The UK's Sectoral System of

Biotechnology Drug Innovation:

Structure, Networking and Knowledge Production

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Abstract

The drug discovery and development subsector lies at the heart of the pharmaceutical and biotechnology industry. However, previous studies have not distinguished this subsector from the industry as a whole. Little detailed analysis has looked at the firms that discover and develop new therapies. From a perspective of the Sectoral Systems of Innovation, this thesis aims to address this important gap in knowledge by looking at the structure, clustering, knowledge production and networking in the drug discovery and development subsector, and to stress the relevant policy implications.

This study intends to objectively examine the best available indicators for the knowledge produced by this subsector and industry dynamics, therefore a broad design of methodology was chosen. Data was collected from government databases, scientific databases, commercial databases, industry associations and companies' websites, concerning the subsector's structure, clustering and concentration, research and development (R&D) investments, product pipelines, scientific publications and citations, patent publications, and alliance agreements.

This study indicates that the drug discovery and development subsector was geographically clustered. The finding further reveals this subsector's hierarchical structure and divergence in strategy development. This thesis also suggests that the focuses of knowledge production in this subsector were changed when partners changed. Moreover, in arguing that this subsector featured massive knowledge production and expanding collaboration with other actors of the innovation systems, the analysis questioned the notion that domestic industry would benefit much from the

successful knowledge production of this subsector, because much of the knowledge produced by this sector was going abroad through commercial licensing, and through mergers and acquisitions (M&As). The data of this study also indicated that the strategies of companies are co-evolved with its position within the networking and industry structure.

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Content

Chapter One: Introduction

The pharmaceutical industry has been seen by the UK government as a key part of the knowledge-driven economy and an important source of economic growth: the UK not only has one of the largest pharmaceutical market of the world (Towse 1996), but it also has been a major exporter of pharmaceuticals (Earl-Slater 1998). In addition, the pharmaceutical and biotechnology industry is the largest research and development (R&D) investor of this country.

Central to the pharmaceutical and biotechnology industry is the drug innovation process. The UK has already established the strongest research base of Europe (Cooke 2006). Public policies are directed to support drug innovation activities and to establish a virtuous circle of innovation (Reiss et al. 2004). However, there has been a lot of policy debate about how best to support this sector (Walley et al. 2000).

From existing work in social science and innovation studies (see Literature Review Chapter) a number of key factors which influence the development of the drug discovery and development have been identified. However, most of these studies have not distinguished the drug discovery and development subsector from the industry as a whole. In particular, little detailed analysis has looked at the firms that lie at the heart of the industry – those involved in discovering and developing new therapies. This study aims to address this important gap in knowledge.

This chapter aims to provide an introduction to this thesis: to begin with, the first section of this chapter will discuss the procedure of drug discovery and development, followed by the history of drug discovery and development, and a discussion of regulation. These two sections aim to provide

a historical background of how the pharmaceutical industry has been using technology breakthroughs to improve drug discovery and development procedures, how regulation and legislation have changed to ensure drug safety, effectiveness and reasonable pricing, and outlines current policy debates on how to improve the efficacy and effectiveness of the regulatory agencies.

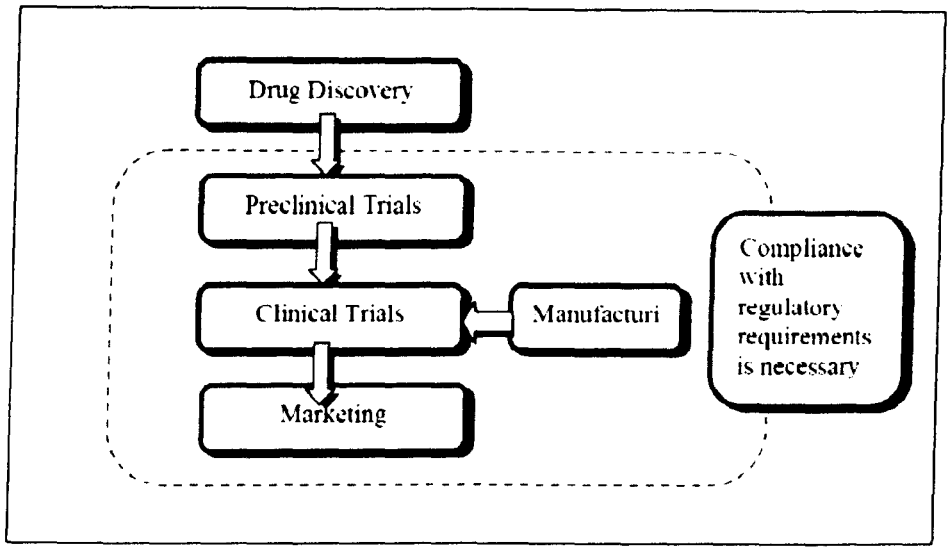
This chapter will also introduce the research questions of this study, and the context where these questions were raised. From a historical and industry dynamical perspective, this study aims to understand the co-evolution of knowledge production, industry structure and networks in the drug discovery and development subsector, and to stress the policy implications of these developments. An outline of the thesis structure will be briefly sketched in the final section.

1.1. Drugs: From Concepts to Markets

It takes a long time to bring a drug from discovery and development to the market. Basically several stages are involved in this procedure: drug discovery, preclinical trials, clinical trials, manufacturing, and marketing application (Figure 1). The last four stages should fulfill relevant regulatory requirements in practice (Rick 2004). This procedure was also described as six phases leading from drug discovery and development to drug registration: drug discovery phase, preclinical phase, clinical phase I, clinical phase II, clinical phase III and registration (Warne 2003).

Figure 1 The stages from drug discovery to marketing approval

(Rick 2004)



There are also six steps of classic drug discovery phase: target generation, lead generation, lead optimization, candidate selection, candidate proposal and candidate acceptance (Warne 2003). The rest of the phases are regulated by different authorities in different countries. However, the tasks and procedures are similar. Take the U.S. for example, the Preclinical phase consists of testing drug candidates on animals, inspecting of the claims on intellectual property rights, and filing an Investigational New Drug Application (NDA) (Schryver & Assellbergh 2003). The NDA serves as a hurdle where the regulator decides if the compound can be tested upon healthy volunteers (Schryver & Assellbergh 2003). After the preclinical phase, there are three consecutive clinical phases: Phase I, Phase II and Phase III, followed by registration.

Phase I: Is the new compound safe for healthy volunteers?

Phase II: Is the compound both safe and effective for the patients?

Phase III: *Are effectiveness and safety demonstrable for the population? And is there a significant socio-economic advantage for the society?*

Registration: *Once a compound passes the clinical phase, a New Drug Application (NDA) has to be filed to convince the regulator of the safety, effectiveness and socio-economic benefit of the new compound.*

(Schryver & Asselbergh 2003)

In the UK, drugs can be licensed in two ways, which will be discussed in detail later in this section, either through the European Medicines Evaluation Agency (EMEA) to apply an EU wide license or through the UK Medicines and Healthcare products Regulatory Agency (MHRA) to apply for a UK only license.

1.2. History of Drug Discovery and Development

1.2.1. History of drug discovery

The pharmaceutical industry has experienced important changes in drug discovery during the last century.

"*...starting with the development and gradual acceptance of the germ theory of disease at the turn of the century and accelerating during the chemo-therapeutic revolution of the 1930s and 1940s. Synthetic organic chemistry and soil microbiology generated significant opportunities for pharmaceutical innovation ... In the 1940s and 1950s, advances in virology provided another set of new opportunities for entrepreneurship, followed shortly by a new wave of breakthroughs in microbial biochemistry and enzymology, breakthroughs that provided the basis for a new style of targeted pharmaceutical research and development...The next, partially overlapping wave of innovation...was grounded in recombinant DNA technology and molecular genetics, and is generally referred to as the biotechnological or 'biotech' revolution.*" (Galambos & Sturchio 1998: 251-252)

The history of the pharmaceutical industry will be briefly reviewed according to these important innovations.

