete.

R&D indicators are broadly of two types namely input and output:

Input indicators: These include the expenditure on R&D and the manpower or personnel involved. Also included are the services, materials, equipment and information used as well as the actual research facility. Such indicators are used to monitor the scale and direction of R&D in countries, sectors of industry, fields of science and other classifications. The input to R&D has received most attention since the data are often available and may have been collected for other reasons for many years by national organizations.

Output indicators: These are far more heterogeneous and involve the embodiment of knowledge in various forms and the use and effects of such knowledge. Arnow has produced a five phase framework for the R&D process with examples of indicators at all points.

For the pharmaceutical industry, it is possible to identify a number of input and output indicators: (33)

Input indicators.	Output indicators
R&D Expenditure	Number of compounds synthesised
Manpower	Number of screening tests performed
	Number of product candidates
	Number of patents filed
	Scientific paper counts
	New drug applications (CTCs,PLs)
	Products marketed (+novelty, significance)
	Sales achieved

Each of these will be taken in turn and the availability of data assessed.

4.5 R&D expenditure as an input indicator

4.5.1 Definitions and sources of data

The use of data concerning expenditure on R&D is complicated by problems of definition. What is included as R&D varies not only from country to country but from firm to firm. The harmonization of definitions and the regularity of OECD surveys has helped to make much of the available data comparable throughout industry. For the drug industry R&D includes 'all activity directed towards the discovery and development of human or veterinary medicines or animal health products' and includes process development (34). The OECD define research and experimental development as, 'creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society and the use of this stock of knowledge to devise new applications' (35).

Fringe activities such as pilot plant development, quality control and process control may or may not be included in R&D but the NEDO study found that if they were included, they comprised 5-7% of total R&D costs. Given this variation in interpretation they concluded that, 'reported figures for expenditure in Britain fairly accurately reflect the actual R&D input in financial terms' (36). The degree of accuracy for comparison of expenditure between firms was found to be between 5 and 10%.

R&D data are often categorized by the function of the expenditure, the definitions adopted by the OECD in the 'Frascati Manual' are as follows:

Basic research: 'experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view'.

Applied research: 'original investigations undertaken in order to acquire new knowledge...directed primarily towards a specific practical aim or objective.'

Experimental development: systematic work, drawing on existing knowledge gained from research and/or practical experience that is directed to producing new materials, products or devices, to installing new processes, systems and services, or to improving substantially those already produced or installed.'

Schwartzman, amongst others, has emphasised the over-simplification that this gives to the R&D process and maintains that such subdivision is arbitrary, each firm having their own interpretation.

In the drug industry 'basic' research may be thought of as goal orientated or orientated basic research as the research is generally towards a commercially attractive area. The OECD recognise this problem and recommend that the data be treated with circumspection, only being used in conjunction with additional qualitative information. The categorization is however used by the industry to argue that the relative spending between the areas has changed over time and that less resources are now devoted to basic research and more to development, a trend they argue that has been caused by drug regulation.

The OECD provide information by institutional class, the drug industry being in the business enterprise sector due to its principal (economic) activity. The basic measure is 'intramural expenditure' that is all expenditure for R&D performed within a statistical unit or sector of the economy. Current and capital expenditure is included but depreciation is excluded. Current expenditure includes labour costs and other current costs. Capital expenditure includes land and buildings and instruments and equipment.

For the UK drug industry, OECD data are available from 1967 to 1975 (38) and are shown in Table 4.3. Immediate problems are due to the fact that the agencies collecting the data for the OECD in the UK changed over the period so that, for example, the data for 1971 and 1973 are not comparable. Data for 1967 are inconsistent, the short time span of available figures makes any trend analyses prone to inaccuracy since little data are available for the period before the introduction of drug regulation in the UK. The OECD data are not the only available, other sources exist and provide useful additional figures, they will be reviewed in turn starting with official government statistics.

U.K. Government statistics. (39)

Table 4.4. gives all available figures for R&D in the UK pharmaceutical industry. The most recent figures result from surveys using OECD definitions and are more comprehensive.

ABPI data (40)

Table 4.5 gives data for all R&D expenditure incurred in the UK for all companies.

Table 4.3

	£mill, Year ending						
	1967	1969	1971	1973	1975	1978	1980
Total intramural expenditure	29.6	18.9	24.2	41.9	78.7	160.3	295.8
Labour costs	14.0	8.8	10.6	18.7	38.8	-	
Other current costs	9.4	6.6	7.9	14.5	27.4	-	
Total current costs	23.4	15.4	18.6	33.3	66.3	-	
Land & buildings	-	1.8	3.1	-	5.9	-	
Instruments & equipment	-	1.5	2.4	-	6.3	-	
Total capital costs	6.1	3.4	5.5	8.5	12.3	-	
As percentages of overall total							
Labour costs	47.3	46.7	43.9	44.8	49.4	-	
Other current costs	31.8	35.0	33.0	34.8	34.9	-	
Total current costs	79.2	81.7	76.9	79.6	84.3	-	
Land & buildings	-	10.0	12.9	-	7.6	-	
Instruments & equipment	-	8.3	10.2	-	8.1	-	
Total capital costs	20.8	18.3	23.1	20.3	15.7	-	
By type of activity							
Basic research	1.2	0.6	1.1	-	-	-	
Applied research	13.4	9.1	10.3	-	-	-	
Experimental development	8.8	5.6	7.1	-	-	-	
As percentages of total							
Basic research	5.2	4.2	6.0	-	-	-	
Applied research	57.2	59.1	55.8	-	-	-	
Experimental development	37.6	36.6	38.1	-	-	-	

RESEARCH AND DEVELOPMENT EXPENDITURE IN THE PHARMACEUTICAL INDUSTRY IN THE UNITED KINGDOM

Source: compilation from ISY surveys, OECD Paris, various years. Data supplied to the OECD by the Department of Education and Science, Boards of Trade and the Department of Trade and Industry.

* From, OECD (STI), 'Basic Statistical Series D: R&D in the BES 1963-79 OECD March 1983

Table 4.4

	£ millions and % of total													
	1967	%	1968	%	1969	%	1970	%	1973	%	1975	%	1978	%
Total expenditure	16.98	100	16.41	100	18.93	100	24.21	100	41.90	100	79.80	100	160.50	100
salaries/wages	8.18	48.2	8.25	50.2	8.84	46.7	6.97	28.8	18.78	44.9	39.30	49.2	66.90	41.7
materials/equipment	2.06	12.1	2.08	12.6	2.10	11.1	1.34	5.5	4.10	9.8	10.60	13.3	19.20	12.0
other expenditures	4.45	26.2	3.84	23.4	4.52	23.9	1.90	7.8	10.50	25.1	17.30	21.7	37.50	23.4
total current	14.69	86.5	14.17	86.3	15.47	81.7	10.21	42.1	33.40	79.7	67.30	84.3	123.70	77.1
land/buildings	0.95	5.6	0.90	5.5	1.90	10.0	3.12	12.9	-	-	-	-	22.90	14.3
plant/equipment	1.34	7.9	1.35	8.2	1.57	8.3	2.47	10.2	-	-	-	-	13.80	8.6
total capital	2.29	13.5	2.25	13.7	3.47	18.3	5.59	23.1	-	-	-	-	36.80	22.9
Basic research	0.59	4.0	0.48	3.4	0.66	4.2	1.12	6.0	2.46	7.4	4.60	6.9	6.90	5.6
Applied research	8.25	56.2	9.24	65.2	9.15	59.1	10.40	55.8	17.49	52.4	37.3	55.4	61.00	49.3
Development	5.84	39.8	4.46	31.4	5.67	36.6	7.10	38.1	13.44	40.2	25.40	37.8	55.70	44.9
Total on R&D	14.69	100	14.17	100	15.48	100	18.62	100	33.39	100	67.30	100	123.70	100

Intramural R&D expenditure in the U.K. pharmaceutical products industry 1967-1978

Sources:

1. 1964-1965; data included in 'petroleum and plastics' so not available. First survey of R&D by the DES/Min Tech.
2. 1968; Min Tech/Board of Trade, 'The cost of R&D in the U.K.1961-62, 1964-65, 1966-67', only data for 1966-67 broken
3. 1966-67; in 'Statistics of science and technology', (1968)
4. 1967-68; in ibid, (1970)
5. Department of Trade and Industry figures in, 'Studies in official statistics No. 21' published by the CSO gives data for 1968-69 and 1969-70.
6. 1972-73; in 'Studies in official statistics No. 27'. Conforms to 'Frascati definitions'.
7. 1975; in Trade and Industry,(24th June, 1977), pps 638-644.
8. 1978; in British business,(8th August 1980).
9. 1980; figures in British business,(9th December 1983), p 750. Private R&D expenditure given as £ 295.8 mill. No breakdown

Table 4.5

Year	Expenditure (£ millions)
1953	2.8
1954	3.0
1955	3.5
1956	3.9
1957	4.2
1958	5.1
1959	6.3
1960	7.5
1961	7.8
1962	8.3
1963	na
1964	10.4
1965	11.6
1966	13.0
1967	16.4
1968	18.9
1969	24.2
1970	29.0
1971	35.0
1972	41.9
1973	44.1
1974	50.0
1975	82.6
1976	120.0
1977	150.0
1978	190.0
1979	222.8
1980	280.0
1981	332.5

Research and development expenditure by the British pharmaceutical industry. 1953-1981, ABPI surveys

Source: ABPI surveys compiled from annual reports of the ABPI. All figures are in current prices.

4.5.2 Problems associated with the use of R&D data.

A number of problems are posed when attempting to use the sort of expenditure data presented above:

* The expenditures are for all pharmaceutical companies conducting R&D in the UK irrespective of their nationality. Since this study concerns itself with the UK owned companies, further disaggregation would be preferred.
* No details are given for expenditure by UK owned companies outside the UK. This will vary from company to company.
* The expenditure figures shown include a proportion for veterinary products and other animal health items which are outside the scope of this study.
* Research data for new chemical entities specifically are not available.
* No details of the effect of price increases over time are given. Figures are in current prices and need to be deflated to take into account the effect of inflation and R&D specific price increases.

Each of these problems can be dealt with but with varying degrees of success.

To determine the proportion of R&D expenditure accounted for by the UK owned companies a number of previous studies allow some estimates to be made for this sector of the industry as a whole. Furthermore it is possible to obtain the figures for the UK owned companies individually and obtain a total figure by addition. The first approach only provides figures for a short time span, for example, the Sainsbury study (41) found that the British companies spent the following on R&D for NHS products (table 4.6).

A point worth noting is the expenditure in general of between ten and eleven per cent of total sales on R&D at this time. A survey by the ABPI

concluded that about fifty per cent of overall expenditure was due to the UK owned companies, an underestimated figure as not all firms responded. Michael Cooper in a significant early study surveyed the industry and obtained data for the British owned companies relating to all products for the period 1964-65. Again, a few companies refused to provide data, a major UK company included, ensuring that the total figure of £6.6 million is again an underestimate (42). This total again represents about 56% of the total expenditure for all companies in the UK.(Table4.7)

Few government statistics are available on a disaggregated basis but approximate figures were calculated. The Department of Industry were not able, for reasons of confidentiality, to provide figures for individual companies but gave the percentage of total R&D expenditure due to the UK owned companies for 1972, 1975 and 1978. From these figures calculations based on 75% of gross intramural expenditure were made to provide the figures for UK owned companies. In doing this it must be assumed that the proportion of expenditure due to these companies has remained constant with time. (Table 4.8)

Interestingly, the DOI estimate that the UK firms account for over 70% of total R&D expenditure, the data are very susceptible to error but are borne out by a figure of 69% found by a ABPI survey in the mid-1970'S (44). US.firms in the same survey were found to have spent around 20% of the total and European firms about 11%.

Such surveys are prone to error particularly if a few companies fail to respond since there are only a small number of UK owned firms that undertake any significant R&D. The availability of data from the companies themselves is not only restricted by confidentiality but by the accounting methods adopted.

Table 4.6

Year	£mill R&D	As % of sales
1961	4.3	10.5
1962	4.7	10.6
1963	5.5	11.4
1964	6.1	10.6
1965	6.9	10.3

R&D EXPENDITURE ON NHS PRODUCTS BY BRITISH COMPANIES 1961-65

Table 4.7

Company code	Expenditure £mill	As % profits	As % NHS sales	Proportion of output devoted to ethicals
A	1.9	1	73	1
B	1.3	-	68	91.5
D	1.0	10	13	-
E	1.0	7	91	-
F	0.8	-	267	15
L	0.2	13	67	-
M	0.2	10	22	11
O	0.1	2	25	91.7
Q	0.1	6	35	-
Total	6.6			

RESEARCH, PROFIT AND SALES 1964-65, BRITISH-OWNED COMPANIES

Table 4.8

	All UK firms		UK owned firms	
Year	Intramural	Gross	Gross	% gross
1967	16.98		12.74	*
1968	16.41	-	12.31	*
1969	18.93	-	14.21	*
1970	24.2	-	18.15	*
1972	41.9	43.9	33.10	75.4
1975	79.8	83.1	58.50	70.4
1978	160.5	170.5	123.30	72.3
1980	295.8		221.85	

R&D EXPENDITURE FOR UK OWNED COMPANIES IN £MILLION

Source: (43)

R&D expenditure is generally charged to profits in the year in which it is incurred, small amounts may be capitalised as part of the cost of new plant and subsequently annual reports and other company information may be of little use. Companies with a number of divisions may not give the expenditure figures for pharmaceutical R&D but for the group as a whole. If data are given then veterinary research may be included as well as other non-pharmaceutical expenses such as health foods.

All UK owned firms of interest were contacted and asked to provide details of their expenditure on R&D for human medicines. Few were able to provide any information, most stated that the figures were not available in any disaggregated form and would require considerable effort to extract.

Figures were, however, obtained from annual reports when available and also from specialist surveys, market research reports and any incidental secondary sources. The data are reproduced below for each company in turn. The cumulative figure for 'all' UK owned companies compares favourable with data from official government sources. However as the data shown is at the most disaggregated level available and considering the possible inherent errors, any interpretation must examine trends rather than absolute values. One further major obstacle remains before a realistic analysis is possible, that of variation in prices over time, necessitating the adoption of R&D deflators which will be discussed next.

Table 4.9

Current expenditure in UK on R&D	£mill		
	All companies	UK owned	As %
In-company R&D Human medicine discovery	37.88	26.3	69.4
Total R&D including animal grants	44.1	30.45	69.03
Outside UK		7.13	

R&D EXPENDITURE 1972-1973 - Source: ABPI

Table 4.10

Year	£mill	Year	£mill	% sales
1946	0.1	1977	19.4	2.7
1962	0.5	1978	24.9	2.9
1969	2.3	1979	31.3	-
1971	6.0	1980	35.1	
1975	11.2	1981	40.4	3.4
1976	15.3	1982	50.6	

BEECHAM R&D EXPENDITURE 1946-1982 (45)

No data on a temporal basis was found for Boots in the sources used.

Table 4.11

Year	£mill	Year	£mill
1971	3.0	1979	8.0
1973	11.0	1980	9.0
1974	3.1	1981	9.0
1975	3.5	1982	10.0(13)
1976	4.4	1983	5.5
1977	6.0		
1978	7.0		

FISONS: PHARMACEUTICAL DIVISION R&D EXPENDITURE 1973-1983 (46)

Table 4.12

Year	£mill	% sales
1971	4.0	-
1975	11.0	-
1976	14.2	-
1977	17.4	4.1
1978	20.2	4.6
1979	25.0	-
1980	32.0	-
1981	38.0	-

GLAXO, R&D EXPENDITURE 1971-1981 (47)

Table 4.13

Year	£mill	Year	£mill
1942	0.079	1970	123*
1943	0.125	1974	11.5
1944	0.193	1975	15.0
1945	0.191	1977	27.0
1946	0.237	1978	31.0
1947	0.313	1980	45.0
1948	0.339	1981	56.0
1949	0.368	1982	70.0
1950	0.372		
1951	0.420		
1952	0.493		
1953	0.549		

ICI R&D EXPENDITURE 1942-1982 (48)

* all ICI Divisions

Table 4.14

Year	£mill
1974	1.2
1975	1.5-1.75
1976	2.0

RECKITT & COLMAN R&D EXPENDITURE 1974-1976 (49)

Table 4.15

Year	£mill	% of Profit
1967	2.9	31.1
1968	3.6	28.5
1969	4.5	31.8
1970	5.7	40.1
1971	7.5	45.6
1972	8.7	42.8
1973	9.9	34.1
1974	11.5	33.8
1975	15.9	37.8
1976	23.1	35.8
1977	29.3	
1978	33.4	
1979	39.1	
1980	47.3	
1981	52.0	
1982	66.3	
1983	80.9	

WELLCOME FOUNDATION R&D EXPENDITURE 1967-1983 (50)

Table 4.16

Year	£mill
1967	6.8
1975	58.0
1977	99.0
1978	116.0
1980	168.0
1981	195.0

R&D EXPENDITURE, ALL UK OWNED FIRMS 1967-1981 (51)

4.5.3 Deflation and R&D expenditure figures.

Since R&D data are given in current prices, any trends in real expenditure are often hidden by changes in prices by inflation. To determine how the cost of R&D has changed over time the data must be deflated using some weighting system, the use of the implicit GDP deflator is only acceptable in cases of extended periods of low inflation, a situation that has not always existed in the UK. Furthermore, economists argue that rises in costs of R&D have exceeded the general rate of inflation and thus makes the use of a general deflator invalid.

Attempts at calculating R&D deflators have been made by the OECD who calculated an experimental price index in 1975, which was improved for 1977 and applied to R&D data for a number of countries for the period 1967-1975 (52). Three main difficulties exist:

* Choosing an index number
* Establishing a weighting system
* Finding suitable price data

The approach adopted by the OECD for the experimental index was firstly to use a Laspeyres average index of 1970=100 as the base, the weighting was derived from the relative expenditures on the subdivisions of current and capital expenditures using ISY averages. Prices were calculated in a proxy series using such information as salaries, the implicit deflator of the Domestic Product of Industry (DPI) and that of the Gross Fixed Capital Formation and its subgroups. For the UK the indices were as follows: 1970=100

1967	1968	1969	1970	1971	1972	1973	1974	1975	1976
84.2	88.7	93.1	0.0	0.0	118.2	128.4	0.0	190.0	0.0

Source (53)

Since this time much work has been done on improving the indices and the 1980 edition of the'Frascati Manual' describes three possible methods of calculating R&D deflators.

1. Composite price index with fixed weights

2. Composite price index with changing weights

3. Deflating each industry's R&D separately

The first approach is the simplest and is similar to the one described above. Examples of approaches to deflating R&D data were presented to a 1977 OECD workshop (54). Calculating an R&D deflator for each industry has attractions as weights specific to that industry may be applied allowing greater accuracy. An example of applying industry-specific deflators to R&D data is provided by Bosworth, among the industries selected was 'Chemicals and allied', the closest relevant industry to the pharmaceutical industry. Using similar weights and price indices as described above he showed that real expenditure with a base year of 1972=100 had peaked in 1969 and had declined ever since. Current expenditure figures on the other hand reveal an almost exponential growth (55).

The R&D price indices for all categories of expenditure for the 'Chemicals and allied' industry were as follows:

1958	1961	1964	1966	1967	1968	1969	1972	1975
46.47	52.41	59.44	64.09	65.03	67.45	72.24	100	171.25

It is possible to use these deflators on the R&D data for the pharmaceutical industry. As an example the ABPI data for the general industry was deflated using both of the indices described. The results are presented in Table 4.17 and Fig. 4.2. In later chapters, the R&D data will be used in conjunction with other indicators. The figures used are those for the UK owned sector of the industry and to this end the deflators were applied to the estimated data for this sector. The results are given in Table 4.18 and Fig. 4.3. What is evident from the deflated figures is that the massive increases in R&D expenditure in the mid-1970's shows a much more gradual but still obvious real

increase over the period 1958-1975. The real increase over this period being about five times as compared with the twelvefold increase in current prices. Deflators could be applied to the separate categories of expenditure and to the UK companies alone (resulting in a real increase in expenditure of two times over the period 1967-1975).

In the late 1960's the Council for Scientific Policy estimated residual growth rates net of inflation ('Sophistication factors') to examine whether the cost of scientific work per scientist had become progressively greater (56). They examined the budgets of a number of academic and government funded research stations and found, for example, that a growth rate of 20% per annum in real terms in major equipment costs had occurred. This type of information is important if the intensity of research calculations are to be based on estimates of R&D expenditure whether alone or coupled with other indicators such as sales or profit figures.

An assessment of the trends in R&D expenditure will be attempted in the concluding chapters in conjunction with other quantitative and qualitative indicators of the research and innovatory processes in the pharmaceutical industry in the UK. The next input indicator to consider is that of R&D manpower or personnel engaged on R&D work in the industry.

Table 4.17

	R&D Expenditure £mill		
Year	ABPI current	OECD index	Bosworth index
1958	5.1	-	10.9
1961	7.8	-	14.8
1964	10.4	-	17.4
1966	13.0	-	20.2
1967	16.4	19.4	25.2
1968	18.9	21.3	28.0
1969	24.2	25.9	33.5
1970	29.0	29.0	-
1971	35.0	35.0	-
1972	41.9	35.4	41.9
1973	44.1	34.3	-
1974	50.0	50.0	-
1975	82.6	43.2	48.2

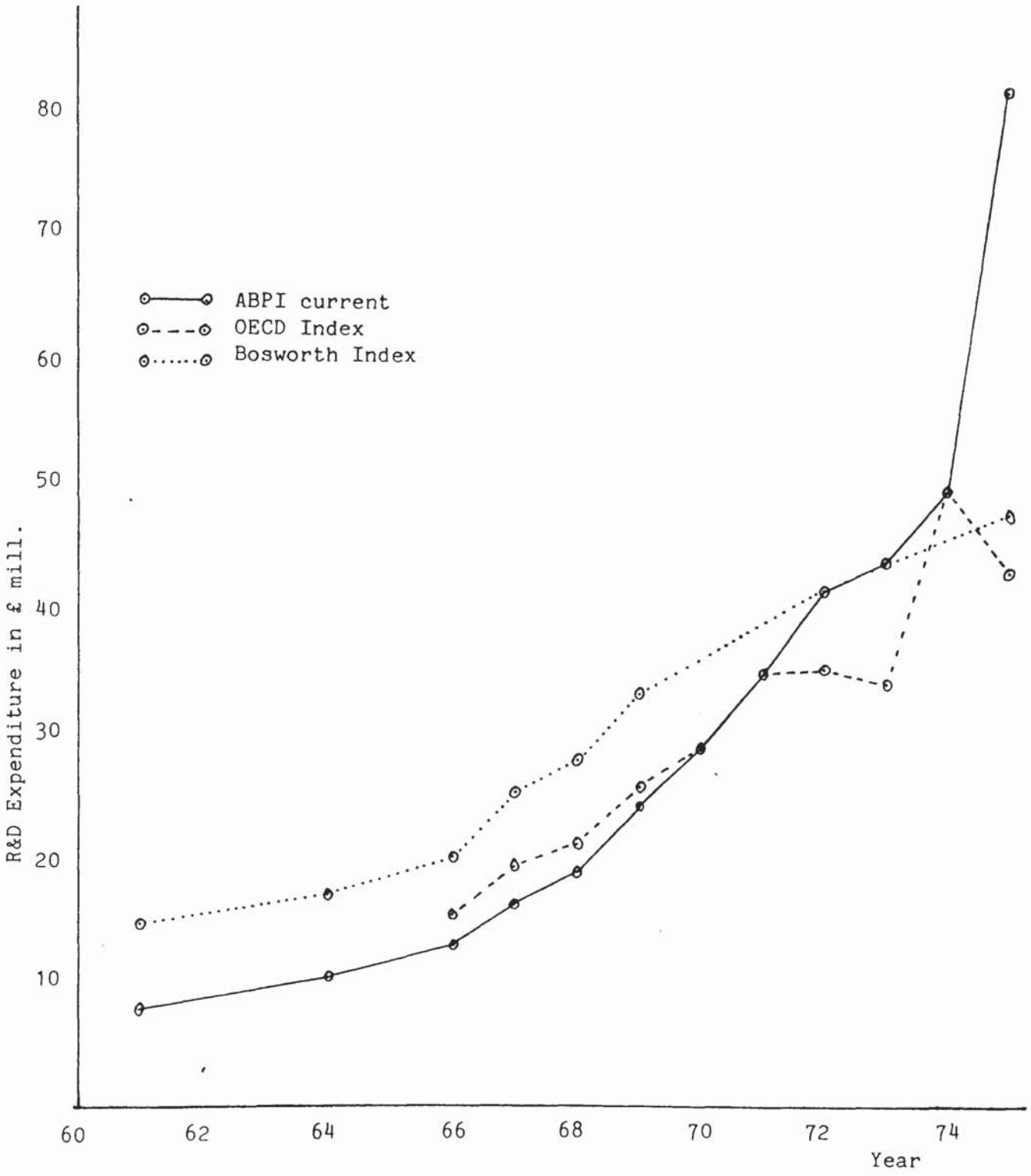
DEFLATION OF ABPI CURRENT R&D EXPENDITURES

Table 4.18

	R&D Expenditure £mill		
Year	DOI current	OECD index	Bosworth index
1967	12.7	15.1	19.6
1968	12.3	13.8	18.3
1969	14.2	15.2	19.7
1970	18.1	18.1	-
1972	33.1	28.0	33.1
1975	58.5	30.6	34.1
1978	123.3	-	-
1980	221.8	-	-

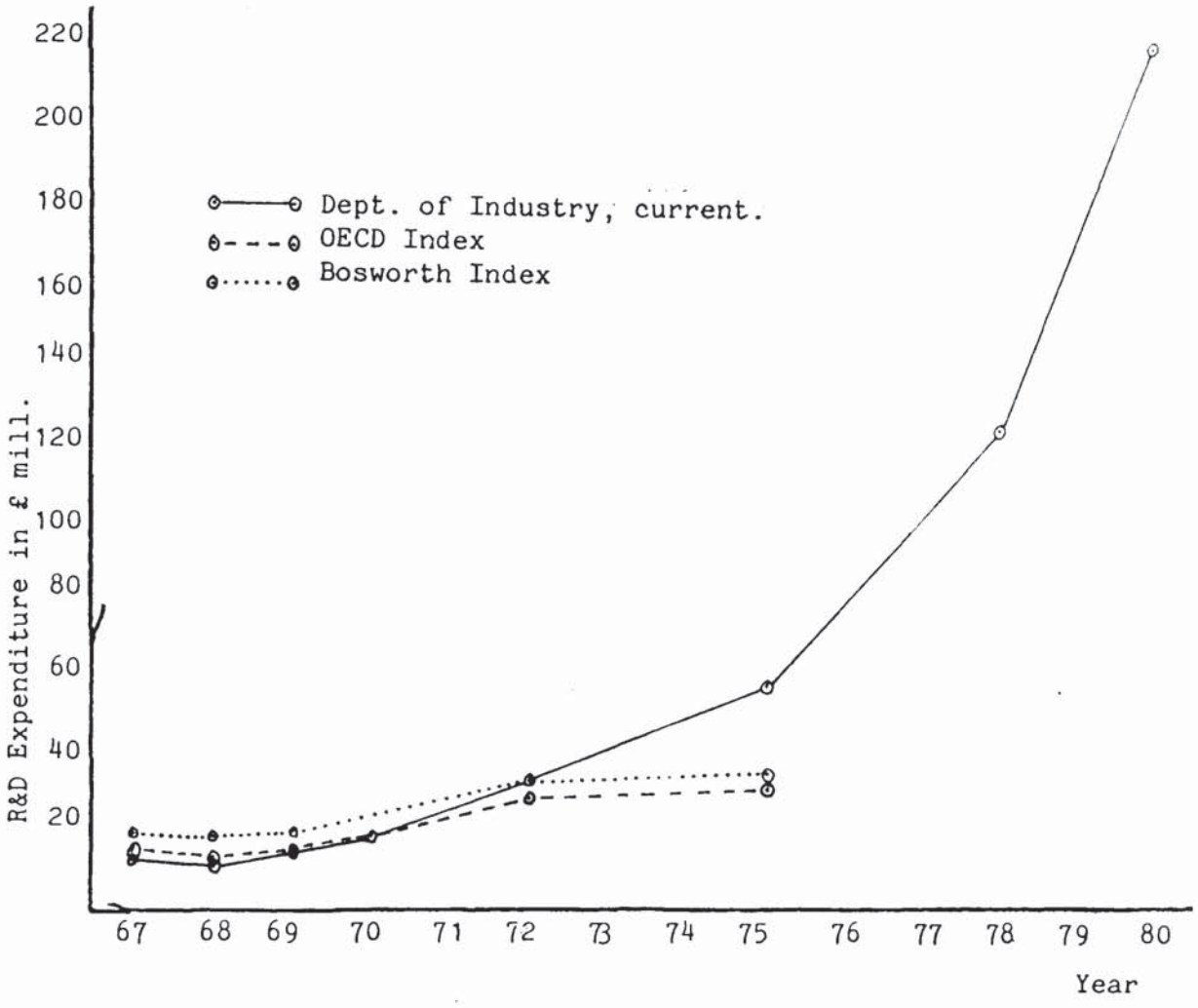
DEFLATION OF DOI CURRENT R&D EXPENDITURE
(UK OWNED COMPANIES)

Figure 4.2



Deflation of ABPI current R&D expenditures

Figure 4.3



Deflation of D. of I. current R&D expenditures.

4.6 Manpower statistics

Manpower statistics may be used alone as a general indicator of research activity or more commonly in combination with expenditure data eg. as expenditure per scientist. The use of manpower statistics is hindered by the same sort of classification and convention problems as outlined earlier for R&D expenditure.

The first major problem concerns the definition of occupations that can be included under the banner of R&D, should non-technical and service staff be included? The OECD definition states that, 'All persons employed directly on R&D should be counted as well as those providing direct services such as R&D managers, administrators and clerical staff' (57). The approach adopted in the NEDO study is that if the staff are directly costed to R&D they should be included in manpower figures but if the costs are apportioned then they should be excluded. Again the practice differs from firm to firm but services such as patent and trade mark work, information provision and computing and statistical services are usually included in the R&D budget but staff are not directly employed on R&D. The NEDO study recognised a lack of consensus and recommended the adoption of a classification system as used by the US Pharmaceutical Manufacturers Association (PMA) (58).

A second problem concerns the classification of staff involved in R&D, should this be by qualifications or the type of work done? The rise in the number of highly qualified staff in research based industries is more a reflection of changes in the education system than academic standards. Highly qualified staff may now undertake more routine repetitive work than was the case previously. The accepted approach is to define the tasks or classes of occupation as based on the International Standard Classification of Occupations (ISCO) as used by the OECD.

Researchers: Scientists or engineers engaged in the conception or creation of new knowledge, products, processes methods and systems. This includes managers and administrators and postgraduate staff generally.

Technicians and equivalent staff: Perform scientific and technical tasks normally under the supervision of scientists and engineers.

Other supporting staff: Includes skilled and unskilled craftsmen, secretarial and clerical staff participating in R&D projects or directly associated with such projects.

This level of disaggregation may however not be necessary, the NEDO study felt that, 'simple counts of either higher graduates or 'QSEs' (59) employed on research must be treated with caution. The total numbers employed on R&D regardless of qualification may be at least as meaningful a measure of the input' (60).

The final major problem to account for is part time working on R&D, some workers may only devote part of their effort to R&D activities. To allow for this the OECD adopted the concept of the Full Time Equivalent (FTE) which is equal to one person-year on R&D, use of this measure goes some way to avoiding over and underestimates but involves complicated accounting procedures for collecting organizations.

Since personnel costs account for a major proportion of total R&D costs (around 50%) it is thought that manpower statistics are a useful short term indicator of R&D effort. Other problems are more difficult to account for including the possibility of automated testing and analysis replacing much of the routine work done by technical staff. However the general trend in manpower remains upwards as will be shown in the data below.

4.6.1 Manpower statistics, sources

A 1959 Federation of British Industry survey noted that even at this time the British drug industry employed the highest ratio of scientifically qualified staff in the country (61). Estimates of the percentage of all personnel in the industry engaged on R&D are in the order of 14% (10,000) to 16% (12,000) with a rise anticipated during the mid 1980's (62). Table 4.19 gives the available data.

Table 4.19

	1967	%	1968	%	1969	%	1972	%	1975	%	1978	%
Total	6800	100	6800	100	7100	100	8579	100	10100	100	12157	100
QSE/RSE			2138	31	2257	32	2509	29	3859	38	4264	35
Technical							4101	48	3500	35		
Other							1969	23	2800	28		

R&D MANPOWER IN THE UK PHARMACEUTICAL INDUSTRY: ALL COMPANIES (63)

Data for individual companies or for the UK owned group as a whole is extremely limited, little information was obtained from the companies following written requests. One example was however provided by ICI who stated that they have a UK workforce of four thousand in the pharmaceuticals division, 1,400 of whom are involved in R&D with a further six hundred involved in R&D outside the UK (64).

Having demonstrated the range and accuracy of input indicators for the UK pharmaceutical industry, the next stage is to examine the possible output indicators.

4.7 Indicators of R&D output

Historically, output indicators have received less attention than input indicators and are still in the early stages of development. One of the main problems is that the type of indicators now accepted as output measures make use of data not collected for that purpose and therefore often require considerable manipulation before use. This

is recognised by the Science and Technology Indicators Unit (STIU) of the OECD, 'While indicators of the output of R&D are clearly needed to complement input statistics, they are far more difficult to define and collect' (65).

Arnow (66) gives a comprehensive list of output indicators including the 'outputs of knowledge production', published papers by author, discipline, source of funds and employer are involved in this category, as well as prizes received, citation counts and patent applications. 'Use of knowledge outputs' include purchase and payment for information, prototypes, patents, designs and licences. 'Initial operational use and effects of new technology' recognises a further type of impact indicator.

Many of these types of indicators require considerable effort for their extraction and the only output measures that have received serious and extended analysis include patent counts, bibliometric statistics including citation counts and finally, counts of inventions and innovations.

In an earlier section a number of possible output indicators were listed for the pharmaceutical industry and were incorporated into the model of the innovation process. From the model it is evident that output indicators may be terminal or intermediate to the process and thus indicate output from various stages of the process. The possibility of using these indicators and the problems associated with their use will be assessed in turn in the following chapter.

4.8 Conclusions

Given the importance placed on the innovation process and the belief that regulations have a detrimental effect on such activities, the lack of objective and consistent information prevents any generalisations being made.

In order to begin to assess the impact of regulations or any other external factors on the drug innovation process, a model must be constructed in order to identify 'indicator points' and distinguish between the innovation process in the drug industry and the more traditional 'academic' system.

A model is outlined and,although it is essentially linear in order to illustrate the temporal features of the process, gives a number of possible science and technology indicators for use in a study of the industry

A summary of the R&D process shows that although firms adopt different approaches to the organization of research and the development of new products, essentially the process has become more sophisticated. This can be accounted for by increasing regulatory stringency and difficulty in developing products of increasing novelty and efficacy.

Traditional indicators of R&D input have been reviewed, with R&D expenditure data being prominent. A number of problems have been shown to be associated with the use of such data in a temporal study of the U.K. owned sector of the pharmaceutical industry. The need for a 'bottom-up' approach is derived from a lack of disaggregated data, This approach, however, results in some inconsistency in the data with periods for which no data are available.

The use of R&D data requires the use of a deflator to account for price fluctuations over time. Two such deflator indices are suggested and their suitability assessed. The short temporal cover of the indices used points to the need for a more specific, long-term deflator for the pharmaceutical industry.

Manpower statistics are shown to be less useful as their availability is limited. This shortcoming precludes their use in subsequent analyses except as general indicators.

Having assessed the availability and suitability of input indicators along with the problems associated with their use, the next stage is to conduct a similar analysis for output indicators which, from the model, appear to be more varied. The next chapter is devoted to this analysis.

CHAPTER FIVE: INTERMEDIATE R&D OUTPUT INDICATORS.

Introduction

Since the rate and direction of innovative activity must, by definition, be measured by the number and type of products and processes made available to some end user, intermediate output indicators must measure the rate and direction of research, inventive or potential innovative activity.

The model of R&D described earlier includes a number of possible output indicators occurring at various stages in the process. The extent to which these can be used or are available will be outlined in this section, ideally, the optimum criteria for an indicator will be their availability over a reasonable and appropriate time span comparable with those for the input indicators chosen. All indicators then should be incorporated into a general framework for the companies of interest so that tentative conclusions may be drawn regarding temporal changes in R&D activity, rate and direction of innovation and the relationship, if any, between these and the implementation of government regulation.

Furthermore, the intermediate indicators should be available at the level of the firm or UK owned sector of the pharmaceutical industry as well as for the UK industry as a whole. Since the terminal output indicator, that of NCE output has been considered already, the intermediate indicators that remain will be discussed in turn and their suitability assessed.

5.1 Types of intermediate output indicator and their use.

5.1.1 Screening tests performed and compounds synthesised

The use of counts of tests performed or compounds synthesised by a company raises a number of problems. The use of such indicators depends on the variable research methods adopted by companies, so that the number of compounds made and screened will vary between the extreme

positions of random screening and the rational approaches outlined earlier. Such indicators may be of more use as indicators of the research method adopted by a company than of research activity. The use of such data is usually restricted to internal research purposes by management to monitor activity at this level (1). However, such data are not generally available outside the companies other than incidental references and thus were deemed inappropriate for this present study.

5.1.2 Counts of new product candidates.

Counts of such active molecules indicate a position further along the R&D process than the above counts and the use of such data was favourably received by companies during the NEDO study, 'There was a general feeling in the companies that the number of product candidates provided the earliest meaningful measure of R&D success within a company' (2). Given the useful nature of such counts it is unfortunate that little data are available. Any information released by industry is intermittent, appearing in specialist journals. To obtain such information even at a superficial level for a short period would have required extensive searching and thus was again deemed an inappropriate measure to use.

5.1.3 Counts of scientific papers.

The application of well-established bibliometric techniques to a study of the pharmaceutical industry initially appears attractive. Publication counts, that is counts of the number of publications emanating from a specific source were seen by NEDO respondants as relevant indicators of whether 'good' science was being conducted in industrial laboratories, the assumption being that publication of the results of a research programme indicate good original work. Difficulties with this measure include the high degree of industrial secrecy, major process innovations may not be revealed in publications for fear of duplication. A number of companies visited during the course of research did indicate that individuals were encouraged to publish results in certain selected

journals but no indication of the level of publication or the timing of publication were given.