Early 20th century – World War I

The development of colour-dye technology in Europe in the 19th century was a milestone in drug innovation. The main reason for this was that both drug innovation and dye research involved applications of organic chemistry (Bogner 1996;Thayer 2002). In 1883, one of Germany's leading dyestuff makers, Hoechst, decided to establish a separate scientific laboratory to investigate the "the possible link between synthetic dyes and biologically-active substance" (Goodman 2000:142). The first pharmaceuticals emerging from the dye companies in Germany were antipyretics and analgesics (Goodman 2000). *Antipyrin* (1883), *pyramidon* (1896), and *novocain* (1905) were introduced to the market by Hoechst, and *phenacetin* (1887) and *aspirin* (1897) were introduced to the market by Bayer (Da Rin 1998).

The second milestone for drug innovation was the research in anti-infectants, which also emerged in Europe (Bogner 1996). Gerhard Domagk, the research director of the Hoechst laboratory, synthesized the red sulphonamide dye, *Prontosil*, which cured lethal streptococci infections, for which he won the 1939 Nobel Prize (Bogner 1996).

World War I not only gave American pharmaceutical companies an opportunity to conduct drug innovation and development (Liebenau 1987), but also an opportunity to consolidate their positions and to plan long-term development (Liebenau 1990). From 1905, the strategy of German pharmaceutical companies to patent every chemical around marketable drugs in the US, was "successful in discouraging competition (from US drug companies) because there was little incentive to work through a development phase when patents were already held on every conceivable related products" (Liebenau 1987: 110). In the 1916 edition of *New and Non-official Remedies*, 228 drugs out of 592 drugs listed were imported from Germany (Liebenau 1987). During World War I the Adamson Bill authorized the President of the US to "license citizens to operate enemy patents" and this enabled the US pharmaceutical industry to synthesize and produce drugs patented by German companies, e.g., *Salvarsan.*

British pharmaceutical companies in the 19th century were importers and retailers, relying on cartel, convention and licensing agreements with German and Swiss companies to offer new products (Liebenau 1990). Except for Burroughs Wellcome, who maintained a well established company laboratory, there were no other industrial laboratories doing product development (Liebenau 1984). The outbreak of World War I also caused a drug shortage in the UK, because of this dependence on German imports. In 1915, the British Medical Journal published a long list of products which were in shortage (Liebenau 1988). With the aid of its North American and Australian branches, Burroughs Wellcome not only developed a substitute for *Salvarsan*, but also manufactured *Aspirin*, *Urotropine* and vaccines (Corley 2003).

The Swiss industry also benefited from the market of the war, e.g. Hoffmann-La Roche, which grew from a medium-sized drug manufacturer to a European-wide pharmaceutical company (Liebenau 1990).

Interwar period– World War II

Major new products of the interwar period bolstered the industry, e.g. sulphonamides, insulin, and chemotherapeutics. However, it was still a very small industry (Liebenau 1990). Vitamins, which could be used both as nutritional supplements and drugs, were exploited by firms such as Glaxo in the UK (Liebenau 1990).

The period during World War II was characterized by large scale technology development, and close collaboration of the industry, universities and government (Freeman 2003). In the UK, Boots, British Drug Houses, Wellcome, Glaxo and May & Baker founded the Therapeutic Research Corporation (TRC) in 1941 (Corley 2003). By the end of 1941, the anti-malaria drug *Paludrine* was developed through the collaboration of May & Baker, ICI and Boots (Corley 2003). The discovery of *Penicillin* in 1928 and the subsequent research at Oxford until the 1940s, before *Penicillin* research moved to the US, is strong evidence of the research competence of the UK academic institutes. However, the US companies benefited from the *Penicillin* research, and they created a new drug research industry based on antibiotics. Bogner suggested that the main reasons for this were "the lack of early government support in the UK, the movement of *Penicillin* research from Oxford to the US and the formation of the Midwest Group[1] for collaborative research"

[1] With the US government approval, several firms were brought together to collaborate on penicillin research and to share information (Merck did its own research, but agree to share information). The others-Squibb, Pfizer, Abbott, Eli Lilly, Parke-Davis, and Upjohn-all agreed to form a consortium, known as the "Midwest Group", to develop technology for the mass production of penicillin production through deep-tank fermentation (Bogner 1996).

(Bogner 1996: 65). However, the different roles of the UK and the US in World War II and the relatively scarce resources of the UK during that period were also major reasons.

A survey of leading British companies in 1942 showed the variation in the research capacity of companies: between 1936 and 1941, May & Baker, which was the leading British company, held 40 patent applications, published 11 scholarly articles and 15 of their staff held doctorates; Burroughs Wellcome only had 6 patent applications, but they had published 220 articles and 24 of their staff held doctorates; Glaxo had only 6 staff who held doctorates, but they published 345 articles and held 13 patent applications (Liebenau 1990).

1950s -1970s

Two new types of drugs stimulated the rapid growth of the industry after World War II: antibiotics and psychoactive drugs. The industry also began to have new international and transnational characters (Liebenau 1990).

After the discovery of *Penicillin* and related substances, many companies established a microbiology and fermentation department (Drews 2000). This period was named the "antibiotic era" (Bogner 1996), mainly because of the major role played by antibiotics in drug innovation research and production. The US companies, in particular, played important roles in basic research. The development of antibiotic research was improved by the results of basic research across the industry, together with the knowledge of infections gained in the war (Bogner 1996). The combination of soil sample screening, observations and trial-and-error testing, was the core technology during this period. In Pfizer's research on *Oxytetracycline*, around 100,000 soil samples were examined (Bogner 1996). The major reason for maintaining large scale sample

screening and trial-and-error testing was the lack of understanding of the chemical structure of the antibiotics. This also limited further drug development (Bogner 1996).

During the antibiotics era, many other new drugs were also developed by using the companies' microbiological capabilities, for example, *Invermectin*, a drug against tropical filariosis (Drews 2000). Other non-antibiotic drugs were also developed, e.g. insulin by Lilly (Bogner 1996).

Patent laws during this period were mainly concerned with the patentability of drugs. Patent law prohibited the patent of drugs which were naturally occurring substances, e.g. some antibiotics, and some countries even prohibited patenting of any drug products (Bogner 1996). To be patentable, any drug discovery should be patented within one year after it was created. However, some synthetic substances' effectiveness as drugs was only discovered a few years later, and those drugs were excluded from patents (Bogner 1996). In 1948, the patent law of the US allowed modified naturally occurring substances to be patented, because "the modification of the naturally occurring products made it sufficiently nonnatural and product patents could be issued", and this change encouraged the development of more substitutes (Bogner 1996).

Bogner argued that during this period, the US industry lacked the vertical integration from raw material through R & D to firm sales (Bogner 1996). In the US, firms were either chemical producers e.g. Merck and Pfizer, or sellers of brand drugs, e.g. Abbott and Upjohn (Bogner 1996). In the UK, however, the pharmaceutical industry had already established drug and raw material distribution systems during World War II, e.g. Boots maintained both manufacturing systems and the largest retailing systems (Corley 2003).

1970s- The present

During the 1970s, the pharmaceutical industry was "in the early stage of mastering drug development by design, applying across a broad front the molecular insights provided by microbial biochemistry and enzyme inhibition" (Galambos & Sturchio 1998:255), and recombinant DNA technology also become possible (Galambos & Sturchio 1998a).

During the last two decades, the development of the pharmaceutical industry has been influenced by many factors. One of them is the application of biotechnology. Biotechnology refers to the application of genomic and molecular biology to the health, food and agriculture sectors (Powell & Owen-Smith 1998). Biotechnology products include antibacterials, antibodies, gene therapy, stem cells, proteins and peptides, therapeutic vaccines and other vaccines, immunology therapy, toxins, hormones and other biological molecules. The differences between biotechnology products and small molecules are shown in Table 1. Both biotechnological and small molecule drugs will be examined in this study.

Table 1 Differences between biotechnology products and small molecules

(Ho & Gibaldi 2003)

	Biotechnology products	Small molecules
Sources	Derived from living sources-human and animal tissues and cells and microorganisms	Chemically synthesized
Size	Macromolecules	Small molecules
Purity	Standard degree of purity	High degree of purity

Different from other industries, small companies play important roles in adopting new drug innovation technologies, and the large pharmaceutical companies have to develop new strategies in order to enter this field (Galambos & Sturchio 1998a). The big pharmaceutical companies needed "not merely scientists working with nucleic acids, but scientific leaders with diplomatic skills and

links to the relevant (molecular genetics) networks that would enable them to build the teams and productive programs necessary to sustain biotech R&D over the long-term" (Galambos & Sturchio 1998: 261).

In summary, the three decades after World War II could be divided into three periods. This first period is from World War II to the 1960s, when antibiotic drugs were the main products of the pharmaceutical industry and the main innovation process adopted was soil sample screening and trial-and-error testing. The second period was characterised by application of chemical drug design. Although chemical drug design had emerged in the 1950s, it was not adopted as a major innovation technology until the late 1960s, when more and more knowledge on the relationship between chemical structure and biological processes was accumulated. The third periods began with the emergence of recombinant DNA technology and monoclonal antibody technology in the late 1970s. Although Bogner argued that the biotechnology applied in the drug innovation process was another type of rational drug design, the biotechnology was based on a different knowledge base from chemical drug design (Bogner 1996). The representative technology in different eras did not totally take the place of other technologies; instead, the industry adopted a combined discovery process.

1.2.2.History of drug development

The history of drug development is not as long as drug discovery. Drug development is based on clinical pharmacology – today pharmacology could be described as "the study of the properties of drugs and how they interact with/affect the body" (Walsh 2003, P69). It was only established as a science discipline in the US in the late 1950s, and was recognized by the World Health

Organization in 1970 (Malinowski & Westelinck 2004). In the last four decades, clinical pharmacology research has emphasized different aspects (Table 2) (Sjoqvist 1999):

Table 2 Four decades of clinical research (1960-2000)

(Sjoqvist 1999)

1960-1970	Controlled clinical trial, adverse drug effects, drug metabolism, clinical pharmacokinetics
1970-1980	Drug interactions, pharmacogenetics, therapeutic drug monitoring, improved methods to assess drug response, improved drug evaluation (phase I and III)
1980-1990	Pharmacoepidemiology, pharmacovigilance, individualization of drug dosage scheduling, drug information.
1990-2000	Molecular pharmacogentics, pharmacokinetic-pharmacodynamic modeling, population-based dose evaluation, pharmacokinetic optimization of drug effects, eveidence-based pharmacotherapy, pharmacoeconomy.

Current major animal tests undertaken in preclinical trials include pharmacokinetic profile, pharmacodynamic profile, bioequivalence and bioavailability, acute toxicity, chronic toxicity, reproductive toxicity and teratogenicity, mutagenicity, carcinogenicity, immunotoxicity, local tolerance (Walsh 2003).

As discussed earlier in this chapter, the clinical trials included three phases: Phase I, Phase II, and Phase III. Some drugs are under post-marketing safety surveillance, which also refers to Phase VI. Table 3 is an example clinical trial for typical chemical based drugs.

Table 3 Clinical trial for typical chemical based drugs

(Walsh 2003)

Trial phase	Evaluation undertaken	Usual number of patients	Average duration (year)
I	Safety testing in health human volunteers	20-80	1
II	Efficacy and safety testing in small number of patients	100-300	2
II	Large scale efficacy and safety testing in substantial number of patients	1000-3000	3
IV	Post-marketing safety surveillance undertaken for some drugs that are administered over particular long period of time	varies	Several

A typical new molecular entity (NME) has most likely been studied preclinically for 5-7 years and will be in clinical trials for 6-7 years (Health & Colburn, 2000). The average cost of bringing an NME to market is between 500-800 million dollars including the costs of lost opportunities and lead-compound failures (Health & Colburn, 2000).

1.2.3.Regulation and legislation

Liebenau suggestes the 'ethical' status of the industry should be maintained by its regulation. He argues that although the technical specification, coverage and administration of regulation are similar in different countries, the genesis in each country is different, revealing "much about the character of governmental attitudes towards regulation, about the state of the pharmaceutical industry, and about the perception of the role of law within the respective medical communities" (Liebenau 1990: 86).

The UK regulatory framework

In the UK, there were a series of regulations and legislation regarding the registration and qualification of chemists and druggists from 1841, e.g. Act of 1868 for qualification examination (Corley 2003). The first list of drugs with information on how they should be prepared was the *London Pharmacopoeia*, published in 1618 (MCA 2005). However, except for the Food and Drug laws which prohibited adulteration, there was no practical regulation on drug production (Liebenau 1988) until World War I. Germany, in contrast, passed the Act of 1902 regarding hygiene, packaging and labelling during drug production, as well as inspection of company premises. The first British legislation that included a form of licensing for medicinal products was the 1925 *Therapeutic Substances Act* which applied to medical substances such as vaccines, sera, toxins, antitoxins, antigens, insulin, pituitary hormone and surgical sutures (MCA 2005). Inspection of manufacturing sites and record keeping are included in this Act and labelling requirements were also introduced in order to identify the manufacturer of each batch of material produced (MCA 2005).

After the National Health Service (NHS) was established in 1948, the UK government paid much more attention to drug prices, safety and R & D (Corley 2003). Since 1957, the UK government and industry have collaborated on the regulation of drug price and reward system (Earl-Slater 1998). A voluntary agreement, the Pharmaceutical Price Regulation Scheme (PPRS), was made between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI) (Earl-Slater 1998). This agreement was not only applied to the members of the ABPI, but to all organizations who supplied drugs to the NHS (Earl-Slater 1997). One of the aims of the PPRS was to encourage R & D in this industry (Corley 2003;Earl-Slater 1998) and penalize firms if they were merely followers (Corley 2003).

After one of the biggest medical disasters, *Thalidomide*[2], which caused as many as 10,000 babies worldwide to be born with severe deformity during the 1950s and early 1960s, the UK government set up the Committee on Safety of Drugs (CSD) in 1964. The members of CSD were medical experts on behalf of the industry, and they introduced many standards which are still in use today (Corley 2003). After the Medicines Act 1968, the CSD became an independent official body, the Committee on Safety of Medicines (CSM) (Corley 2003). Corley suggests that the industry was shaped by government policies during this period and the rate of change in the industry "accelerated markedly" (Corley 2003:18).

The Medicines Control Agency (MCA) was launched in 1989, and became an executive agency of the Department of Health in 1991. This agency aimed to reduce licensing times for medicines and to ensure that all medicines on the U.K. market had met "appropriate standards of safety, quality, and efficacy" (American Chemical Society 2008). In 2003, the MCA and the Medical Devices Agency (MDA) merged to form the Medicines and Healthcare products Regulatory Agency (MHRA).

In 1999, the National Institution for Clinical Excellence[3] (NICE) was established, and its main responsibility was to evaluate clinical cost-effectiveness of drugs entering the England and Wales market (McDonald 2000). However, there are different views about NICE. Besides the criticism from the pharmaceutical industry, it has also been described as a sign of direct government intervention in the market (McDonald 2000). On the other hand, many researchers argued that NICE was a key element of the national pharmaceutical policy framework and it should be supported by integrated pharmaceutical policies (Walley et al. 2000).

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[2] Thalidomide, 2-(2, 6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione, is a sedative, hypnotic, and multiple myeloma medication. Thalidomide was mainly sold during the late 1950s and early 1960s to pregnant women to combat morning sickness. More than 10,000 children in 46 countries were estimated to have been born with deformities as a consequence of thalidomide use (FDA 2001).

[3] In Scotland, the Scottish Health Technology Assessment Centre (SHTAC) plays a similar role.