To further assess the possibility of using counts of scientific papers from the UK industry, a trial search in the Science Citation Index by name of company and location of research facility for a number of years was conducted but proved fruitless. It became apparent that only a count by author would give any adequate results but since this required temporal details of the names of all researchers employed by each company, a mammoth task, this approach was not pursued.

Analysis of specialist journals did however reveal information concerning products in the latter stages of clinical trials. A comprehensive search of selected journals for papers emanating from individual companies would enable a case study approach in a limited sense but whether this would be at the level of aggregation and for the required time period is open to debate. Further research possibilities exist in this field but were outside the scope of this study.

5.1.4 Animal experimentation statistics

One possibility considered during the course of this study was that statistics on animal experimentation might, if available, provide an indication of the level of pre-clinical research in the industry. Data was subsequently found to be readily available and all relevant figures were assimilated.

Tables were drawn up based on the publication 'Statistics of experiments on living animals' collected by the Home Office in Britain. Statistics are compiled under the Cruelty to Animals Act of 1876 which aimed to ensure that no excessive pain or cruelty due to experimentation is caused to any animal. All experiments are conducted under licence in registered premises with the exception of tissue culture, bacterial culture etc.

The testing of drugs under, initially, the 1965 Therapeutic Substances Act or the Diseases of Animals Act 1950 had to be recorded and since the inception of the 1968 Medicines Act experiments under the latter have been differentially recorded. Statistical returns are collected and published by the Home Office as Annual reports.(3)

Table 5.1 records the number of experiments conducted under the Therapeutic Substances Act and the Diseases of Animals Act as well as the number of registered premises. The number of Home Office inspectors and their visits may give some indication of the increase in regulatory pressure since 1960.

Table 5.2 is more specific and includes the number of experiments involving medical, dental or veterinary products and appliances. This level of aggregation is insufficient for the needs of this study as non-human medicines are included. However, figures in table 5.3 are more useful as they include experiments conducted in order to register under the 1968 Medicines Act or any equivalent overseas legislation. Table 5.4 includes quality control experimentation on a similar basis.

Since separate figures are not available for experimentation involving drugs for human use or for the UK owned companies of interest and detailed data are only provided for the post-1977 period, the information is of limited use. Trends in the figures may be the result of changes in research practices rather than variation in levels of activity over time.

Table 5.1

Year	Number of expts * TSA/DAA	Registered places	Visits	Inspectors
1960	1,236,585	524	1506	-
1961	1,113,874	529	1407	-
1962	1,214,276	536	1755	6
1963	1,173,535	556	1941	6
1964	1,411,872	575	2170	8
1965	1,331,288	596	2038	8
1966	1,182,365	609	2147	9
1967	1,238,294	614	1952	10
1968	1,204,860	609	2224	9
1969	1,453,939	605	2850	13
1970	1,473,225	607	3140	13
1971	1,300,844	596	3650	13
1972	1,072,801	592	4052	13
1973	1,260,765	607	4181	14
1974	1,375,829	601	4284	14
1975	1,188,774	594	5095	14
1976	1,263,400	583	5861	14
1977+	-	574	5442	14
1978	-	573	6410	14
1979	-	578	5791	15
1980	-	559	6574	15
1981	-	527	6743	15

Statistics of experiments on living animals 1960-1981

Source: Home Office,"Statistics of Experiments on living animals", Annual Reports HMSO London. Various years.

* Mandatory testing for the standardization of sera vaccines and drugs under the 1956 Therapeutic Substances Act and the 1950 Diseases of Animals Act.

+ New report format introduced.

Table 5.2

Year	Number of experiments
1977	2 932 557
1978	2 925 740
1979	2 680 760
1980	2 680 081
1981	2 403 014

Experiments on living animals. 'To select, develop or study the use etc. of medical, dental and veterinary products or appliances'.

Table 5.3

Year	Number of experiments and location		
	Total	Commercial labs	%
1977	212 059	146 819	69
1978	227 864	192 286	84
1979	223 497	156 066	69
1980	220 536	154 858	70
1981	184 539	135 938	73

Total number of experiments and locations. 'Intention to register under the Medicines Act 1968 or equivalent overseas legislation'.

Table 5.4

Year	Number of experiments and location		
	Total	Commercial labs	%
1977	707 179	474 863	67
1978	703 423	387 870	55
1979	641 409	381 543	59
1980	637 739	405 007	63
1981	546 640	351 158	64

'Intention to present batch quality control data under the Medicines Act 1968.'

Pressure from anti-vivisectionists, the increasing costs of animal experimentation and the development of in-vitro techniques are variables that need to be accounted for if the Home Office data are to be used as indicators. The decline in all categories of animal experimentation since 1970 needs to be considered in the light of such general variables.

In conclusion, data on animal experimentation lack sufficient detail and disaggregation to be used in conjunction with input indicators but are useful in providing background information concerning research activity and regulation in the pharmaceutical industry.

5.1.5 Applications for clinical trial certificates and product licences.

Counts of applications for certificates and licences may indicate the level of research and development activity for products that warrant testing in humans and subsequent marketing respectively. The origins of the licensing system and how CTCs and PLs fit into the system have been discussed in Chapter One. Considerable statistical information is available regarding the licencing activity of the Medicines Division of the DHSS and its expert committees including the CSM and its predecessor the CSD. The activities are recorded in table 5.5.

Clinical trial certificates.

Trends in application rates were affected in the late 1970's by delays in licensing and apparent severity of regulations resulting in much clinical work being diverted overseas with subsequently no CTC application thus underestimating U.K. clinical research activity.

The clinical trial exemption scheme resulted from administrative problems, data collected under the CTX scheme may be more representative of research activity in the UK. However, the popularity of

Table 5.5 (a)

Year	Applications		Granted		
	CTC	PL	CTC	PL	NCEs
1964	66	-	-	-	55
1965	168	-	-	-	69
1966	203	705	174	597	66
1967	202	563	186	512	56
1968	239	552	194	475	56
1969	218	630	170	524	66
1970	178	536	155	344	69
1971(1)	172	521	123	398	na

Licensing activity of the CSD

Table 5.5 (b)

	Clinical trials certificates				Product licences				
	Applications		Granted		Applications		Granted		
	M.D	Ref'd	M.D	Ref'd	M.D	Ref'd	M.D	Ref'd	
Year	Total	to CSM	Total	to CSM	Total	to CSM	Total	to CSM	
1972	170	153	172	102	-	406	337	336	
1973	194(194)	172	179	113	514	359	312	281	(2)
1974	138(169)	131	143	130	704	418	329	277	
1975	144(139)	104	121	78	623	328	346	235	
1976	123(140)	127	108	91	762	506	326	237	
1977	97(105)	120	93	45	660	601	504	158	(3)
1978	107	108	100	30	835	589	597	113	
1979	106	62	-	48	922	180	608	81	(4)
1980	87	46	-	39	1180	167	604	63	
1981	-	46	-	27	-	159	721	70	
1982	-	7	-	2	-	182	-	60	(5)

Licensing activity of the CSM and Medicines Division (6)

Source: Annual reports of the CSD, CSM and Medicines Commission.

Notes:

(1) CSM take over from 1.9.71

(2) Figures in brackets given by J.P. Griffin

(3) CSM application data includes those carried over from previous year. All subsequent years also.

(4) New report format introduced

(5) CTX scheme started 1981

(6) The Medicines Division refers applications to the CSM for a number of reasons.

the scheme meant that many applications for exemptions would not have been submitted under the original system or tested abroad and thus there is a possibility of the figures suffering from inflation. CTX data does however include figures for the British owned companies as well as total figures. Table 5.6 gives the information for one year of operation of the scheme.

From this table, it is possible to estimate the proportion of the total activity due to the UK companies as around 18% but it would be inappropriate to use such a figure to estimate the research activity of the earlier data. CTX data are not directly comparable with earlier application figures and as the earlier data do not show the same level of disaggregation it is not possible to use such data directly in the study of the UK owned companies.

Product licences.

A problematic variable associated with the use of product licence applications as indicators is that each novel drug may have several associated product licences,one for each formulation of the drug. Since drugs may be marketed in a variety of presentation forms it would be necessary to determine all possible product licences for the drugs of interest. Data are not available by nationality of firm or by company and as a result the use of product licence application data is similarly restricted. Product licensing applications have increased over time which may be an indication of a trend toward maximum product formulation rather than an increase in new product development.

The Medicines Division of the DHSS were contacted to determine whether aggregated data for the companies of interest or indeed company data could be made available. For reasons of confidentiality the request was turned down and the only data available is as presented.

Table 5.6

Nature of applicant	Total CTX	NCEs
British owned	38	11
Foreign owned	81	28
US owned	25	2
EEC owned	40	21
European	21	6
Other	5	2
Total	210	70

Applications for exemptions from clinical trials
April 1981-March 1982

Source: Spiers and Griffin (1983) (36)

Application and grant data may be used as input and output indicators for the assessment of the activity of the regulatory authority rather than the industry. Processing times, workload and temporal changes in these criteria may be analysed using this type of data and Griffin has published research findings in this field. Regulatory stringency may also be assessed as the decline in CTC application rates was correlated with regulatory stringency as mentioned earlier, as regulations were relaxed application rates rose dramatically, more rapidly than could result from an increase in research activity.

5.1.6 Patent counts.

Patents have received more attention than any of the indicators mentioned so far but the companies concerned with the NEDO study were sceptical of their validity as indicators of innovative activity and cited methodological and theoretical problems.

The OECD, DSTI secretariat accordingly stated that, 'problems posed by the use of such data should not lead to their rejection as they are, at the moment, the only data which are available to measure output'.(4).

Having reviewed, albeit briefly, the types of intermediate output indicators available, it was evident that fundamental weaknesses existed in the availability of suitable data for the time period of interest. It was known that patent statistics, despite their associated problems, were available for a long time span and could be searched by a variety of criteria.

The use of patents as indicators has only recently received widespread attention probably because of the specialised nature of the statistical information. Again, using OECD terms, 'The analysis of these indicators requires specialised knowledge, it is difficult

even impossible to analyse with precision patent statistics or to do bibliometric analyses without the help of patent experts or scientists who are well acquainted with the field that one proposes to analyse' (5).

The above statement may explain why many studies, particularly exploratory ones have failed to come to terms with the use of patents as indicators and why they are often rejected as research tools. Given the weaknesses of other indicators and the lack of extensive studies of patenting activity in the pharmaceutical industry in the UK it was decided to review any history of research in the field. Making use of patent information within and outside the industry, an overview of the patenting process in general and for the pharmaceutical industry specifically was to be developed.

Once the theoretical background to patenting was understood the next aim was to develop a methodological approach to a patent study of the pharmaceutical industry and to determine whether the production of useable indicators was possible. If so a patenting profile of the inventive activity of the companies of interest for two decades was to be drawn up. The remainder of this chapter will review previous studies, attempt to justify the use of patents as indicators, explain the patenting process in general and, by means of interview material, describe patenting in the UK owned drug companies.

5.2 The use of patent statistics as indicators: historical perspective

Probably the best known early study using patent statistics on a large scale was that of Jacob Schmookler. His 'Invention and economic growth' published in 1966 used US patent data for a selection of industries (6). He concluded that sales of goods preceded patenting and this was used as evidence that a 'demand pull' model of economic growth had operated in the US over the period of study. This pioneering study was followed by many articles on the economics of innovation and patents were accepted as possible tools for economic analyses.

Mueller, in his 1966 investigation of the measurement of inventive activity in US industries (including chemicals and drugs), used patent statistics for the period 1962-1964. Research and development expenditure statistics and employment data for the period 1958-1960 were correlated with the patent data. For the Chemicals and Drugs sector, expenditures on applied and basic research were found to be better correlated with patents than was the development expenditure. Generally for all industry Mueller found that R&D expenditure and patents were highly correlated(7).

The chemical, drug and petroleum industries were the subjects of research by Grabowski in 1968 into the determinants of industrial R&D. The number of patents granted to ten drug firms was used as one of three output measures, the others being product sales and the number of significant inventions. Patent data was obtained for each company. His results led him to the conclusion that an increase in size of firm did not automatically lead to an increase in research intensity (8).

In 1969 Comanor and Scherer again used patent statistics in a measure of technical change in the US pharmaceutical industry. By using a limited time period they hoped to eliminate temporal variation.

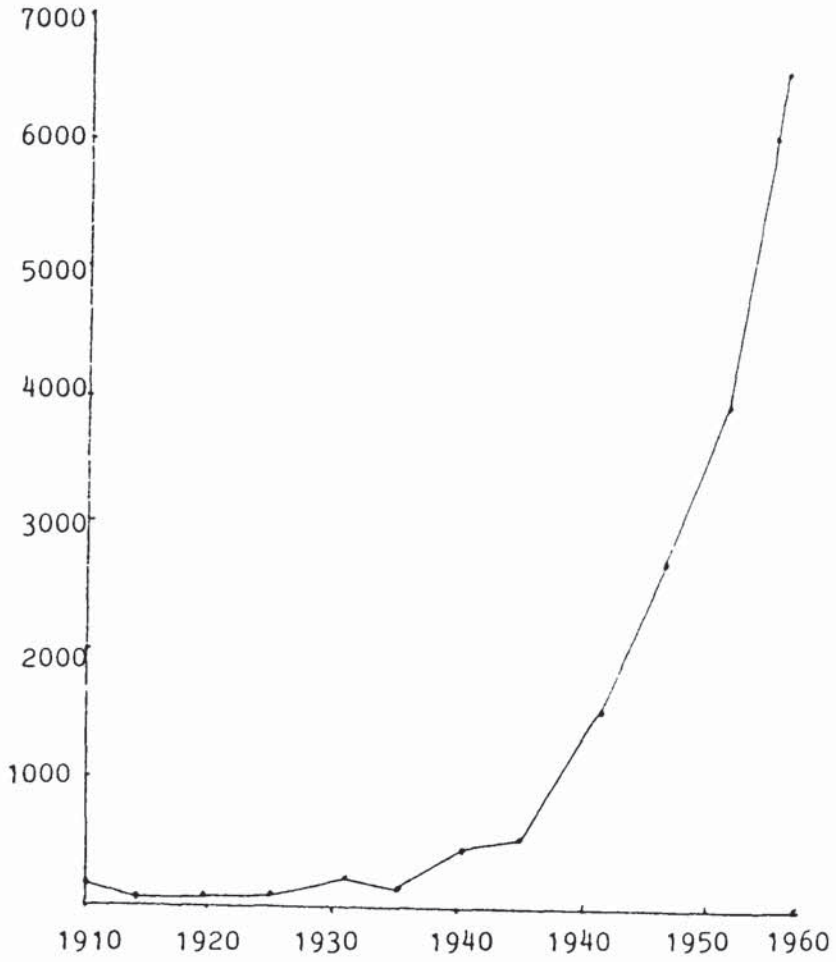
Other data used included details of NCE introductions between 1955-1960 weighted by sales, qualified R&D staff and total staff (9). Patents and new products were correlated and patent lags calculated.

The main conclusions of the above studies were that patents were a better measure of technical advance than the rate of innovation. They also indicate that patents may be a better measure of research input than research output.

The next piece of research of interest is that of Duncan Reekie in 1973. In his PhD thesis on the economics of the pharmaceutical industry (10), Reekie uses data available at the UK Patent Office for patents granted over the period 1900-1966 for 'chemico-pharmaceutical' products. Attempting to measure the technological progress of the industry using the patenting activity he proceeds to demonstrate almost exponential growth. Some doubts are expressed by Reekie over the data used but the use of patent acceptance dates rather than application dates, the classification adopted and the time period studied makes the study of limited use for the present study. A fuller critique of this work and others can be found in a paper presented to the OECD (11). Although Reekie's data is, in his own view, to be regarded with caution, it is one of the most important dealing with patenting in the UK and is a useful starting point for research. See figure 5.1.

Around this time the whole subject of science and technology indicators was becoming of importance to researchers of technological change. The US National Science Foundation began to publish the Science Indicators series, the OECD had already begun collecting data on R&D expenditure and this had been used by workers such as Freeman. One of Freeman's early studies used patents as a measure of inventive output in a series of reviews of industries including the plastics industry where patents and product output were studied (12).

Figure 5.1



U.K. Chemico-pharmaceutical patents in 5 year periods

Source: (10)

The use of patents as measures of research effort was taken further by Aries (13) who provided surveys of the international patenting activity of the pharmaceutical industry. Total international filings and the number of drug patents for a number of companies are calculated. From these data he calculates the relative number of drug patents compared with total patent applications and hence the level of pharmaceutical activity.

Returning to themes developed by earlier workers, Schwartzman in his substantial book on Innovation in the pharmaceutical industry (14), gave the results of a study testing Schumpeterian theory in the US drug industry. Patents issued to a number of US based companies between 1968 and 1970 are used as one of six broad indicators of research output in attempting to assess the economies of scale in research and the relationship between innovation and firm size.

International comparisons were the subject of a paper by Schiffel and Kitti in 1978. The concern at that time over the apparent increase in foreign patenting in the US relative to domestic applications was challenged. Studying the activities of various industries they found that other reasons could explain the increased foreign patent activity including an increase in world trade and a greater propensity for foreign companies to patent internationally generally. They concluded that studies on a more disaggregated level were necessary as a background for international studies where unforeseen technical problems occurred (15).

Two studies of particular interest to the present research were those of Withers (1977) and Nolan (1979) both being MSc theses from the City University, Centre for Information Science (16, 17). They provide substantial and useful information. Using a variety of methods

they both demonstrated a decline in patenting in the UK but increasing activity in the field of drug patenting. One important discovery by Nolan was that over 50% of patents studied which claimed a pharmaceutical composition were not classified under the Patent Office classification A5B. This classification was used by Reekie in the study mentioned above and shows the care that must be taken when extracting drug patents.

In an attempt to obtain clearer data Nolan then used a Name Index search for specific companies followed by painstaking manual retrieval of relevant patents. The aim was to collate the patents with a master set of drug products introductions obtained from the drug industry publications MIMS. She then presented data on a company basis giving counts of patents by year of publication and application. The figures are reproduced in table 5.7 Over the period of study a decline was evident in the patenting activity for Beecham, Boots, Glaxo, Allen & Hanbury and Fisons. Unfortunately, more detailed breakdowns of the patents by product, process or therapeutic significance were not conducted. This is an important point and the significance of this study to the present one was one consideration that was taken for the present study.

Table 5.7

Year	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77
A & H	-	2	1	7	4	2	4	5	1	6	8	4	5	4	-	-	-	-
	1	1	1	-	2	1	6	3	1	3	6	3	5	5	2	9	4	-
BEECHAM	29	12	3	4	12	12	17	7	13	14	21	36	22	23	7	-	-	-
	-	20	24	9	5	3	10	10	12	10	8	14	16	19	17	22	29	15
BOOTS	1	2	2	5	3	1	-	-	1	2	3	2	4	2	-	-	-	-
	-	-	4	-	2	1	5	5	-	-	-	2	1	2	2	4	2	1
FISONS	-	-	-	-	6	5	3	4	2	5	7	8	5	5	6	-	-	-
	-	-	-	-	-	-	-	1	7	3	4	3	6	4	4	8	5	7
GLAXO	5	2	5	8	3	5	4	4	12	14	16	15	9	6	2	-	-	-
	2	6	3	2	4	2	5	6	4	7	6	2	18	10	11	18	10	5

Pharmaceutical Patents by year of application and publication.

From: Nolan (1979). First line by year of application,
Second line by year of publication of the patents.
UK Patent Office Data

Other interesting calculations made by Nolan included the time delay from filing a complete patent specification to publishing which was found to have remained fairly constant over time. Time delays from patenting to marketing for each product were also found with nine years being the average but with extremes of 3.5 to 15.6 years. The percentage of patents that led to marketed products over the period were also calculated for each company and was found to be small (1.12-2.44%). This type of analysis needs to be qualified because of the initial classification of patent examined and it may be more interesting to examine the percentage of patents for each type of product that eventually lead to marketed products, eg NCE patents versus NCEs.

The problems of data extraction led Withers to adopt a computer based retrieval system. She provided data for 20 drug firms including 8 UK owned companies. Patent Office files were again used but additionally, the services of Derwent were utilized. One hundred patents per year for five years were traced for each company to determine their progress through the patent system. The rate of opposition was found to be higher for drug patents than for all patents in general. The finding that only 28% of all patents studied reached the full term of 16 years under the 1977 Patent Act has implication for those that argue for an extension of the patent term.

Data on a company basis was obtained using the Derwent Company Card Index, this being inaccurate for the period 1958/9 and 1973/4. The patent application rates for each company are reproduced in table 5.8. No general trends were seen with patenting activity being erratic. 'Lows' in patenting activity did appear to follow the introduction of a new product. Ranking of the firms by turnover and patenting activity

Table 5.8

Year of application	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
Glaxo	1	5	9	16	21	23	16	13	19	13	10	8	7	20	26	37	43	30	23	13	3
Fisons	-	-	-	-	-	1	-	3	2	6	10	15	7	12	18	13	15	11	21	15	4
Wellcome	4	3	12	22	50	37	31	30	26	24	17	15	7	14	14	26	10	22	16	14	9
Beecham	1	1	6	6	48	22	11	15	10	16	18	25	21	27	38	51	61	47	45	39	26
Boots	3	2	2	4	5	4	9	7	8	5	4	14	6	2	4	5	2	6	4	-	1
R&C	-	-	-	-	-	2	3	-	-	1	4	5	7	6	2	3	4	4	-	1	1
ICI	-	5	8	28	38	31	35	42	28	43	39	42	39	33	26	58	65	46	36	38	16

Patent applications per year from Farmdoc Company Card Index.

Source: (16)

gave a positive correlation. Her conclusion was that the 'results overall indicate that patent counting is a valid measure of innovative activity and economic effectiveness'.

Both of the above studies made an important contribution to any patent based study of the drug industry and many of the methods pioneered by the researchers were incorporated into the present study. However the emphasis and aims of the present study differed markedly from the previous ones and the retrieval methods and analysis of data will be shown to have important differences.

An 'internal' study of the drug industry by Hanna Mlodzik of Ciba Geigy in 1979 showed that the industry was interested in the use of patent statistics as a means of monitoring the technological activity of firms. Concentrating on the anti-rheumatics product area and again using the Derwent 'Farmdoc' drug patents data base, patents were considered to give an 'indication of the innovative potential of the companies' (18). Company activity was followed closely using patent statistics for the period 1963-1978 for all firms in the product area. For the first time, patent family size (all patents incorporating the main invention claimed) was suggested as an indicator of the importance of any invention. The reflection of patenting policy of the companies in the statistics was also noted.

The ideas of Schmookler reappear in a document prepared for the SSRC by Walsh et al of the Science Policy Research Unit (19). They attempted to identify the determinants of scale and direction of scientific activity in a number of industries including pharmaceuticals. A series of indicators were used including patents, scientific paper counts and more specific economic measures. The pharmaceutical industry was selected and the relationship between patent activity and the NCE introductions in the US was investigated with the conclusion that patents provided a better indication of inventive activity than innovative output. Chemical Abstracts was used as a patent database as well as a source of scientific papers. One difficulty encountered was that the classification adopted by Chemical Abstracts for drug products also includes many medical items unconnected with drugs. See fig. 5.2.

The patent data tended to be a rather broad generalisation of the actual activity in the area of NCE R&D. The pattern that emerged was one of increasing patenting and publishing activity with a corresponding decline in NCE output. This 'world' pattern for patenting and drug

Figure 5.2

World 'pharmaceutical' patents in Chemical Abstracts 1940-1976

Source: (19)

output confirms earlier studies. The problems of classification result from the adoption of a readily available database of patents which was not designed for use as an indicator source. It is evident that very serious thought should be devoted to the selection and modification of databases for such studies. Some progress towards producing acceptable patent databases for such studies has been made.

The OECD organised seminars in 1978 and 1979 on the use of input and output indicators which included the use of patent statistics. The work of the US Office of Technology Assessment and Forecasting (OTAF) was outlined by Lawson in a paper on the use of patents as output indicators (20). He gave suggested uses of patent statistics including identification of the 'actors' in the technology and tracking technologies. He also forecast improvements in the quality of patent statistics with the application of computer technology. In the same seminar the work of Pavitt at SPRU on the relationship between R&D, patenting and innovative activity was presented (21). Pavitt argued that patents and R&D statistics show different aspects of the process of industrial innovation. The study focussed on patenting and R&D comparisons between firms, industries and countries over time. He concluded that R&D data may be a better indicator of innovation in large firms whilst patent statistics were of more use in studies of smaller firms.

The theme was continued in a 1980 OECD Science and Technology Indicators Conference (STIC). In one paper, Soete, also of SPRU, explained the use of patents in International trade analyses (22). Foreign patenting was shown to be a more reliable indicator of output than domestic patenting. The use of foreign patent applications will be discussed in a later section, including the limitations of the approach. Grief (23) discussed the relationship between input and output in research

using German patent statistics. On a gross basis he argued that patenting appeared to decline as R&D effort increased.

The 1982 OECD conference continued the investigation and many papers contained research findings making use of the techniques adopted for the analysis of publication output. In the same year Prusak published an account of the economic impact of the patent system. He stated that, 'although they have limitations, patent data represents one of the best available output indicators of inventive activity' (24).

Subsequent research by Soete and Wyatt (25) into the use of foreign patenting as an internationally comparable output indicator used patenting by foreign companies in a common market, the USA. They viewed this as one step towards eliminating methodological problems associated with the use of patent statistics. These studies outline the problems faced by researchers of science and technology policy faced with a lack of objective measures of innovation. Major initiatives have been taken by the OECD and the NSF in collecting patent data and formulating comparable techniques to bridge the gap between mainstream economic measures and the range of alternative, cruder indicators.

One aim of this section was to outline the development of the use of patent statistics and to introduce the organizations and interest groups that will provide the impetus to the use of patent data in future policy studies. Many of the studies reviewed provided valuable background for the present study of the UK pharmaceutical industry. Given the wealth of data and approaches presented so far, the next stage is to determine, more specifically, how patents may be used for the purposes of this present study. Initially a justification for their use will be demonstrated followed by more detailed analysis of the patenting process.

5.3 Justification of the use of patent statistics in a study of innovative activity in the pharmaceutical industry

The use of patent statistics is linked to the importance placed on the patent system by the inventor. The extent to which the inventor makes use of the system is related to the economic benefit that the system provides and this will be reflected in the statistics. If the propensity of the inventor towards patenting is low the statistics will give a poor indication of the gross unweighted output of R&D. Many of the studies of technological changes mentioned above have justified the use of patent statistics on the grounds of unparalleled availability and coverage.

Most studies include some reference to these factors, 'the analysis of patent information remains one of the most established directly available and historically reliable methods of quantifying the output of a science and technology system' (26), 'The most readily available index of innovative activity' (27), 'most useful, systematic and complete set of information about inventive activity which is available over a long period' (28), 'Unparalleled as a source of information about technological progress in the distant and more recent past' (29), 'Unfortunately, in most instances the choice is not between patent statistics and better data but between patent statistics and no data' (30).

At this early stage, it may be opportunate to emphasise the fact that patent statistics have advantages, the drawbacks are complex and the use of patents as solitary indicators is not to be recommended if alternative indicators are available. Measures including lists of innovations where available, publication counts and so forth can and must be used in conjunction with patents. Together patents and the more traditional indicators should provide a better overall perspective of the nature of technological activity and changes in the rate and direction of that activity.

There are many criticisms of the use of patent statistics as indicators which is not surprising when one considers that patent statistics have been historically collected for legal and administrative reasons by the national patent offices and are not readily comparable to other more recent statistics of research and development such as R&D expenditure statistics collected by the OECD as possible indicators. Some recently designed patent data bases are purpose built with their use as assessment criteria implicit in their collection. Criticisms of the use of patents are in many cases justified, often, however, the criticism is due to a poor understanding of the patent system. The level of criticism also depends on the use made of the statistics. In a later section the problems associated with using patents in a study of the pharmaceutical industry will be reviewed, outlined below are some of the more general criticisms of the use of patents as indicators.

5.4 Criticisms of the use of patent statistics.

1) Firms' propensity to patent vary.
2) Industries' propensity to patent vary.
3) Variation in International patent legislation prevents International studies.
4) The economic or technical importance of each patent varies.
5) In many cases patenting may not occur eg. if:
   The invention lacks commercial application
   Trade secrets may be preferred
   Expense or difficulty with the application
   Legal problems etc Anti-trust legislation in the US.
6) Patents may be taken out for strategic purposes eg. Blocking patents
7) Patenting may occur after commercial exploitation (US)
8) Statistics only reflect the activity of the patent offices!
9) Statistics do not reflect the output of R&D, may reflect input
10) Problems may disrupt the statistics eg. wars.

Each of these points will be dealt with in turn in relation to a patent study of the pharmaceutical industry but some generalisation is possible.

With reference to the differing propensities to patent that may exist between firms and sectors, some criticism is justified. A high technology industry such as aerospace may surprisingly account for a small percentage of national patenting activity in relation to its level of research. In such cases alternative protection methods such as trade secrecy may be adopted. Some companies are in a highly monopolistic position, with specialised products which may not require patent protection. In many industries process improvements are not patented particularly if the process adopted cannot be determined from the end product. The pharmaceutical industry is seemingly in a unique position, being research-based with innovation supplying the competitive behaviour. This fact coupled with the obsessive attachment to the patent system as legal protection ensures that the propensity compared with other industries is high. One reason for this may be that the product which may have taken years to develop may be synthesised by a rival in a matter of days once a sample of the original is obtained.

The question of propensity and the interfirm variation in this behaviour is considered later but the simplistic view presented above must be analysed in more detail as there appears to be little agreement over the concept of propensity.

Variation in national patent legislation is a considerable hindrance to international studies because the patents issued, if any, are a reflection of the patent system and will contain inventions that fit or are fitted to the patentability requirements of that country. In some cases chemicals per se are not patentable, process patents may only be available. Temporal changes in patent legislation and

requirements must be studied if long term historical reviews of patenting behaviour are conducted. Many studies have taken scant account of these problems and as a result their findings must be viewed with caution. Recent changes in patent systems and a move towards harmonization will inevitably lead to more comparable data. For differences in national patent systems and the patentability requirements see Table 5.9 and figure 5.3

One of the severest criticisms concerns the unequal weighting of individual patents. The fact that some patents may reflect major inventive steps whilst others may only demonstrate minor technical improvements would appear to reduce the effectiveness of patent indicators. The economic or technical importance of individual patents is difficult to monitor unless impact studies or patent tracing studies are conducted. This problem was evidently important to Sanders (31), who stated that for patent data to be a useful indicator of inventive activity:

1. The proportion of inventive activity resulting in patented inventions must have remained invariant with time and,
2. The input per average patent must have remained similarly invariant.

These seem unlikely and are criticisms of any similar aggregate measure including well-established techniques such as counts of important inventions, qualified scientists and engineers and so forth. Statistical techniques have been employed to eliminate some of this error (32) but some error is inevitable. The problem is reduced if patents are not used in isolation, the effect of this problem on the pharmaceutical industry's output is considered later.

Some patents may be of strategical importance, the best known being the so-called 'blocking patents' taken out by a firm in order to prevent competitors entering a research field. The significance of this problem in terms of statistics is difficult to quantify unless

Table 5.9

Country	*Claims to chemical compounds generally*	*Claims to chemical compounds where a pharmaceutical*	*Claims to pharmaceutical compositions*	*Chemical process cover including pharmaceuticals*	*Novelty*
Argentina	Yes	No	No	Yes	World
Australia	Yes	Yes	Yes	Yes	Local
Austria	No	No	Yes	Yes	World
Belgium	Yes	Yes	Yes	Yes	World
Brazil	No	No	No	No	World
Bulgaria	No	No	No	Yes	Local
Canada	Yes	No	Yes*	Yes	World
Ceylon	Yes	Yes	Yes	Yes	Local
Chile	No	No	Yes	Yes	World
Colombia	No	No	No	No	Local
Czechoslovakia	No	No	Yes	Yes	Local
Denmark	Yes	No	Yes*	Yes	World
Finland	Yes	No	Yes*	Yes	World
France	Yes	Yes	Yes	Yes	World
Germany West	Yes	Yes	Yes	Yes	World
Germany East	No	No	No	Yes	Local
Greece	Yes	No	Yes	Yes	Local
Holland**	Yes	Yes	Yes	Yes	World
Hungary	No	No	No	Yes	Local
India	No	No	No	Yes	Local
Ireland	Yes	Yes	Yes	Yes	World
Israel	Yes	Yes	Yes	Yes	World
Italy	Yes	Yes	Yes	Yes	World
Japan	Yes	Yes	Yes	Yes	World
Yugoslavia	No	No	No	Yes	Local
Mexico	No	No	No	Yes†	Local
New Zealand	Yes	Yes	Yes	Yes	Local
Norway	Yes	No	Yes	Yes	World
Pakistan	Yes	No	Yes	Yes	Local
Paraguay	Yes	No	No	Yes	Local
Peru	Yes	Yes	Yes	Yes	Local
Poland	No	No	No	Yes	Local
Portugal	No	No	Yes	Yes	World
Rumania	No	No	No	Yes	Local
South Africa	Yes	Yes	Yes	Yes	World
Spain	No	No	No	Yes	World
Sweden	Yes	Yes	Yes	Yes	World
Switzerland	Yes	Yes	Yes	Yes	World
Taiwan	No	No	No	Yes	World
Turkey	Yes	No	No	Yes	Local
Uruguay	No	No	No	No	World
U.S.A.	Yes	Yes	Yes	Yes	World
U.S.S.R.	No	No	Yes*	Yes	World

*Pharmaceutical composition should possess some novelty *per se*, *e.g.* a new composition of a known pharmaceutical.

**New law.

†Inventors certificate only.

Types of claim allowable and novelty requirements

Source: (Murphy 1979) (35)

Figure 5.3

Comparison of patent systems [source:(33)]

detailed studies are done. This type of analysis was outside the scope of the present study. The fact that inventions may not be patented has been mentioned but since this seems to occur predominantly in process inventions and whenever possible these were eliminated from the present study, it was hoped that this difficulty could be avoided.

As the commercial application of an invention is difficult to assess with any accuracy at the time when the initial patent application is made the tendency is to patent at a high initial rate and allow less important inventions to lapse. Alternatively the firm may choose to patent late when more is known of the invention. The former is one argument for using patent application data whenever possible in order to assess overall inventive activity. The situation in practice is more complicated as will be demonstrated in later sections.

Application for a patent after commercial exploitation is a situation that arises in the USA due to the nature of the patent system that allows one year's grace before application is necessary. In the UK any prior disclosure of the invention will preclude subsequent application for a patent for that invention and therefore is a situation that will not arise in this study. Additionally, the long lead times for drug products makes this tendency unlikely.

If patenting activity over time is to be analysed it is important to ensure that any backlogs that have developed in the patent system at any time in the past are accounted for. This sort of problem occurred following the World Wars when few patents were issued and the resulting post-war activity shows up on temporal data. Figures 5.1 and 5.2 show such disruptions. The remaining problems are concerned with the factors that patent statistics are seen to measure. Most researchers agree that they are a reflection of the inventive activity of a company, industry or country. Others argue that they reflect innovative

output, R&D productivity, research effort, technical change or even R&D input. This disagreement may be due to the variation in the model of technological change used and how innovation and R&D fit into the model. Basic errors in understanding where patents locate into the R&D process are also obvious.

For the pharmaceutical industry the policy regarding timing of patent applications varies but it is generally agreed that patenting is one of the earliest phases of research and development. The patent portfolio of a firm will contain some key patents that relate to commercially important products and processes that can be considered innovative, also included will be many other inventions that are never utilised but are of importance to the firm in terms of experience. Patent data will therefore include inventions and subsequent innovations with alternative indicators necessary to identify this latter set.

Given all the problems outlined so far it seemed useful to present some information regarding patent systems and the type of data available. A more comprehensive understanding, it was thought, would allow a more satisfactory and accurate study of the patenting behaviour of the pharmaceutical industry and would be of use to researchers hoping to use patent data with more confidence in the future. Many of the problems given earlier seemed to be surmountable given a more detailed knowledge of the patent system.

5.5 Introduction to the use of patent data.

In order to utilise patent statistics it is essential to understand much of the background to the patent system; the philosophy and administrative aspects being particularly important. The patent system is not fundamentally a source of a science and technology indicators database but impinges on the industry in terms of the incentive to innovate that the patent system is said to provide. The patent system and the pharmaceutical industry must, therefore, take complementary positions in a study of innovation in the industry in terms of patent protection.

Patent Systems

The earliest patent law passed was that of 1474 in Venice whilst the earliest legal landmark in Britain was the Statute of Monopolies of 1624. Recent types of G.B. specifications date from 1618, with the introduction of patent specification No. 1. In the United States the patent system dates from a 1790 Act, French patenting was established in 1791. The types of systems that existed in terms of examination procedure varied with Britain taking a moderate line in severity. Another important legal landmark was the 1883 Paris Convention which had the futuristic aim of establishing an 'International' patent. This trend is evident in many legislative changes and is presently embodied in the European patent system and the Patent Co-operation Treaty.

A patent is a document that provides the applicant with a degree of monopoly power to 'work' an invention and recoup the investment made in bringing the invention to the commercial arena.

The degree of protection conferred on the invention can vary from country to country and even with time in any one country due to changes in patent law. The most useful patent system to review in the context of this research being the British one. In 1916 the Parker Committee

in their study of the system advocated the restriction of patent protection to methods of production or manufacture and the product when so made eg. process and product by process cover. This was made law in the Patent Act of 1919 thus revoking the protection of products per se for chemical inventions that had existed previously. It was not until the Swan Committee of 1944-47 until the restoration of patentability of products per se was achieved, with surprisingly little opposition.

In order to summarise the differences between national patent systems it is necessary to consider the following criteria:

1) Patentability of subject matter

2) Criteria for novelty

3) Type of examination used

4) Sanctions for the abuse of monopoly

As already stated, patentability can include products, processes, product by process or pharmaceutical uses depending on the patent system. This is important because the number and quality of patent applications will to a large extent depend upon what can be claimed.