The current regulatory framework in the UK is primarily the system of licensing and conditional exemptions from licensing laid down in the European Medicines Evaluation Agency (EMEA) (MCA 2005). In 1965, the European Commission (EC) issued its first Directive in order to reduce national differences in drug regulation, and in 1975, the EC established the Committee of Proprietary Medical Products (CPMP) which was authorized to review all the drugs applying for licences in EC members (Vogel 1998). In order to build a single European market, the European Medicines Agency (EMEA) was established in London in 1995 (Vogel 1998). London was chosen because of the leading role of the UK pharmaceutical industry in the EU and the experience of the UK government in pharmaceutical regulation (Vogel 1998). EMEA was mainly responsible for the evaluation and supervision of medicinal products throughout the European Union (EMEA 2005).

In 2004, the EU Clinical Trials Directive (2001/20/EC) was implemented in the UK as the Medicines for Human Use (Clinical Trials) Regulations 2004, and replaced the clinical trial provisions of the Medicines Act 1968 and its secondary legislation (MHRA 2004). The major changes included that Pharmacology studies in healthy human volunteers (Phase I) require authorization from the MHRA where previously they only needed a favourable opinion of an ethics committee (MHRA 2008). Other changes included that each trial must have an identified sponsor, investigational medicinal products (IMPs) must be manufactured to Good Manufacturing Practice (GMP) and the manufacturer must have a license (MHRA 2004).

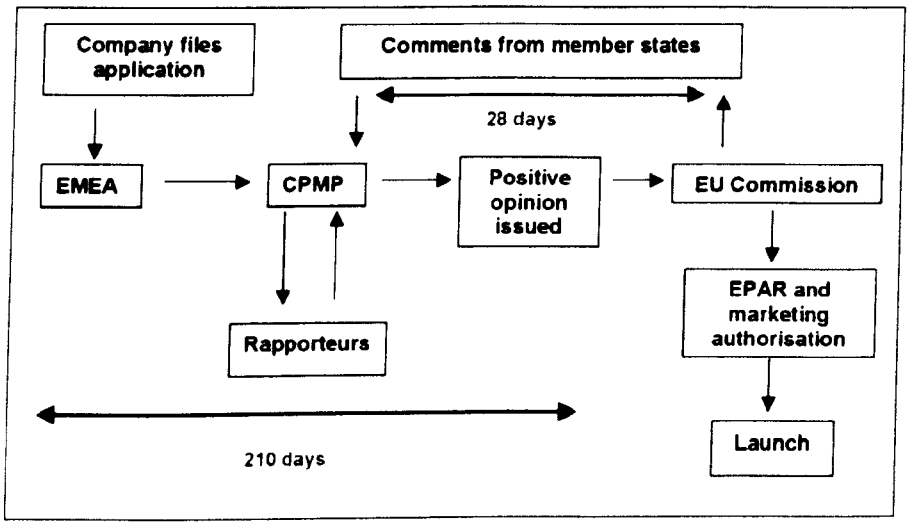
Drug approval in the UK

In the UK, drugs can be licensed in two ways: either companies send applications directly to the UK MHRA to apply for a UK only license, which is assessed by CSM, or through EMEA to apply an EU wide license. There are two systems within the EMEA: 'Centralized system' which grants 10 years exclusivity, was compulsory for biotechnology products, as well as new drugs on AIDS,

cancer, neurodegenerative diseases and diabetes (NHS 2003). Companies send their application to EMEA, and EMEA passes them to CPMP. Based on assessments of selected representatives from two member states, CPMP will make recommendations for or against an EU wide license. If CPMP makes a recommendation, a European Public Assessment Report (EPAR) and marketing authorisation will be issued (NHS 2003) (Figure 2).

Figure 2 The European Union centralised system

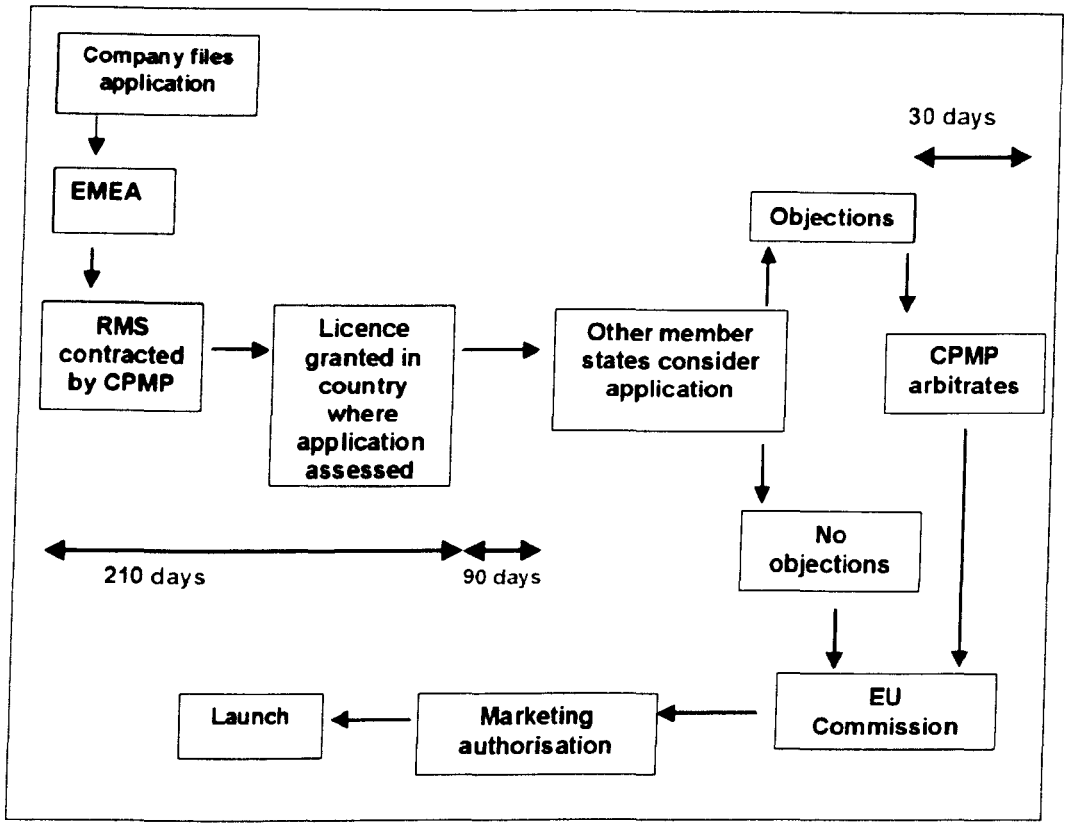
(NHS 2003)



In "decentralized system" (or "mutual recognition system"), one member state will assess the drug application and grant the license (8 years exclusivity). In the UK, MHRA is the agency to consider these applications. After the license is granted, other member states will mutually recognise or object to the decision (Figure 3). Under this system, CPMP only intervenes when there are disagreements between member states (NHS 2003). Because reviews in different countries may lead to different results, companies are inclining to choose the member states where approval is less doubtful and the procedure is faster (NHS 2003).

Figure 3 The European Union decentralised (or mutual recognition) system

(NHS 2003)



Besides the Medicines for Human Use Regulations 2004, Medicines Act 1968 and revisions, the Pharmaceutical Price Regulation Scheme (PPRS), the existing regulations and legislation regarding the UK pharmaceutical industry also include the Intellectual property rights, advertising of drugs, prescription charges, profit controls, generic prescribing targets, commercial competition, trade and parallel imports, drug tariffs, the Consumer Protection Act, and the production liability directive (Walley, Earl-Slater, Haycox, & Bagust 2000).

Walley et al. argued that the integrated policy should "go beyond the regulation of drugs, the industry and the prescribers, but it would combine all of these", and the aims of the integrated

policy should be "effective and safe drugs that are readily accessible at an affordable price—and it would support continuing research into areas of unmet need" (Walley et al. 2000: 1525).

Policies to promote drug innovation

The policies aimed at promoting overall UK innovation and technology performance, and the specific policies to promote biotechnology development both had positive impacts on the drug discovery and development subsector. The Biotechnology and Biological Sciences Research Council (BBSRC) was established in 1994 by incorporation of the former Agricultural and Food Research Council (AFRC) with the biotechnology and biological sciences programmes of the former Science and Engineering Research Council (SERC). The Industrial Biotechnology Innovation and Growth Team (IB-IGT) was formed in November 2007 by Department for Business Enterprise & Regulatory Reform (BERR), and it was divided into three groups: Policy Measures work group, Technology and Manufacturing work group, and Finance and Investment work group.

Cleff et al. suggested that the most important tax incentives for biotechnology innovation are direct ways of support - grants and subsidies - followed by indirect ways of support - tax credits and R&D allowances (Cleff et al. 2008). These include generic policies and biotech-specific policies to promoting innovation (D'Este, Senker, & Costa 2007). This section will first discuss the grants and subsides, and then introduce tax credits and R&D allowances.

As direct ways of support, government annual expenditure on bioscience research exceeds US$ 960 million (The UK government's inward investment agency 2001). These policies included enhancing networking, strengthening linkages between academic institutes and industry,

facilitating biotechnology commercialization, promoting business, helping increase manufacturing potential and improving industry competitiveness (Zechendorf 2004).

Programmes to facilitate biotechnology commercialization included Harnessing Genomics which was a £25 million programme to help businesses to take up and commercialize genomics science. One important part of this programme was the DTI Bioscience Beacons project, which aimed to help the universities to commercialize their research. These projects included Imperial College's "imaging changes in diseases" and "computer models to detect toxicity", also, University College London's project "computer models to predict drug action", University of Edinburgh's "new rapid approach to detecting diseases", University of Glasgow's project "biochemistry 'in silico'" and University of Liverpool's project "development of a high-throughput platform for functional gene analysis".

The Biotechnology Mentoring and Incubator (BMI) Challenge was a competition to encourage the provision of incubators and specialist business mentoring services to young biotechnology companies. BMI provides funds of up to £500,000 for each project, and from its beginning to 2006, has funded 11 with two extensions. According to DTI Bioscience Unit, BMI has catalyzed 137 new biotechnology companies that employ over 900 staff. Many companies studied in this thesis benefit from BMI, such as Vectura, Ark Therapeutics and ReNeuron. Bio-Wise was a £13 million programme which aimed to improve the competitiveness of UK industry through the use of biotechnology, and support the development of the UK biotechnology supplier industry. Up to and including 2006 Bio-Wise helpline took over 25,000 enquires and organized 92 events.

The UK Biotechnology Finance Advisory Service was a free service sponsored by DTI. Its aim was to assist both existing biotechnology companies and new companies to access financial support. Small companies could get Small Firms Loan Guarantee Fund from Regional Venture Capital Funds and the UK High Technology Fund to finance business proposals.

The general government grants for R&D were administered by the nine English Regional Development Agencies. Four types of grants were available: up to £20,000 for Micro Projects lasting less than 12 months, up to £100,000 for Research Projects lasting six to 18 months, up to £250,000 for Development Projects lasting six to 36 months and up to £500,000 for Exceptional Development Projects lasting six to 36 months. A similar regionally based programme was the Biotechnology Exploitation Platform (BEP) Challenge launched in 1999, which aimed to promote technology transfer. This programme covered technologies such as therapeutics, medical devices, diagnostics, plant sciences and environmental sciences. According to the DTI Bioscience Unit, by May 2006, 2085 technologies were indentified with commercial potential in BEP, 958 projects were selected for commercialization, 415 patents were filed and 58 were granted.

In order to help small to medium sized companies improve their manufacturing potential, a two-year initiative, 'Manufacturing for Biotechnology', was launched in 1999, which provided help in the form of workshops, information, management tools, training grants and grants for feasibility studies (UK Trade and Investment).

Policies also facilitated clustering of biotechnology companies. Zechendorf suggested that clusters and incubators had been supported with £50 million annually from regional innovation funds since 2001. In addition six Genetics Knowledge Parks were also built (Zechendorf 2004).

Besides encouragement of basic research and commercialization, there are also programmes to enhance the network and linkages of companies and academics. For example, the EU Fifth Framework Programme (FP5) for the period 1999–2002 was designed to enhance linkages between countries, and between industry and academia. Similar programmes included EUREKA, a pan-European network for market-oriented industrial R&D, which aimed to enhance partnerships between companies and organizations in EUREKA member states. The UK LINK scheme aimed to strengthen linkage between academic institutes and industry via cooperation in various life science fields. The government departments and Research Councils provided up to 50% of the cost.

According to the DTI Bioscience Unit, the LINK Applied Genomics, from its launch in 2000 to 2006, has supported 21 projects in healthcare with around £29 million investment. Successful examples include development of prototype biochips for human protein expression profiling and antibody selection, and development of novel automated protein expression systems to accelerate drug discovery. Collaboration between the UK and the US was also encouraged, for example, the UK/US Texas Bioscience Collaboration Initiative aimed to bring together researchers from UK and US academia and industry.

Besides the direct support, there are also indirect fiscal incentives. Cleff et al. have summarised the UK R&D allowances and tax credits for innovative companies:

R&D allowance:

Small and medium-sized companies: 150% deduction of expenditures on R&D, if at least GBP 10,000 p.a. is spent (c. EUR 15,000); also applies in principle to R&D expenditure on contracted research; benefits and subsidies received reduce the tax base. Restriction: Income tax and social security payments must not exceed an additional 50% reduction in any year (capping). SMEs can benefit from the concessions for large companies (see below), if they are unable to take up the concessions for SMEs because of government benefits or subsidies; SMEs are defined in accordance with the EU subsidy regulation (e.g. turnover of GBP 25M (c. EUR 37M) p.a. or less).

Large Companies (all companies other than SMEs): 125% deduction of R&D expenditure; also usually valid for R&D expenditure on contracted research; Restriction: The 125% reduction in any year must not exceed the income tax and social security payments (capping); any benefits and subsidies may be offset.

SMEs and large companies may deduct an additional 50% on R&D expenditure to combat epidemics.

Tax Credit

SMEs that do not make a profit and therefore cannot use the 150% deduction of expenses can apply for a rebate of 24% of R&D expenditure (cash costs) as a tax credit.

(Cleff et al. 2008, P86)

Tax allowance enables firms to claim back R&D expenditure and tax credit allows firms to directly deduct part of their tax (Cleff et al. 2008). Compared with the direct grants from government, there are many advantages of indirect fiscal incentives: they require less administration costs for both companies and government, avoiding long term project management and monitoring; there are less barriers for small and medium sized companies to obtain support; moreover, they are more neutral on the process and content of the R&D project (Cleff et al. 2008, P53). Therefore, the tax allowances have impact on all industries, while most direct grants and subsides discussed in the earlier section are biopharmaceutical sector-specific.

In short, the UK and EU government have made policies to directly and indirectly promote the development of biopharmaceuticals. These policies are characterized with wide coverage, including basic research, technology commercialization, networking and industry development, from small and medium sized firms to large companies. However, there are also debates on these policies, in particular arguments from different actors. In the next sub section, policy debates will be discussed from perspectives of different stockholders.

Policy debates

The policy disputes of biopharmaceutical regulation arise from the conflict of interests between different actors. First of all, there are conflicts of interest between industry and government. The drug discovery and development process "has developed into an evolutionary struggle between manufacturers, who wish to maximise sales and profits, and regulators, who wish to ensure that new agents are safe and effective" (Gale 2001, P1870). One Sociological concern is the impact of drug developers on regulation. On the one hand, the delay of drug approval may cost the company as much as one million each day (Montaner, O'Shaughnessy, & Schechter 2001); on the other hand, only the company whose drug is first approved will win when there is competition to develop similar compounds (Gale 2001). Therefore, the drug developers are actively influence the regulatory body and the regulation process making them important "political players" (Abraham 2002b).