When undertaking a temporal study any changes in the nature of the patent protection must be considered. Fortunately in the UK the only main changes in recent times occurred with the introduction of the 1977 Patent Act. Patents applied for under the old 1949 Act cover a satisfactory time period for an examination of the recent activity of the drug industry. The policy regarding foreign patent applications although not vital in a study confined to the UK apart from estimating the importance of individual patents will be determined as a result of commercial criteria and the degree of protection offered. If international studies are to be attempted, these problems must be taken into account. An example of a case where these problems were not identified occurred in the US in relation to the Drug Regulation Reform Act of 1978

where decisions were made using data on the patent protection offered by a number of countries some 6 years prior to the debate and which had in the meantime changed, thus altering the significance of the proposed Act. The subject of differences in patent systems is adequately covered in the publications of Jucker (33), Kemp (34) and Murphy (35).

The signing of the European Patent Convention in October 1973 by 16 States has led to a unification of criteria regarding patentability, patent term and examination procedure. The use of the new patent data resulting from applications made under the recent system is to be expected.

Basically the two extreme types of examination system that can operate are one in which the granting of applications is almost automatic with little or no formal examination resulting in weak patents or one in which the application undergoes a substantial referred type of examination for novelty, obviousness and inventiveness resulting in much stronger patents. The European Patent System includes such a substantive search and is preferred by the pharmaceutical industry due to the strong, highly defendable patents that result.

Patent families ie, groups of equivalent patents filed in different countries will often have as a 'basic' or first published,a patent originating in a country that operates a simple registration type examination system eg. Belgium, Netherlands or Denmark.

If a patent study is confined to one country then these problems are manageable. This study attempts to concentrate on extracting patents granted to the seven major UK owned research based pharmaceutical companies, namely Beecham, Boots, Fisons, Glaxo (and Allen and Hanbury), ICI, Reckitt and Colman and Wellcome. The availability of patent data for pharmaceutical products in general as well as the more specific company information will be reviewed in the next chapter.

5.6 Patenting policy in the pharmaceutical industry

5.6.1 Introduction and approach

One of the major criticisms of using patent data was that individual patents may protect inventions of varying commercial importance and to allow for this, some weighting system was needed. It was also argued that patenting policy varies between industries and also within any one industry. Some firms and industries were thought to patent all inventions with little apparent concern for the significance of the invention whilst other firms and industries were more selective, patenting only those inventions that were potentially of commercial or industrial importance. This variation would not be accounted for if aggregate patent data was used and it seemed important to determine the behaviour of the pharmaceutical industry prior to the use of patent statistics on any scale.

A further factor for consideration was the assessment of the timing of patenting in the R&D process. Patents were thought to give a reasonable indication of project initiation. Furthermore, it was hoped that a more comprehensive understanding of the patenting process in general and in the pharmaceutical industry specifically would allow a more successful methodological approach to any subsequent patent search to be developed.

Following the advice of the OECD described earlier, it was decided to conduct a series of interviews with staff of the patent departments of the U.K. owned pharmaceutical companies. Initially, all companies were contacted with a view to obtaining permission to interview patent staff. No response was forthcoming from Boots or Reckitt and Colman, Glaxo gave a written reply to a series of questions but the remaining companies agreed to be interviewed.

Interviews were conducted with patent managers (36) at company sites, they were asked a series of questions ranging from general industry and company policy to specific details of patenting behaviour. From the replies a draft of this section was written and circulated to the interviewees for comment. Alterations, mainly on points of clarity and emphasis were made and the section rewritten and re-circulated.

Patenting activity is a complex activity and the following account somewhat arbitrarily divides up the process into logical stages allowing inter-company comparisons to be made. Inter-industry variation was not considered in depth, being outside the remit of the study, as was any major attempt at international comparison. The account begins with a review of the organisation and location of the patenting department within the R&D process.

5.6.2 The company patent department

Patent departments in all firms have a similar role, what does vary is the relationship of the patent department to other departments as well as some organizational and policy characteristics. Some firms adopt a rigid patent policy whilst others are more flexible in their approach. One consensus was that a close relationship between the patent and research departments was essential for innovation. Personal relationships were often established between staff from both departments on an informal basis and Fisons emphasised the valuable assistance given to the patenting process by a research manager who understood the requirements of the patent department and was aware of any likely problems. Wellcome staff found that personal contacts made sure that the patent department was aware of any prospective activity in all research areas.

The linking of the two departments was in some instances a more formal affair. Two companies adopting this approach were Beecham and ICI. In the words of the patents controller at Beecham:-

> 'Beecham adopts a system whereby the patent department runs very much in parallel with research and the project basis on which research is organised is mirrored in the organisation of the patent department. Accordingly, the three main groups of related research projects have led to the setting up of three distinct groups within the patent department to handle this work. In this way the patent agents in the department have been able to build up considerable expertise in certain project areas'.

Previously a less structured approach was adopted and found to be less efficient.

At ICI the structure is similar with the department split up into disease areas with patent agents responsible for each area. Each agent deals with the processing of foreign applications for his project area with no outside agents used whenever possible. All the patent agents are ex PhD chemists and are encouraged to maintain close links

with the research departments. Interestingly a role in stimulating innovation was attributed to the patent department by one spokesman who argued that suggestions for likely 'leads' into research areas are gleaned from searches of the patent literature. These close links between departments would seem to indicate that the flow of inventions from research to patenting is unimpeded and that whenever possible an invention will be made available for patenting at a very early stage in its life.

If the research department is seen as a source of inventions then the patent department must be the earliest point outside research at which the rate and direction of inventive activity can be monitored. The process by which inventions are selected is complex but results in a reduced quantity of inventions passing on to the next stage. The role of the patent department in deciding whether to continue the processing of a drug has three main stages: application for initial or priority application, proceeding from an initial application and the foreign filing stage. These decision points will be considered in turn.

5.6.3 Priority application stage

There are inter-firm variations in the process of patent application. The initial suggestion that an invention is patentable can come from several sources. Fisons encourage research staff to approach the patent manager with ideas. At this stage no senior research staff may be involved for reasons of speed. Applications may then be initiated if the invention is thought to have commercial significance. A patents committee is involved, consisting of a senior pharmacist, biologist, chemist and other research and commercial department staff. In this way selection of likely inventions fulfilling the requirements of the committee then takes place.

Wellcome adopt a system of sending copies of routine R&D reports to the patent staff. The reports are then scrutinised for possible patent applications. An internal, patent department, committee then undertakes a general review and if any of the candidates proves interesting, help is sought from commercial and technical staff. A consensus decision-making process is used to select applications. A full time patents committee had been tried but was found to be uneconomic due to the necessarily large number of individuals needed to deal with all the various project areas.

Beecham has adopted a comprehensive patent policy and they summarise it thus:

> 'In Beecham, the close working relationship between the patent agents and the research projects ensures that the patent department is made aware of inventions almost as soon as they are made; in the majority of cases no formal application being necessary. Normally, a priority application will follow as a matter of course provided the invention is of interest, no formal decision-making body being involved in view of the minimal expense involved'.

They continue:

> 'On the other hand, when the invention is considered for foreign filing it is then closely scrutinised in view of the considerable expense of foreign filing'.

> At ICI the process can be more complex in certain situations:

> 'At ICI although patents are obtained in the name of the company each Division is autonomous and extent of filing for an invention is determined after consultation with technical and commercial departments. In the event that an invention may be of use to more than one Division, eg. fungicidal products for agricultural and pharmaceutical uses, the procedure may be more complicated as each Division's interest has to be accommodated.'

Therefore for technical and commercial reasons only a percentage of initial output of the research department will result in patent applications. This percentage may vary from firm to firm, the minimum 'standard' at which the invention becomes worthy of patenting can vary. There did not appear to be any consensus of the term 'propensity to patent'.

Generally, however, the firms interviewed were of the opinion that Beecham, Wellcome and Fisons were of a high propensity whilst Boots and Reckitt and Colman were lower. Some foreign firms, notably Squibb and Sandoz were thought to be of the highest propensity. This was taken to mean that these firms were more likely to patent inventions irrespective of the commercial significance. It is important to distinguish between the tendency to patent many inventions and the tendency to patent many of the possible inventions. A high research output does not necessarily indicate a high patenting propensity. A further important consideration is the timing of the patent application.

5.6.4 Timing of patent applications

The most important factor here is that the application for an invention must be filed before novelty is destroyed. This may result from publication of research findings in scientific journals or by third party patenting. Patents with priority dates as early as possible in the invention's life are often required. The timing of the initial patent application often depends on what one manager called 'the fear factor', this can be thought of as the degree of external pressure placed on the company. Pressure can take the form of known competition in the research area, in a 'hot' field of research where the pressure to patent early is greatest a company may be forced to apply for a patent very early in the product life cycle, well before the technical feasibility is determined. If the compound discovered is technically close to that of a competitor, further applications may be made in areas of overlapping technology. In a new field the pressure from competitors is reduced and the application may be delayed.

The policy of Wellcome illustrates the criteria used in the decision making process. Three main factors are considered, the application is delayed for as long as possible in order to extend subsequent patent life and in order to increase knowledge of the invention. There are limits to the delay that is possible, for example no product should leave the research laboratory for external testing until adequate legal protection has been obtained. Secondly, filing in active areas is accomplished with some haste and this is the other extreme, usually however, applications fall between these extremes. The patent is seen by Wellcome as an 'insurance policy not an absolute control' and each patent is viewed as an 'island'. Wellcome consider that they tend to file later than most companies for reasons of maintaining secrecy as long as possible. A patent will, of necessity, reveal a certain amount of information regarding the area of interest of a company. If the patent is demonstrating a piece of unique research it may allow a competitor entry to a field in which they are not as technically advanced. If on the other hand the patent illustrates a 'failed' research area this will also be recognised by competitors.

Beecham, in general, take an alternative view and tend to file as early as possible in the product life cycle with the application costs for patents at this stage considered minimal compared to the protection offered. They state that:

> 'One possible disadvantage is that the earlier an application is filed, the less relevant information it may contain, although the company has devised ways of minimising this disadvantage. Moreover on the basis of the company's extensive litigation experience, it is felt that this disadvantage is completely overshadowed by the advantage of early filing' .

This then appears to be a case for the use of patent statistics other than just those dealing with national application data on a company basis. The problems of differing company policy and variation in time

of filing are reduced as elimination of the less significant inventions takes place. In the case of a company with a high propensity the application data will give a good indication of the total output from research.

In summary it is obvious that products that are considered to be of significance will result in complete patents in all firms and it is the process by which these are obtained that will be considered next.

5.6.5 Decisions made after filing a priority application

These decisions are broadly of two types, firstly a decision to proceed from a priority to a complete application for a GB patent and secondly a decision to apply for foreign cover for the invention. Other options do exist including abandonment where there is no further commercial interest in the invention and secondly re-filing at a later date if the invention is not at a stage where a decision can be made with accuracy. Both main decisions must be made at about the same time, within twelve months of filing priority in the UK.

Selection of the priority applications that are deemed to be of significant commercial importance occurs at regular intervals after initial application, usually after 8-9 months. The research departments may be questioned concerning the progress made by an invention and depending on the status report the decision to abandon or proceed will be made. Each patent is usually considered in turn, the review may involve a patent committee and it is usual for the commercial department to be involved. Even in the case of a patent that has been granted, constant reviewing of the patent is necessary to ensure that patent fees are not being allocated to patents that are redundant. At this stage the total number of inventions carried over from each year will decrease.

At the foreign filing stage the applications are heavily scrutinised due to the high costs of international protection. Companies considered it to be vital to obtain patent protection in as many countries as deemed necessary by the type and importance of the invention claimed. Protection in the UK alone was not seen as satisfactory and the usual minimum cover for any invention of significance would include all major developed countries.

Decisions regarding the countries in which to file applications were again made on an individual patent basis using a similar decision making structure. Fisons utilise the services of a commercial manager who decides on the basis of present or estimated future significance of the invention in the countries of interest. Considerations taken into account included legal and technical factors including whether patent protection could be obtained and whether enough was known of the invention to obtain adequate cover.

The choice of countries in which to claim protection is risky at this stage due to the limited knowledge of the invention. Fisons' staff used a list of countries arranged by disease area. For example, if the compound has a likely use in the treatment of malaria, the lists would indicate the areas where the disease was prevalent and protection would be sought in these areas. This system is satisfactory if the invention falls within any known field of interest but for unexpected inventions this may be inappropriate.

Wellcome staff agreed with the proposition that the minimum cover for a useful invention should include Britain, USA, France, West Germany and Japan but should also take into account the countries where major manufacturing of the product could take place. The likelihood of copying in areas including Israel, Korea, Taiwan and the

Latin American states meant that any product with anticipated sales in excess of £10 million per annum should be covered in these areas whenever possible. This should be borne in mind when attempting to assess the importance of future drugs using patent literature and their weighting of importance. Apparently, some firms outside the UK use rankings of importance and decide on the extent of foreign cover depending on the invention's score. Problems arise in areas where patent protection offered by Patent Laws may be weak or non-existant.

Beecham staff select on the basis of three main criteria for their eighty or so foreign patent decisions per annum. Firstly, notice was taken of the importance of the market for the product, secondly an assessment of the type of protection offered by the countries in which the markets occurred and thirdly an estimation of the threat posed by that country's domestic drug industry. These decisions are important as they have to be taken early in the product life cycle (10 months for ICI) and with foreign protection for a NCE estimated at £20,000 in fees alone.

At Beecham:

> 'a general policy has been established in consultation with all of the commercial Divisions which takes into account all of the above criteria and against which, candidates for foreign filing are considered. It has been found that this approach considerably simplifies the decision to foreign file and yet assures that the decisions that are taken reflect current commercial thinking without the need to refer each case to the commercial Divisions'.

ICI generally filed in all the developed countries and then more selectively in other countries. Disease lists were not used as they considered that a disease may develop in an area where there was no previous significant incidence. An example given was that of gastric ulcers developing in areas in response to dietary changes. The long product development time of a drug they considered necessitated

thinking along these lines. Foreign filing is a useful point of analysis at which inventions considered to be of future commercial or technical benefit to the company gain international legal protection. A flow diagram of the traditional patenting process is summarised in figure 5.4.

5.6.6 Recent changes to the patent system

Certain aspects of the foreign filing process have changed with the recent introduction of new patent systems. The two most significant being the system developed by the European Patent Office (EPO) and the Patent Cooperation Treaty (PCT). The extent to which the pharmaceutical industry has adopted these new approaches and the impact that they have had on the patenting policy of the firms of interest was investigated.

The significance of the new systems, it was proposed, would cause fluctuations in patent output statistics and make collation of data more difficult. The PCT system was unanimously viewed by patent managers as unacceptable for general use in the industry. The major criticisms concerned the excessive costs and complexity of the PCT system. This route, they considered, was only acceptable when protection for an invention was sought 'late in the day' and where a decision to file an application was made on the basis of the advantage of rapid registration via the U.K. Patent Office. Additionally, most firms agreed that the PCT route was of more use to the 'small inventor'.

Figure 5.4

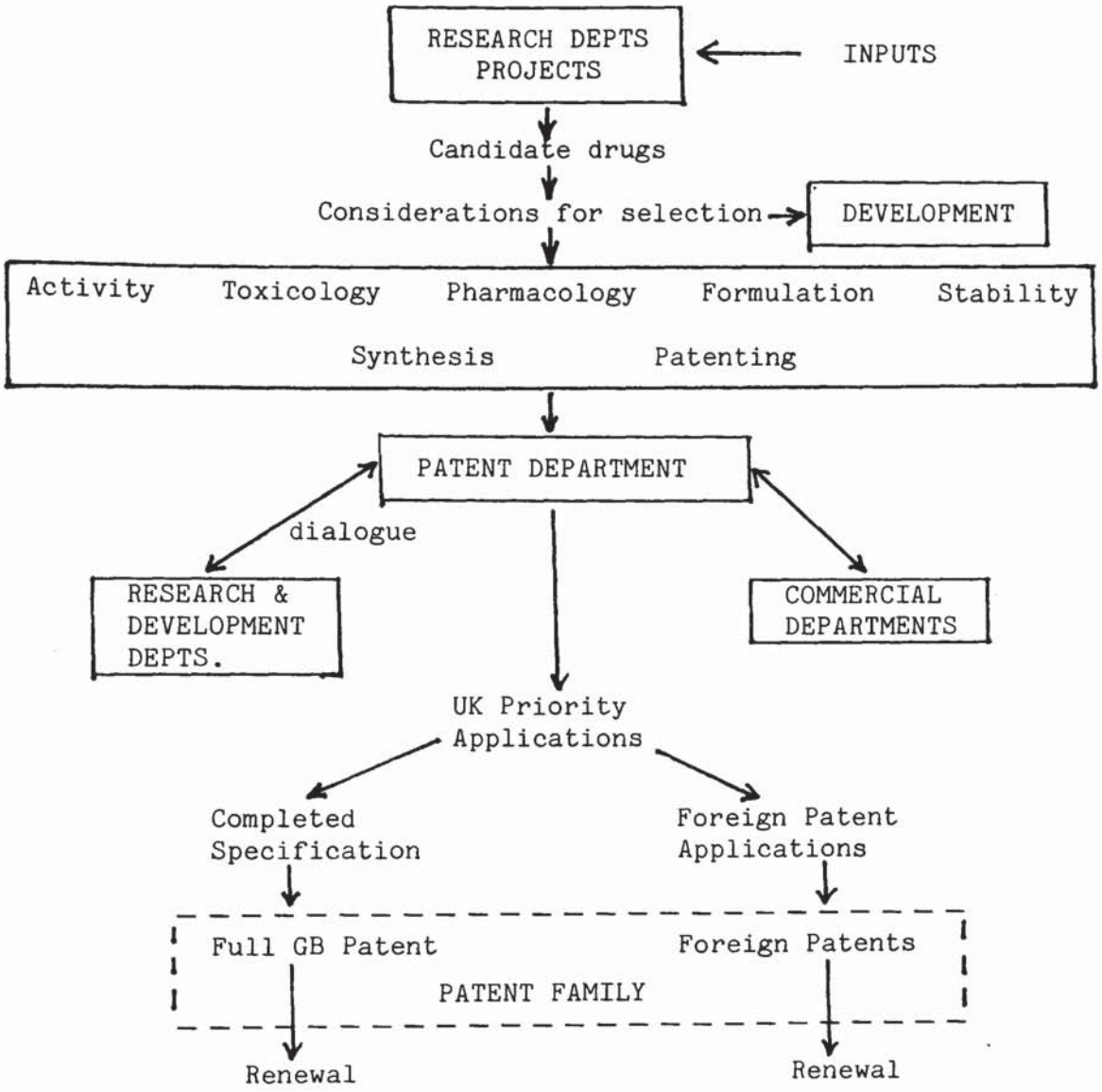


DIAGRAM OF THE PATENTING PROCESS

The EPO route was deemed as acceptable by all interviewed with most managers stating that considerable use had been made of the route since its introduction in June 1978. The advantages of the EP route were in terms of easier administration, reduced overall costs if filing applications in more than 3 countries and finally, delayed translation costs. Staff in some firms eg. ICI, referred to an initial reluctance to depend solely on the EP route with Britain as a designated state and for this period they filed British applications in conjunction with or instead of designating Britain within a European patent. As no serious problems arose this procedure was largely dropped but Fisons' staff believed that patents granted following national applications in Italy, Sweden, Luxembourg, Belgium and France were stronger than those included as designated states within a EP.

In some former colonial states the reluctance to accept the GB designation as a British patent meant that the usual automatic protection of British patents was not provided. This resulted in the need to file a normal national patent in order to claim protection in these states. Recent changes in the constitutions of the states in question have been implemented and partly clarified the problem. A further reason for retaining the British application was cited, due to the necessity to file such an application in order to claim priority for a substantive application. Most UK drug companies in the present study will file priority in the UK as a matter of course.

The above demonstration of the importance placed on the new European Patent route means that any future study utilising patent statistics must take these changes into account and make use of European literature.

5.6.7. General policy considerations

One interesting point relevant to the use of patent statistics concerns the number of patents that arise from the discovery of a novel chemical entity. The use of aggregate patent data does not allow for there to be any variation in the patent coverage between inventions. It would also be useful to be able to identify the patent that first claims the invention of interest. Some progress was made in answering these questions.

Ideally a NCE will have only one patent protecting it, this is, however, not the usual case and most drugs will have a number of patents protecting various aspects of the invention. In the case of an improved production method being developed for a product, it will be necessary to obtain legal protection for this process. For incremental process improvements, industrial secrecy is preferred. Some defensive patenting takes place, particularly in the case of intermediate products in order to establish a priority date. With the introduction of the 'whole contents' approach in recent times, this reason has become redundant. Blocking patents may also be used but the staff interviewed were reluctant to discuss such matters.

As a general guideline the 1:1 NCE:patent relationship will exist unless any of the following need legal protection:

Selection patents; new leads out of an early general patent
New processes
New presentation
Intermediates

A number of process patents may be generated around the time of a new drug launch.

In order to test the accuracy of patent numbers given for drugs in such sources as the Merck Index, the firms interviewed were asked to check these numbers for substantive claims. The replies received

indicated that, often, the numbers published referred to minor process patents and few were product patents for the drug of interest. This data was used in later analyses of patent output.

5.7 Conclusions

Many prospective intermediate output indicators for use in a study of the pharmaceutical industry have been reviewed and most are unavailable in the disaggregated form required. Those cited by industry as useful are only available within industry. The number of screening tests performed, counts of product candidates and scientific papers are cases in point. Animal experimentation statistics are a useful background indicator. Licensing information, if available in a consistent and disaggregated form would make an important contribution to any analysis of the industry. Patenting statistics remain as one of the few indicators available over the required time period and in the required disaggregated form. These factors, together with the weaknesses in alternative indicators, provides a justification for their use.

Studies using patents indicate the diverse uses made of such output data. Patents have been used as indicators of technical change, innovative activity, innovative potential and inventive activity. More detailed studies may indicate that patents may be of more use instudies of innovation in small firms with other indicators used for large firms. However, the use of patents in isolation is not recommended.

Criticisms of the use of patent statistics are described, particularly the possible variation in propensity, weighting of inventions and disagreement over what patent data can measure. This problem will be addressed in later chapters, using correlations.

Since patents are seen as important indicators the need for a fuller understanding of their background and use is paramount. A summary of the history of patent systems provides some of the necessary background to any patent study. Variation in national patent systems is emphasised, this being important if international patent analyses are attempted or foreign patenting information used. Patenting in the pharmaceutical industry is considered in some detail given the importance of patents as indicators and the significance of patenting as part of the drug innovation process.

The review of patenting in the pharmaceutical industry illustrates the variation in the process of patenting of inventions. Differences in propensity to patent may result from internal patent policy regarding the timing of patent applications, the involvement of other departments and external pressure due to competition.

Late or early filing habits of a company are only significant when data on patent applications are needed. At this stage the policy of the company regarding timing must be understood in order to assess inter-firm variation. A high propensity may mean that the quality and commercial significance of the total research output is high. This is, however, unlikely to be the case in most companies. The lack of empirical data necessary to establish the actual propensity of any firm necessitates the use of subjective measures. The confusion of propensity with research output needs to be clarified.

Propensity becomes less of a problem during the later stages of the patenting process as the elimination of those patented inventions that are found to have low or unsatisfactory commercial status takes place. If one assumes that this occurs in a similar way for all

the companies of interest, then we may infer that at least the non-important patented inventions may have been generally removed by the foreign filing stage. A case may be made therefore for the use of statistics of patents issued to each company.

Some idea of the relative importance of each patent could be gained from an investigation of the scope and magnitude of foreign patent applications for any one invention. The patent departments can be thought of a filter through which only those inventions that at that time are regarded by that company as being of important can pass.

Certain aspects of patenting policy are due to the nature of the invention, for example, the nature of competition in the field. Other policies may be specific to the firm, for example, the late or early filing behaviour. See the summary in table 5.10.

It is possible to identify three specific stages at which the patenting activity of a company can be monitored;

1. The priority application stage
2. The grant of a G.B. patent
3. Foreign application stage

Changes in patent laws have complicated the searching procedures for patent information and these changes need to be understood if patent statistics are to be used effectively in innovation studies.

The methodologies that are available to obtain patent data are considered in the next chapter. If full attention is given to the factors considered above the analysis of patent data becomes more meaningful.

The variation in patenting activity and policy outlined for the companies interviewed illustrates the care that must be taken in making any generalisations from aggregate patent data.

Table 5.10

Company	Timing of applications	'Propensity' to patent
Beecham	Early	High
Boots	-	Low
Fisons	Early	High
Glaxo	Late	-
ICI	Early	-
Wellcome	Late	High
R & C	-	Low

Summary of patenting policy in the U.K. companies

CHAPTER SIX : SEARCHING FOR PHARMACEUTICAL PATENTS

Initial sections of this chapter will outline the availability of patent statistics in the U.K. and will be applicable to any patent-orientated study. The sources of information regarding patents broadly divide into 'Official' and 'Non-official' sources. Official sources can be considered as those provided by national Patent Offices while the non-official sources include the relatively recent commercial sources. Both types of source may be manually or computer searchable. This study will consider examples from both types of source.

6.1.1 Official sources of patent documentation

The Patent Office, London is responsible for the administration of patent law and handles all patent applications and enquiries. Patent documentation is complex with certain documents produced for Patent Office internal use and some for public use as required by law. As well as published patent specifications, any invention may be located by means of Indexes, Journals and abridgements or abstracts. Each of these sources will be dealt with in turn, with an indication given of the nature of information provided in each case.

The documentation of the patent system covers an extensive time period and is therefore ideal for temporal studies. Some changes in the type and timing of patent publications occurred with the introduction of the 1977 Patent Act. The searches depend to a great extent on the classification schemes available for searching. Classification schemes adopted by the Patent Office have altered over time and this factor as well as general patent classification will be considered next.

6.1.2 Patent classification

The most important step in deciding whether to proceed with the use of patent statistics on an industry basis is determining whether the

inventive output of the industry can be correlated with its patents. The suitability of patent classifications for industrial searching is hindered by the fact that classifications are not provided for the benefit of external searchers but mainly for the use by Patent Office staff when searching in order to determine the novelty and prior art aspects of a new patent application (1).

Therefore if anything other than gross national patenting data is sought, the selection of appropriate classification from which to extract data must be a compromise between what is required by the researcher and what is provided by the Patent Office. This limitation is unavoidable but can and should be reduced whenever possible.

When searching for patents the two main classification schemes generally used are the U.K. domestic classification and the International Patent Classification (IPC). The US has its own scheme which may be used when extracting or cross referencing US patents. Since 1963 the U.K. classification had been moving towards a scheme in line with the IPC and as a result of the 1977 Patent Act, the two schemes have become very similar.

Subject matter fields are identified as Headings in the U.K. system, there are over 400 such headings which are grouped into 40 Divisions. The Classification Key is divided into 25 units for the purposes of abstraction, these units are divided out of eight main sections A to H which also correspond to IPC Sections. The classification outlined so far is summarised in figure 6.1. The Classification Key is revised every 50,000 patent specifications, a point that must be recognised in any temporal study using patents and earlier editions consulted if necessary.

Figure 6.1

Classification level	U.K.	IPC (WIPO)
First	Sections A-H (8)	Sections A-H (8)
Second	Divisions (40)	Sub-sections (20)
Third	Headings (400+)	Classes (116)
Fourth	Sub-divisions	Sub-classes (614)
Fifth	----	Main groups (5000)
Sixth	----	Sub-groups (46000)

Classification levels

Source: (6)

U.K. Classification Scheme	International Classification
Section A: Human necessities	Section A: Human necessities
Division A5: Medicine, surgery pesticides and fire fighting	Class A61: Medical and veterinary science, hygiene.
Heading A5B: Pharmaceutical preparations etc.	Sub-class A61K: Preparations for medical, dental or toilet purposes
Heading C2C: Organic compounds	
Sub-divisions C2C801 etc.	Main group 31/00: Medical preparations containing organic active ingredients.

Classification of pharmaceuticals etc.

U.K. Classification	International Classification
A5B	A61J, A61K
C2A	C07G, C12D
C2B	C07F
C2C	C07B , C07C, C07D, C07G, C07H
C2J	C07F C11C, C12P
C2P	C07F, C07H
C2S	C08B, C13K
C2U	C07J
C2V	C07C, C07D, C07G, C07H, C12P

Patent Classification Concordance

Patent Classification

The Catchword section of the Reference Index allows one possibility to assess the availability of relevant headings under which to search for pharmaceutical patents. A direct approach to the Classification Key is an alternative. Catchwords such as 'drugs', 'pharmaceuticals', 'compositions' and 'medical' lead directly to the classification A5B with occasional reference to C2C. These were the classes used by Reekie and Nolan in the previously mentioned studies. It is preferrable to use several synonymous catchwords to cover all possibilities.

This approach results in a table of possible Headings and Sub-divisions which should theoretically contain all patents relating to new pharmaceutical inventions. The next difficulty is finding a means of collecting the data on an annual basis under these headings. The following options are available.

1. Abridgements
2. Official Journal
3. Name Indexes
4. File lists

6.2 Sources of official patent statistics

6.2.1 Abridgements

The abridgements contain a standard number of patent specifications (25,000 per volume since 1974) and are arranged in 25 Units depending on the classification. Unit 3 contains A5-A6, Unit 11 contains C2. Each Unit contains a subject matter index with Sub-division codemarks, a name index to applicants and a list of abridgements by numerical patent number. The Sub-divisions can be examined and the number of patents per volume under any classification extracted. This is a laborious process but relatively straightforward. Searches by name of applicant are also possible using the Abridgement volumes.

6.2.2 Official Journal

The Journal is a weekly Patent Office publication and contains lists of applicants, their applications and complete specifications published listed in order of serial number, application number, applicant's name and subject matter heading. Again, it is possible to search for the number of patents in each Journal issued and attempt to relate this figure to an annual total. This again is a time consuming process having to search each weekly issue manually for data.

6.2.3 Name Index to Complete Specifications

This Index lists patents granted by name in alphabetical order of applicant. Each Index contains 20-25000 specifications according to the year. Each volume contains the patent specifications for 7-12 months and is therefore more convenient to use than weekly Journals. Subject matter searches are not possible using this method, this results in difficulties if the company of interest has industrial activities outside the scope of the research. This is obviously the case for some UK owned drug firms with wide range of business interests such as ICI.

In order to assess the feasibility of using Name Index searching in the present research, searches were conducted for all companies of interest for the period 1960-1970. This fulfilled a further role in providing data for a period not covered by later search methods. Data generated could be compared with alternative samples from other sources. In the Name Index a short title is given for each specification as well as the name of the inventor. In recent volumes the patent classification assigned is also included. A preliminary search was conducted for Beecham, the results were published (2) and are presented in figure 6.5

6.2.4 File Lists

These are lists of specifications assigned to a particular coded term or combinations of terms in the classification. The data is held on computer at the Patent Office and forms the basis of subject matter searches. Lists of patents classified under certain codes can be purchased from the Patent Office and are relatively inexpensive. They are used by patent staff as alerting information or as a means of ascertaining the novelty of an invention before application for a patent. The most current edition of the Classification Key is used for the searches. This method was used for checking the patenting activity of the drug industry in general at the UK Office. The search itself will be discussed later.

From the above sources it is possible to conduct two main search types using official Patent Office data,

a) a search by inventor or applicant or in this case, company or firm

b) a search of subject matter.

Problems arise when both are required together ie, a specific subject matter search involving known applicants. This was necessary in order to conduct an analysis of the patenting activity for novel chemicals in the UK owned companies of interest.

The use of raw subject matter application statistics is not satisfactory since this will include applications made for British patents by all firms irrespective of nationality. To determine the patenting activity of the limited number of companies that make up the UK owned sector of the pharmaceutical industry requires a 'bottom-up' approach using data for each company. As an illustration of the number of patents involved in the study prior to extraction of the relevant data, the number of patents in relevant subject matter areas are given in Table 6.1

Table 6.1

YEAR	A5	C2	A5B
1957	367	1608/265	207
1958	349	1608/214	183
1959	412	1710/323	256
1960	445	1968/42	403
1961	427	2211/379	558
1962	478	2204/372	328
1963	340	2427	290
1964	565	2718	308
1965	576	2883	375
1966	745	3049	412
1967	807	3606	490
1968	693	3005	479
1969	667	3013	481
1970	729	3216	525
1971	805	3180	503
1972	941	3329	559
1973	887	3189	553
1974	785	3012	503
1975	872	3260	538
1976	1093	3236	610
1977	940	2818	-
1978	995	2948	-
1979	1064	2810	-
1980	1243	2951	-
1981	1290	2675	-

Complete Specifications Accepted/Published by the Patent Office

For 1957-1962 the two figures show the number of patents classified under the primary and subsidiary subject.

Source: Annual Reports of the Comptroller General of Patents, (HMSO, London.)

A5B data from Withers (1977)

Having completed preparatory studies of the various search possibilities a number of searches using these methods were conducted. The first approach made use of the File Lists available from the Patent Office.

6.3 Method 1: File List searches for pharmaceutical patents

Patent Office literature includes a recommendation that, 'It is essential to express as precisely as possible, the technical subject to be searched for' (3). Four separate series of File List are available from the Office according to the searcher's requirements.

Series A: 1911-1965 (up to specification No. 1,000,000)

Series B: Specification No. 1,000,000 to present.

Series C: As for Series B but with Series A for some Headings.

Series D: For combination searches using algebraeic expressions.

Series A Lists use the 1965 Edition of the Classification Key whilst the others use the most recent Edition available.

A visit to the classification section of the Patent Office revealed weaknesses in previous assumptions. The heading A5B used by previous researchers was found to contain pharmaceutical chemicals in formulations, fulfilling known functions as well as novel chemicals. Some indication of this problem was given by Nolan who found that many chemical patents were not included under A5B. The Heading C2C, 'organic chemicals' contains novel chemicals in general and has sub-divisions for therapeutic chemicals. This type of sub-division was the most likely to contain patents for novel drugs.

As a search procedure it was decided to search a limited number of specific code marks to test the retrieval of relevant patents. In order to determine how many patents were classified as novel chemicals of a

specific type, having a therapeutic use, the C2C Heading was used. A set of code marks was chosen from the options available, see table 6.2. The figures in brackets refer to the number of patents classified with that code mark under the present edition of the Key. The final search profile adopted is given in table 6.3. The search included all organic chemicals with a therapeutic use as well as more specific classes including steroids, antibiotics and phosphorus containing compounds with a therapeutic use. The search profile was constructed with the assistance of the member of the Patent Office staff with responsibility for classification of drug patents. Excluded from the search were vitamins, organometallic compounds, organoboron and inorganic compounds as these were outside the field of interest.

Once identified, File Lists containing the patents classified with these marks were ordered. The Lists contained patent specifications in numerical order from 1965 to 1981. As expected, some patents had been assigned more than one of the code marks. Lists also contained patents granted under the European patent system as well as those granted under the 1977 Patent Act. Therefore the data for the most recent period is complex.

Analysis of the codings presented little difficulty with the exception of the C2C Heading and its associated C790 code mark. It was evident that this mark was producing a high number of patents. It was recommended that it would be cheaper to search the C790 mark manually using the Abridgement volumes. Additionally, the C790 mark was replaced in 1979 by two codes namely C801 and C802. The mark C790 included patents with a 'use as a pharmaceutical of a novel organic compound'. C801 includes 'novel organic compounds having antibiotic activity' and C802 includes, 'novel organic compounds having other activity'.

Table 6.2

Heading	Codemarks	Classification details
A5B		Pharmaceutical preps. & c.
C1A	A530	Inorganic substances; medicinal, pharmaceutical or cosmetic uses (13)
C2A	A3A1	Antibiotics; pharmaceutical uses (334)
C2B	B3A, B3A1	Organic compounds containing boron, pharmaceutical uses (17)
C2C	C790, C801/2	Organic compounds; bioactive, pharmaceutical (3393)
C2J	JA, JA1	Organometallic compounds, pharmaceutical uses (26)
C2U	U8A1	Steroids; pharmaceutical uses (1474)
C2V	VA1	Vitamins; pharmaceutical uses (121)
C2P	PA, PA1	Organic compounds containing phosphorus; pharmaceutical uses (84)

File List codemarks; search options

Table 6.3

Heading	Codemark	Subject
C2A	A3A1	Antibiotics; pharmaceutical uses
C2C	C790	Organic compound; pharmaceutical uses
C2P	PA	Phosphorus compounds; pharmaceutical uses
C2U	U8A1	Steroids; pharmaceutical uses

File List Search profile

Approximately 8000 patents were listed under the codes C801/2 and these were included on a File List. Some double counting was inevitable as the specific codes such as C2P will be assigned to patents as well as the general coding C790. The latter coding, therefore, provides an overall assessment of chemicals patenting with the specific codes illustrating trends within chemical groups. It must be remembered that these Lists include all patents granted at the Patent Office irrespective of nationality of the applicant and can only provide an indication of the level of pharmaceuticals patenting in the U.K.

File List data was analysed by year of publication of the patents, the number of the first specification to be published each year being extracted from the Official Journal, see table 6.4. This is not a wholly satisfactory approach but is preferable to checking individual patent specifications. Table 6.5 gives the number of patents coded with the relevant code marks in each year. Table 6.6 gives the C790 data by Abridgement volume and approximate date. The data is not directly comparable with the other marks but may illustrate trends. This data was represented graphically on a temporal basis using three year moving averages as a curve smoothing technique. The graphs are reproduced in figures 6.2, 6.3 and 6.4.

The patenting activity for novel chemicals with a pharmaceutical use (C790) shows a gradual increase since 1969 with a levelling off around 1975. From 1979 the C801/2 data operate. Patenting in antibiotics shows a rapid increase from 1965 until a peak in the early 1970s from which time activity declines until the late 1970s when a return to the levels of the mid-1960s is seen. A slight increase in patenting activity in recent years is also evident. Activity in the field of phosphorus-containing compounds shows a similar trend to that of antibiotics. For the steroid compounds a very different pattern

emerges, a high level of activity in the mid-1960s is followed by a constant decline with only minor fluctuations.

Such results must be viewed with caution given the changes in classification outlined. This method may be appropriate for monitoring trends within specific subject matter fields in a case-study approach. Since patent numbers are supplied with the File Lists, this method is a useful starting point for further in-depth studies. It can be argued that patenting in the U.K. Office is a good indicator of world patenting trends as Britain is a major market and location for pharmaceuticals activity with patent protection in the area deemed important by national and international firms.