Abraham is one of the most important researchers in the field of pharmaceutical policy: he published a series of papers and books to discuss the regulation and policies relating to the pharmaceutical industry (Abraham 2002a;Abraham & Lewis 2000;Abraham 1995;Abraham 2002b;Abraham 2007;Abraham & Davis 2005;Abraham & Davis 2007;Abraham & Lewis 1999;Abraham & Sheppard 1997). He argued that when the interest of public health and drug developers diverge, the company may influence the regulatory body via "subtle ways" (Abraham 2002b). For example, one method is described as the "revolving door", that is that many regulatory officials started their careers in the pharmaceutical and biotechnology industry and frequently move back to the industry where they may be promoted to higher positions than before (Abraham 2002b). Therefore, the policy making process is influenced by employee movement between industry and regulatory bodies.

Another factor which may influence the policy making process is the financial linkages between industry and the regulatory body. Abraham describes this as "regulatory capture", and suggested

that the "regulators too often consistently award industry the benefit of scientific doubt when reviewing products", and one important reason is that part or all of the running costs of the regulatory agency are provided by industry (Abraham 1995;Abraham 2002b). In the US, FDA scientists have claimed that their recommendation of approval of a drug is more welcome than recommendation of non-approval (Abraham 2002b). Furthermore, the pharmaceutical and biotechnology industry also paid attention to the financial links with experts: in 1996 only a forth of expert advisers on Committee on Safety of Medicines (CSM) or the Medicines Commission did not have financial interests in the industry (Abraham 2002b). Therefore, the regulatory body needs financial dependence from industry, and regulatory agencies also need more representation from patients and public health (Abraham 2002b).

The industry also has impact on the globalization of drug testing and assessment standards: in order to reduce the cost and time of drug development, the industry organized the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and 17 countries' regulatory agencies also attended (Abraham 2002b). Abraham argued that the ICH adopted low scientific standards suggested by industry, for example, minimum clinical trial treatments in initial marketing applications were reduced from 12 months to 6 months, although evidence showed that one forth of serious adverse drug reactions, and one eighth of all reactions, occurred after 6 months treatment (Abraham 2002b).

Besides the direct impacts from the industry, there are also problems of the regulatory bodies and regulatory systems. For example, Abraham & Lewis suggested that the mutual recognition system of EU drug approval procedure will result in a competition between agencies to shorten approval time to attract applications and thereby increase the regulatory body's income (Abraham & Lewis 1999). However, shortened time of review process was likely compromising drug safety (Abraham & Davis 2005).

Although there was no direct evidence to claim that the current mutual recognition system of EU drug approval procedure would have negative impacts on drug safety, there is evidence indicating that the shortened approval time does have impacts on the rates of drugs withdrawn. Based on the fact that there were twice the number of new drugs withdrawn because of safety reasons in the UK than in the US between 1971 and 1992, Abraham & Davis suggest five hypotheses to explain the difference: 1) the UK approved more new drugs than the US, 2) differences in firms' strategy, 3) UK regulatory agencies were more strict at post-marketing surveillance, 4) because the approval process in the US is slower than that in the UK, the US regulatory agency learns from and avoids safety problems that emerged in the UK or European market, 5) the US regulatory agencies were more strict and they approved fewer unsafe drugs (Abraham & Davis 2005). Their conclusion was that the main reason was that the US regulatory agency has a more strict approval review process, which takes longer and prevents safety problems that have emerged in the UK or European market (Abraham & Davis 2005).

However, the patients groups who benefit from long and strict approval processes raise another issue: the cost of the review process. The US researchers argued that the US regulatory systems need to speed up the review process and reduce the cost sharing of patients (Cohen et al. 2006). From a perspective of patients, drug safety and administration cost are both important requisites for drug approval process.

From a perspective of pharmaceutical and biotechnology industry, the strict regulation may cause them to relocate their companies to other countries, and further damage export and employment; in addition, the slow and ineffective approval process will influence the public health (Abraham 2002b). The indications of pharmaceutical and biotechnology industry were also controversial: as found in this project, companies are reluctant to invest in diseases such as tropical disease and tuberculosis because the development processes are costly, risky and have a low return. In order to balance the drug pipelines, public-private partnership and incentive packages have been offered to encourage the drug development of neglected diseases (Trouiller et al. 2002).

From a perspective of government, they must both support drug innovation *and* ensure drug safety and efficacy. Therefore, the policies and regulations should embody both restrictions and drive drug innovation. The current policy comments focus on these two directions: more strict control on drug approval and encouragement of drug innovation. There are several important reports in these two streams: "*The Influence of the Pharmaceutical Industry*" published by House of Commons Health Committee in 2005 suggested more strict control; while the report of Bioscience Innovation and Growth Team published in 2003 and Cooksey's report "*A review of UK health research funding*" published in 2006 both suggested the reform of regulatory agencies to encourage the drug innovation.

In the report *The Influence of the Pharmaceutical Industry,* recommendations are focused on how to improve industry and the regulatory agency (House of Commons Health Committee 2005). The report suggested that for industry research the register of clinical trials needs to be more transparent and the design of trials should be improved to more accurately predict the performance of drugs; for industry marketing, company promotion needs to be controlled more strictly. For the regulatory agencies, the report suggested data submitted by companies to MHRA should be accessible to patients and the public rather than kept in secrecy, furthermore, the MHRA also need to review the standards developed by ICH. It also suggested that the MHRA need to be reviewed in-depth. Several principles were outlined: "the need for greater independence from government; the need for greater independence from the pharmaceutical industry; the need for policies of greater transparency and accountability in light of recent freedom of information legislation; the need to increase effectiveness of the post-licensing department and the need for the MHRA to become pro-active rather than re-active; scrutiny of the regulatory standards underpinning clinical and non-clinical new drug review and reporting and evaluation of adverse drug reactions; the prioritisation of new marketing applications; and inclusion of the public in policy-making and implementation" (House of Commons Health Committee 2005, P106-107). Based on the data from telephone interviews, other research suggested that the UK regulation systems need to improve the

fairness of the process and "provide guidelines for implementing recommendations" (Mitton et al. 2006, P208).

There are also reports which give comments on policies and regulations to encourage drug innovation. The report of Bioscience Innovation and Growth Team, suggested creation of the National Clinical Trials Agency (NCTA) to support clinical trials, create a public and regulatory environment supportive of innovation, provide sufficient funding for bioscience companies, and attract and retain scientific and managerial employees (Bioscience Innovation and Growth Team 2003).

Cooksey suggested that there are two gaps in the translation of research: translating basic ideas and clinical research into new drugs or treatments, and implementing these new drugs and treatments into clinical practice, therefore, the UK government will increase the amount of R&D, from basic laboratory to clinical trials to new drug approval and evaluation (Cooksey 2006). The result of this report is to carry out potential reform of regulatory systems, that is establish an Office for Strategic Coordination of Health Research (OSCHR) to "achieve better coordination of health research and more coherent funding arrangements to support translation" (Cooksey 2006, P4). Moreover, there were several schemes set up to facilitate the translation of basic research: Higher Education Innovation Fund (HEIF), Public Sector Research Exploitation Fund (PSRE Fund), Science Research Investment Fund (SRIF), DTI's Equity Investment Programmes, Small Business Research Initiative (SBRI), DTI Technology Programme, etc. Take DTI's Equity Investment Programmes for example, which included several schemes such as Regional Venture Capital Funds (RVCFs) which provide up to £500K risk capital to SMEs which have growth potential; the Early Growth Funding (EGF) which is designed to help start-up companies (136 companies have benefit from this scheme); The UK High Technology Fund (UKHTF) which was founded to invest venture capital firms and further invest in high technology companies; and The Enterprise Capital Fund (ECF) which was developed to provide equity funding to small business (Cooksey 2006).

To conclude, the current arguments over policy and regulations are focused on establishing a reliable and efficient framework, which can, at the same time, mediate the conflict of interests among different actors: ensuring the safety of patients and their access to the new drugs, while ensuring the healthy development of the pharmaceutical and biotechnology industry.

In summary, this section has provided a historical background of how the pharmaceutical and biotechnology industry has been using technology breakthroughs to improve drug discovery and development procedures, how regulation and legislation has changed to ensure drug safety, effectiveness and reasonable price, how policy has been used to promote the growth of the biotechnology industry and how policy disputes have been addressed and analysed. The next section will discuss how the research questions of this study have been raised and developed.