The major failing of this method is that it reveals little, specifically, of the activities of the U.K. owned drug firms. It was apparent that more structured and selective searching techniques were needed to obtain the type of statistical information required. The second method attempted makes use of searching by company name in Patent Office documentation.

Table 6.4

Volume Number	Date of first in year	Complete Specifications accepted
71	1-1-1959	809,321 - 829,180
72	6-1-1960	829,181 - 861,800
73	4-1-1961	861,801 - 889,570
74	3-1-1962	889,571 - 918,310
75	2-1-1963	918,311 - 949,030
76	2-1-1964	949,031 - 982,550
77	1-1-1965	982,551 - 1,020,000
78	5-1-1966	1,020,001 - 1,058,500
79	4-1-1967	1,058,501 - 1,102,800
80	3-1-1968	1,102,801 - 1,142,500
81	1-1-1969	1,142,501 - 1,180,650
82	1-1-1970	1,180,651 - 1,222,450
83	6-1-1971	1,222,451 - 1,263,600
84	5-1-1972	1,263,601 - 1,306,400
85	4-1-1973	1,306,401 - 1,346,400
86	3-1-1974	1,346,401 - 1,384,030
87	2-1-1975	1,384,031 - 1,424,100
88	2-1-1976	1,424,101 - 1,464,400
89	6-1-1977	1,464,401 - 1,500,800
	5-1-1978	1,500,801 - 1,540,350
	4-1-1979	1,540,351 - 1,562,750
		2,000,001 - 2,026,290
	6-1-1980	1,562,751 - 1,584,610
		2,026,291 - 2,050,130
	7-1-1981	1,584,611 - 1,605,150
		2,050,131 - 2,078,070
	6-1-1982	2,078,071 -

Patent Office Official Journal dates

Table 6.5

Year of publication	Number of patents given code mark		
	C2A3A1 antibiotics	C2PA phosphorus	C2U8A1 steroids
1965	7	6	73
1966	13 (13)	9 (9)	158 (136)
1967	19 (15)	13 (12)	178 (145)
1968	12 (18)	13 (16)	99 (129)
1969	23 (21)	21 (20)	111 (104)
1970	29 (29)	25 (30)	103 (106)
1971	34 (40)	45 (35)	105 (113)
1972	56 (32)	35 (37)	130 (107)
1973	3 (39)	31 (26)	87 (96)
1974	57 (24)	13 (25)	72 (70)
1975	13 (28)	30 (22)	50 (69)
1976	13 (13)	22 (23)	85 (60)
1977	14 (12)	18 (21)	46 (69)
1978	9 (16)	23 (23)	77 (57)
1979	25 (16)	29 (30)	48 (57)
1980	15 (15)	39 (34)	46 (49)
1981	6	34	51

Series D File List results

Note: Figures in brackets are 3 year moving averages.

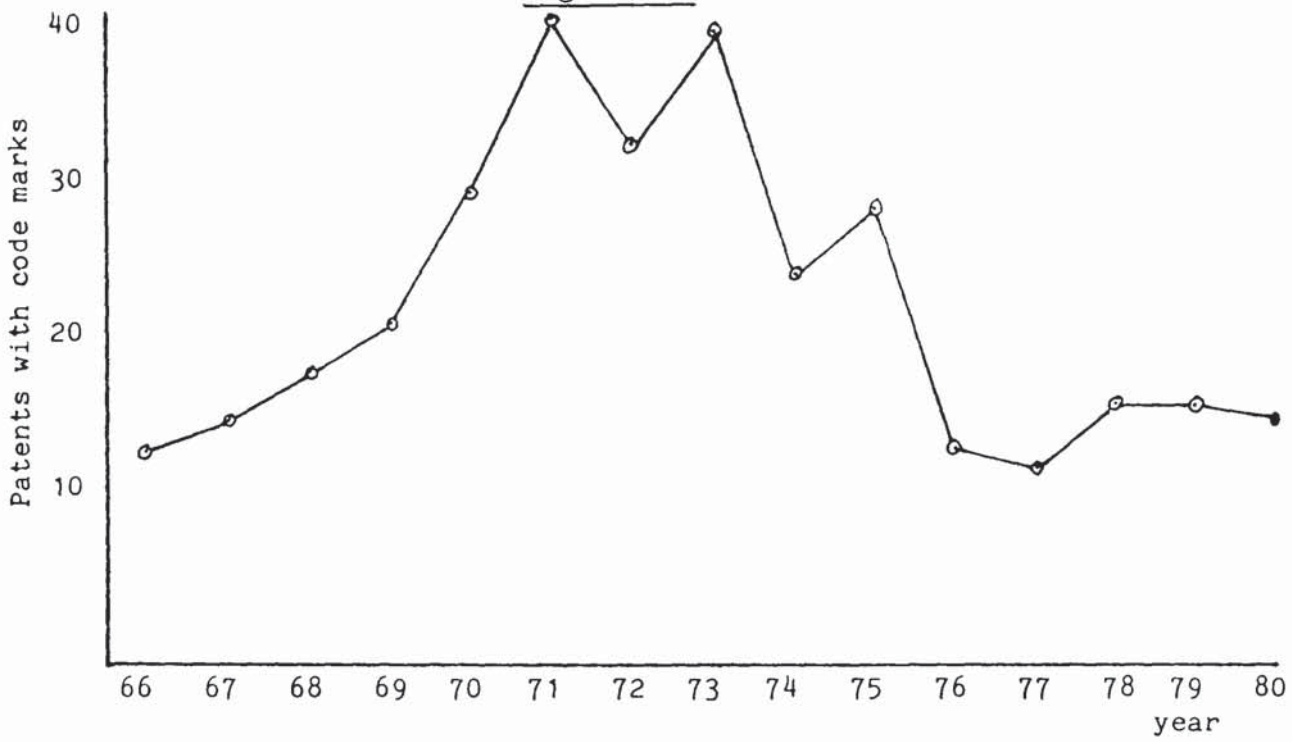
Table 6.6

Abridgements covered in Volume	Approximate year of Volume	Patents with C790 codemark
1150001-1175000	1969-70	305
1175001-1200000	1969-70	324
1200001-1225000	1970-71	307
1225001-1250000	1970-71	325
1250001-1275000	1971-72	468
1275001-1300000	1971-72	410
1300001-1300001	1972-74	542
1325001-1350000	1972-74	484
1350001-1375000	1974	600
1375001-1400000	1974-75	730
1400001-1450000	1975-76	677
1425001-1450000	1976	676
1450001-1475000	1976-77	686
1475001-1500000	1977-78	?
1500001-1525000	1978	633
1525001-1537580	1978	278

Note: prior to 1969 there was no codemark C790. In 1978, the new codemarks C801 and C802 came into operation. Data from 1979 is affected by the introduction of the EPC which has reduced overall patent application under the concurrent system.

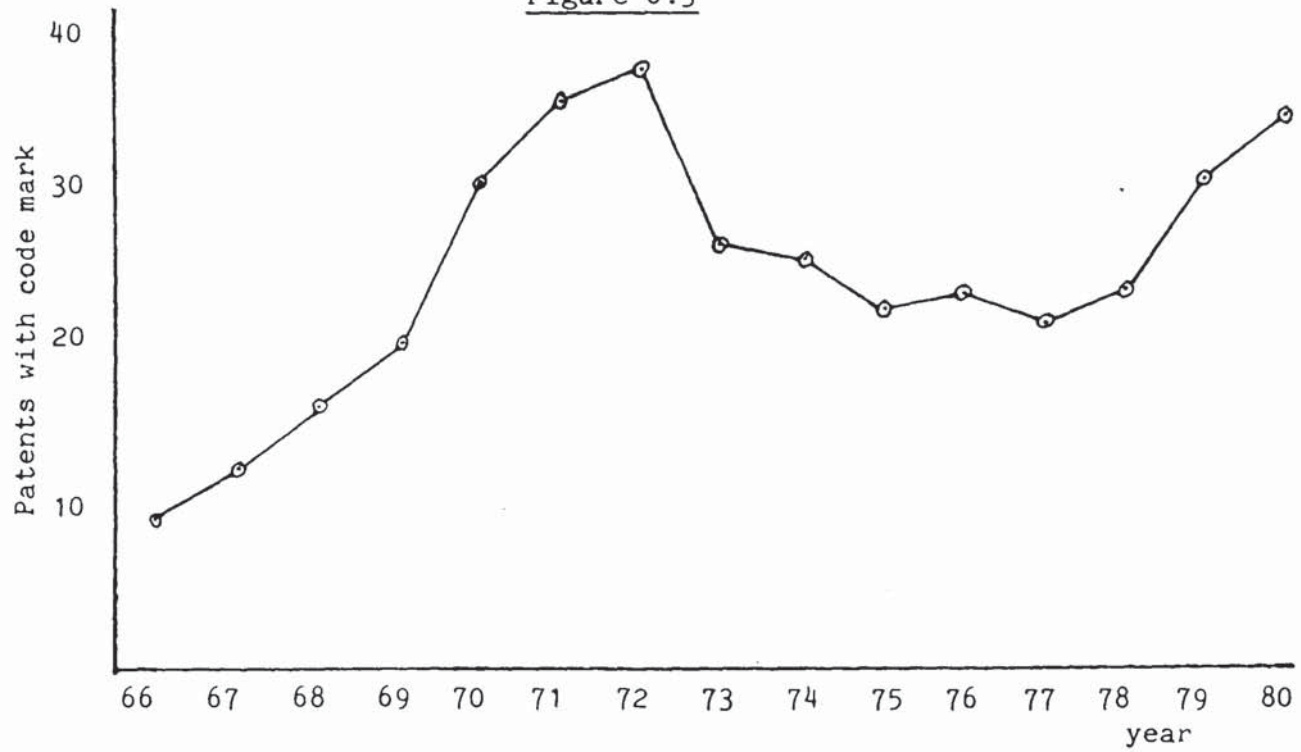
File list search for organic chemicals patenting-therapeutic uses

Figure 6.2



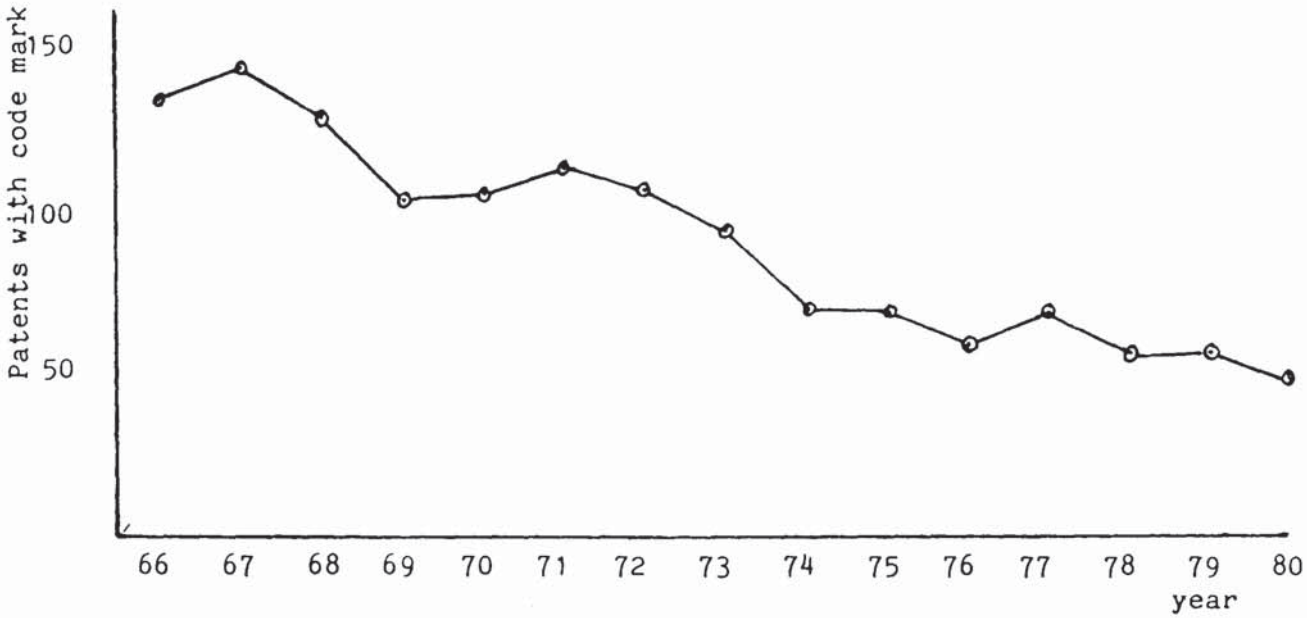
Antibiotics patenting activity in the U.K.

Figure 6.3



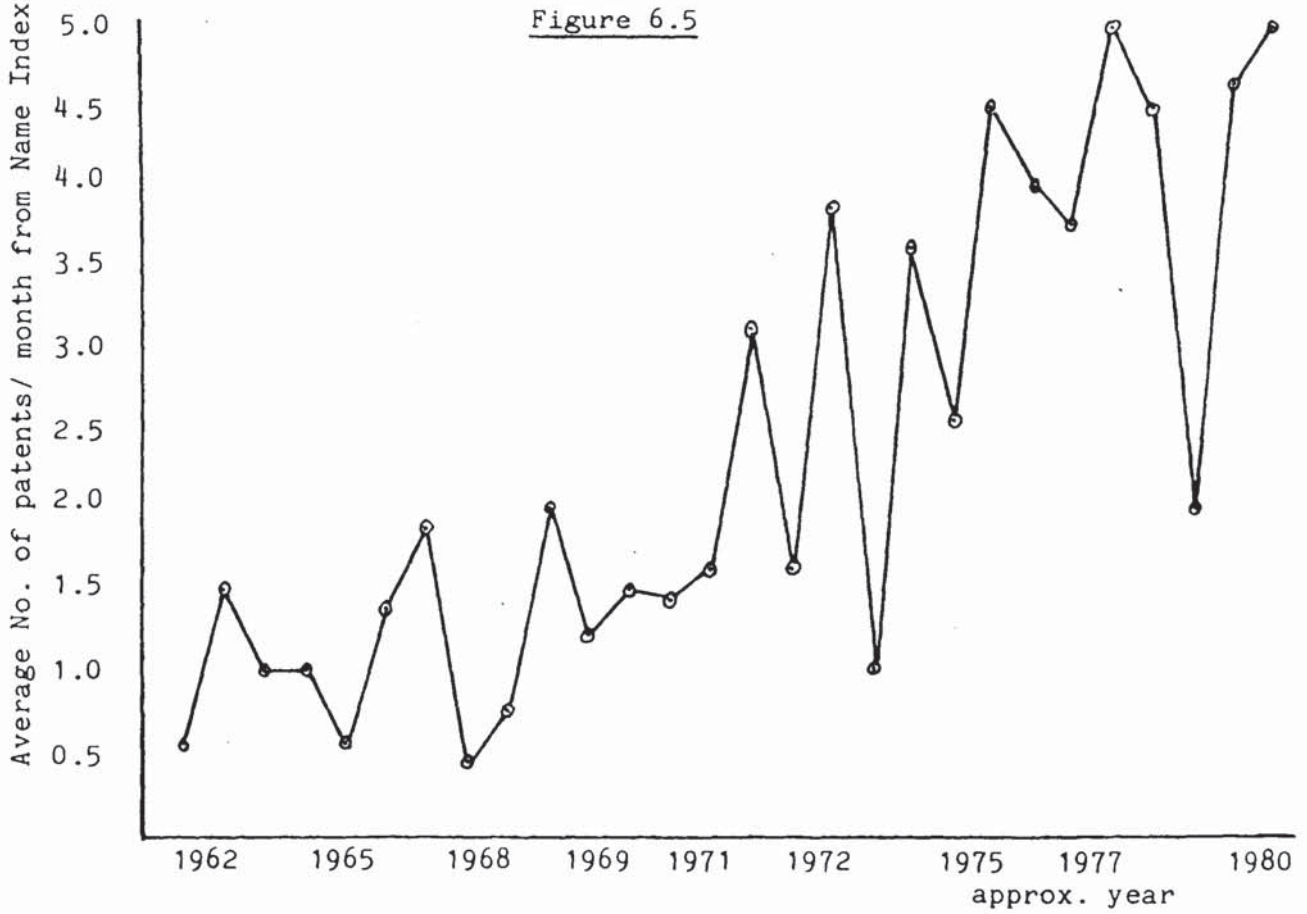
Phosphorus-containing compounds patenting activity in the U.K.

Figure 6.4



Steroid compounds patenting activity in the U.K.

Figure 6.5



Beecham patenting activity 1963-1980 from the Name Index

6.4 Method two: Name Index searching

The Patent Office produces Indexes containing lists of specifications by alphabetical name of applicant. As patents taken out by companies are usually filed under the name of the company and not the inventor, this method can provide insights into the level of patenting activity of the firm and the nature of that activity. Under name of applicant the patents are arranged by name of inventor together with a short title and the specification number. Titles are useful but are not an absolutely accurate guide to the nature of the invention, for pharmaceutical patents a sound knowledge of chemical terminology and nomenclature would be necessary to gain full benefit from short titles. The names of the inventors are a good indicator of those involved in the field at the time.

This approach is particularly useful if the company of interest has research in one subject area and where patents will predominantly reflect this research area. Difficulties arise when a firm has interests in a number of fields and much manual searching and extraction is necessary to eliminate those areas outside the area of interest. A company with diverse commercial interests such as ICI, where drug patenting is a minor activity compared with all patenting activities in general, will be less amenable to study than a company where the main commercial interests lie in pharmaceuticals.

As an example of the level of analysis and accuracy offered by this method, a study of Beecham's patenting activity was conducted. Beginning at 1960, Name Indexes were examined and all patents granted to Beecham were noted. From this list all non pharmaceutical patents were eliminated. These included dental compositions, animal health products and all surgical and medical aids. The final list contained patents relating to single chemical

substances, from 1960-1980. In presenting this information on an annual basis more difficulty was encountered since the Name Index volumes are in patent specification numerical order and not chronological order. The Name Index volumes from which the data was extracted covered varying time periods usually about 8 or 9 months. In order to present the information on a temporal basis the average number of patents published per index volume was calculated. The averages were plotted graphically by index volume number with a rough time comparison. The data is presented in table 6.7 and plotted in figure 6.5.

This method is extremely labour intensive and time consuming and would be inappropriate if large numbers of patents needed to be investigated or if companies with diverse interests were examined. The method was used mainly as a back up to fill in missing time periods from other methods and as a comparison of retrieval effectiveness.

The London Patent Office also maintains an index of all applications for patents made for the previous 5-6 years. These applications may never result in a published specification but are a useful alerting literature. Their utility in a long term study is limited by the short temporal nature of the index, as well as the fact that this index is only available in London, unlike the Name Index or patents themselves which are available for public scrutiny at a number of main city libraries. The index was used by Nolan and Withers but with little success.

6.5 Method three: Chemical Abstracts patent searches

Attempts at retrieving patent data from the Patent Office documentation revealed the limitations of the system, inability to search by company and subject areas being the main hinderances. In order to complete the review and tests of all possible patent sources, it was necessary to examine the non-official patent documentation the most readily available being the Chemical Abstract volumes.

Table 6.7

Volume "Number"	Period covered	Months	Number of patents	Average number of patents per month
1	Jan-Sept 63	9	5	0.55
2	Sept 63-Apr 64	8	12	1.50
3	Jun 64-Jan 65	8	8	1.00
4	Jan-July 65	7	7	1.00
5	Aug 65-Apr 66	9	5	0.55
6	Apr-Nov 66	8	11	1.37
7	Dec 66-July 67	8	15	1.87
8	July 67-Jan 68	7	3	0.42
9	Jan-Aug 68	8	6	0.75
10	Aug 68-Apr 69	9	18	2.00
11	Apr-Dec 69	9	11	1.22
12	Dec 69-July 70	8	12	1.50
13	July 70-Mar 71	9	13	1.44
14	Mar-Oct 71	8	13	1.62
15	Oct 71-May 72	8	25	3.12
16	May-Dec 72	8	13	1.62
17	Dec 72-July 73	8	31	3.87
18	Aug 73-Apr 74	9	9	1.00
19	Apr-Nov 74	8	29	3.62
20	Nov 74-July 75	9	23	2.55
21	July 75-Feb 76	8	36	4.50
22	Feb-Sept 76	8	32	4.00
23	Sept 76-May 77	9	34	3.77
24	Jun 77-Feb 78	9	45	5.00
25	Feb 78-Sept 78	8	36	4.50
26	Sept 78-Dec 78	4	8	2.00
27	Jan 79-Dec 79	12	56	4.66
28	Jan 80-Dec 80	12	60	5.00

Patents granted to Beecham 1963-1980 from the Name Index

In the course of compiling Chemical Abstracts many patents are encountered and included. Some previous research using this source has been reviewed already (4) and the results given in figure 5.2 . Patents for pharmaceutical inventions are indexed under the following sections of Chemical Abstracts.

1950: Section 17: pharmaceuticals, cosmetics & perfumes
1962: Section 39: pharmaceuticals
1963: Section 30: pharmaceuticals
1967: Section 63: pharmaceuticals

The classification adopted by the abstractors results in some very broad 'pharmaceutical' patents as well as apparatus, prostheses, dental and cosmetic products being included. This meant that little information of the type needed for the present study was readily available from the source. There was no way of searching by company, country of origin, or subject (other than abroad). Chemical Abstracts also produce other useful indexes of interest. The most useful is the Patent Concordance, this provides patent family information and allows equivalent patents to be found. If a foreign patent number has been found the Concordance allows a UK or USA patent number of an equivalent to be extracted. Chemical Abstracts patent data may be of more use as indicator of world pharmaceutical or health care activity. The immediacy of Chemical Abstracts publication makes it a useful patent monitoring source.

Having completed studies on all possible official patent data sources the next stage involved the use of commercially available databases, a number of which have been developed over recent years. The use of such sources seemed essential if data of the appropriate type was to be found.

6.6 Method four: Computerised commercial databases

Specialised computer databases have developed as the requirement for rapid retrieval of patent data has increased. Various sources exist, those containing patent data exclusively and others offering patent data within broader databases. Table 6.8 gives some common computerised sources.

The most popular and well known of the computer, on-line sources containing patents pertinent to the pharmaceutical industry is the FARMDOC system developed by Derwent. This system has been available for about 20 years and is widely used by the information services departments of most drug companies. Some academic studies have already utilised this system, the most notable being those of Nolan, Withers and Oppenheim which have been reviewed earlier. The FARMDOC database is most useful in that it is searchable by company and subject area. The methodology and results of a patent search using this system will be described in the following sections.

The appeal of a computerised patent retrieval system revolves around the ability to search by various terms or combinations of terms and have a 'hard copy' of any data obtained which can be further analysed. The use of such a method was necessary given the type of data needed, and a review of the available patent databases placed the FARMDOC option at the top of the list.

World Patent Index (WPI) is the property of Derwent Publications Ltd. and covers patents issuing from 24 leading countries as well as EP and PCT activity. The system allows searching by inventor, patentee, subject matter and year using an on-line interactive format. Patents for pharmaceutical related products have been abstracted from 1963 under the FARMDOC file name. Other Derwent files include agricultural patents from 1965 (AGDOC), plastics patents from 1966 (PLASDOC), and general chemicals since 1970.

Table 6.8

Database covering patents exclusively

1. CLAIMS/US: US patents and foreign equivalents from Belgium, France Britain and W. Germany, 1963-1977
   IFI Plenum Company: Lockheed (USA), via IPSS

2. INPADOC: Published patent specifications in 42 countries.
   i) IFS: Inpadoc Family Service
   ii) IPG: Inpadoc Patent Gazette
   INKA Germany. INKA via Euronet, Lockheed via IPSS

3. INPI Brevets: French patents, all patents deposited and published in France 1969 on.
   INPI: telesystemes (France), via Euronet/DIANE

4. Patent Register (PR): European published applications and granted patents according to EPC
   EPO: via Euronet/DIANE

5. Patent Search Documentation (PSD): Patent documents of the major patent issuing countries.
   EPO: via Euronet/DIANE

6. PATSEARCH, PATCLASS, PATHELP: US patents 1970-1980 including chemicals.
   PIIC: Pergamon Infoline (UK)

7. World Patent Index (WPI):
   Derwent: SDC via IPSS

Databases including patents

CA SEARCH: In association with INPADOC.
Chemical Abstracts Service, USA

Lockheed USA, SDC USA, BRS USA, IRS Italy.
Access all on Lockheed except IRS on Euronet/DIANE

Computerised databases containing patent information

The System Developments Corporation's ORBIT IV programme contains WPI, Central Patents Index (CPI) and the predecessor files. Pharmaceutical patents are available in the following files for the stated periods:

1963-1969: FARMDOC: pharmaceutical and veterinary patents
1970-1973: CPI, Section B.
1974- WPI.

Within these files the patents can be searched using the following directly searchable elements:

1. Accession number
2. Entry year
3. Patent number
4. Patent country
5. Designated states (EP,PCT)
6. Cited patents
7. Priority number/country
8. Priority date
10. Patent assignee
11. Patentee code (company code)
12. Inventor
13. Derwent class/section
14. IPC
15. Index terms (Derwent thesaurus)
16. Title terms (Derwent assigned)
17. Manual codes
18. Fragmentation codes
19. Registry names

Manual searching using coded cards and the Derwent company code are alternatives to the use of the on-line system. The latter has the advantage of being time saving and also requires less initial manual effort. The card files were used by Withers. From the searchable elements above, it seemed that patents for pharmaceuticals could be searched by company over a reasonable period. The search methodology adopted is given below.

6.6.1 Search methodology used.

Two preliminary searches were conducted at the Science Reference Library, London using the FARMDOC database. Only two firms were chosen for this initial study, namely ICI pharmaceuticals and Glaxo (including Allen & Hanbury). This was because ICI was found to be almost impossible to search efficiently using other methods outlined and Glaxo was suspected of being the most prolific patentee. Prior to comprehensive and specific searching it seemed useful to have an indication of the volume of patenting to expect.

FARMDOC files were used to extract all the patent families resulting from equivalents patenting by the companies concerned over the period of

coverage of the database.Section B7 of the file was eliminated from the search leaving B1-B6. B7 was thought to be too general and was likely to contain few patents of interest (see table 6.9). The advice of library staff was sought in making this decision. The resulting print-outs contained a list of all patent families in the file together with the relevant priority information. The number of patent families for each company up to the end of 1980 was as follows:

	All FARMDOC WPI 1963-80	FARMDOC B1-B6
Glaxo	223	219
ICI	625	605

Data was further analysed on an annual basis, the number of priority patents per year was counted. This was not equal to the total number of patents as each priority patent may have given rise to more than one patent. However, priority patents were thought to provide a better indication of total inventive activity. This point will be returned to when the substantial searches are analysed.

Results were presented graphically showing the number of priority patent applications per year. It must be recorded that only if an application led to a published patent would the patent be contained in the data. This meant that some patent applications were not included but as these seemed to be of little commercial importance they were of secondary importance to this study. The graphs are given in figures 6.6 and 6.7.

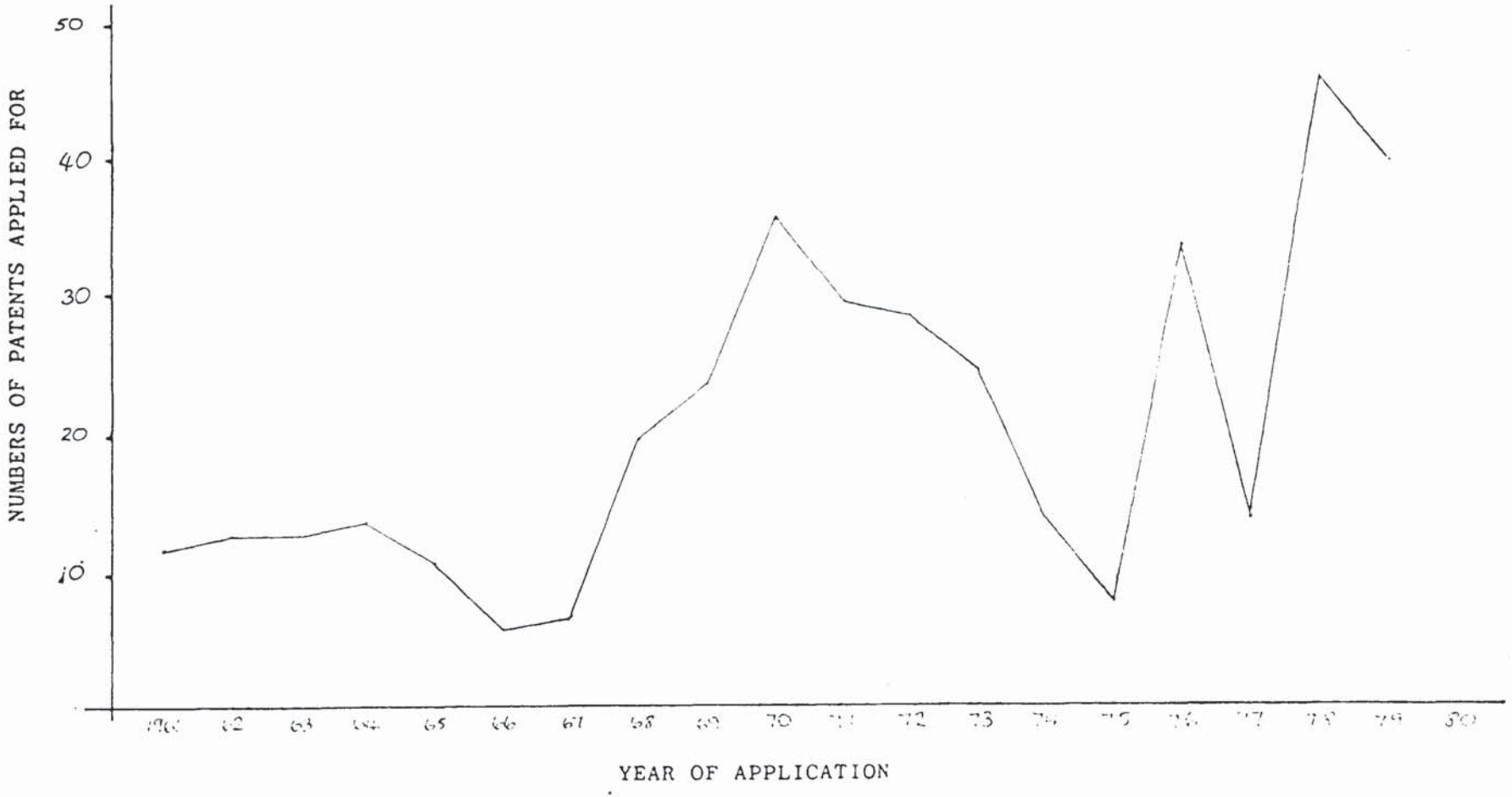
Problems existed in the database, with initial inaccuracies and at a later time when the Patent Laws changed. Patent family size could also be determined from the print-outs and some analysis of patenting policy seemed possible.

Table 6.9

B1	Steroids - includes systems containing carbocyclic and/or heterocyclic rings fused onto the basic steroidal ring structure but excludes compounds where the basic steroidal cyclopentano-phenanthrene ring structure has been modified by heteroatoms (E.G. azasteroids), additional ring atoms (e.g. homosteroids) and bond breakage (secosteroids).
B2	Fused ring heterocyclics
B3	Other heterocyclics
B4	Natural products and polymers - including oligo or poly peptides with at least four amino acid units (but not homopolymers of any amino acid), testing of body fluids (other than blood typing or cell counting), pharmaceuticals or veterinary compounds of unknown structure, testing of micro-organisms for pathogenicity, testing of chemicals for mutagenicity or human toxicity and fermentative production of DNA or RNA.
B5	Other organics - aromatics, aliphatics, organometallics, compounds whose substituents vary such that they would be classified in several of B1-B5 and general compositions.
B6	Inorganics - including fluorides for toothpastes etc.
B7	General - tablets, dispensers, catheters (unless for drainage), encapsulation etc. but not systems for administration of blood or saline or i.v. feeding etc. or machinery for general tabletting etc.

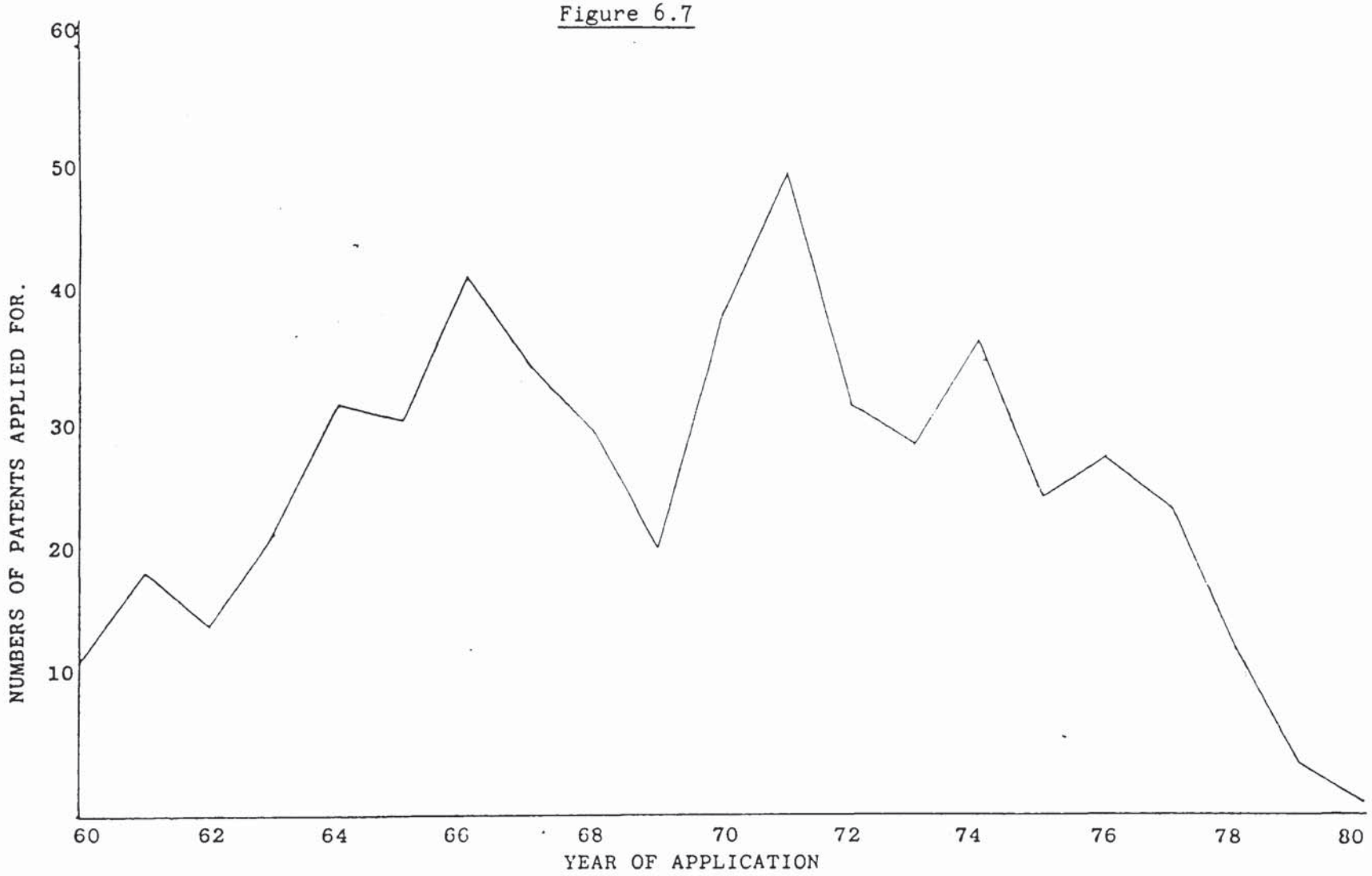
Farmdoc Classifications B1-B7

Figure 6.6



Patents granted to Glaxo (1961-1979) for pharmaceutical products by year of application

Figure 6.7



Patents granted to ICI (1960-1980) for pharmaceutical products by year of application

6.6.2 Initial Results

For ICI a substantial amount of foreign priority patenting was evident particularly in the U.S., Australia and Japan for the mid-1970s. Patent family sizes showed an increase for the most recent period for which data was available. For the early 1960s, little priority information was available and for this reason the patent output for this period is underestimated. A decline in patenting activity in the later 1970s can be attributed, in part, to the time lag in patent publication. This will be common to all the companies studied. The broad trend for ICI is that of a fluctuating decline from a peak in the early 1970s.

For Glaxo, more evenly sized patent families were evident over the whole period of study, large patent families were less common. An interesting observation, highlighted by the method adopted, was that numerous priority applications were taken out in Japan around 1976. Apart from this, few priority patents were applied for outside the U.K. for Glaxo over the period. In terms of patenting activity, Glaxo appeared to increase output until 1971 with a decline in the mid-1970s followed by an upsurge in activity to a new peak in 1978. The most recent data may underestimate the patenting activity but the difference between the patenting profiles of Glaxo and ICI is clearly demonstrated.

From even such a limited company study, it was obvious that contrasting trends in patenting activity existed between firms and this required more detailed analyses of patenting activity for all the companies of interest. Reasons for the variation needed to be produced, the database was generating the type of information needed but to produce the more refined statistical information assistance was ought. The search profile needed to be improved to eliminate the limited number of non-relevant patents, in order to do this technical assistance was sought from Derwent.

6.7 Detailed patent search of U.K. owned companies

The preliminary Derwent searches revealed sources of error. To improve the search format assistance was sought from Derwent Publications (5) and by negotiation a revised search format was developed with the aims of removing any unwanted 'hits' in the original data and also to expand on some alternative patent information. Beginning with the whole range of search qualifiers in the Derwent unit record a search profile was developed which contained more relevant data. The unit record and profile adopted are given in tables 6.10 and 6.11.

6.7.1 Search format

The patent output of the companies was again extracted using sections B1-B6 of the FARMDOC file or its predecessors. Whenever possible novel single chemical patents were extracted but this proved impossible for the pre-CPI period prior to 1970. As accurate data was needed it was decided to use the present search for the period 1970-1982 and to make use of manual searching using Name Indexes and the previous, more general, FARMDOC search for the earlier data. This does mean however that the earlier data is not as accurate as could be hoped. The search method itself utilised fragmentation coding which Derwent assured would give a very complete retrieval. The coding used was as follows.