1.3. Research Questions

There are two main reasons for choosing drug discovery and development companies: first, the pharmaceutical industry plays an important role in the British economy: it accounts for 0.6% of UK GDP, employs around 73,000 people and generates 250,000 jobs in related industries (DTI, 2006). The importance of the pharmaceutical industry can also be shown in international trade: in 2005 it exported £12.2 billion and created a trade surplus of £ 3.4 billion (DTI, 2006). The pharmaceutical industry has been seen by the UK government as a key part of the knowledge-driven economy and an important source of economic growth. According to the *Department of Trade and Industry* (DTI) *1998 Competitiveness White Paper*, the UK will only compete successfully in the global economy if it builds a knowledge-driven economy, based on knowledge, skills and creativity. Moreover, this industry also provides large social benefits, e.g. increased

longevity, enhanced quality of life and improved labour force participation (DiMasi, Hansen, & Grabowski 2003;Grabowski 2002).

Second, central to the pharmaceutical industry is the drug discovery and innovation process. Innovation is critical to Britain's long-term competitiveness, because innovation is a determinant for productivity growth and social gain (HM Treasury 2002). The potential of scientific and technological discovery to benefit the economy and society will only occur through successful and effective conversion into innovation (HM Treasury 2002). Therefore, the drug discovery and development subsector has the greatest potential for wealth and job creation of the pharmaceutical industry. Public policies are directed to support drug innovation activities (Reiss et al. 2004), and to establish a virtuous circle of innovation: e.g. the UK government launched the R&D Credits Scheme to encourage companies to invest in research and development (R&D) in the form of tax relief.

From existing work in social science and innovation studies (see Literature Review Chapter) a number of key factors which influence drug discovery and development have been identified, e.g. policy and regulations, market, alliances, R&D and management skills. There is a large body of research on the pharmaceutical industry, a fraction of which focuses on British companies. These studies mainly address topics of policy and regulation (Abraham & Lewis 2000;Earl-Slater 1997;McMeekin, Green, & Coombs 2002;Sally 1998;Smith 2005b;Walley, Earl-Slater, Haycox, & Bagust 2000), innovation (Casper & Matraves 2003;Walsh 2002), drug markets (Franco & Orsenigo 2002;Green 2002;McMeekin & Green 2002a), alliances (Simon & Martha 1996) and clustering (Peter & Martha 1996;Van Reenen 2002).

There are many debates among researchers. One important reason for researching the innovation systems of biopharmaceuticals is based on the debates of performance of this sector (Patel, Paunov, & Arundel 2008). On one hand, the pharmaceutical and biotechnology sector is regarded as a key driving force of the knowledge economy by many researchers and policy makers (Earl-Slater

1998;Van Reenen 2004); on the other hand, many researchers argue that the performance of biotechnology does not meet people's expectations (Hopkins et al. 2007;Pisano 2006).

For the UK biopharmaceutical sector, the arguments focus on comparisons of its performance with those of other countries. In terms of volume of activities of the biotechnology sector it is ranked top of Europe (Patel, Paunov, & Arundel 2008). However, considering the R&D expenditure as a ratio of GDP and output per million capita (PMC), the UK is under performing. Patel, Paunov, & Arundel have compared the performance of the biotechnology sector of different countries and suggest that Switzerland and Denmark have the best performance of biotechnology innovation, followed by Ireland, Sweden and Belgium; and these countries' performance is better than the countries which had the largest "volume of biotechnology related activates"—UK, Germany and France (Patel, Paunov, & Arundel 2008, P3). Their research used 17 indicators of three areas of innovation: human resources and knowledge creation, commercialization and finance, and outputs and markets (Patel, Paunov, & Arundel 2008). These indicators included "post-graduates in life science PMC, biotech publication PMC, citations per publication in biotech, government biotechnology R&D as a ratio of GDP, biotech business sector R&D expenditures as a ratio of GDP, biotechnology patents PMC, employment in dedicated biotechnology firms PMC, number of biotech start-ups PMC, strategic alliances in biotechnology PMC, total venture capital for DBFs as a ratio of GDP, total finance available for DBFs as a ratio of GDP, revenues of DBFs as ratio of GDP, revenues per employee for DBFs, number of approved biopharmaceuticals as a ratio of GDP, number of clinical trials of biopharmaceuticals as a ratio of GDP, index of optimism in biotech", and a non biopharmaceutical related indicator-"genetically modified organism field trials as ratio of agriculture output" (Patel, Paunov, & Arundel 2008, P7). The large majority of the data were about biopharmaceuticals which placed the overall performance of UK biotechnology sector in the third level (Patel, Paunov, & Arundel 2008). Results of a Biopolis Final Report indicated that the best performing countries were Switzerland, Denmark, Sweden and Finland, with the UK ranking as second level, together with Austria, Belgium, the Netherlands, Ireland, Norway, Germany and France (Enzing et al. 2007).

Therefore, the UK biopharmaceutical industry is still under pressure of competition from other countries. Policies and regulation which support the development of this sector are required, in particular for drug discovery and development companies which are core for biopharmaceutical innovation. However, without understanding the development and structure of this sector, it is very difficult to make policies for the drug innovation sector.

One gap in the research is that the performance of the drug discovery and development sub-sector has not been evaluated separately: most of these studies have not distinguished the drug discovery and development subsector from the industry as a whole. Take Patel, Paunov, & Arundel's study for example: it did not map the biopharmaceutical sector separately, although biopharmaceuticals accounted for "the large majority of all biotechnology R&D, employment and revenues" (Patel, Paunov, & Arundel 2008, P18). Obviously, the policies and regulations regarding the biopharmaceutical sector are different from those for agriculture and environment. In many other studies, the drug discovery and development companies were considered as part of the health care industry, and were studied together with reagents and equipments companies, contract service companies, and manufacturers etc. In short, the development and contributions of the drug discovery and development sector were not properly evaluated in these studies.

This subsector is the key part of knowledge production of the pharmaceutical and biotechnology industry, and its major activity is drug innovation. As discussed in an earlier section, there are many government policies and regulations to promote the development of this sector, and comments from academics to enhance the efficiency of policy implementation, however, little is known about this subsector, e.g. How has this sector evolved and what factors have shaped its development? How does this subsector contribute to knowledge production within the pharmaceutical industry? Is it realistic to expect this subsector to make a significant economic contribution in future? Do policies which were designed to promote this sector achieve their goals? As this sector evolves, are new policies required to enhance its development? However, these questions are not answered by previous literature, because in most cases the drug discovery and

development sector was either discussed with the pharmaceutical industry as a whole, or analysed together with other biotechnology sectors (agricultural, environmental biotechnology etc.).

As suggested by the Biopolis Final Report, in order to design successful policies, "a broad and up-to-date information base and the inclusion of different perspectives are important prerequisites" (Enzing et al. 2007, P17).

Therefore, to answer these questions firstly requires a detailed analysis of the subsector and the key factors influencing its development. Besides analyzing the current structure of this subsector, e.g. number of companies, size, and age, it is also important to study the industry dynamics, i.e. how the industry knowledge production and networking had changed over time. What technologies have been involved in the alliances between drug innovation companies and other pharmaceutical companies? How successful are these technologies in developing new drugs? There are two main reasons for this. First, it often takes a long time for a technology invention to transfer to commercial innovation, and even longer for this to come into widespread use (Charles Edquist 1997). Second, understanding the dynamics of this industry will also help us to understand the accumulation of the influences of different factors upon the development of the biotechnology industry. Previous studies have only drawn a rough picture of the network and alliances: more studies are needed to understand the networks of the UK drug innovation subsector and its alliances, e.g. how are these drug innovation companies allied with other companies? How successful are these alliances in drug innovation?

This study aims to understand the co-evolution of company strategy and networks, and co-evolution of company strategy and structure from a historical and industry dynamics perspective, and to analyse the policy implications of these developments.