M 710/M1, M2 for any compound

M 720/M1, M2 for production of a known compound

The latter coding was adopted to attempt to determine the relative levels of product and process patenting in the companies of interest. A complication meant that steroid patents were not included in the format above and had to be extracted using the alternative coding SS 17. In practice only Glaxo had any significant activity in the steroid field.

Table 6.10

SEARCH QUALIFIER (Synonyms)	ELEMENT NAME	PRT/STRS QUALIFIER	STANDARD PRINT COMMANDS			
			PRINT	FAM	FULL	CODE
/AN (AC)	Accession Number (Prints with Derwent Week and Entry Year)	AN	X	X	X	X
/XR	Related Accession Numbers	XR	X	X	X	X
*/EY (AY)	Entry (Accession) Year	-	(Prints in AN)			
/DC (CL)	Derwent Classes and Sections	DC	X	X	X	X
/IT	Index Terms - preferred form, Thesaurus controlled	IT	-	-	-	-
			(Addl words print in AW)			
/TT (TI)	Derwent Title (searchable as individual words as they appear)	TI	X	-	X	-
-	Additional Words (searchable in IT)	AW	-	-	X	-
/PA	Patent Assignee (searchable as individual words) Print Line also has patentee code	PA	X	-	X	-
/CC	Company (Patentee) Code	-	(Prints in PA)			
/IN (IV)	Inventors	IN	-	-	X	-
**/PN (FM)	Patent Numbers (print with Derwent week)	PN	-	X	X	-
/PC	Patent Publication Country		(Prints in PN)			
/DS	Designated States	DS	-	X	X	-
/CT	Citations and Language indicator	CT	-	-	X	-
*/PD	Publication date of Basic YYMMDD (Print includes basic patent no.)	PD	-	-	X	-
/PR (PY)	Priority (Year, Cty-Serial) Prior Country (Print includes priority date).	PR	-	X	X	-
/PRD	Priority Date YY.MM.DD		(Prints in PR)			
/IC	International Patent Classes	IC	-	-	X	X
/MC	Manual Codes	MC	-	-	X	X
/KS	Plasdoc Key Serials	KS	-	-	-	X
/KT	Plasdoc Key Terms	KT	-	-	-	-
/KP	Plasdoc Key Terms Descriptors (searchable as individual words)	KP	-	-	-	X
@ A,R,1 thru 6	Fragment Coding	A,R,1-6	-	-	-	X
/RR	Ring Index Numbers	RR	-	-	-	X
/RN	Registry Names	RN	-	-	-	X
/UP	Update Code for Basics	-	-	-	-	-
/UPEQ	Update Code for Equivalents	-	-	-	-	-
/UPA	Update Code for A Fragment Coding +PKT	-	-	-	-	-
/UPB	Update Code for BCE Fragment Coding and RR	-	-	-	-	-
/AB	Abstract Text	AB	-	-	-	-
-	Derwent Section for manual codes	XL	-	-	-	-

Derwent Unit Record.

Table 6.11

Search qualifier	Element name
AN	Accession number (prints with Derwent week & entry year)
DC	Derwent Classes & Section
TT (TI)	Derwent title
PA	Patent assignee/Patentee code
IN	Inventors
PN	Patent numbers/Derwent week
PC	Patent publication country
DS	Designated states
CT	Citations & language indic.
PD	Publication year of basic (includes basic patent No.)
PR	Priority year (includes priority date)
PRD	Priority date
IC	International patent classes
MC	Manual codes

Search profile adopted

The Derwent Company Code was used in which all large companies have a designated code with all identifiable subsidiaries collected under the same code. Using this method Glaxo and Allen & Hanbury patents will be extracted together and similarly, Beecham and Bencard patents will be retrieved together. For the benefit of lower costs and technically better prints, off-line sorting was advised with the prints sorted by accession number in descending chronological order.

Until 1974 some priority dates were given the code 00.01.00 and required manual checking for chronological age. Each unit record gave one patent family or set of equivalents. An example of a unit record from the search is given in figure 6.8. Separate data files were obtained for each company covering all published patents in the area of interest. The product/process data and a summary of the total patent output for each company are given in table 6.12.

6.7.2 Organization and use of data

Each company file consisted of a list of patent families arranged in chronological order by year of priority. Steroid patents were sorted separately and added to each company file. From the files the following elements of the unit record were noted for initial analysis;

1. Priority date and number
2. Date, country and number of the basic patent
3. Patent family size
4. The G.B. equivalent (if not the basic patent)
5. The Derwent Accession Date

As noted earlier, even such a refined search could not hope to eliminate all non-relevant patents due to the nature of the patent classification. By means of visual scanning the following patents were eliminated from the files;

Figure 6.8

-277-
AN - 16901C/10 (80)
TI - 3-Alkenyl:thio-7-oxo-1-aza:bi:cyclo:heptene-2-carboxylic acids - useful as broad spectrum antibacterials
DC - B02
PA - (BEEC) BEECHAM GROUP LTD
IN - SOUTHGATE R,SMALE TC,PONSFORD RJ
CT - (E)DE2736482 FR2356649 FR2392996
PD - 80.03.05 EP---8497-C10
PR - 79.01.06 79GB-000503 78.07.26 78GB-031223 81.00.00 81EP-104385 81.00.00 81EP-104411
IC - A61K-031/40 C07D-487/04
PN - EP---8497-C10 J55022676-C13
AW - BETA LACTAM
DS - BE CH DE FR GB IT NL SE

-278-
AN - 27718C/16 (80)
TI - Di:methyl-cyano-trans-4-pyrrolidinyl-3-chromanol derivs. - useful as vasodilatory, antihypertensive agents
DC - B02
PA - (BEEC) BEECHAM GROUP LTD
IN - EVANS JM
CT - (E)GB1495526 GB1548221
PD - 80.04.16 EP---9912-C16
PR - 79.01.10 79GB-000901 78.10.04 78GB-039303 78.10.20 78GB-041306
IC - A61K-031/44 C07D-311/68 C07D-405/00
PN - EP---9912-C16 J55049371-C21 DK7904153-C22 ZA7905275-C43
DS - BE CH DE FR GB IT LU NL AT SE

-279-
AN - 57360C/33 (80)
TI - 1-Hydroxyalkyl-5-omega-hydroxyalkyl-hydantoin derivs. and analogues - having anti-gastric secretion, antihypertensive, bronchodilator activity etc.
DC - B03 C02
PA - (BEEC) BEECHAM GROUP LTD
IN - WOOTTON G
CT - (E) EP---1238 EP---2258 EP---2259 FR2362839 FR2427331
PD - 80.08.06 EP--14076-C33
PR - 79.01.18 79GB-001887
IC - A61K-031/55 C07D-233/78 A61K-000/00 C07D-000/00
PN - EP--14076-C33 J55100371-C37 ZA8000297-D05 DK8000173-D47
AW - ANTIULCER CARDIOVASCULAR BLOOD PLATELET INHIBIT AGGREGATE ANTIFERTILITY SMOOTH MUSCLE ANTIARRHYTHMIC
DS - BE CH DE FR GB IT NL AT SE

Example of unit records from the patent search

Table 6.12

Company	Total 1963-82	New Compounds CPI only *	Production of known compound	Steroids 1963-82 *	Pre-CPI incl. steroids
Beecham	797	408	117	20	177
Boots	75	21	8	11	35
Fisons	149	62	13	3	29
Glaxo/A&H	451	190	77	89	125
ICI	682	238	78	14	311
R&C	50	21	2	1	21
Wellcome	430	124	32	8	218

* offline prints provided

Summary of patent search of U.K. owned firms

Table 6.13

NCE	Family size
Amoxycillin	18
Talampicillin	52
Flurbiprofen	18
Cephaloridine	25
Fazadinium Bromide	12
Cefuroxime	34
Clofibrate	4
Etoglucid	5
Ertryptamine	1
Propranolol	25
Tamoxifen	15
Practolol	17
Viloxazine	20
Atenolol	29
Acyclovir	49

Patent family sizes for some NCEs

a) Veterinary products

b) Intermediates

c) Production of a known compound

d) Processes (purification, extraction, fermentation etc.)

If the patent claimed a process to prepare a known compound and had also been designated the International Classification A61K then that patent was included. If the patent was classified C07D then it was excluded as being purely a process patent. Counts were made before and after this preliminary cleaning.

The resulting list of patents needed to be further organised on an annual basis either by year of application or publication of the patent. Initially a count using the Derwent Accession Year was used for the whole data file, this being similar to a publication count by basic patent. Early 1970s patents were given the accession year 1966 and this introduced errors into the data for this period. For this reason as well as the general inaccuracy of Derwent dates in the search, the alternative method of using a list by year of publication of the G.B. patent was adopted.

Patents were placed into publication date order using the Official Journal dates given earlier. The adoption of the application date approach is more difficult as the nearest date on the Derwent unit record is the priority date, in some cases this was not given and these patents would require manual searching. Additionally if the title was vague then the patent specification would require a manual examination to check the validity of the patent for the study. This task was undertaken and required many visits to the patents section of the Birmingham Public Library which contains one of the regional patent libraries.

For each unit record the family of equivalents occasionally contained more than one G.B. patent. The problem was whether to count the number of families or absolute numbers of patents. The former was decided on as it was considered that for two patents to be included in the same family, the inventions claimed must be technically linked and thus could be considered to represent one research output. However, the number of instances of this occurring were few and a count of families seemed acceptable.

6.7.3 Pre-1970 patents; methods adopted.

For ICI and Glaxo the previous FARMDOC data was used and rechecked manually. For the other companies the Patent Office, Name Index to Complete Specifications was used to generate a list of all patents relevant to the study. Fortunately this presented few problems for the remaining firms as the annual output of published patents was low. Beecham had previously been examined using this approach and data was collected in a similar way.

The lists of patents extracted from the Name Index were cleaned by first removing all patents of obvious non-relevance. Once this had been done the remaining patent specifications were checked at the library. As intimated earlier this was a formidable task and remains one of the problems with using patent data. Specifications were individually scrutinised, figure 6.9 gives an example of a typical G.B. specification front page as retrieved from the library.
Using this approach a final list of patents resulted. The time period of patents examined in this way was extended to overlap with data available from the FARMDOC search in order to test the accuracy of the manual method and search comparability. The fact that the Name Index

search gave absolute numbers of patents rather than the number of patent families and also failed to provide any details regarding equivalents are weaknesses of the manual method illustrates the advantage of computerised patent searching.

6.7.4 Analysis of patent family sizes

Analysis of the data thus far was on a purely quantitative basis, establishing the patenting output of the companies on an annual basis. It seemed possible to extract a certain amount of qualitative information from the statistics. Two options were available, the importance of each patent family could be assessed using family size as a proxy measure, whilst therapeutic/chemical classification of the patents would be a guide to the direction of research activity.

The use of patent family size information was demonstrated by Mlodzik who used such data to show variation in company patenting policy when filing international patents. Aspects of international patenting have been considered earlier but given that important inventions will generally receive wider patent cover whenever possible, patent family size represents an assessment of the importance placed on an invention by a company.

For each invention the associated set of patents that comprise a patent family give an indication of the areas where patent application has been sucessful. The Derwent data contained all necessary information regarding family size to allow some analysis. Data for each company was added to the company lists by taking each patent family in turn and counting the number of equivalents assigned. This information was added to the final cleaned data for each company and is presented in the company lists in the appendices.

Counting the total number of equivalents was not completely acceptable for a number of reasons. The family may have contained more than one equivalent from each country in order that the full breadth of the invention may be claimed. However, multiple patents surrounding one invention indicate an invention of some significance and thus did not seem to preclude the use of the method. A further assumption inherent in the method was that all equivalents were of equal weighting. Thus a patent taken out in a minor country was of equal weighting to a patent taken out in a major industrialised country.

Given these conditions the patents that comprised the final application lists were assigned all family data, if more than one G.B. equivalent existed then all members were attributed with the total family size. This obviously leads to some degree of double counting emphasising those patents of significance. The family size data was further analysed in terms of the family size of identifiable NCE patent families. Cross checking of known NCE patents revealed that there appeared to be a lower limit of around 15 equivalents for the NCEs of interest. Table 6.13 gives details of family sizes for the NCEs examined.

For subsequent analysis the number of families with sizes of greater than 5 and greater than 15 were counted for each company and recorded. It was hoped to use this data in a temporal study of patenting output. The patent families were organised on an application date basis for this analysis.

6.7.5 Analysis of patents by therapeutic/chemical classification.

Classification of patents on the basis of their therapeutic application and chemical structure is possible using the full Derwent records. The procedure utilises the Manual Coding (M.C.) system. This is assigned to basic patents in the WPI database and is more detailed than the more general Derwent Classification (D.C.). Codes are applied to the 'main inventive features of the patent', a hierarchical system is used with many levels of classification. Derwent Classification makes use of the first two levels only. To assess the benefits of full coding separate print-outs were requested for one company only, namely Beecham. The accession year sort was used, this being acceptable as only broad trends were to be examined at this stage. For each accession year a list was compiled of each set of equivalents in that year together with their full manual coding.

The chemical codes B1-B10 are assigned to each set of equivalents by a priority rule, B1 before B2 and so forth. If the structure of the compound is known the patent may also have a classification B5-B10, except for antibiotics which are designated as B2. Some degree of double counting is possible and for the purposes of this study the first code was used with the second code providing more information on the same patent. Data on the number of patent families coded with B12 (a therapeutic use) was extracted with all instances of this coding being noted. Some patents were allocated more than one B12 code and in these cases all were noted as the use of a hierarchical system was not considered adequate for this aspect of analysis.

For each accession year lists were compiled containing the number and percentage of families in each sub-section, the number of families with a therapeutic code and the number and percentage of instances of B12 coding.

6.8 Conclusions

Extraction of patent statistics requires a thorough knowledge of the sources of patent documentation. Patent documentation can be divided into Official and Non-official sources depending on whether they are assembled for the purposes of fulfilling patent law or for a range of alternative uses. Searching both types of source requires an understanding of patent classification systems and the advice of experts in the field should be obtained whenever possible.

Searches of various types of official patent documentation are outlined but most suffer from search parameter limitations. The two most useful search sources are the Name index to Complete Specifications and File Lists. Name Index searching is a valuable method of searching by company name or inventor but for some firms with interests outside pharmaceuticals, a considerable amount of manual sorting is necessary to eliminate non-relevant patents. This method was used to extract patents for all firms of interest for the period prior to 1970. Beecham was used as a case study initially and details are supplied of the results of Name Index searching for Beecham patents.

File lists can provide a considerable amount of patent data on a subject matter basis. Again, a knowledge of the coding system used to extract File Lists is necessary to obtain relevant patents. Examples of the type of data that may be obtained using this method are given; antibiotics, phosphorus compounds and steroids are chosen as case studies. Differences in patenting trends were observed between these categories over the period of interest. The method is, however, not suitable for searching by company or even by nationality of patentee. This made the method unacceptable for any detailed patenting study for the U.K. owned companies.

Computerised patent databases provide more acceptable and varied search criteria, allowing searches to be made by company and subject matter field together. Databases available for the extraction of pharmaceutical patents are outlined, the Derwent Farmdoc database is considered in more detail and its suitability assessed. The database is deemed to be suitable for a study of patents related to NCEs for the U.K. firms.

The methodologies of preliminary and detailed Farmdoc searches are described with details of classification, search profiles and the type of results obtained. Essentially, the final search profile is similar to that of earlier researchers but differs in aspects of specificity, coverage and subsequent analysis. All aspects of patent data searching outlined may be of use in studies of patenting in all industries and may be useful in providing the type of background necessary for such studies.

From the patent searches, lists were compiled for each firm of interest with patents listed by year of application. This listing method required extensive manual searching in patent libraries. Family size data was added to these company files whenever possible. This information may be used as an indicator of the importance of a patented invention. A final level of searching outlined was that of therapeutic and chemical classification. This was thought to be a reasonable indicator of the direction of inventive activity. One firm only was chosen for this analysis as a test case.

Having extracted and collated all the necessary patent data for use as an intermediate output indicator in the U.K. owned pharmaceutical industry, some assessment of the value of such data was required. The next chapter describes the conclusions that may be drawn from the data and correlates patent data with other input and output indicators described in earlier chapters.

CHAPTER SEVEN: ANALYSIS OF RESULTS AND CONCLUSIONS

7.1 General comments

A central problem identified in early stages of this research was whether the rate and direction of innovation in the U.K. drug industry had been influenced to any measurable extent by external factors, the most identifiable being regulation of new drug products. A review of previous research highlighted a number of reports of the effect of drug regulation in the United States. Most of these studies failed to convincingly relate changes in drug innovation rates for new products directly to the increase in regulatory stringency. Other factors were identified as contributing to these changes in innovation rate.

Prior to a study of the effects of U.K. drug regulation some effort was put into an examination of the history of drug regulation in Britain in order to identify phases of regulatory stringency and provide a background to an impact study. This also provided an assessment of the U.K. regulatory authority's response to demands for a relaxing of testing demands by the industry. Such accounts were not well documented elsewhere.

In order to conduct a manageable study of innovation in the drug industry, the U.K. owned sector was selected as a focus for research. The U.K. owned companies had not received attention specifically in earlier studies but were also thought to be fairly representative of the industry in general.

In attempting a detailed study of the rate and direction of innovation in the U.K. owned companies a number of methodological problems arose. The need for accurate indicators of innovation led into an examination of possible science and technology indicators and an assessment of what each indicator measured. Innovation rates in the

pharmaceutical industry had traditionally been measured by counts of new chemical entities introduced. For the British drug industry lists of drug introductions were available for a reasonable time period and had been used by previous workers. Some sorting of this data was necessary to extract the NCE introductions originating in U.K. owned companies. This was achieved using patent information for each drug. Data was presented in two ways, by year of marketing and by year of invention as indicated by patenting dates.

The use of NCE data as an indicator of innovation rates revealed little of changes in the research and development process. The effect of external factors on the R&D process had not been examined in detail in most earlier accounts of innovation and this aspect of the industry was examined in detail. Each company comprising the U.K. owned sector was reviewed on a case-study basis and their research interests and methods were detailed.

An analysis of the R&D process pointed to possible indicators of research activity at various stages. Possible indicators included counts of applications for clinical trials certificates and product licences, product candidates, publications, animal experiments conducted and patents obtained. Research and development expenditure was also included as an input indicator.

Obtaining such data on a U.K. industry basis was problematic and required a method which aggregated the separate companies' data. This involved a number of sources and in some cases estimates needed to be made. Some gaps occurred in the case of R&D expenditure and patent data whilst data for most of the other indicators was limited. Examples of the data available for most of the indicators were presented. A further complication was accounting for inflation in R&D costs. This necessitated

the use of R&D deflators and examples of expenditure series deflated using two price indices were given.

Selection of patenting data was on the basis of unparalleled availability and the direct relationship between patenting and inventive activity. A review of past research using patents as indicators revealed a certain degree of misunderstanding of patenting and in many cases patent data was used without sufficient understanding of how such data is collected and classified. Additionally, since patenting is an important part of the drug R&D process, a fuller account of the patenting process in the industry seemed important. This type of information would be of use to researchers using patent data in any study.

A study of patenting in the companies of interest by means of interviews indicated variation in patenting policy between firms. The use of patent data in international studies would be enhanced by a more complete understanding of such matters. Some conception of the patenting propensity of drug firms was obtained, this being one criticism of patent data.

To obtain patent data for the companies concerned on a subject matter basis proved difficult. Since patents related to single novel chemicals were needed most of the common patent sources proved unacceptable. Sources were taken in turn and included 'official' and 'non-official', for each source searches were conducted to assess the type of data available. Again, such information may prove useful to other researchers using patent statistics. The advantages and disadvantages of each source were given. Given the search requirements, only one type of source namely,computerised databases allowed for searching by company and subject matter in conjunction.

The Derwent-operated, Farmdoc patent file was selected as it had proved valuable in previous research. The requirements of the present search were, however, different to that of earlier workers in that only patents relating to single chemicals were required and the companies used were different in some cases. Assistance was sought from patent experts to ensure an accurate search profile. Patent data was obtained for all companies of interest, including details of patent family size and, in some cases, therapeutic and chemical classification of the patents. Additional patent information from earlier manual searches was used to compliment and extend the time period of computer searches.

Data was organized on an application date basis to allow subsequent correlation with R&D expenditure and NCE marketing. All the indicator data obtained was then used in analyses to determine whether any changes in the rate and direction of NCE output for the firms concerned could be related to changes in the R&D process as monitored using patent data and R&D expenditures. Other indicators were used as background information.

The organization and use of the indicator data is outlined in the next section which includes conclusions generated from the results of the empirical sections.

7.2 Results and conclusions of the patent study

Much of the research presented has been essentially empirical in nature describing the nature of research and development activity in the U.K. pharmaceutical industry and demonstrating possible methods of obtaining science and technology indicators for the industry. Conclusions regarding the methodologies adopted and the limitations to many previous research efforts in this field have been made in the relevant chapters. The major empirical work resulting in a series of indicators of innovative and inventive activity needs to be analysed beginning with the patent data obtained from the various searches conducted.

The results of the patent study in its final form may be presented in a number of ways. Patent output may be collated on an application date basis as in table 7.1, by year of publication as in tables 7.2 and 7.3, by accession year of the basic patent as in table 7.4 or by year of priority as in tables 7.5 and 7.6. For the present study the most appropriate method is a count by year of application for the patent. This allows all the indicators to be given a common time base. The full results are, however, given for completeness.

The size of patent family or set of equivalents associated with each patent is a further measure that is recorded. Two sets of data are reproduced, the first based on family sizes of greater than 14 and the second based on family sizes greater than 4. These results are presented in tables 7. 7 and 7.8 respectively. These measures will be used in the analytical section as indicators of importance. To avoid reproducing earlier data reference will be made to earlier tables and figures or summaries will be presented.

The analysis is presented in the following way; the limitations of the methods adopted and sources of error are considered followed by more detailed examination of patent data. This is followed by a series

of correlations using earlier indicators as well as patent data. This leads into a discussion of the effectiveness of patents as science and technology indicators with particular emphasis on their use as monitors of the effects of regulation on the drug industry and as innovation or invention indicators..

From the data it is evident that the patenting activity for the early 1960s and the most recent period is underestimated due to the incomplete nature of the databases used. The effects of the 1977 Patent Act and other recent changes in international patent laws has resulted in a change in patenting policy in the companies of interest and this will affect data for the recent period. Furthermore, some periods have no associated patenting activity again, presumably, due to the sources used.

The retrieval patterns of the patent databases used coupled with the severe demands of the search profiles introduces a degree of subjectivity with some trade-off being necessary between completeness and search definition. Finally, when in later sections attempts are made to correlate the various input and output indicators used it will be evident that obtaining data for each indicator for a comparable time period presents difficulties. This is unavoidable given the range of measures used and the diverse sources.

Given these inherent weaknesses, common to any study using data for reasons other than for those for which they were collected, the study does emphasise the problems involved in collecting data related to inventive and innovative activity and describes improved methods of retrieval together with an analysis of previously misunderstood variations in policy and practice.

Table 7.1

Year	Beecham		Boots		Fisons	Glaxo	ICI *		R&C	Wellcome		All	
1956	3	1	7	6		1				5	5	16	13
1957	6	5	4	3		4	6			14	10	38	28
1958	3	3	4	4		9	25			19	10	60	56
1959	30	29	5	5		5	28			30	11	98	78
1960	19	18	3	2		5	26		1	24	7	78	59
1961	10	5	5	3		5	29		-	20	12	69	54
1962	13	7	5	3		5	32		-	18	9	73	56
1963	7	5	6	5		14	24		-	15	5	66	53
1964	15	13	3	3	6	13	35		1	13	4	86	75
1965	18	12	2	1	5	7	31		3	14	8	80	67
1966	20	14	5	2	4	8	31	1	3	10	4	81	66
1967	13	9	3	0	6	9	20	7	7	5	3	63	54
1968	19	14	1	1	3	14	2	10	4	4	1	55	47
1969	11	9	2	2	5	14		10	-	7	3	49	43
1970	20	17	3	3	8	21		17	3	13	3	85	72
1971	25	23	3	2	8	14		16	-	8	1	74	64
1972	16	13	4	4	4	13		14	3	7	7	61	58
1973	23	20	2	2	4	10		11	-	3	1	53	48
1974	25	24	0	0	8	2		10	-	5	2	50	46
1975	33	31	1	1	0	4		13	2	3	3	56	54
1976	34	31			1	15		12	1	13	8	76	68
1977	23	17			4	16		12	2	14	12	71	63
1978	5	3			5	22		16	2	7	6	57	54
1979	4	4			2	16		10	0	15	15	49	49
1980	5	4			2	13		3	2	4	4	29	28

Patent Count by year of application

Notes: Column 1 = Total Column 2 = Products
*Column 1 from Farmdoc 1 Column 2 from Farmdoc 2

Table 7.2

Year	Beecham		Boots		Fisons		Glaxo		R&C		Wellcome	
1959	3	3	7	5							1	1
1960	6	6	10	7			12	9			14	14
1961	32	32	6	5			18	14			11	11
1962	24	22	6	2			17	9			17	13
1963	11	11	9	3			13	5	1	1	37	35
1964	14	13	14	8			19	16	-	-	41	30
1965	11	8	7	2			10	9	-	-	33	30
1966	17	16	10	9			20	14	-	-	15	9
1967	12	9	8	7	2	1	21	12	-	-	26	20
1968	24	21	2	1	16	7	11	9	5	4	20	15
1969	12	9	8	7	8	3	12	11	10	0	14	10
1970	19	13	6	3	9	8	12	12	2	1	12	9
1971	28	18	3	1	5	4	17	16	6	3	6	4
1972	7	7	-	-	-	-	20	20	-	-	-	-

Patent count by publication year of G.B. equivalents, Name Index data

Second column gives 'cleaned data'

Table 7.3

Year	Beecham		Boots		Fisons		Glaxo/A&H		ICI		R&C		Wellcome	
1970	5		-	-	2	1	-	-	8		1	1	1	
1971	17		2	2	0	0	10	10	9		2	2	3	
1972	12		3	2	11	7	13	12	18		1	0	4	
1973	23		4	4	4	4	18	12	25		2	2	9	
1974	26		2	2	9	5	27	16	19		1	1	11	
1975	26		4	4	8	8	24	17	18		2	2	5	
1976	26		2	2	5	5	29	24	32		1	1	15	
1977	38		1	1	8	4	13	7	17		0	0	5	
1978	34		1	1	4	2	8	8	28		2	2	10	
1979	60	29/31	0	0	7	6	15	14	25	15/10	2	2	21	7/14
1980	76	36/40	1	1	8	7	36	32	26	10/10	2	2	20	13/7
1981	88	27/61	1	0	6	2	44	36	17	8/9	3	3	34	18/16
1982	19	5/14	1	1	1	1	10	10	14	0/4	1	1	4	2/2

Patent count by publication year, Farmdoc families

Note: GB/EP. First column uncleaned, second column cleaned in other cases.

Table 7.4

Year	Beecham	Boots		Fisons		Glaxo/A&H		ICI	R&C		Wellcome
1970	11	2	2	10	8	13	10	15	4	3	4
1971	22	4	3	3	3	23	19	15	3	3	9
1972	30	3	3	9	8	35	23	30	1	1	12
1973	27	4	4	6	6	19	14	24	2	2	8
1974	22	4	4	7	6	28	21	17	1	1	9
1975	24	1	1	4	4	13	8	24	0	0	8
1976	29	1	1	3	3	8	8	25	2	1	6
1977	44	0	0	3	2	19	15	15	1	1	11
1978	35	0	0	3	3	19	16	17	4	4	5
1979	46	1	1	4	3	17	16	20	2	2	19
1980	50	1	1	7	6	17	15	19	0	0	16
1981	63	0	0	5	1	19	16	12	1	1	21
1982	19	1	1	-	-	9	9	5	1	1	2

Patent count by accession year of basic patent, Farmdoc families

Table 7.5

Year	Beecham	Boots	Fisons	G/A&H	ICI		R&C	Wellcome
1958	-	-	-	2				
1959	-	-	-	6	2	-		
1960	-	1	-	2	12	-		
1961	-	4	-	11	19	-		
1962	-	0	-	11	14	1		
1963	-	0	-	11	21	1		
1964	-	0	-	10	30	0		
1965	-	1	-	18	32	1	-	-
1966	3	2	2	5	34	1	-	-
1967	2	2	0	9	35	8	2	1
1968	10	2	2	19	29	12	3	4
1969	15	3	6	10	19	10	1	8
1970	27	5	6	30	26	18	2	9
1971	30	2	11	23	39	29	0	9
1972	24	4	2	26	33	21	3	3
1973	25	1	6	21	28	22	0	12
1974	30	1	7	13	38	26	0	11
1975	29	1	1	4	26	23	2	4
1976	42	1	4	22	23	18	1	9
1977	42	0	5	10	22	16	4	16
1978	45	0	4	23	8	19	1	12
1979	53	1	5	8	2	13	0	16
1980	44	0	3	0	1	8	1	8
1981	7	1	1	-	-	4	1	1
				*	(a)	(b)		

Patent count by year of priority, Farmdoc families

* 43 pre-1958. F.1. data

(a) F1 (105 pre-1958)

(b) F2

Table 7.6

Year	Number of Families		
	Ordinary	Steroid	Total
1958	-	2	-
1959	-	3	-
1960	-	0	-
1961	-	2	-
1962	-	2	-
1963	-	2	-
1964	-	4	-
1965	-	7	-
1966	-	2	-
1967	-	1	-
1968	3	8	11
1969	11	6	17
1970	22	13	35
1971	17	4	21
1972	16	10	26
1973	16	3	19
1974	8	4	12
1975	6	0	6
1976	20	2	22
1977	13	1	14
1978	22	1	23
1979	16	0	16
1980	17	0	17

Glaxo/Allen & Hanbury: count by year of priority. Farmdoc 2 data.

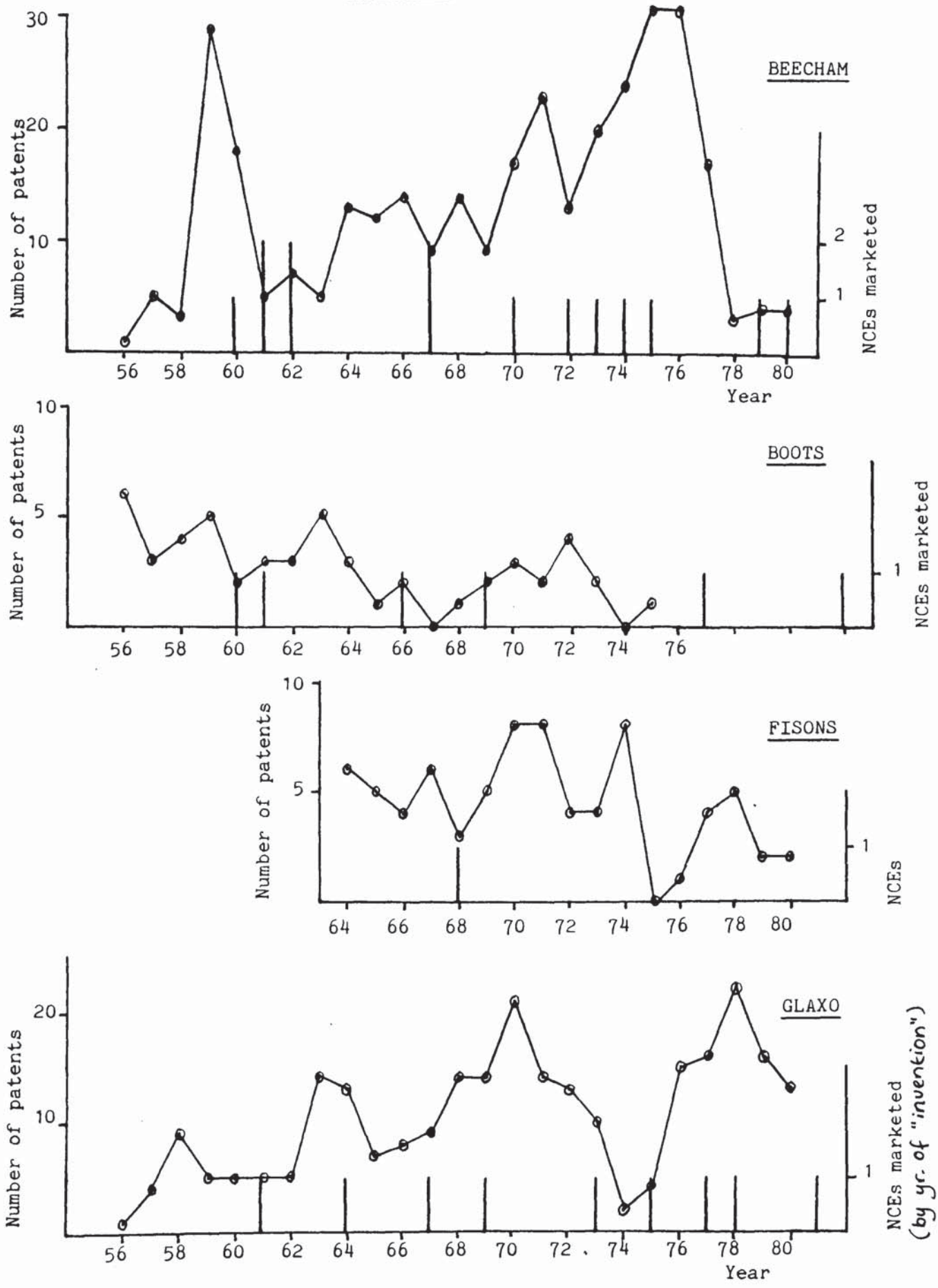
7.3 Examination of patenting trends

A number of criteria are open to examination in this area, a fact which encourages the adoption of computer-based searching of patent data on a wider basis. For the companies studied it is possible to identify areas of divergent patenting activity. The type of claim made, location of priority application, size of patent family and the general level of patenting activity can all be studied in detail.

In terms of the type of claim, Boots, for example, make use of the 'product by process' claim in many cases which makes for some difficulty when attempting to distinguish between product and process patenting activity. Other firms studied used this approach to a lesser extent and are therefore easier to study. Priority applications exhibit wide variations with Beecham, for example, using Britain almost invariably whilst Boots make use of priority in the United States in many cases. Glaxo tended to patent priority applications in Japan around the mid-1970s particularly. ICI, as expected of a multinational company, exhibit a substantial degree of foreign priority patenting with, in some cases, no British priority given, Reckitt and Colman as a smaller pharmaceutical operation use Britain for the majority of patents. Fisons as a relatively late starter in the field use the Eurpoean patent for most applications. These considerations are important if international patenting is to be examined as an indicator of industrial strength. Additionally, if output is to be studied then foreign patenting policy must be considered if an accurate assessment of inventive activity is to result. Although these aspects are not of major importance to the present study they may be of assistance to future researchers.

If the patent output of the companies over the period of study is examined (see figures 7.1) a number of points are evident.

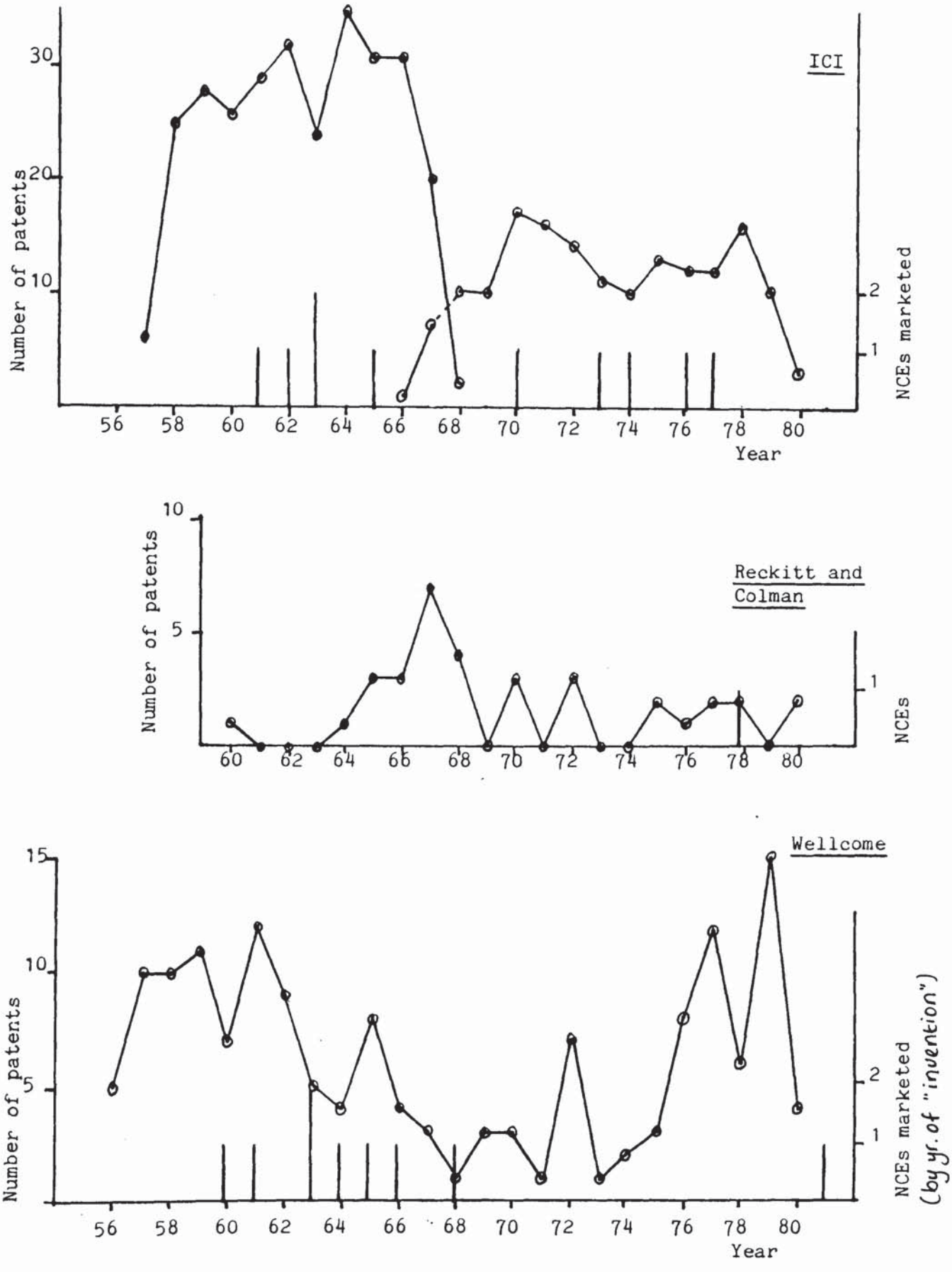
Figure 7.1



Patents Granted to U.K. Owned Companies (1956-1980) by Year of Application-

Novel Single Chemicals

Figure 7.1 cont.



Patents Granted to U.K. Owned Companies (1956-1980) by Year of Application-

Novel Single Chemicals

Major pharmaceutical companies such as ICI, Wellcome, Beecham and Glaxo may apply for a large number of patents for single chemicals each year. The former three companies show peak patenting rates of over 30 published patents per annum whilst Glaxo had a peak of around 20 per annum. The smaller firms such as Boots, Fisons and Reckitt & Colman may have less than 10 patents per annum as a peak. On this basis patents may be fair general indicator of the level of inventive effort.

Analysis of trends in patenting rates show inter-firm variations between firms of similar size. Figures are presented whenever possible for total patent output as well as patenting for novel single chemicals. Even though the patent searches were designed to eliminate most non-chemical patents and non-pharmaceutical inventions there were considerable non-relevant patents included. The extent of this error is given in the tables presented earlier.

Specific differences between firms include the decline in overall patenting rate for Wellcome from a peak of 30 in 1959 to 3 in 1975 and subsequent recovery to 15 in 1979. Their single chemical patenting shows a similar trend but with lower levels.

Beecham's patenting rate for both sets of data indicates a sharp peak in 1959 with a decline in the early 1960s followed by a sustained increase to a new high of 35 in 1976. Glaxo patenting activity also shows a decline but in the mid 1970s. The ICI pattern is complicated by the availability of two sets of data generated from separate computer searches with slightly different profiles. Both sets were made as comparable as possible by manual elimination of non-chemical patents in the original, more general, search. Allowing for these constraints, the trend for ICI is a gradually declining output. The early data must be regarded with some caution but since this pattern is not confined to ICI the trend may be given some credence.

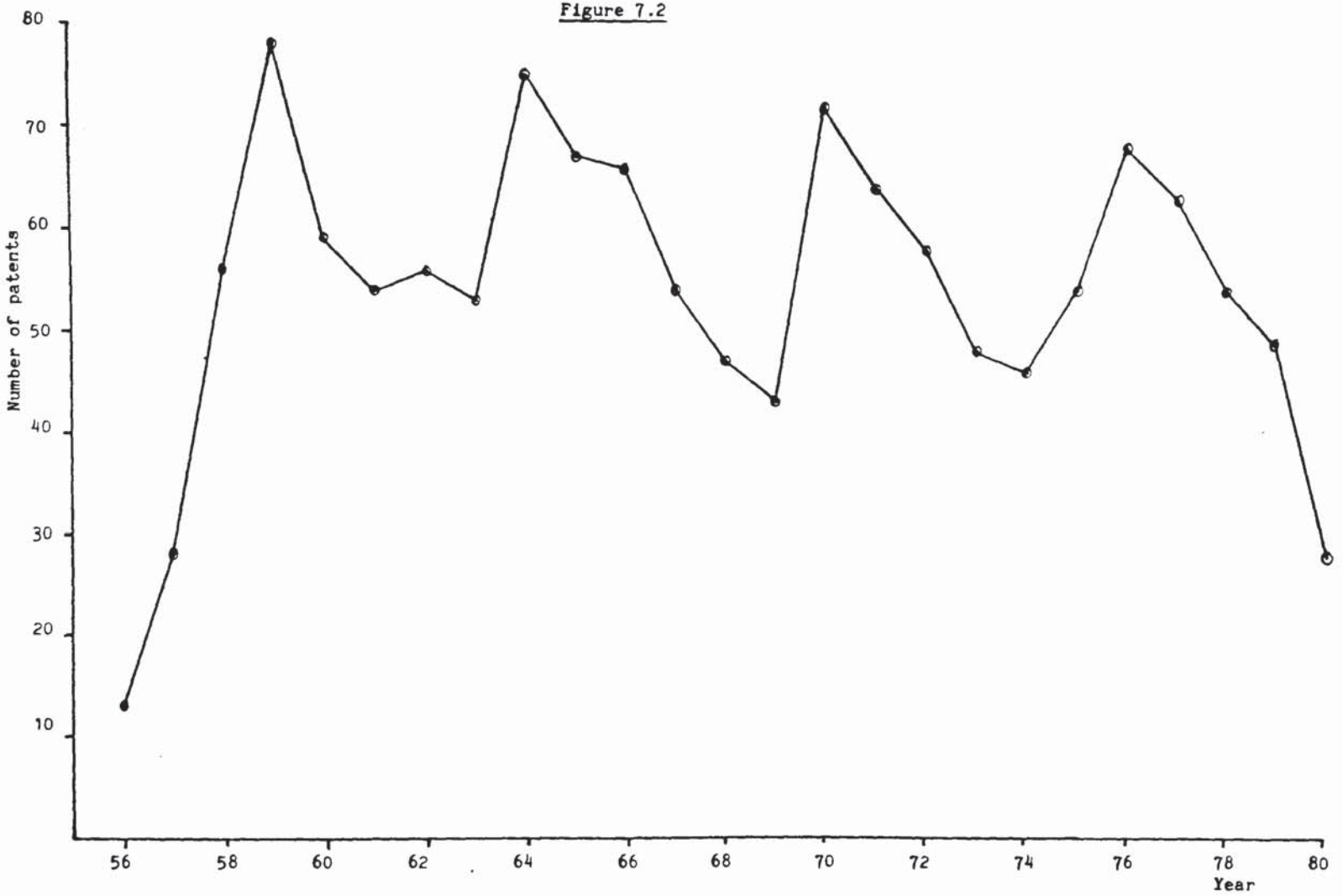
The smaller firms are more difficult to analyse with fewer published patents generally. For these firms the most significant findings include the constant decline in activity for Boots over the period. Although starting from a low output of 7 patents in 1956, this level has not been repeated. Fisons' peak activity was for 1970 and 1974 with 8 patents in each year, since then their output has declined. Reckitt and Colman had a peak patenting activity in 1967 with 7 applications followed by a very low and erratic output ever since. The activity for Fisons and Reckitt & Colman may accurately reflect the research activity of companies with interests in a few product areas and having limited research facilities.

Overall the data obtained compares well with the more general patent outputs presented by Nolan and Withers in earlier chapters. The decline in patenting activity that they described for the most recent period they studied does in fact turn out to be a result of the incomplete nature of the database for the later period. As mentioned earlier the decline in activity in the most recent period in this study must similarly be attributed, in part, to the database.

From the above evidence there is a degree of variation in patenting activity between the companies studied. This variation may be explained by a number of factors including company size and structure, nature of business interests outside pharmaceuticals and a number of other policy, organizational and commercial factors. This inter-firm variation would not be evident in any aggregate study of the industry. Patent data at this level may be used in an analysis of the effects of external factors on individual firms as well as on the industry in general.

If the data are aggregated to give the information for the U.K. owned industry (see figure 7.2), a small but significant decline

Figure 7.2



Patents Granted to the U.K. Owned Pharmaceutical Industry (1956-1980) by Year of Application- Novel single Chemicals

in overall patenting activity is evident as well as a smaller decline in single chemicals patenting. This result compares markedly with the findings of Reekie and Walsh et al in studies of general chemico-pharmaceutical patenting. Both of these previous studies showed a constant increase over the period since 1956. It appears that pharmaceutical patenting in Britain on a general aggregated basis may have risen over this period but patenting by the U.K. owned firms for single chemicals has declined. This decline may be important if it can be correlated with a slight decline in the output of NCEs. The relationship between patenting as an indicator of inventive activity and product marketing as an indicator of innovative output is important to determine. Earlier chapters have contained arguments for the use of patents as indicators of inventive activity but also have indicated the effect of variations in company policy on the timing and rate of patent application. The fact that patenting activity may be a result of inventive activity combined with company patenting policy necessitates a more detailed examination of the patenting activity of the industry and its relationship with the other indicators used. Before attempting such analyses, one further factor needs to be studied, that of patent family size and the utility of such indicators.

7.4 Examination of patent family size data

Patent family size data appeared to be a potentially useful indicator of the importance placed on an invention by a company. Variation in company policy regarding the number of equivalents allocated to any invention tends to complicate the issue. In an earlier section it was noted that two measures of family size were chosen as measures of importance. The first makes use of all patents with a family of equivalents of greater than 14 and the second of greater than 4. The former measure

was assumed to be a good indicator of significant inventions as most NCEs identified as being related to specific patents had family sizes of greater than 15. Amoxycillin had 18 equivalent patents and Talampicillin had 52. The second measure was chosen as a more general indicator of importance as any patent with more than two or three equivalents can be assumed to have more than a minor level of importance to a company.

A broad analysis of equivalents patenting revealed inter-firm variation over the period of study. Beecham generally favour large families whilst ICI have increased their average family size over the period. Smaller firms such as Boots, Reckitt & Colman and Fisons tended to use large families, a behaviour based on economic reasoning as these firms patent relatively few inventions and may be able to justify the expense of wide international protection for their inventions. The use of family size as an indicator of importance is only wholly satisfactory if, over the whole period, the policy of a company regarding family size is constant. Since this does not appear to be the case the use of family size must remain tentative.

If the industry as a whole is examined then it is clear that patents with the largest family sizes have declined over the period. This may be due to either a decline in patentable important inventions or a change in patenting policy. If the former is true then this has implications for the inventive and innovative output of the industry. If family size is proven to be unrelated to inventive or innovative output then this concern will be unjustified. The following sections will attempt to establish relationships between family size and other aspects of patenting statistics and other science and technology input and output indicators.

Table 7.7

Year	Beecham	Boots	Fisons	R&C	Wellcome	Glaxo	ICI	all
1966	-	-	-	-	-	-	2	2
1967	-	-	-	-	-	1	-	1
1968	1	1	1	-	-	-	1	4
1969	-	-	1	-	3	-	1	5
1970	-	1	2	-	7	2	2	14
1971	3	-	1	-	6	5	3	18
1972	3	3	-	-	2	-	7	15
1973	13	1	1	-	-	4	1	20
1974	7	-	3	-	2	-	2	14
1975	17	1	-	1	2	-	6	27
1976	6	-	-	-	7	2	4	19
1977	6	-	-	1	3	2	5	17
1978	5	-	3	1	1	3	9	22
1979	12	-	2	-	2	4	5	25
1980	1	1	1	-	1	5	2	11

Number of patents with family sizes of 15 or greater, by application year

Table 7.8

Year	Beecham	Boots	Fisons	R&C	Wellcome	Glaxo	ICI	all
1966	0	-	-	-	-	4	18	22
1967	0	-	1	0	-	3	7	11
1968	4	1	1	1	-	7	4	18
1969	6	1	4	0	7	10	6	34
1970	13	1	5	1	10	19	8	57
1971	15	2	5	0	7	11	8	48
1972	12	3	1	2	6	12	12	48
1973	19	2	4	0	2	9	6	42
1974	18	0	4	0	4	2	7	35
1975	24	1	0	1	3	4	9	42
1976	28	0	0	1	11	15	9	64
1977	21	0	1	2	13	15	7	59
1978	33	0	5	2	5	19	16	80
1979	45	0	4	0	14	16	10	89
1980	39	1	2	0	4	12	3	61
1981	-	1	-	2	-	0	-	3

Number of patents with family sizes of 5 or greater by application year

Data were available for 1957-1965 for ICI and Glaxo and are as follows:
ICI: 0,1,2,1,9,14,13,19,16. Glaxo: -,1,2,4,3,4,6,3,5.
all: 0,2,4,5,12,18,19,22,21.

7.5 Relationship between patent data and other indicators.

From the results obtained two measures of patenting may be regarded as the most appropriate to use in subsequent analyses, those of family size and overall patenting output for patents for single chemicals. Since patent information on a family size basis was only available for a relatively short timespan (1967-1980)for families of 15- and for a longer period (1958-1980) for families of 5- the extent to which these measures can be used with any accuracy is limited. Patenting of single chemicals was seen as a general output that could be correlated with NCE output with large family patents as a sub-set of potential importance.

To test the validity of patenting output in terms of large family patents as a proxy measure of overall patenting output, correlations may be attempted to assess the relationship between these two measures. It was assumed that any relationship between overall patenting levels and the patenting of inventions with a large numer of equivalents would be tenuous given the variation in approach to patenting, R&D and innovation identified in the companies of interest in earlier sections. In order to test these assumptions Product-Moment Correlation Coefficients (Pearsonian coefficients of correlation) were calculated.

The first calculation examined the relationship between overall patent output for the aggregated industry and patents with family sizes of more than 14. The resultant coefficient of +0.005 was statistically insignificant. This demonstrated the lack of correlation between the two measures and validated the assumptions made. A further calculation used the overall patenting output against patents with family sizes of more than 4. For this calculation, more data was available for family size and the data was grouped into five year blocks to eliminate minor fluctuations in patenting. The data used is presented in table 7.9. A resultant

Table 7.9

Years	Patent applications	Family size 15-	Family size 5 -	NCEs
1956-1960	235		11	16
1961-1965	305	12	92	15
1966-1970	282	24	142	11
1971-1975	270	94	215	7
1976-1980	262	94	353	-

Summary of patent data for use in correlation calculations

coefficient of +0.00003 indicated that there was little relationship between overall patenting output and the output of relatively important inventions. It may be concluded from this analysis that a high level of patenting bears little relationship to the output of patents with large families of either type. A further series of analyses needed to be conducted to determine whether family size was statistically related to any other indicator of important inventions.

Similar calculations were made to determine the extent to which patenting was an acceptable indicator of inventive or innovative activity. Correlations for innovative activity were conducted using NCE output for the industry as a measure of innovation. The NCE data used was as described in Chapter two and given in Appendix A. The data are summarised in table 7.10, dates refer to the date of application for the patent that contained the chemical of interest. This method was necessary to avoid having to use estimated invention dates for every drug. For some drugs, particularly those marketed from about 1978, little patent data could be obtained and for these products estimated invention dates were used. The estimates were based on average times from invention to marketing for all available accurate lags. The estimates are outlined in table 7.11. A list of NCEs by date of marketing is also given for comparison in table 7.12 and also in figure 7.3. Since the output of NCEs, even on an industry level, per annum is low, aggregation into five year blocks was again thought to be appropriate. The aggregated data are again presented in table 7.9.

For correlations between overall patenting rates and the NCE output of the industry, a result of -0.00004 for NCEs by invention date against patent output and +0.008 for NCEs by marketing date showed a lack of any direct relationship between patent output and NCE output. This is an

Table 7.10

Year	Number of NCEs patented in year
1956	2
1957	0 (1)
1958	2
1959	5 (3)
1960	3
1961	4
1962	5
1963	2
1964	3
1965	1
1966	3
1967	0
1968	2
1969	1 (2)
1970	1 (2)
1971	1 (1)
1972	0 (2)
1973	1 (1)
1974	1

NCEs Marketed by U.K. Owned Companies by Year of Patenting (1956-1974)

Note: Figures in brackets are drugs originating in companies other than the introducing company. These are excluded.

Table 7. 11

Year of introduction	Average time to reach market (yrs)
1960	3.2
1961	2
1962	2.5
1963	4
1964	6.5
1965	7.5
1966	8
1967	6
1968	8.3
1969	5.5
1970	6
1971	-
1972	10
1973	8.3
1974	8
1975	5.5
1976	11.5
1977	9
1978	5
1979	-
1980	-
1981	7
1982	-

Time lags from patenting to marketing in the UK

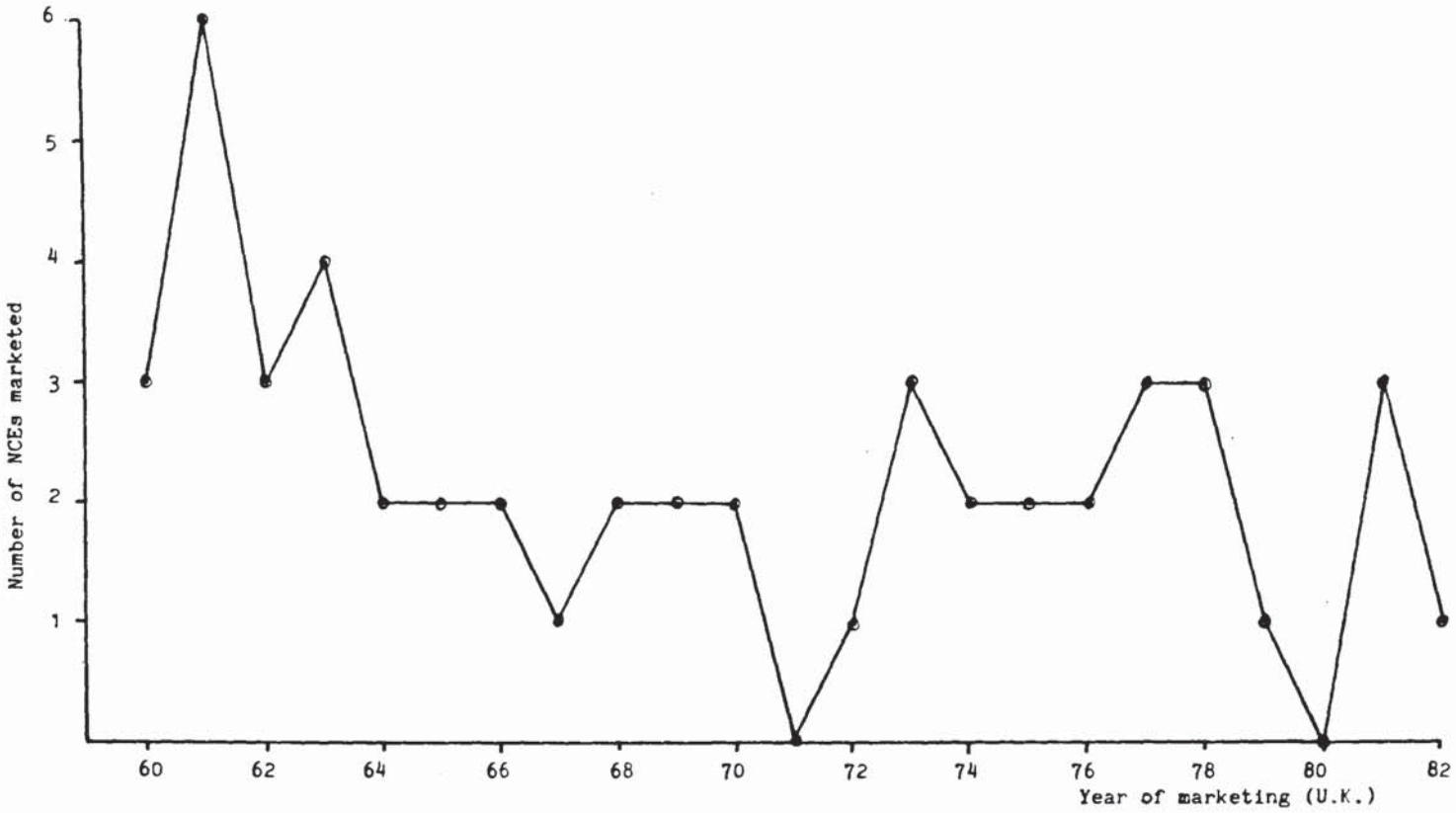
Table 7.12

Year	Number of NCEs
1960	3(1)
1961	6(3)
1962	3(1)
1963	4
1964	2
1965	2
1966	2
1967	1(3)
1968	2
1969	2(2)
1970	2
1971	0
1972	1
1973	3(1)
1974	2
1975	2
1976	2(1)
1977	3
1978	3(1)
1979	1
1980	0(1)
1981	3
1982	1

NCEs Marketed by UK Owned firms and attributed to them

() means that these NCEs have been eliminated from the table because they had a patent reference originating in another company indicating that the UK company was not responsible for the innovation. This process is more difficult for Wellcome who have a large US research base and a patenting policy that results in inventions being patented in both countries regardless of origin. In this case the inventions are deemed to be Wellcome inventions and are included.

Figure 7.3



NCEs Marketed by U.K. Owned Companies 1960-1982

important finding because it indicates that patent output data may be a poor indicator of innovative activity in the pharmaceutical industry. Few companies had sufficient NCEs on which to base any correlation for NCE output against patenting activity. An exception was Beecham and a similar calculation to the one above for NCEs by invention date against patenting activity gave a result of +0.091 which, although still statistically insignificant, is a better relationship than for the industry as a whole.

A second set of correlations between NCE output and the measures of family size outlined earlier were attempted. This was to assess the relationship between important patents and NCE output. From the earlier findings large families were a poor indicator of innovation and this was borne out by a coefficient of -0.003 for families of greater than 4 against NCE inventions 1956-1975. Insufficient data were available for the calculation using families of greater than 14. Large family size patenting may therefore bear little relation to subsequent innovative output in the idustry. However, given the limited amount of data available for patent families and NCEs, it may be that more information over a longer timespan may be required to obtain accurate conclusions.

A final series of correlations involved the use of R&D expenditure data. It was necessary to determine whether there was any relationship between the amount spent on R&D and the inventive or innovative output of the industry. Both measures of patenting activity (absolute numbers and family size) were correlated with R&D expenditure and NCE output. However, before such calculations could be attempted, a number of problems needed attention. The first, that of deflating the expenditure to account for price fluctuations had already been addressed in Chapter four. The second problem, that of the time lag from expenditure to patenting and subsequent marketing of the product is more complex.

NCE output had already been lagged to the date of invention or patent application, it remained to consider the lag between R&D expenditure and patenting. It may be argued that R&D expenditure on a drug continues in parallel with drug development but for this study the approach adopted was to lag R&D expenditure by three years, this being an estimated period from expenditure to patenting. This is a very conservative estimate but does take some account of time delays.

Deflated R&D expenditure data were used as calculated earlier and reproduced in table 7.13. Expenditure data were correlated with patents having family sizes of greater than 4 and this resulted in a coefficient of +0.005 which was again insignificant. For family sizes of greater than 14, the coefficient increased to +0.02 but remained insignificant. This meant that important inventions as measured by family size do not increase in frequency as R&D expenditure increases. This was not unexpected in some respects due to the unpredictable nature of the R&D process described earlier. For overall patenting activity and R&D expenditure 1967-1975, the coefficient was -0.001. The effect of not lagging the R&D expenditure was assessed by using R&D expenditures and patent activity for the same years. The result for this calculation was +0.004 which was again not significant.

The last correlation investigated was that of R&D expenditure and NCE output. However, from the data available there were insufficient pairs of variables from which to construct any meaningful correlation and this was not attempted. Clearly there was a need for more data over a longer timespan as well as a more specific R&D deflator

Summing up the limited number of statistical correlations possible, it seemed unlikely that any simple relationship existed between patenting activity and innovative output in the pharmaceutical industry.

Table 7.13

	£millions									
	Beecham		Wellcome		ICI		Fisons		All firms	
Year	Current	Real	Current	Real	Current	Real	Current	Real	Current	Real
1962	0.5									
1967			2.9	3.44					12.7	15.08
1968			3.6	4.04					12.3	13.86
1969	2.3	2.47	4.5	4.83					14.21	15.26
1970			5.7	5.70					18.1	18.10
1971	6.0	6.00	7.5	7.50			3.0	3.0		
1972			8.7	7.36					33.1	28.00
1973			9.9	7.71			11.0	8.56		
1974			11.5	11.50	11.5	11.50	3.10	3.10		
1975	11.2	5.80	15.9	8.32	15.0	7.85	3.50	1.83	58.5	30.64
1976	15.3	15.3	23.1	23.10			4.40	4.40		

R&D expenditures deflated*

* Used OECD deflator as described earlier.

Patents may be a better measure of inventive activity but more detailed information may be needed to eliminate the possibility of patents bearing some relationship to innovative output. Given the limitations of the data and the assumptions made in the methodology adopted, the results from the statistical analysis point to the following conclusions. Patent indicators fail to measure the level of innovative activity in the drug industry in the U.K., this allows for patents to measure some other aspect of the research and development process. If patents are better indicators of inventive activity, there is little evidence to suggest that large family patents are any better indicator of the level of inventive activity than overall patenting activity.

Statistical analysis of the data presented above resulted in some contradictions with earlier findings. In a preliminary study of three major U.K. firms (ICI, Beecham and Glaxo) published for an OECD patent workshop (see chapter six), there appeared to be some degree of correlation between patenting activity and the NCE output of the companies studied. Furthermore there was a remarkable correlation between patenting activity for the firms on an aggregated basis and R&D expenditure. Patenting activity appeared to increase in line with increasing R&D expenditure in real terms. The variation between these earlier findings and the more comprehensive current research needs to be explained.

The earlier findings were not tested statistically, additionally, the correlation between R&D expenditure and patenting was based on expenditure data for all companies operating in the U.K. rather than for U.K. owned firms. The current research used R&D expenditures for U.K. owned firms only. Generally, the current findings were based on more refined and selective data.

The results obtained from the correlation analyses tended to be unsatisfactory due to the limited amount of data available for correlations at a company level. It was considered that more information could be obtained from analysing each company in turn, making use of the case histories of the companies developed in an earlier chapter. The relationships between patenting, product output and R&D expenditure at a company level needed to be determined to assess whether there was any variation between firms. The methods employed in data collection and the results obtained allowed for a discursive approach to these questions. It may be suggested that aggregate correlations fail to take into account the differing characteristics of the firms of interest. To determine whether patenting, NCE output and R&D expenditure can be interrelated at a company level, each firm will be discussed in turn.

Figure 7.1 presents the patenting activity of each firm and the NCE marketing dates have been added to each company profile in order to assess the relationship between patenting and NCE invention. Since NCE invention dates are only accurate up to those marketed in 1978, only tentative conclusions can be drawn for the period since this time. Additionally, the last year for which NCE output data was available at the time of writing was 1982, this represents a cut-off point. NCEs marketed since 1978 will obviously have been patented some years earlier and these will be difficult to relate to patenting activity with any accuracy other than by using published research reports. Patent output data is similarly limited for the period 1978 on and is complicated by changes in patent law. Given these weaknesses, some analysis of each company is possible.

Beecham

The discovery by Beecham of the 6-APA molecule in 1957 and its extraction in a pure form in 1958 led to a large number of semi-synthetic then fully synthetic antibiotics. A patenting peak around 1959 seems to correspond to this increased research activity. Bencard merged with Beecham at this time increasing the scale of R&D activity. Launches based on research at this time followed in 1960, 1961 and 1962. This indicates a lag of only 3 years from research to marketing at this time.

The early surge in patenting activity ceased abruptly, followed by a more consistent patenting activity increasing as consolidation of research took place. Launches on a similar theme took place during 1967 and 1970. During 1972 Beecham reduced expenditure on antibiotics and this corresponds to a decline in patenting activity at this time. New research interests at this time helped maintain the level of patenting activity. A new peak patenting activity in the mid-1970s can be linked to the discovery and testing of clavulanate with an associated launch of a clavulanate-based product in 1981. This would indicate a lead time of about 6 years.

Therefore in terms of correlation, there appears to be a visibly good relationship between patenting activity and NCE output if the differing lead times are taken into account. This may be difficult to confirm on a statistical basis. R&D expenditure over the whole period increased gradually in current terms. A patenting peak in the mid 1970s may indicate the possibility of future Beecham launches in the mid to late 1980s.

Boots

Boots' antiinflammatory products research was accelerated in 1956 with a screening programme. The first product from this research was launched in 1966, a lead time of 10 years. This research continued throughout the 1960s with resultant launches in 1969 and 1977. Research appears to have declined in the late 1960s as difficulty was encountered in producing more

effective products. The increased patenting activity in the early 1970s may be explained by a switch to research into antiulcer products, a product of this type being launched in 1982. The lead time being 10 years. Boots' patenting activity in the mid-1970s declined to very low levels indicating that it is unlikely that the company will launch any significant in-house products in the near future. Any correlation between patenting and NCE output is less clear in this case as once again the tendency for increasing lags from patenting to marketing complicates any simple relationship. R&D expenditure data for Boots was not available in the sources examined and any correlation between patenting, NCE output and R&D expenditure is not possible.

Fisons

Fisons' patenting activity compared markedly with that of other companies. Research into antiasthmatics began as late as 1966 and resulted in the launch of disodium cromoglycate in 1968. Subsequent research and patenting centred on improved and novel drug delivery systems with which to administer the drug. Process patenting and drug delivery systems will not be fully represented in the patent data generated by means of the methods employed in the present study. Patenting of products has consistently been at a low level for Fisons.

A resurgence of patenting activity in the early and mid 1970s can be attributed to research into drug delivery systems as well as some continued research for new antiasthmatics. The decline in patenting in the mid 1970s may be a result of a lack of follow up innovation. A subsequent increase in activity in the late 1970s is consistent with the diversification policy adopted at this time.

The withdrawal of a new drug, proxichromil, just prior to launch in 1981 left Fisons with few research leads and a very low level of patenting activity. For correlation purposes, Fisons have few products (as NCEs)

on which to base any analysis, as well as a low level of patenting. Similarly, few details of R&D expenditure were available, R&D expenditure increased gradually over the period 1971-1983 (the figure for 1973 is probably for all research activities not just pharmaceutical). A halving of research expenditure in 1983 reflects Fisons' delicate economic position in pharmaceuticals at this time. The decline in patenting activity at this time may be due not only to the database but also to the restructuring of Fisons' research activities.

Glaxo

Glaxo, on the other hand, have demonstrated a consistent rate of drug innovation with product launches at regular periods since the early 1960s. However, it is difficult to relate the constant rate of innovation to the patenting activity of the company over the period. More information is available on product launches than research activity at various times. Product launches in the late 1960s may be related to patenting activity in the early part of the decade. Similarly, products launched in the late 1970s may correlate with patenting activity in the latter part of the 1960s and early 1970s. A patenting peak in the latter half of the 1970s may indicate possible products due for marketing in the future.

In terms of R&D expenditure, steadily increasing R&D expenditure throughout the 1970s correlates with a decline in patenting activity followed by a steady increase indicating that there may be no simple relationship between the two factors. Gaps in the R&D data do, however, prevent any generalisation and additionally the lag from patenting to marketing must also be accounted for.

ICI

The situation for ICI is similar to that of Glaxo in that patents and NCEs are difficult to correlate due to the frequency of output of marketed products and the methods employed in data generation. Increased patenting

activity was evident following ICI's relocation at Alderley Edge in 1957. The 1960s patenting activity is a resultant of two main policy decsions, a policy of diversification of research interests and a strengthening interest in a major field, that of antihypertensives. These interests led to product launches in the 1960s and 1970s. Continued interest in all fields resulted in a constant level of patenting activity throughout the 1970s. R&D expenditure increased throughout the 1970s and early 1980s and this corresponded to a fluctuating patenting activity for the same period. Patent information for the most recent period is incomplete and this prevents any assessment of the relationship between R&D expenditure and patenting for this period.

Reckitt & Colman

Reckitt and Colman have few product launches consistent with in-house R&D activity. Early ventures into pharmaceuticals in the late 1950s and early 1960s were conducted on a joint basis with J.F. Mcfarlane and it may be assumed that patents taken out were assigned to the latter company. From the time when Mcfarlane were acquired by Reckitt and Colman in 1963 patenting activity increased. The major product, Buprenorphine was launched almost 15 years after research on the product began in the mid 1960s. In the late 1960s an interest in cardiovascular drugs began but few patents appear to have resulted from this interest.

From the early 1970s a gradual decline in research activity can be correlated with a decline in patenting activity. For the period up to the halting of research in the early 1980s, few patents were taken out. Using the patent record the demise of pharmaceutical activities at Reckitt and Colman may, in hindsight, appear obvious. Insufficient R&D data are available for this company in order to make any reasonable assessment of the relationship between expenditure and patenting.

Wellcome

Any simple correlation between patenting activity and NCE output for Wellcome is complicated by the fact that the company has two major research and development facilities, one in the U.K. and one in the U.S. For Wellcome inventions in general it appears that NCE patents are attributed to the U.K. base. IF Wellcome patenting activity is compared with the output of NCEs by the company then the peak patenting levels of the late 1950s and early 1960s compares well with the NCE introductions of the early and mid 1960s. A lead time of 3 to 4 years from patenting to marketing seems reasonable for this period.

A reduced level of patenting activity in the mid 1960s to mid 1970s can be related to a gap in NCE product launches of approximately twelve years. Increased patenting activity in the latter part of the 1970s again may indicate possible future innovations. R&D expenditure figures for the company are more readily available than for other companies and a survey of data shows that Wellcome devoted increasing expenditure to R&D from 1967-1983. This increase was not mirrored in product output or patenting activity for the whole period indicating a variation in the return on investment.

A discursive account of trends in patenting activity, new chemical entity innovation and R&D expenditure using background information on research activities over the period of interest indicates that there may be more evidence for some relationship between these factors than was revealed in the statistical correlations for the aggregated U.K. owned industry. For the first decade of the period studied from about 1958 on, there appears to be evidence for a relationship between patenting activity and subsequent product innovation. Whether this relationship could withstand analysis at a statistical level requires further research.

A method needs to be developed which takes into account the lag from patenting to product launch and the variation in this period over time. Additionallly, the limited number of product launches for each company over the period restricts statistical investigation.

For Beecham, Glaxo and Wellcome, the relationship between patenting activity and NCE output is more obvious than for the other companies studied. These latter companies are generally smaller pharmaceutical companies and may merely be accounted for by the limited number of NCE launches involved. The most obvious conclusion may be that a low level of patenting activity does correspond to a low rate of product innovation. This is not very surprising given the importance placed on patenting by innovative pharmaceutical companies. Product launching without previous patenting activity can usually be explained by licensing from other drug companies, a tendency that is increasing and is most obvious in the smaller pharmaceutical companies. Any quantitative relationship between patenting activity and NCE output may not be simple but a high level of patenting activity appears to indicate future drug launches.

Patenting activity may therefore still be a reasonable indicator of inventive activity in the pharmaceutical industry and further research is necessary to determine whether patenting is a satisfactory indicator of potential innovation. From the documentary evidence presented and its relationship with the empirical findings, patent output appears to be a reasonable indicator of the level and diversity of research activity. Large swings in the patenting output of the companies could usually be explained by changes in research policy, changes in investment or other economic criteria.

The difficulty in relating patenting activity to NCE output or R&D expenditure in the companies concerned may indicate that the process that generates patents may have changed over time due to additional factors.

The observation that patenting related well to NCE output in the late 1950s and early 1960s but failed to do so in many cases for the subsequent period may be a result of additional variables affecting the R&D process. The impact of drug regulation is a factor that is obviously important. Two possible scenarios were formulated for the impact of drug regulation on the industry. In the first one, regulations would have little direct impact on the rate and direction of inventive activity and companies would continue to invent drug candidates as normal with any impact taking place at the marketing or late development stage as drugs were tested. This should result in no major fluctuations in patenting activity following the introduction of drug regulations. The second possibility was that the inventive activity of the companies would be directly affected by drug regulation and that this would result in a decreased level of patenting activity.

These hypotheses are more complex than outlined above and the non-regulatory factors including technical constraints and financial criteria would also have an impact on patenting activity. To partly elucidate the problem, the patenting activity of each company and the industry as a whole was examined with reference to the phases of regulatory stringency outlined in chapter one.

7.6 The influence of regulations.

In chapter one a number of regulatory phases were identified for the U.K. regulatory system based on the stringency of regulatory pressure at various times in the past. If the patenting activity of the industry is examined over the period of interest (Figure 7.2) it is possible to identify points where overall activity has declined significantly. A decline in patenting rate is apparent prior to 1964 which may be construed as a response to the anticipated formation of the CSD in 1964. A similar but more marked decline is seen in the period prior to 1971, the date of introduction of the 1968 Medicines Act. However, patenting activity is seen to peak at 1964 and 1970 confusing this simplistic analysis. Furthermore, if the effects of the 1964 CSD factor and the 1968 Act introduction are lagged by approximately 3-4 years to allow for the effects of regulatory change to be reflected in patenting behaviour, there is some evidence for a more direct effect of changes in regulation on patenting activity. The mere coincidence of events does not, however, imply cause.

The simple relationship between regulatory stringency and patenting activity does not withstand scrutiny at a company level. If the individual company patenting profiles are examined (figure 7.1), it must be noted that wide variations exist between companies in their apparent response to regulatory change. Clearly patenting activity must be influenced by factors other than purely regulatory criteria. The identification and elimination of these non-regulatory factors has been a constant problem associated with studies anlaysing the effects of regulation. It has been a problem that cannot be explained by purely economic factors. If the patenting trends for the larger firms are studied, divergent responses are seen. Firm size therefore cannot alone account for the differences and any decline in patenting activity or NCE output must be a result of the effects of different research

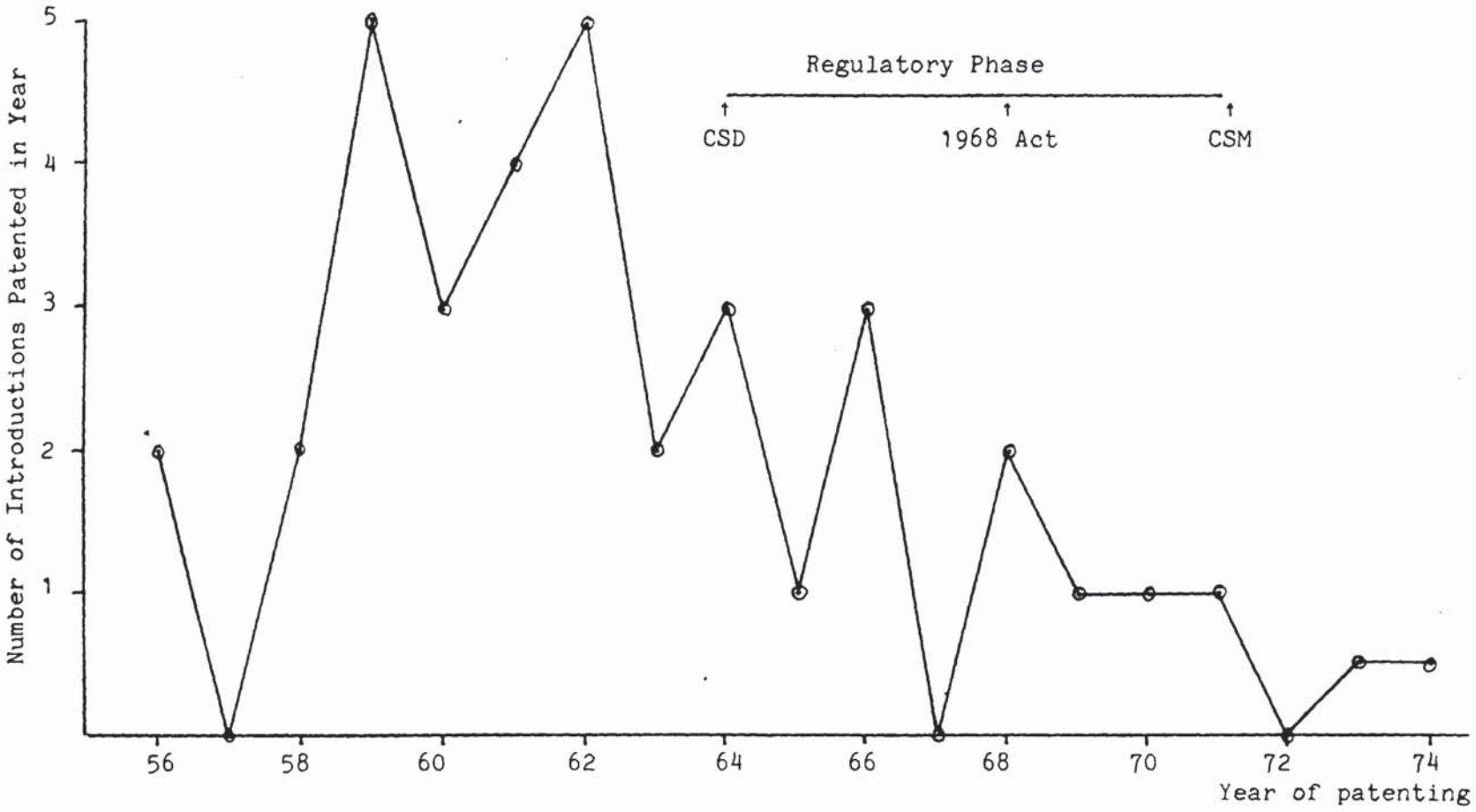
policies, pharmaceutical interests and, other technical and economic factors. The diversity in business practices and the complexity of the R&D process has been described and such criteria have been difficult to account for in any quantitative way in this study.

In terms of the effects of regulation on the rate of innovation as measured by NCE output, patenting of NCEs peaked in the early 1960s prior to the introduction of mandatory drug testing legislation but some account must be taken of the anticipatory effect. Figure 7.4 shows the number of NCEs by year of patenting together with an indication of the timing of major regulatory activities. From the figure it is apparent that the number of NCEs patented per annum declined since the early 1960s. However, the number of NCEs patented in this period appears similar to that following the implementation of drug legislation. Drugs may yet to be introduced but which were patented in this period.

A further explanation may be that firms increased their development and marketing activities shortly before legislation to pre-empt any regulations. Such questions may be elucidated by means of assessing the chemical and therapeutic significance of the pre- versus post legislation introductions in a similar approach to those outlined in earlier chapters.

If introduction dates are used instead of patenting dates, a different pattern emerges with a slight increase in introduction rates in the mid 1970s. The use of patenting dates may be a better perspective on the effects of external factors on inventive activities. The use of estimated invention dates for a few drugs does, however, complicate the picture and a lack of information on recent introductions is a further variable.

Figure 7.4



NCE Introductions by U.K. Owned Companies by Year of Patenting of the drug (1956-1976)

7.7 Analysis of patents by therapeutic and chemical classification

In chapter six the collection of data concerning the therapeutic and chemical coding of patents was described. A case-study approach was adopted with data being collected for one firm only, namely Beecham. Two codings were extracted from the patent files described, one for the therapeutic indications for each patent and the other for basic chemical classification. The results are presented in tables 7.14 and 7.15, the patent output is arranged by publication year rather than application year as the main object of the exercise was to determine the type and level of information available from searches of this type.

Since antibiotics patenting is coded under the chemical nature of the invention rather than under therapeutic classification, the latter illustrates Beecham's interest in other areas. Beecham appear to have research interests in all categories of drugs but trends can be seen in each of the categories. A severely reduced patenting activity in the field of antiparasitic compounds and antimicrobials conflicts with a considerable increase in products in the field of the autonomic nervous system and respiratory system.

Continuing interest is shown in the field of central nervous systems whilst new activity is seen in metabolism-active and blood active drugs..Strengthened interest in respiratory diseases occurred in the middle of the period of interest.

In terms of chemical classification, there appears to be a lack of any activity in steroids patenting. Beecham's main interest, that of antibiotics shows up as a high rate of patenting over the whole period with, in some cases, patenting in this area making up over 70% of all chemicals patenting as classified. Chemical classification details as outlined may be of interest to researchers interested in changes in research interests. It may be possible, given more information for

other firms, to determine relationships between patenting activity in various therapeutic and chemical fields with changes in technolgy and breakthroughs in basic understanding of disease processes and the industry's responses to these.

Since only one company was studied, few conclusions may be drawn other than to suggest the adoption of similar search criteria in more detailed analyses of innovative activity.

Table 7.14

	70	71	72	73	74	75	76	77	78	79	80	81	82
Antimicrobial	31.5	22.8	8.3	13.5	0	4.6	9.3	5	1.4	10.5	1.9	4.5	12.1
Antiparasitic	42.1	8.7	1.6	0	6.0	0	0	0	1.4	0	0	1.5	2.6
CNS active I	10.5	20.0	36.6	27.0	15.1	9.3	18.6	15.0	16.4	6.5	5.8	8.3	11.3
CNS active II	5.2	22.8	20.0	10.8	27.2	25.3	6.9	12.0	19.4	17.1	7.1	19.0	13.0
Autonomic N.S.	0	0	5.0	0	3.0	2.3	9.3	12.0	8.9	7.8	21.4	7.6	6.9
Cardioactive	0	8.5	10.0	10.8	3.0	11.6	6.9	9.0	5.9	2.6	13.6	6.1	4.3
Metabolism	0	8.5	1.6	13.5	0	4.6	16.2	11.0	11.9	22.3	16.2	9.1	12.1
Blood active	0	0	1.6	8.1	6.0	2.3	4.6	7.0	7.4	7.8	9.7	10.6	6.9
Gastrointestinal	5.2	2.8	1.6	0	6.0	13.9	9.3	9.0	5.9	3.9	8.4	12.9	12.1
Respiratory	0	0	1.6	2.7	24.2	20.9	9.3	15.0	8.9	7.8	11.0	8.3	3.4
Cosmetic	5.2	5.7	10.0	13.5	9.0	4.6	9.3	4.0	10.4	13.1	4.5	11.4	14.7
Formulations	0	0	1.6	0	0	0	0	1.0	1.4	0	0	0	0

Therapeutic Classification of Beecham Patents 1970-1982-Percentage of Total Therapeutic Classification

Table 7.15

	70	71	72	73	74	75	76	77	78	79	80	81	82
Steroids	0	0	0	0	0	2.9	4.4	0	0	0	0	0	0
Antibiotics	50.0	34.4	34.1	44.1	34.4	20.5	60.0	47.4	63.4	72.7	57.4	35.6	42.8
Vitamins	6.2	0	0	0	0	0	0	0	0	0	0	0	0
Natural polymers	6.2	13.8	7.3	8.8	3.4	8.8	6.6	6.7	4.8	5.4	14.8	8.2	8.9
Miscellaneous	6.2	0	0	5.8	3.4	0	0	0	0	0	0	2.7	0
Heterocyclics [1]	0	20.6	21.9	20.5	20.6	35.2	11.1	22.0	14.6	9.0	14.8	26.0	26.7
Heterocyclics [2]	18.7	13.8	26.8	14.7	27.5	11.7	6.6	13.5	14.6	7.2	7.4	12.3	17.8
Aromatics (1)	0	0	2.4	2.9	0	2.9	4.4	3.3	0	0	0	0	0
Alicyclics(2)	0	0	0	0	0	0	0	0	0	0	0	0	0
Aromatics and cyclo-diphatics	12.5	17.2	7.3	2.9	10.3	17.6	6.6	6.7	2.4	5.4	5.5	15.0	3.5

Chemical Classification of Beecham Patents 1970-1982-Percentage of Total Chemical Classification

[1] = Fused ring

[2] = Mononuclear

(1) = Polycarboxylic

(2) = Polycarboxylic

7.8 Suggestions for Future Research

Suggestions arise both directly from the research presented and from comments made by individuals contacted. The conclusions reached from the empirical studies were, in some cases, undermined by a lack of sufficiently accurate and extended series of data. In the case of R&D expenditure figures on the basis outlined, no recommendations can be made regarding additional sources other than direct contact with the companies concerned. This proved futile in the present study. Some progress should be possible in calculating specific price indices for the drug industry as R&D expenditure deflators. This was recommended by the OECD but requires detailed knowledge of price changes in current and capital expenditures including equipment prices, salary levels etc.

More sophisticated and flexible patent searches may be possible with the constant development of computerised databases. Derwent, for example, were interested in the use of patent statistics for reasons other than normal patent activity and encouraged researchers to detail specific search requirements in order to update databases so that the type of data required could be extracted. Similar approaches have been documented for similar systems in other countries. A specific suggestion would be to obtain more extended data on patent families in order to allow more accurate correlation analyses.

A number of interesting points arose from discussions with individuals in the drug industry and those involved in patent activities. Some of their suggestions were followed up to a limited extent but were usually outside the constraints of this study. Patent studies of specific drug areas using similar search methods as in the present research could be used to determine any differences between therapeutic field in terms of the rate of invention at various times. Linked to

this type of study could be studies tracing the rise and maturity of patentable subject areas. Bibliometric approaches could be used to identify key patents and citation mapping could be used to plot the development and relationships within the subject area.

A study of the role of the NRDC in stimulating drug innovation could begin with a study of the patents taken out by the NRDC followed by location of the companies in which these patents were being 'worked'. Interviews with staff at the NRDC were encouraging in that they had similar interests and intimated that data could be made available. Glaxo, for example, made use of NRDC held patents in several research programmes. The research into prostaglandins and their subsequent development was one major area of interest of the NRDC.

The subject of drug regulation has many associated issues which present interesting research problems. The effects of limited deregulation by means of the CTX scheme could be studied to determine whether there are any measurable effects on innovation and invention rates. This type of analysis is of obvious interest to the licensing authority as well as the companies. A number of projects have already been initiated to examine this issue. On a more historical basis, the identification of changes in testing regimes as a response to drug regulation is not well documented and would be worth examining.

Changes in social attitudes to drug regulation following the impact of specific drug related incidents such as those associated with Opren and Depo-provera could be studied. This could be linked to a study of the decision making process adopted in the regulatory authority which has come under criticism following such incidents.

External factors such as the implementation of limited drug lists as a cost cutting exercise by the DHSS and the effects of these on the

direction of inventive activity in the drug industry provide an interesting focus for research. A related issue was suggested by staff at the NEDO, SWP, they were interested in the relationship between the direction and rate of innovative activity in the drug industry and the mortality and morbidity characteristics of the population. This is a complex issue as drug research has world targets. Similarly, assessment of the relationship between drug output and 'social need' is complicated by various definitions of social need. These issues were investigated in a limited way during the present research but no detailed empirical studies were conducted.

Generally, the drug industry cannot be taken in isolation from social and governmental factors as well as financial and general economic criteria. This means that any study of the industry will result in a number of side issues and a need for a flexible and inter-disciplinary approach to research in this field is paramount.

APPENDIX A

NEW CHEMICAL ENTITIES INTRODUCED BY U.K. FIRMS 1960-1982

YEAR	APPROVED NAME	PROPRIETARY NAME	U.K. COMPANY	PATENT No.	APPLICATION	GRANT	COMMENTS
1960	Methicillin Sodium	Celbenin	Beecham	880400	150759	181061	
1960	Diloxamide furoate	Furamide	Boots	2912438	220754	101159	G.B. priority
1960	Bephenium hydroxy-naphthoate	-	Wellcome	819681	290356	221259	U.S. 2918401
1960	Procyclidine HCl	Kemadrin	Wellcome	2891890	190254	-	Lilly *
1961	Ampicillin	Penbritin	Beecham	873049	061058	190761	
1961	Propicillin K	Brocillin	Beecham	877120	250559	-	G.B. priority
1961	Cetoxime	Fibramine	Boots	895495	200160	020562	
1961	Fluocinolone acetonide	Synalar	ICI	965658	070959	060964	Syntex *
1961	Ertryptamine acetate	Monase	ICI	933786	120161	140863	
1961	Triprilidine	Pro-actidil	Wellcome	2712020	200748	-	Burroughs
1961	Betamethasone	Betnesol	Glaxo	901092	220757	110762	Scherico *
1961	Tigloidine HBr	Tiglyssin	D. F.	J. Am. Chem. Soc. (1937)			*
1961	Hydroxycortisone, 21-sodium succinate	β-Corlan	Glaxo				
1962	Cloxacillin	Orbenin	Beecham				
1962	Phenbenicillin	Phenspec	Beecham	877120	250559		
1962	Griseofulvin	Grisovin-FP	Glaxo	934527	040560	210863	(1931) *
1962	Etoglucid	Epodyl	ICI	901876	270460	250762	
1963	Bethanidine sulphate	Esbatal	Wellcome	973882	231259	151060	
1963	Azathioprine	Imuran	Wellcome	878646	210360	021062	Burroughs
1963	Clofibrate	Atromid-S	ICI	860303	200658	010261	
1963	Mebanizine	Actomol	ICI				
1964	Cephaloridine	Ceporin	Glaxo	1028563	141262	040566	
1964	Melphalan	Alkeran	Wellcome	783292	170353		U.S. priority
1965	Methisazone	Marboran	Wellcome	783292	170353		U.S. priority
1965	Propranolol	Inderal	ICI	994918	231162	100665	
1966	Allopurinol	Zyloric	Wellcome	798646	100855	230758	
1966	Ibufenac	Dytransin	Boots	971700	020161	300964	
1967	Bupivacaine	Marcain	D. F.	869978	290554		Swiss priority *
1967	Beclomethasone	Propaderm	A & H	912378			
				901093	220757	110762	Scherico *
1967	Carbenicillin	Pyopen	Beecham	1004670	230463	150965	Berk *
1967	Metoclopramide HCl	Maloxon	Beecham	994023	250761	020665	

1968	Trimethoprim and sulphamethoxazole	Septrim/Bactrim	Wellcome	875562 2888455	030959 040956		Burroughs
1968	Disodium cromoglycate	Intal	Fisons	1144906	250365	120369	
1969	Diazoxide	Eudemine	A & H	982072	190960	030265	Scherico *
1969	Cephalexin	Ceporex	Glaxo	696026	(Belgian)		Lilly *
1969	Salbutamol	Ventolin	A & H	1200886	230966	150970	
1969	Ibuprofen	Brufen	Boots	971700	020161	300964	
1970	Flucloxacillin	Floxapen	Beecham	905778			
1970	Practolol	Eraldin	ICI	1078852	300964	090867	
1972	Amoxycillin	Amoxil	Bencard	978178	021162	161264	
1973	Clobetasol propitionate	Dermovate	Glaxo	1253831	190168	171171	
1973	Tamoxifen	Novaldex	ICI	1013907	130962	221265	
1973	Fluocortolone	Ficoid	Fisons	990284	220261	280465	Scherico *
1973	Benapryzine	Brizin	Beecham	1007845	220863	221065	
1974	Viloxazine HCl	Vivalan	ICI	1138405	281266	010169	
1974	Carfecillin sodium	Uticillin	Beecham	1133886	051166	201168	
1975	Clobetasone butyrate	Molivate	Glaxo	1253831	190168	171171	
1975	Talampicillin HCl	Talpen	Beecham	1364672	090671	290874	
1976	Mianserin	Norval	Bencard	1064629	200765	050465	Organon *
1976	Fazidinium bromide	Fazadon	D.F.	1342713	030670	030174	A&H ?
1976	Atenolol	Tenormin	ICI	1285038	210269	090872	
1977	Labetalol	Trandate	A & H				
1977	Razoxane	Razoxin	ICI	978724			
1977	Flurbiprofen	Froben	Boots	1091403	240164	151167	
1978	Cefuroxime sodium	Zinacef	Glaxo	1453049	210873	201076	
1978	Buprenorphine	Temgesic	R & C	969262	020363	090964	J.F. McFarlane *
1978	Cephamandole						
1978	Fenclofenac	Flenac	R & C				[34645-84-6]
1979	Ticarcillin sodium	Ticar	Beecham				[34787-01-4]
1980	Ketazolam	Anxon	Beecham				[27223-35-4]*
1981	Ranitidine	Zantac	Glaxo				[66357-35-5]
1981	Acyclovir	Zovirax	Wellcome	1523865	020974	060978	
1981	Clavulanate/Amoxycillin	Augmentin	Beecham			[23256-39-5]	+ [74469-00-4]
1982	Pirenzepine	Gastrozepin	Boots				[28797-61-7]

[ ] indicates a Chemical Abstracts Registry Number as no patent numbers were obtained for these drugs.
* indicates a drug originating outside the U.K. company. These were not included in the lists of drug output.

APPENDIX B

PATENTS GRANTED TO U.K. OWNED PHARMACEUTICAL COMPANIES 1960-1982

Note: The following acronyms are used as column headings.

PN - Patent number (G.B. or E.P.)

DOA - Date of application or priority for 2 million series & EPs

DOFCS - Date of filing complete specification

DOP - Date of publication

Numbers in brackets are patent family sizes (equivalents for that patent)

NCEs related to the patents are given whenever possible.

B1. BEECHAM

PN	DOA	DOFCS	DOP	COMMENTS
820503	090756	300957	230959	
820954	020556	250457	300959	
823733	071256	271157	181159	
833807	100757	240658	270460	
833820	171057	250958	270460	
836280	200158	121258	010660	
838974	300457	090458	220669	
845021	290357	100358	170860	
859260	281157	221058	180161	
861377	100157	020158	220261	
870395	020858	150758	140661	
870396	020858	150758	140661	
873049	061058	230959	190761	Ampicillin
873244	100459	010460	190761	
873533	230359	110360	260761	
876508	090659	230560	060961	
876516	080659	230560	060961	
876662	150659	250560	060961	
877120	250559	100560	130961	Propicillin
877323	170759	050760	130961	
877497	170759	171159	130961	
877531	170759	050761	130961	
878233	220159	010160	270961	
880042	090659	270560	181061	
880400	150759	200460	181061	Methicillin sodium
882335	020759	200660	151161	
885424	290659	250560	281261	
885425	150659	250560	281261	
886436	170659	310560	100162	
886437	150759	280660	100162	
888110	221059	211060	241060	
889066	131159	031160	070262	
889069	131159	031160	070262	
889070	131159	031160	070262	
889168	161159	101160	070262	
890201	091159	291160	280262	
891279	161159	101160	140362	
891586	041159	031160	140362	
891777	131159	031160	210362	
891938	301159	181160	210362	
892144	300159	120160	210362	
893518	221059	211060	110462	
894247	250160	240161	180462	
894457	131159	131160	180462	
894460	160260	120261	180462	
900666	130560	020561	110762	
902703	250860	190561	090862	Ampicillin POA
903785	150860	090661	220862	
905427	020759	220660	050962	
905778	310360	140361	120962	Flucloxacillin
906383	180760	140761	190962	
910456	210960	170861	141162	
911482	061060	010961	281162	
911888	150960	100961	281162	
913441	120860	210761	191262	
914419	141060	270961	010163	
914451	100859	270760	020163	
916548	260161	290961	230163	
920176	250860	220861	060363	
920177	250860	220861	060363	
920300	251160	241161	060363	
931567	251160	241161	170763	
939708	010661	010661	161063	
940488	210761	230762	301063	
940489	210761	230762	301063	
940711	230661	190662	301063	
940712	230661	190662	301063	
943608	131260	120362	041263	
948074	240660	250961	290164	
949405	170561	300462	120264	
950662	180861	150862	260264	
952283	130262	310163	110364	
954243	230661	230762	020464	
958478	130362	280263	210564	
959853	280262	040263	030664	
960665	160362	280263	190664	
961627	060662	220563	240664	
962024	210562	130563	240664	

962025	210562	130563	240664	
975379	180862	010863	181164	
978178	021162	251063	161264	Amoxycillin PVA
978299	171062	171063	231264	Flucloxacillin
980777	271162	181163	200165	
986554	111262	111263	170365	
989882	040761	290662	220465	
991376	140263	130264	050565	
991586	280263	130264	120565	
1004670	230463	280464	150965	Carbenicillin
1007845	220863	290764	221065	Benapryzine
1016875	220663	110664	120166	
1029222	281163	061164	110566	
1033257	230464	140465	220666	
1034788	040564	140465	060766	
1035780	280564	200565	130766	
1038367	280563	280864	100866	
1039455	030764	220665	170866	
1040166	290764	070765	240866	
1041987	030964	180865	070966	
1044301	240464	230463	280966	
1048907	290764	190765	231166	
1051675	031264	111165	141266	
1053415	290764	190765	040167	
1053817	031264	221165	040167	
1053818	031264	261165	040167	
1054209	031264	221165	040167	
1057697	030964	090865	080267	
1059303	220165	060166	150267	
1060034	180165	060166	220267	
1061335	100265	060166	080367	
1064893	230365	110366	120467	
1066107	180365	020366	190467	
1067965	220165	140466	100567	
1071435	290565	180566	070667	
1080247	270765	080766	230867	
1092714	141065	131066	291167	
1114311	030764	300865	220568	
1118566	251164	181165	030768	
1122306	080765	040766	070868	
1122658	211065	211066	070868	
1123954	140566	120567	140868	
1125339	250366	220367	280868	
1125557	130566	090566	280868	
1128235	030366	200267	250968	
1128637	130966	040967	250968	
1130445	280466	180467	101068	
1130935	281066	231067	101068	
1131741	060265	240166	231068	
1133341	010165	211265	131168	
1133448	160265	080266	131168	
1133886	051166	301067	201168	Carfecillin
1134237	120666	110767	201168	
1134682	071065	300966	271168	
1134687	280466	280767	271168	
1138745	080966	081267	010169	
1139041	250566	170567	060169	
1140975	220966	200967	220169	
1141781	190167	100168	290169	
1154434	230167	230568	110669	
1157613	310765	210766	090769	
1160211	151266	131267	060869	
1162784	100468	110468	270869	
1169027	191166	061267	291069	
1169696	181165	311066	051169	
1172864	160266	310167	031269	
1174051	301165	251166	101269	
1174124	300667	300968	101269	
1175590	090867	060868	231269	
1180745	041068	021067	110270	
1185080	071267	051268	180370	
1192011	071267	190567	130570	
1192012	150767	150768	130570	
1192599	071267	011268	200570	
1193302	070367	060368	280570	
1197973	180467	180468	080770	
1199731	230466	240767	220770	(1)
1205741	140666	120967	160970	(1)
1205742	140666	120967	160970	(1)
1210472	190168	170169	281070	

1210472	100168	170169	281070	
1217143	130267	120268	311270	
1217415	040768	090669	311270	(6)
1220201	070269	020769	200171	
1224619	140868	120869	100371	(10)
1229805	180368	170369	280471	
1230911	060168	201268	280471	(2)
1230115	011168	311069	280471	(1)
1231093	061267	051268	050571	
1234426	231068	081069	030671	
1236076	040768	200669	100671	(1)
1237283	180767	180767	300671	
1241844	230868	200868	040871	Amoxycillin
1243241	061168	311069	180871	
1243242	011168	311069	180871	(1)
1243243	131168	131169	180871	(1)
1243244	131168	131169	180871	(1)
1250531	010169	101269	201071	(14)
1250611	030268	310169	201071	
1250985	110968	120869	270971	
1255033	260768	150769	241171	
1255034	060968	050969	241171	(1)
1255035	130269	050270	241171	
1257266	050869	300770	151271	(15)
1260723	110169	260370	190172	(1)
1267433	140869	130870	220372	
1267936	280569	260570	220372	(7)
1268259	181169	021170	290372	(1)
1268424	041069	180070	290372	(8)
1269279	290769	280770	060472	(9)
1270831	221168	041169	190472	(13)
1284150	230470	190471	020872	(8)
1286199	100370	190471	230872	(10)
1297273	040470	190471	221172	(8)
1297555	220970	040871	221172	(5)
1297835	180870	080771	291172	(1)
1300261	050570	050571	201272	(9)
1307645	011070	011070	210273	(5)
1307646	311069	051070	210273	(6)

1314427	170770	080771	260460	(10)
1314428	260471	260471	260473	(9)
1314553	091070	300971	260473	(2)
1315397	250970	300971	020573	(11)
1315443	020371	090272	020573	(1)
1316612	131070	270871	090573	(1)
1318221	221070	131071	230573	
1321296	100970	090971	270673	(11)
1321815	020769	290670	040773	(10)
1322938	100970	090971	110773	(7)
1324752	040671	230572	250773	(4)
1335345	130170	040172	241073	(8)
1336170	141070	131071	071173	(5)
1340531	280171	120172	121273	(7)
1357633	020371	020372	260674	(9)
1359863	051171	031072	100774	(6)
1359992	301270	031171	170774	(8)
1360009	140970	090971	170774	(9)
1360457	091071	021072	170774	(1)
1360982	270870	240871	240774	(12)
1364312	270171	250172	210874	(1)
1364472	090671	230672	290874	(52) Talampicillin
1366513	241171	221172	110974	(6)
1371507	181271	101172	231074	(11)
1373346	091270	061271	131174	(11)
1373347	290971	120972	131174	(8)
1341449	170771	040772	191273	(2)
1377817	090771	230672	181274	(52) Talampicillin
1378381	180871	130772	271270	(11)
1383765	040871	060972	120275	(8)
1383766	040871	060972	120275	(8)
1389822	110571	200472	090475	(9)
1390402	240272	010273	090475	(5)
1390754	090671	230672	100474	(52) Talampicillin
1393981	200172	020173	140575	(12)
1400480	111172	1110 73	100775	(7)
1405758	210472	081172	100975	(8)
1406239	121071	101172	170975	(1)
1406993	091071	021072	240975	(1)
1407691	200172	061272	240975	(12)

1409947	161071	011072	081075	(1)
1412291	250172	071272	051175	(20)
1417745	070773	270674	171275	(12)
1421787	011272	121273	230176	(8)
1424166	081071	080972	110276	(5)
1426872	180173	170174	250276	(9)
1430074	130772	280673	310376	(11)
1432899	190473	190474	220476	(21)
1434645	111073	190974	050576	(14)
1435892	040772	200673	190576	(8)
1437088	250572	160573	260576	(11)
1437781	040472	180573	030676	(17)
1439878	291273	191274	100676	(1)
1441252	200672	100773	300676	(1)
1443441	240273	070274	210776	(20)
1444558	170273	210174	040876	(2)
1448366	041172	311073	080976	(10)
1448437	240273	070274	080976	(20)
1450043	080972	280873	220976	
1450764	140972	210873	290976	(2)
1451151	200374	040375	290976	(15)
1453863	190573	150574	271076	(25)
1454247	190473	190474	031176	(21)
1455529	270275	270275	101176	(6)
1456992	030473	210374	011276	(24)
1460269	111272	261173	311276	(1)
1460936	011074	230975	060177	(1)
1468012	090873	090774	280377	(2)
1470493	120875	120875	140477	(1)
1471235	180974	030975	210477	(7)
1472174	220973	090974	040577	(13)
1474377	110973	200874	250577	(23)
1476721	110973	200874	100677	(23)
1476906	190375	290176	100677	(12)
1479267	040573	080674	130777	(29)
1479297	040774	010775	130777	
1479711	120673	040674	130777	(33)
1479712	120673	040674	130777	(33)
1479713	120673	040674	130777	(33)

1480737	111073	300974	200777	(16)
1480747	180174	191274	200777	(2)
1482195	230873	310774	100877	(18)
1483142	150376	030376	170877	(22)
1486001	300774	180775	140977	(24)
1486272	270474	140475	210977	(9)
1489235	280374	120575	191077	(27)
1489332	111073	041074	191077	(12)
1489333	111073	041074	191077	(12)
1492393	210275	190275	161177	(21)
1493197	040775	300676	231177	(5)
1493848	240775	220776	301177	(18)
1493998	030675	250576	071277	(20)
1495526	310574	120575	211277	(15)
1495640	280775	230776	211277	(2)
1497109	291075	201076	051078	(6)
1497161	190775	230176	060178	(17)
1498025	151174	011075	180178	(8)
1501643	281074	260975	220278	(9)
1503918	180674	300575	150378	(11)
1504424	090875	050876	220378	(17)
1504426	131075	011076	220378	(11)
1504442	210176	251176	220378	(1)
1505345	100474	210375	300378	(2)
1505859	151275	121076	300378	(5)
1508314	101274	211075	190478	(2)
1508977	200474	110475	260478	(59)
1508978	200474	110475	260478	(59)
1509200	291074	270176	040578	(1)
1509400	151275	291176	040578	(10)
1509853	270176	151276	040578	(3)
1509904	040574	280478	040578	(12)
1509924	060674	040675	040578	(1)
1511187	020476	230377	170578	(11)
1512006	280574	210475	240578	(11)
1515241	270176	091276	210678	(9)
1524260	220176	231176	060978	(1)
1524818	291174	101175	130978	(29)
1524819	291174	101175	130978	(29)
1524950	181074	240975	130978	(1)
1525434	300776	270777	200978	(14)

1529434	221074	061075	181078	(12)	
1531141	170876	120877	011178	(14)	
1534508	181274	041275	061278	(15)	Clavulanic acid.
1538051	170175	080176	100179	(24)	
1538052	170175	080176	100179	(24)	
1538227	230375	270276	170179	(19)	
1538473	130576	011076	030577	(13)	
1542405	150475	080476	230379	(4)	
1544467	140475	180376	100579	(18)	
1546622	200276	091276	230579	(1)	
1546937	290776			(11)	not found
1547165	150875	230776	060679	(5)	
1547169	131075	121076	060679	(6)	
1548221	270176	171276	040779	(10)	
1548222	080476	171276	040779	(10)	
1551416	270876	220777	300879	(16)	
1552122	100575	100576	050979	(1)	
1552123	180276	251176	050979	(1)	
1554897	101276	221177	311079	(10)	
1555335	210675	140576	071179	(5)	
1555753	110277	100278	141179	(9)	
1560726	280476	270677	060280	(13)	
1560942	251075	201076	130280	(17)	
1561592	050576	250477	270280	(2)	
1561023	220477	290378	130280	(12)	
1563427	040377	270278	260380	(2)	
1565083	200276	110277	160480	(8)	
1565209	131075	150976	160480	(31)	
1566706	131075	081076	080580	(27)	
1568962	311075	181076	110680	(22)	
1570146	271175	161176	250680	(17)	
1570147	271175	161176	250680	(17)	
1570495	161275	251176	020780	(10)	
1570582	271175	161176	020780	(17)	
1572184	251075	201076	230780	(24)	
1572185	251075	201076	230780	(24)	
1573153	260277	270278	130880	(2)	
1574906	310176	110177	100980	(20)	
1576007	110276	240177	011080	(13)	
1577725	300676	140677	291080	(5)	
1577931	290176	110277	291080	(5)	
1578730	240676	240677	051180	(7)	
1579362	160377	280378	191180	(5)	
1581598	250577	110578	171280	(1)	
1582884	190577	100578	140181	(4)	
1582944	030676	300577	210181	(11)	
1584762	010477	280378	180281	(2)	
1585181	220576	200577	250281	(11)	
1587403	220576	200577	010481	(10)	
1587612	301076	181077	080481	(4)	
1593146	051176	230178	150781	(11)	
1595176	031276	151177	120881	(10)	
1595177	031276	151177	120881	(10)	
1598073	181276	151277	160981	(14)	
1598074	181276	151277	160981	(14)	
1598662	181276	151277	230981	(17)	
1598663	181276	151277	230981	(17)	
1598664	181276	151277	230981	(17)	
1598665	181276	151277	230981	(17)	
1601107	100577	050578	281081	(12)	
1601688	050377	270278	041181	(9)	
1602960	250577	160578	181181	(14)	
1604672	190377	100378	161281	(6)	
1604673	190377	100378	161281	(6)	
1604822	220477	070478	161281	(18)	
1604823	220477	070478	161281	(18)	

2001966	140777	120778	140279	(5)
2004273	140977	020878	280379	(4)
2004541	160977	230878	040479	(15)
2006762	111077	021078	100579	(4)
2009154	101177	081178	130679	(5)
2013670	020278	010279	150879	
2014993	031177	111078	050979	(6)
2030134	130978	240779	020480	(1)
2030135	130978	080879	020480	(2)
2034694	111078	270979	110680	(6)
2037277	221278	311079	090780	(2)
2037770	101177	081178	160780	(5)
2042508	140279	311079	240980	(1)
2049660	79	160579	311280	(1)
2052981	020779	260680	040281	(5)
2061268	021079	260980	130581	(8)
2078217	140680	020681	060182	(1)
2084152	011080	230981	070482	(3)
2084568	160880	130881	150482	(4)
2083462	160880	110881	240382	(4)
2085438	210880	180881	280482	(3)

(EP) PN	DOA	DOP	COMMENTS
252	290677	100179	8(8)
254	200677	100179	19(7)
804	040877	210279	4(7)
816	060877	210279	4(7)
828	060877	210279	3(5)
1333	280678	040479	-
1914	051177	160579	4(5)
2310	270778	130679	9(8)
2312	261177	130679	6(7)
2371	031277	130679	8(9)
2562	101177	270679	4(7)
2564	121177	270679	4(3)
3069	011177	250779	11(7)
3254	260178	080879	3(7)
3410	120579	080879	5(8)
3740	190178	050979	7(6)
4132	040378	190979	2(8)
4134	040378	190979	5(5)
4723	131078	171079	5(8)
4740	010478	171079	6(8)
5006	210478	311079	11(8)
5014	271078	300480	6(9)
5348	300578	141179	6(9)
5349	260179	141179	3(9)
6352	150678	090180	2(8)
6353	150678	090180	8(10)
6718	150678	090180	2(8)
6719	150678	090180	6(10)
6735	271178	090180	4(10)
7152	060578	230180	2(8)
7180	150678	230180	4(8)
7717	290778	060280	4(8)
7727	161178	060280	3(8)
7753	250878	060280	2(8)
8186	080878	200280	4(10)
8497	060179	050380	2(8)
8514	250878	050380	7(8)
8877	090978	190380	3(10)
8884	090978	190380	2(8)
8885	090978	190380	4(8)

8889	230878	190380	-
8899	050978	190380	4(10)
9879	070978	160480	7(10)
9912	100179	160480	4(10)
10369	251078	300480	2(8)
10392	040779	300480	4(7)
11373	141078	280580	3(8)
11935	250479	110680	-
11963	050579	110680	6(9)
13067	221278	090780	2(8)
13138	090879	090780	5(9)
13153	271278	090780	2(8)
13790	050778	060880	4(10)
14076	180179	060880	4(9)
15690	250779	170980	7(9)
17352	240379	131080	5(6)
18107	200479	291080	6(9)
18134	210479	291080	6(10)
18203	210479	291080	4(10)
19457	170579	261180	6(11)
20018	190579	091280	5(10)
20039	230579	091280	5(10)
21587	080679	070181	6(11)
21636	160679	070181	4(10)
21836	020779	070181	7(11)
23083	270679	280181	4(10)
23093	020779	280181	5(10)
23385	160679	040281	4(10)
24105	120779	250281	4(10)
24372	030879	040381	1(11)
24807	280779	110381	3(10)
24832	170480	110381	6(11)
25271	030879	180381	4(10)
25287	210879	180381	1(11)
25288	310879	180381	4(10)
25331	060979	180381	5(10)
26611	280979	080481	6(10)
26644	021079	080481	8(11)
27323	061079	220481	4(11)
27324	270979	220481	4(11)
25064	280979	060581	2(8)
28083	261079	060581	4(11)
28105	251079	060581	5(10)
28449	280979	130581	2(8)
28489	051179	130581	5(11)
28497	291079	130581	4(11)
28883	101179	200581	1(10)
29320	151179	270581	4(10)
31219	201279	010781	4(10)
31653	191279	080781	5(10)
32048	080180	150781	2(7)
32314	090180	220781	2(7)
32821	190180	290781	2(7)
33612	020280	120881	3(7)
33613	020280	120881	2(7)
34002	220180	190881	3(7)
34004	190180	190881	4(10)
34015	300180	190881	4(10)
34443	140280	260881	2(11)
36269	150380	130981	2(7)
38629	120480	281081	2(6)
39552	220480	111181	4(9)
40000	080580	181181	4(9)
40915	220580	021281	4(9)
41322	300580	091281	4(9)
41768	240480	161281	4(9)
41813	060680	161281	3(8)
41817	100680	161281	2(8)
42232	060680	231281	2(8)
42705	180680	301281	3(8)
42706	210680	301281	2(8)
43197	020780	060182	2(8)
43205	260680	060182	3(8)
43659	090780	170282	2(8)
44142	030780	200182	3(8)
44170	110780	200182	3(8)
45150	240780	030282	3(9)
45219	300780	030282	3(8)
46031	020880	170282	3(9)
46349	160880	240282	3(8)
46363	160880	240282	4(7)
46372	160880	240282	4(7)

46652	210880	030382	3(7)
48096	130980	240382	1(8)

B2.

PN	DOA	BOOTS DOFCS	DOP	COMMENTS
820180	180956	260857	160959	process
822199	180956	260857	211059	
822978	150557	170658	041159	
825875	270656	140657	231259	
826995	091156	251057	270160	
828962	150757	080758	240260	process
840121	030256	240157	060760	
840122	030256	240157	060760	
840239	210158	080159	060760	
841824	240256	240157	200760	
845916	170957	040958	240860	
850394	081157	291058	051060	
855556	060558	140459	071260	
862226	291058	131059	080361	
883199	070959	240860	291161	
888684	260258	100259	310162	
895495	200160	020161	020562	Cetoxime
897854	080260	110161	300562	
904797	231259	030161	290862	
909102	230759	240660	241062	
911484	241259	131260	281162	
916242	070159	141259	230163	
936590	301260	130362	110963	process
937556	180561	070562	250963	process
938440	140761	170562	021063	process
966496	150562	290463	120864	
967890	071261	191162	260864	
968210	260661	250662	260864	
969808	080662	210563	160964	
971700	020261	120162	300964	Ibufenac, Ibuprofen
975984	150662	040363	251164	
1012480	260762	150763	081265	
1026921	010463	110664	200466	
1030756	010463	110664	250566	
1030759	310563	220764	250566	
1037658	020764	250665	030866	
1041691	300762	190763	070966	
1057131	210263	190564	010267	
1071815	191064	041065	140667	
1073916	041163	290165	280867	
1073983	280263	250564	280667	process
1082573	120265	280166	060967	process
1082574	120265	280166	060967	
1091403	240164	200165	151167	Flurbiprofen
1158492	090266	180167	160769	process
1159490	151266	180167	230769	process
1160725	251167	201167	060869	process
1167192	080966	290867	151069	process
1180025	020666	240567	040270	
1181673	020966	230867	180270	
1185344	040867	250768	250370	process
1213295	270467	190468	251170	
1246902	270369	120370	220971	9
1253521	270968	180969	171171	23
1287271	090769	061070	310872	1
1307284	160370	190471	140273	29
1309221	160370	190471	070373	1
1352415	300471	300471	080574	5
1315355	050870	020871	020573	3
1382996	260371	070372	050275	14
1396726	150672	060673	040675	18, Flurbiprofen
1398549	061172	061173	250675	16
1400448	250871	140872	160775	12 process
1417402	300372	270373	101275	19
1437783	220972	030973	030676	4
1460295	010673	220574	311275	7
1480591	311073	281074	200777	22
1514812	040475	310376	210678	
2047691	250380	270379	031280	16
2085441	160981	260980	280482	11

B3.

FISONS

PN	DOA	DOFCS	DOP	COMMENTS
1089513	290164	110165	011167	
1108086	110865	101066	030468	
1109502	180464	200465	100468	
1111336	240764	090765	240468	
1111337	240764	090765	240468	
1111338	240764	090765	240868	
1116562	060964	280965	060668	
1120992	240465	070466	240768	
1144905	250365	030366	120369	
1144906	250365	030366	120369	Intal
1147976	211265	131266	100469	
1183940	221066	051067	110370	
1190193	050766	200667	290470	
1190194	050766	200667	290470	
1199951	130567	290468	220770	
1200902	130567	290468	050870	
1204121	190966	080967	030970	3
1223690	171067	071068	030371	-
1230087	170867	300768	280471	-
1242212	080867	230768	110871	-
1271364	220868	310767	190472	-
1290174	200567	270470	200972	8
1291571	290369	060370	041072	7
1291864	120269	020270	041072	16
1291865	120269	020270	041072	16
1292601	301068	101069	111072	20
1292602	301068	101069	111072	20
1294681	010269	221070	010172	8
1297264	150469	240370	221172	6
1319803	030970	240871	130673	-
1320019	010870	050771	130673	5
1321879	301270	061271	040773	9
1326745	250470	190471	150873	11
1356379	270870	130871	120674	15
1362782	260870	130871	070874	17
1368243	250870	020871	250974	32
1368244	250870	020871	250974	32
1382247	100671	160572	290175	7
1384530	290771	100772	190275	20
1388268	240671	250572	260375	11
1389227	160971	080872	030475	5
1389827	230771	100772	090475	11
1391615	300971	110972	230475	6
1397731	080671	110572	180675	5
1399647	151272	051273	020775	4
1410597	301171	161172	221075	5
1447479	151272	291173	250876	4
1447480	151272	291173	250876	3
1448980	190173	181273	080976	9
1449810	031272	161173	150976	15
1461777	080673	280574	190177	11
1476300	211173	121174	100677	18
1477331	050274	310175	220677	4
1484134	211173	111174	240877	14
1488707	100774	300675	121077	21
1499323	220374	180375	010278	19
1499324	220374	180375	010278	19
1504709	071274	211175	220378	7
1517153	301174	261175	120778	30
1517154	301174	261175	120778	30
1517155	301174	261175	120778	30
1548254	110576	130477	110779	4
1583691	260177	130178	280181	14
2000123	060678	210577	040179	8
2009157	071178	301177	130679	17
2022078	060678	040577	121279	1
2028316	260679	150878	050380	6
2035312	191079	311078	180680	15

(EP)PN	DOA	DOP	COMMENTS
8864	131278	190380	8(10)
9874	120978	160480	8(10)
11399	010379	280580	6(10)
12512	051278	250680	2(10)
17332	200379	151080	7(10)
37187	020480	071081	3(7)
43194	190680	060182	5(11)

GLAXO

PN	DOA	DOFCS	DOP	COMMENTS	
820658	100257	060258	230959		
839505	160158	151258	290660		
851180	010257	240158	121060		
851761	270158	210459	191060	1	
855212	190658	250559	301160	-	
863342	250458	270759	220361	1	
863717	030758	190659	220361	-	
864231	070858	270759	290361	5	
873206	310757	220758	190761	-	
875701	231058	131059	230861	1	
875702	231258	041259	230861	1	
876320	081156	100258	300861	-	
884712	220559	190560	131261	2	
884713	220559	190560	131261	1	
890533	091159	261060	070362	-	
898093	061159	021160	060662	6	
899668	190460	040461	170662	6	
902255	191157	111158	010862	3	
926591	230960	220961	220563	8	
929466	080858	290759	260663	7	
956272	200759	120760	220464	13	
959050	041261	221162	270564	-	
962918	100561	010562	080764	-	
974891	120260	030261	111164	9	
977788	090660	090661	161264	9	
977789	021260	301161	161264	-	
980394	120962	130163	280865	-	
1002184	051061	280962	250865	10	
1003082	020861	200762	020965	13	
1012943	160561	020562	151265	10	
1022871	281163	031164	160366	-	
1023205	170963	230364	040966	-	
1023720	170963	230364	020966	-	
1030630	141262	021263	250566	25	Cephaloridine
1036278	191263	200764	081266	-	
1043347	100563	300464	210966	13	
1047518	110663	010664	021166	14	
1047519	110663	020664	021166	14	
1049564	090763	301164	160666	-	
1051600	170963	141264	040966	-	
1054806	200762	280663	110167	11	
1057883	110762	250663	080267	17	
1059562	240962	090963	220267	12	
1060160	050864	010365	200767	-	
1070751	280164	130165	010367	16	
1082943	270363	160364	130967	15	
1082962	280563	160364	130967	12	
1087174	050465	111066	040367	-	
1098105	211065	030166	071068	-	
1101561	041163	290964	310168	-	
1101423	160763	250664	310168	12	
1101562	041163	290964	310168	-	
1101961	100563	100864	070268	1	
1132583	161264	031265	061168	8	
1139506	230665	270566	080169	10	
1141293	231264	101265	290169	11	
1151866	220665	170666	140569	9	
1153421	190565	060566	290569	8	
1159434	160865	150866	230769	10	
1168290	180767	221067	160769	-	
1168845	231266	291067	151269	-	
1170680	211267	121166	261169	-	
1170929	281265	161266	191169	12	
1176173	141166	010167	031170	-	
1183046	280666	040367	200670	-	
1189306	100866	240767	220470	7	
1195203	240666	190667	170670	14	
1195294	210867	170668	010870	-	
1200886	230966	050867	150970	Salbutamol	
1202521	290766	080867	190870	11	
1208014	230367	120368	071070	9	
1208015	230367	120368	071070	9	
1211694	151266	041267	111170	9	
1214012	211267	251168	131270	-	
1215506	060868	091268	060870	-	
1226344	310767	240368	190775	-	
1241656	210867	060868	040871	18	
1241658	210867	040868	040871	-	
1242963	170769	180870	190371	4	
1245711	130169	080970	010171	12	

1253831	190168	200169	171171	Dermovate	
1260463	290168	230169	190172	13	
1260464	290168	230169	190172	-	
1260521	060269	190170	230172	13	
1260465	290168	230169	190172	9	
1261650	120669	120670	260172	9	
1262864	290368	250369	090272	-	
1263987	300569	160270	200572	13	
1265315	050468	260369	010372	-	
1266058	080769	080370	290672	16	
1268771	150368	140369	290372	6	
1268772	150368	140369	290372	9	
1268773	150368	140369	290372	-	
1272769	020868	180769	030572	10	
1277415	140668	300569	140672	-	
1279402	140668	300569	280672	10	
1281689	141068	131069	120772	9	
1289521	230169	120170	200972	8	
1296469	050270	151171	190172	9	
1298494	170670	161271	180572	10	
1301720	080570	040171	190473	8	
1304583	100370	240171	190473	9	
1312620	271169	040470	121173	13	
1313659	250769	130770	180473	9	
1315484	250769	020770	020573	9	
1316964	240769	020770	160573	8	
1317184	200669	010670	160573	26	
1326531	260869	060870	150873	18	
1332784	211169	201170	031073	6	
1334382	240470	190471	171073	11	
1339008	050870	281171	200773	12	
1339010	271170	281171	211073	5	
1342241	230170	120171	030174	17	
1342242	230170	120171	030174	17	
1342713	030670	030171	120574	12	Fazadinium bromide
1351754	020770	010571	220674	-	
1357733	280770	100971	260674	6	
1361183	060870	150771	240774	12	
1368233	310770	300771	250974	12	
1372175	061170	051171	301074	10	
1376892	121170	121171	111274	13	
1377608	171270	161271	181274	8	
1377609	171270	161271	181274	9	
1377624	210771	070772	181274	5	
1379730	171270	161271	080175	11	
1380246	171270	161271	080175	9	
1380248	171270	161271	080175	11	
1383088	030772	050273	120675	14	
1384372	200171	200172	190275	12	
1385683	010371	280272	260275	3	
1385895	010371	280272	050375	3	
1389194	290171	140172	030475	25	
1389195	290171	140172	030475	25	
1391443	050771	280672	230475	11	
1397073	190571	180572	110675	7	
1399087	140571	120572	250675	23	
1399088	140571	120572	250675	23	
1399089	140571	120572	250675	23	
1400789	131172	230772	231075	9	
1400999	191171	230772	231075	12	
1401287	081271	300772	211175	12	
1410011	230971	151072	120975	13	
1430932	050572	040573	070476	10	
1430942	050572	040573	070476	11	
1432135	050572	040573	140476	8	
1433141	070772	140673	220476	6	
1434919	150672	150673	190576	9	
1436324	120573	110573	190576	9	
1436549	150672	150673	190576	-	
1438940	190772	170773	090676	11	
1440064	110872	100873	230676	10	
1443950	251072	081073	280776	6	
1445979	251072	081073	110876	14	
1453049	210873	130874	201076	34	Cefuroxime
1458012	030173	030174	081276	13	
1468349	060373	060374	230377	13	
1468673	070573	020574	300377	12	
1472534	060773	050774	040577	13	
1496757	211273	201274	050178	31	
1496758	211273	201274	050178	31	
1496759	211273	201274	050178	31	
1497039	051273	041274	050178	11	

1499655	310174	150175	010278	12
1529972	290775	150776	251078	10
1532957	041174	231075	221178	12
1555471	190675	160676	141179	11
1555958	270276	080277	141179	8
1565966	040876	220777	230480	24
1565967	040876	220777	230480	24
1567902	151075	141076	210580	10
1571683	160276	150277	160780	15
1572993	160276	150277	130880	12
1573503	171275	161276	280880	9
1579531	270276	250277	191080	9
1581234	050476	040477	101280	14
1581235	050476	040477	101280	14
1583146	130776	120777	210181	6
1583911	090277	270178	040281	10
1584461	250377	230378	110281	12
1585124	040676	030677	250281	12
1591438	090976	090977	240681	6
1591439	011076	300977	240681	7
1593651	030277	180178	220781	10
1594934	251076	241077	050881	11
1596278	301176	291177	260881	9
1597359	301176	291177	090981	7
1598568	190477	180478	230981	12
1599907	260478	240478	071081	9
1601459	170477	020478	281081	13
1602725	270477	270478	181181	4
1602736	120877	260578	181181	6
1603659	031077	190578	251181	9
1603989	260578	260578	021281	10
1604674	170577	080578	161281	12
1604675	170577	080578	161281	12
1604722	260578	260578	161281	5
1604723	260578	260578	161281	18
1604724	260578	260578	161281	18

2006769	101077	091078	100579	5(7) EP1516
2006771	111077	111078	100579	9(7) EP1699
2014561	231277	201278	300879	10(7) EP2930
2014574	160278	150279	300879	4(7)
2014579	080278	080279	300879	12
2023133	260478	190479	281279	14
2024808	260578	250579	160180	10
2025398	260578	250579	230180	23
2027691	260578	250579	270280	18
2027692	260578	250579	270280	23
2028805	110778	110779	120380	10
2029824	260579	250579	260380	10
2030979	260778	250779	160480	9
2035310	121078	101079	180680	11
2036724	271078	261079	020780	10
2036738	171178	161179	020780	9
2037281	151178	141179	090780	12
2037744	251078	181079	160680	11
2038322	161178	161179	230680	11
2040921	271078	261079	030980	10
2043641	230279	220280	081080	10
2046261	220379	210380	121180	16
2047238	020379	290280	261180	9(10) EP16565
2054572	290679	270680	180281	5(9) EP21840
2058785	050979	040980	150481	6(10)
2058791	260579	250579	150481	23
2060610	190779	180780	070581	9 process
2061915	090879	080880	200581	6(9) EP24843
2062624	021079	011080	280581	7
2062626	031079	031080	280581	11
2063253	221079	221080	030681	4(9) EP29303
2063874	221079	221080	100681	5(10) EP28483
2063875	231079	231080	100681	4(9) EP27744
2064513	021079	011080	170681	8
2064515	231079	231080	170681	4(9) EP29306
2070591	090180	080181	090981	4(10)
2072662	050380	050381	071081	3(10) EP35412
2075007	280280	270281	111181	10
2079281	040780	030781	200182	6

2080300	150780	150781	030282	5(11) EP44704
2080301	150780	150781	030282	5(11) EP44705
2080308	160780	150781	030282	8
2081717	120880	110881	240282	17
2082584	270880	270881	100382	5(11)
2083463	120880	110881	240382	17
2085434	111077	111078	240482	9(7) EP1699

(EP) PN	PRIORITY	DOA	DOP	COMMENTS
3415	200178	190179	080879	2(8)
10358	200978	190979	300480	2(9)
44227	160780	150781	200182	2(11)
44705	150780	150781	270182	

B5. ICI

PN	DOA	COMMENTS
841701	050457	1
841710	120857	3
842322	011056	1
842673	250458	1
842797	300458	1
843118	130257	5
843676	311257	1
845235	281057	3
845248	300458	1
845378	060158	4
846611	070258	1
848130	140358	1
857362	031258	1
859287	031058	1
859342	230758	3
860303	200658	4 Clofibrate
860629	220958	1
860940	230558	1
861379	140358	1
861525	060857	-
861822	170658	1
861833	020159	2
862127	040758	1
863719	230758	1
964197	070159	5
864282	080959	1
864731	031058	1
865754	301159	3
868030	051258	5
868573	250359	1
869058	210758	1
869504	090259	5
869575	020558	1
873223	130459	1
874980	171258	1
875717	191258	1
875955	311258	1
876601	030759	5
876719	050259	1
878177	170659	11
884414	021159	1
884629	220559	1
886526	210859	1
886692	040359	3
886693	040359	4
889748	011259	5
891553	131059	1
892450	181159	1
894823	211259	2
895395	241159	2
896245	120859	1
897870	150659	1
898408	260260	1
898409	290260	1
898414	160360	1
898596	100360	3
898633	270160	2
901876	270460	5 Etoglucid
901891	040560	1
901892	040560	2
904893	131159	1
904894	241159	1
904895	161259	1
904896	161259	1
904897	211259	1
906109	260760	1
908110	090660	1
908297	141059	2
917738	020161	1
917869	201059	1
918869	310860	3
919177	140960	5
919491	231258	9
919703	211259	8
921665	021160	1
923182	080860	-
923311	140960	1
924455	241060	1
924612	191260	1
925909	050760	1

927255	221260	1	
928754	040161	2	
932674	030261	5	
933786	120161	1	Ertryptamine acetate
935426	190460	6	
935592	160161	1	
936685	170261	1	
946880	050661	5	
950529	041061	1	
951652	280660	1	
953010	310561	4	
955478	061260	1	
955504	050760	1	
955856	010861	4	
957449	100861	1	
957685	270761	2	
967425	140960	5	
967492	010260	4	
969851	181160	-	
969031	180462	1	
969664	220262	5	
971176	091161	6	
973911	040662	5	
973912	040662	3	
973913	040662	3	
974168	260661	6	
974522	150162	5	
975291	120962	5	
979389	290162	10	
982738	050661	1	
984291	221261	1	
984306	070562	4	
984365	031061	1	
984375	060962	5	
990061	221261	-	
991140	230562	5	
991203	010562	5	
991977	240962	7	
994918	231162	25	Propranolol
995800	231162	11	
997037	190362	2	
998524	290162	10	
999762	260561	9	
1004606	150562	2	
1005021	191061	7	
1005022	191061	1	
1005023	191061	7	
1005024	081161	6	
1005025	221261	11	
1005026	280362	15	
1005027	191061	1	
1013180	301062	3	
1013224	210662	10	
1013907	130962	15	Tamoxifen
1015794	021062	1	
1017691	311061	7	
1017700	150563	1	
1017973	100563	3	
1017974	100563	6	
1018113	061261	4	
1018802	170563	4	
1019225	231062	2	
1019772	210662	10	
1021275	080563	8	
1021393	300562	1	Australia process
1021522	100563	8	
1021933	071262	1	
1023214	171262	24	
1024643	150961	6	
1024914	190961	1	
1025314	111163	2	
1025904	200363	8	
1026726	231162	2	
1028152	311262	1	
1028233	060164	8	
1028234	060164	6	
1028813	280862	2	
1028812	280862	1	
1029221	020963	8	
1031082	040264	9	
1036282	100963	1	
1038332	130263	11	

1038333	130263	8	
1038334	311263	2	
1038335	311263	3	
1038336	311263	3	
1040635	120564	2	
1041028	200164	9	
1041029	200164	9	
1041350	230764	3	Australia veterinary
1042481	250664	1	
1042482	250664	1	
1042483	250664	1	
1042484	250664	8	
1042485	250664	5	
1042486	250664	1	
1042488	020964	6	
1043012	280764	1	
1043104	120564	1	
1043513	060464	6	
1046001	130364	12	
1047927	090364	12	
1048084	140863	11	
1050221	160964	1	
1050511	140264	8	
1050767	140863	10	
1051375	281064	12	process
1054655	240164	16	
1055203	160964	14	
1055413	160964	1	
1055619	301164	5	
1055741	120763	7	
1055786	120763	7	
1056268	060363	1	
1058822	300763	21	
1059034	160164	1	
1059271	050264	1	
1059968	200164	14	
1059990	181264	9	
1061993	200363	1	
1062354	310365	4	
1063727	120465	1	
1063728	120465	1	
1064429	200765	9	Tamoxifen isomer
1066613	030365	18	
1067811	010165	12	
1069341	111262	32	
1069342	190763	13	
1069343	100963	13	
1069344	080464	1	
1069345	111262	32	
1069411	130464	6	
1072579	200565	1	
1078633	210864	8	
1078852	300964	17	Practolol
1079534	240265	1	
1079747	070765	11	
1079989	280965	1	
1080274	120765	9	
1080699	030965	4	
1089769	300665	13	
1090252	130465	17	
1092634	240364	1	
1099093	030965	1	
1099389	071065	22	
1100890	141265	1	
1108532	100366	2	
1109148	101265	11	
1109150	140366	3	
1110846	130566	1	
1115372	150165	1	
1115373	150165	1	
1120310	230566	1	
1120755	130666	1	
1120870	110766	12	
1121027	230666	3	
1121922	170666	14	
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1122435	200466	12	
1122847	141065	2	
1123258	150965	9	
1123601	120365	3	
1124374	270566	1	
1127469	031066	11	

1128052	080665	12	
1128378	200666	1	
1129072	010266	12	
1129563	310366	12	
1129797	310366	12	
1131798	310865	24	Australia process
1131799	190765	24	Australia process
1131800	190765	24	Australia process
1132516	010266	1	
1133800	101166	4	
1135340	071266	1	
1136918	160665	2	
1136919	160665	12	
1138405	281266	20	Viloxazine
1138539	150966	15	
1138540	190966	15	
1139940	300966	21	
1143263	040866	7	
1146668	120765	1	clay
1147068	021266	26	
1148676	130766	2	
1152243	261165	7	
1157100	270966	7	
1158387	130667	1	
1160291	310166	6	
1164510	150666	15	
1166403	210767	1	
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1167249	180867	3	
1169310	240867	15	Australia process
1170538	260767	7	
1170807	210367	14	
1174221	080168	5	
1175219	220667	11	
1175220	220667	11	
1175268	030367	3	
1175269	030367	3	
1175270	030367	3	
1177548	281167	1	
1180268	120967	14	
1183219	270967	3	
1183504	100767	10	
1183781	140268	8	
1183850	241167	-	
1185044	031166	13	
1185045	031166	15	
1185046	240767	-	
1186507	131267	5	
1197755	250767	-	

1133800	102266	4	
1175219	220667	11	
1175220	220667	11	
1177548	281167	1	
1183504	100767	10	
1185046	240767	5	
1197755	250767	2	
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1217925	140668	5	
1227978	130968	5	
1228301	160468	1	
1234635	130968	19	
1236947	150868	10	
1237438	170668	1	
1243991	100668	1	
1252815	170469	6	
1261060	090969	1	
1263956	260969	12	
1268523	291069	5	
1269775	180768	13	
1270099	231068	2	
1270723	020569	1	
1276061	140170	5	
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1284485	160270	7	
1285038	210269	29	Atenolol
1291994	241069	6	
1295447	171169	13	
1305820	280970	4	
1306139	060870	4	
1306839	161070	13	
1306878	290470	4	
1308787	051070	23	
1308832	270770	8	
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1311432	070171	18	
1311521	130270	14	
1311336	070970	7	
1312055	200470	4	
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1313675	070970	1	
1326961	270570	20	
1327331	250171	1	
1331520	270171	1	
1350971	110571	27	
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1356581	091070	9	
1356834	031171	23	
1367163	041071	14	
1377248	250472	10	
1382526	110872	38	
1382965	110872	38	
1386146	030572	13	
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1393675	160672	4	
1394260	241071	2	
1395156	280771	5	
1396322	150671	4	
1399516	061271	7	veterinary
1402035	071272	9	
1407903	210373	6	
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1415011	160671	6	
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1449595	140674	13	Merck ?
1451959	300573	5	
1452701	070574	24	
1455116	151272	33	

1457876	151272	18	
1458315	220474	19	
1460348	031171	4	
1460593	220673	18	
1461105	110974	10	
1461106	110974	10	
1468156	190773	14	
1474399	190874	21	
1486832	050874	15	
1486869	190675	4	
1487535	190575	4	
1487712	150475	5	
1489412	270974	21	
1492431	010275	11	
1492678	110875	17	
1495152	160874	11	
1502312	200375	22	
1508208	220673	5	
1509300	220673	5	
1509527	151272	20	
1512930	200975	2	Australia veterinary
1513742	310175	24	
1513913	200675	12	
1516414	220875	16	
1517562	130675	13	
1523812	080476	14	
1524318	210676	5	
1524319	210676	5	
1524747	110576	21	
1526367	121076	5	
1538201	110876	11	
1539268	231276	4	
1540463	071076	6	
1550399	081276	10	
1550838	151272	6	
1559977	251175	22	
1560880	291275	23	
1569819	070776	2	
1573359	170973	5	
1573421	210576	76	
1582853	160677	5	
1585965	300776	22	
1591618	161276	23	
1599181	010477	5	
1599518	210277	20	
2001624	200477	1	
2002748	230577	18	
2003138	160877	21(8)	
2003855	220877	5	
2004869	220977	5	
2009746	081177	6	Australia veterinary
2031406	080978	23(9)	

(EP) PN	PRIORITY	DOP	COMMENTS
2097	220877	300579	15(7)
2309	121077	130679	6(8)
2892	151277	110779	14(9)
2895	101178	110779	15(9)
2896	221277	110779	13(9)
3640	180178	220879	4(8)
3664	080278	220879	14(9)
4726	120478	171079	6(9)
4727	120478	171079	11(9)
5911	260578	121279	12(10)
6286	240578	090180	4(10)
6298	150678	090180	9(10)
6679	250578	090180	12(10)
10360	241078	300480	2(10)
10418	161078	300480	3(9)
10893	161078	140580	2(8)
10894	161078	140580	2(9)
11372	071178	280580	10(10)
11447	171178	280580	13(10)
13817	190179	060880	4(10)
14057	180179	060880	2(10)
15124	160279	030980	2(6)
19377	150579	261180	4(11)
19411	210579	261180	10(11)
28455	121079	130581	6(7)
28906	131179	200581	7(11)
30092	131179	100681	7(11)

30795	061279	240681	6(11)
31708	241279	080781	8(10)
40932	220580	021281	8(11)
45155	300780	030282	2(11)
45161	240780	030282	6(11)

B6.

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925001	280960	260961	010563	
1111584	030665	020666	010568	
1116595	080764	140665	060668	
1136214	150665	100666	111268	
1136764	130865	090866	181268	
1146271	170166	170167	260369	
1146272	170166	170167	260369	
1154505	151266	041267	110669	
1166510	200667	120668	081069	
1164671	310367	260368	170969	
1164672	310367	260368	170969	
1173215	200667	120668	031269	
1178537	201066	111067	210170	
1179479	200667	130668	280170	1
1179480	200667	140668	280170	1
1207731	140568	070569	071070	7
1222669	211068	061069	170271	-
1223445	180768	080769	240271	1
1224918	180768	180769	100371	1
1308327	140470	190471	280273	13
1337575	071270	241171	141173	13
1337576	071270	241171	141173	13
1374317	200172	281272	201174	8
1395235	070672	010673	210575	4
1395236	070672	010673	210575	9
1513768	241075	201076	070678	1
1523598	080375	190276	060978	17
1578135	170676	080677	051180	8
1587831	230377	220378	080481	15
1593191	230377	220378	150781	16

PN	DOA	DOFCS	DOP	COMMENTS
2004891	080978	290977	110479	11
2013689	301178	151277	150879	17
2068376	020281	040280	120881	10
2085437	020781	090780	280482	-

(EP) PN	PRIORITY	DOP	COMMENTS
43736	090780	130182	5(10)

B7.

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PN	DOA	DOFCS	DOP	COMMENTS
829507	280357	280357	020360	veterinary
830519	150356	150357	160360	
830825	180157	200158	230360	
830913	170557	160558	230360	
832250	180157	200158	060460	
833008	220157	220158	210460	
833463	240655	240956	270460	
834300	220357	210358	040560	
834313	280557	120558	040560	
834453	030157	030158	110560	
836696	220655	240956	090660	US
838820	121056	130158	220660	
838821	220655	240956	220660	
853176	231156	251157	021160	US
864885	181257	151258	120461	process
868552	031257	211158	170561	
872102	311057	311058	050761	process
872300	261056	281057	050761	US
872943	261056	281057	120761	US
873691	030157	030158	260761	
875562	210257	210258	230861	Trimethoprim, ex US
878461	170358	130359	270961	
878646	110358	090359	041061	Azathioprine, US
881265	130658	220359	011161	Bretylium
887409	060657	040658	170162	US
891940				not found
896303	311057	311058	160562	
898855	110360	270161	140662	
899404	011157	031158	200662	veterinary, US
904802	200260	200260	290862	process
906422	020558	170459	190962	
908966	220158	160159	241062	
912949	180458	140459	121262	
913348	090458	080459	191262	ex US
913710	010558	170459	281262	US
915304	130358	090359	090163	US
915514	190859	290760	160163	US

Note: US indicates that the application date is for the US
ex US indicates an invention originating in the US

919124	030358	020659	200263	
919462	150960	060761	270263	process
920127	240759	230660	060363	veterinary
920267	160558	150559	060363	
920412	180458	140459	060363	ex US
921315	310358	260359	200363	process
921316	240758	261059	200363	
921317	190159	190460	200363	
921318	190159	260359	200363	
921978	130359	030360	270363	process
922321	130259	040260	270363	process
922837	120658	120659	030463	US
923076	240758	030759	100463	
923084	120659	260560	100463	process
923727	040260	270161	180463	process
924146	120659	100660	240463	
924246	231258	031259	240463	US process
924961	130359	290260	010563	veterinary
925017	210759	290960	010563	
925988	130259	180260	150563	process
926249	260260	020261	150563	process
927616	170359	090660	290563	veterinary
933605	210160	130161	080863	
933711	121159	130261	140863	process
935282	080759	240660	280863	
935381	151258	201159	280863	US process
935387	230960	140961	280863	
935613	040260	270161	280863	process
936654	091059	091059	110963	process
938042	300361	220362	250963	
941751	050159	101259	131163	process
942309	060259	040260	201163	
942743	220559	120560	271163	
946957	250761	170762	150164	
948730	080459	050260	050264	process
951431	170359	160660	040364	
951432	170359	170660	040364	ex US
951628	291059	311060	110364	US process
952736	160659	160660	180364	
957797	030960	290760	130564	ex US process
960586	100759	110760	100664	US
960587	181159	181160	100664	US
960605	181159	101160	100664	US
960613	040360	230261	100664	US process
960769	200362	140363	170664	process
961434	100260	090261	240664	ex US proce
966849	150959	010960	190864	process
968199	080361	010362	260864	veterinary
970583	190761	050762	230964	ex US proce
970935	300360	130161	230964	veterinary
971307	020361	040662	300964	ex US
973007	150262	090563	211064	ex US
973882	231259	151260	281064	process, Be
975323	120860	210761	181164	ex US proce
975357	041259	011260	181164	process Methisazone
975706	210761	120762	181164	ex US
975850	230562	090563	181164	ex US
975938	300960	200761	251164	ex US
978281	110260	020261	231264	process
979551	290260	020261	060165	process
980854	300562	300863	200165	ex US
981092	230660	200461	200165	
981093	240660	200461	200165	
981458	041261	040363	270165	ex US
981506	220862	160863	270165	ex US process
982572	100660	250561	100265	process
982776	240162	100163	100265	ex US
983600	150562	090563	170265	ex US process
984363	230661	200962	240265	ex US process
985970	150860	240861	100365	
987916	220862	160863	310365	ex US process
988044	200161	110162	310365	process
990857	230660	090661	050565	ex US
990858	230660	210761	050565	ex US
991602	100361	010362	120565	process
991988	250263	130264	120565	ex US process
993581	030360	020661	260565	process
994483	210961	200962	100665	
997036	230262	230563	300665	
997823	290362	210363	070765	
997824	290362	210363	070765	process
999092	241159	101160	210765	

999093	180360	090361	210765	
999094	270560	110561	210765	
999096	241159	240261	210765	
1003889	121261	071262	080965	
1006724	010362	210263	061065	
1009301	240461	221261	101165	US process
1013520	160763	170764	151265	
1013904	190762	041063	221265	veterinary
1014881	131061	100163	311265	ex US
1015011	221260	141261	311265	
1015784	131061	100163	050166	
1016656	011163	221064	120166	
1020611	200461	050462	230266	
1026401	230261	230562	200466	
1026402	121261	110363	200466	
1031165	140761	121062	250566	
1032251	220661	140662	080666	
1049181	210163	090164	231166	process
1050204	210163	090164	071266	process
1051143	080662	070663	141266	
1057666	201262	200364	080267	process
1062895	131262	281163	220367	
1063872	110862	111163	300367	
1074102	220363	140464	280667	ex US
1074103	220363	200364	280667	ex US
1075251	041062	260963	120767	
1075252	161266	161266	120767	
1082964	250663	250664	130967	
1084103	301063	291064	200967	US
1084824	091263	031264	270967	
1088102	100164	070165	251067	process
1090754	010863	300764	151167	E. coli strain
1092286	200364	180365	221167	process
1092287	200364	180365	221167	process
1093121	310563	210564	291167	ex US
1093284	050963	030964	291167	process
1094985	070764	280665	131267	
1097333	100863	300764	030168	process
1101749	170664	140665	310168	
1104292	110763	100764	210268	ex US process
1106076	260564	200565	130368	

1111563	050864	280765	010568	process Beth
1111564	050864	290765	010568	process Beth
1112011	290664	240665	010568	process
1112378	070864	051165	010568	veterinary
1113391	230764	220765	150568	process
1121307	070864	060865	240768	ex US
1125619	151165	111166	280868	
1128234	190266	160267	250968	ex US proces
1129084	180265	180266	021068	ex US proces
1129814	191164	181165	091068	ex US proces
1132453	190365	100366	061168	ex US proces
1134852	200565	190566	271168	ex US
1140353	220265	180266	150169	process
1142654	281065	271066	120269	ex US process
1142782	010465	310366	120269	ex US process
1143940	250565	240566	260269	veterinary
1145278	231265	131266	120369	
1153471	090465	190566	290569	process
1153883	260865	180866	290569	
1153884	260865	180866	290569	
1161201	221065	201066	130869	process
1171112	070965	071266	191169	
1178242	050266	270167	210170	
1188519	271066	201067	150470	process
1188529	090666	080967	150470	ex US
1190413	170567	080568	060570	ex US
1194183	210666	080667	100670	
1194835	070766	210667	100670	
1200444	140766	030767	290770	ex US process
1200445	140766	030767	290770	ex US process
1203027	300966	150967	260870	
1203032	180866	040867	260870	ex US process
1223881	020267	010268	030371	US process
1223882	020367	010268	030371	
1246649	220967	250968	150971	veterinary
1247347	190168	180469	220971	ex US
1250601	190567	150868	201071	2
1295437	061268	191169	081172	2 process
1298192	060968	041269	291172	1 process
1304174	070369	050370	240173	ex US 11

1307978	280269	270270	210273	14	process
1308132	241268	230370	280273	1	
1319056	230669	220670	310573	13	ex US process
1321991	230669	220670	040773	14	ex US process
1336871	020170	231270	141173	5	process
1338905	171169	161170	281173	16	US
1338906	171169	161170	281173	16	US
1340033	041269	031270	051273	20	ex US
1354513	050670	280571	300574	15	ex US
1356937	270870	110871	190674	10	process
1363064	270770	130771	140874	22	process
1363065	270770	130771	140874	22	
1363066	270770	130771	140874	22	process
1363067	270770	130771	140874	22	process
1363068	270770	130771	140874	22	
1366855	300670	280971	110974	1	
1375162	221070	201071	271174	25	ex US
1375163	221070	201071	271174	25	ex US
1380882	010970	261171	150175	1	ex US process
1386585	161170	160272	120375	15	ex US process
1407971	160471	140772	011075	17	ex US process
1407972	160471	140772	011075	17	ex US
1413471	121071	121072	121175	26	process
1413472	121071	121072	121175	26	
1425449	291271	290373	180276	1	
1427508	121071	120173	100376	11	process
1434714	291271	290373	050576	27	process
1434715	291271	290373	050576	27	
1437082	240372	220673	260576	2	ex US
1447032	190572	170873	250876	28	
1451043	010872	011173	290976	9	
1454165	010872	011173	271076	15	
1454166	010872	011173	271076	15	
1458185	060972	061273	081276	16	
1458186	060972	061273	081276	13	
1468171	010273	010574	230377	14	
1476422	230273	230574	160677	3	
1501855	011173	310175	220278	12	
1516642	040674	040675	050778	14	
1519762	090874	071175	020878	26	ex US
1523865	020974	020975	060978	49	ex US Acyclovir
1530912	130275	130276	011178	7	ex US
1532211	251074	241075	151178	12	
1539221	300976	300977	310179	9	viral pr
1543709	081174	090276	040479	6	
1561380	010376	010377	200280	25	ex US
1562899	170675	160676	190380	16	ex US
1566493	010376	010377	300480	9	US
1568401	030276	270177	290580	1	ex US
1569393	010376	010377	110680	16	US
1577114	260176	260177	221080	19	
1579822	101275	070377	261180	17	
1582245	090676	160677	070181	20	
1583961	110576	100577	040281	19	
1583962	110576	100577	040281	19	
1587065	280676	230977	250381	15	
1587250	060876	050877	010481	2	veterinary
1590500	240277	230278	030681	15	US
1595693	080376	080677	120881	11	
1596535	231176	231177	260881	19	
1599740	050977	310578	071081	8	
1600127	230377	190578	141081	2	
1600840	300578	300578	211081	7	ex US
1602188	011277	310578	111181	5(4)	EP2258
1603407	050977	310578	251181	7(6)	EP1238
1603689	260578	260578	251181	1	
1604644	220777	310578	091281	11(5)	EP559
2006752	260877	220878	100579	8(6)	EP950
2008089	260877	220878	310579	8(6)	process
2010813	191077	271178	040779	25(8)	EP951
2024817	150378	140779	160180	12(8)	EP4579
2032419	050978	090579	080580	1	
2044259	220279	210280	151080	8(9)	EP15002
2050371	090579	080580	070180	3(6)	EP19223
2053218	290679	270680	040281	6(9)	EP22229
2061929	191079	151080	200581	2	
2063868	301179	261180	100681	4(8)	
2073740	030380	020381	211081	7(9)	EP35270
2074571	110480	100481	041181	3(9)	EP38046
2083034	260880	250881	170382	3(9)	EP46597

(EP) PN	PRIORITY	DOP	COMMENTS
382	080777	240179	3(4)
383	080777	240179	8(4)
541	200777	070279	9(7)
791	160877	210279	6(3)
2236	231178	130679	1(7)
2259	011277	130679	4(9)
3560	310979	220879	1(9)
7529	130778	060280	4(7)
8356	130778	050380	4(7)
21120	010679	070181	2(6)
21121	010679	070181	7(9)
21292	140679	070181	5(8)
21293	140679	070181	7(8)
25598	130979	250381	2(8)
25599	130979	250381	2(8)
25600	130979	250381	2(8)
28305	130979	130581	2(8)
31563	211279	080781	5(8)
38569	230480	281081	3(8)

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35. Beecham Pharmaceuticals: Mr. D. Roberts, Controller, Patents and Trade Marks Department.
Fisons Pharmaceuticals: Mr. C. Craig and Mr. F. Murphy. No comments were received from Fisons on the original draft of this section.
ICI Pharmaceuticals Division: Dr. P. Kolker, Manager, Patent Department.
Wellcome Pharmaceuticals: Mr. P. Jackson, Head, Group Patents and Agreements.

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