To facilitate the analysis, a conceptual framework of Sectoral Systems of innovation will be adopted in this thesis (details will be discussed in next chapter). As suggested by Malerba, a

sectoral system has a specific knowledge base, technologies, inputs and demand, and agents are individuals and organizations at various levels of aggregation (Malerba 2002). They interact through processes of communication, exchange, co-operation, competition and command, and these interactions are shaped by institutions (Malerba 2002). As discussed in the previous section, the knowledge base of the drug discovery and development sector has experienced long term development and accumulation, and currently several technologies co-exist. The input to this expansion included not only R&D investment, but also human and social capital.

This study is focused on the knowledge base, technology domain and networks of the drug discovery and development companies. One important feature is that a sectoral system undergoes change and transformation through the co-evolution of its various elements (Malerba 2002). Therefore this project will focus on the dynamics and interlinkages of different elements.

In order to meet these aims, the study will focus on the following research questions, and how these questions have been raised which is further discussed in the literature review chapter:

1) Is there a divergence of strategies existing in the drug discovery and development subsector? If so, what are the key factors which determine the divergence of strategy?

2) How does the divergence of strategy influence industry structure?

These research questions reflect the core element of Sectoral Systems of Innovation: co-evolution. Using this conceptual framework, the research questions are firstly broken down into four issues, and then analyzed in a systematic way.

1) The drug discovery and development subsector's structure, the size and age of firms their clustering and concentration;

2) The knowledge contribution of the drug discovery and development subsector and how this has developed over time;
3) Their networking and collaboration with other actors and how this has changed over time;
4) The development of different company strategies.

Each issue is important in describing the drug discovery and development sector and its changes overtime. Central to the analysis of these key issues, is the understanding of the relationship between this subsector and other actors of the pharmaceutical industry. Rather than studying the companies involved in drug innovation separately, this study investigates the role of these companies in a network of innovations.

1.4. Thesis Structure

As introduced above, the first chapter of this thesis provides a historical background of how this industry has been using technology breakthroughs to improve drug discovery and development procedures, and how regulation and legislation has been changing to ensure drug safety, effectiveness and reasonable price. Research questions were also discussed in this chapter.

The second chapter will be the literature review and conceptual framework. In particular it will introduce and define the Sectoral System of Innovation, and discuss pros and cons of this conceptual framework. Literature on the pharmaceutical and biotechnology industry will also be reviewed. It will pay attention to structure and dynamism, clustering, networking and alliances, firm strategies, and policies.

The third chapter will discuss the research design and methodology of this thesis. It will begin with an introduction of data sources, followed by discussion of measurements and indicators and criteria of data collection. It will address the practical issues that arose and how the research process was designed in response. Finally, the limitations of the methods and research design will be discussed.

The first section of the fourth chapter will focus on mapping the current British pharmaceutical and biotechnology industry, giving more details about its activities, structures, and clustering. This section will present an industrial background of the drug discovery and development subsector. The second section of the second chapter will provide an overview of the drug discovery and development subsector, more precisely, the drug discovery and development companies which were established after the 1980s – when biotechnology first started to be applied to the drug innovation process. This group of companies is the focus of this study. An overview of their product pipelines and R&D expenditure will also be discussed in this chapter.

The next two chapters will focus on the R&D output of this subsector: the fifth chapter will focus on scientific publications of this subsector, and the sixth chapter will analyse its patent publications. The seventh chapter will discuss alliances and networking of this subsector, followed by a chapter integrating the four data chapters. The final chapter will be a discussion and conclusion.

Chapter Two: Conceptual Framework and Literature Review

This chapter aims to introduce the conceptual framework used in this study and briefly review literature related to the pharmaceutical and biotechnology industry. The first section will introduce and define the concept of Systems of Innovation and Sectoral Systems of Innovation, and the pros and cons of using this conceptual framework.

The second section will outline how research questions have been developed from the existing literature. It will then introduce a broader context of research and review literatures related to the pharmaceutical and biotechnology industry: first, studies of the structure and dynamics of the pharmaceutical and biotechnology industry will be reviewed to give a background of this industry; second, literature on the clustering of new biotechnology firms will be reviewed, followed by a review of the impact of globalization; third, the literature regarding the formation and performance of alliances in the pharmaceutical and biotechnology industry will be reviewed. The following section will focus on companies' R&D activities: both internal R&D and outsourcing of R&D. The next section will review literature on firm strategy and management, followed by a section to review the literature on policy and regulations. Finally, there will be a discussion and summary of this chapter.

2.1. Conceptual Framework

2.1.1.Systems of Innovation

First of all, definition of Systems of Innovation will be introduced. Innovation, defined by Nelson and Rosenberg, as "encompassing the processes by which firms master and get into practice product designs and manufacturing processes that are new to them, if not to the universe or even to the nation" (Nelson & Rosenberg 1993, P4). According to this definition, there are two types of innovations: product innovations which refer to "new or better material goods as well as new intangible services", and process innovations which refer to "new ways of producing goods and services" (Edquist 2005, P182).

"System" is defined as "a set of institutional actors that, together, plays the major role in the influencing innovative performance" (Nelson & Rosenberg 1993, P4-5). Edquist describes the systems of innovation as "all important economic, social, political, organizational, institutional, and other factors that influence the development, diffusion and use of innovations" (Edquist 1997 , P14).

There are several different perspectives on Systems of Innovation, e.g. national, regional and sectoral systems of innovation. In the *National Innovation Systems and Instituted Processes* (de la Mothe & Paquet 2000), de la Mothe & Paquet suggeste the core idea of National Systems of Innovation was taken from *National System of Political Economy* written by German economist Friedrich List in 1841, and became a conceptual framework in 1980s and 1990s through the analytic and empirical efforts of Freeman (Freeman 1987), Lundvall (Lundvall 1992), Nelson (Nelson ed. Nelson 1993), Niosi et al. (Niosi et al. 1993), the OECD (OECD 1994a;OECD 1994b)and Edquist (Edquist 1997). This conceptual framework is based on two assumptions. First, that knowledge is the most fundamental resource in the modern economy and learning is the most important process; and second, that this process cannot be understood without taking into account the social context (Lundvall 1992).

Similarly, Regional Systems of Innovation also based on the idea of territory, which could be described as "the institutional infrastructure supporting innovation within the production structure of the region" (Asheim & Gertler 2005).

In contrast to the territorial notion, a Sectoral Systems of Innovation is originally defined as a "group of firms active in developing and making a sector's product and in generating and utilizing a sector's technologies" (Breschi & Malerba 1997, P131). The definition of Sectoral Systems of Innovation has been redefined and expanded later and includes more elements:

> *A sectoral system of innovation and production is a set of new and established products for specific uses and the set of agents carrying out market and non-market interactions for the creation, production and sale of those products. A sectoral system has a knowledge base, technologies, inputs and an existing, emergent and potential demand. The agents composing the sectoral system are organizations and individuals (e.g. consumers, entrepreneurs, scientists). Organizations may be firms (e.g. users, producers and input suppliers) and non-firm organizations (e.g. universities, financial institutions, government agencies, trade-unions, or technical associations), including sub-units of larger organizations (e.g. R&D or production departments) and groups of organizations (e.g. industry associations).*
>
> *(Malerba 2002, P250)*

The Sectoral Systems of Innovation is also different from technological systems: technology systems focus on single technology utilized across sectors, while Sectoral Systems of Innovation may utilize many technologies (Malerba 2005).

2.1.2.Sectoral Systems of Innovation

The early study of the elements of Sectoral Systems of Innovation included products; agents (firms and non-firm organizations); knowledge and learning processes; basic technologies, inputs, demand, and the related links and complementarities; mechanisms of interactions both within firms and outside firms; processes of competition and selection; and institutions (Malerba 2002,P250-251). Geels criticized this framework that there were too many "heterogeneous elements", and their linkages are not clear (Geels 2004).

Malerba further improved this framework and suggested that a sectoral systems framework emphasis three dimensions: knowledge and technological domain, actors and networks, and institutions (Malerba 2005).

Although the focus of this project will be the drug discovery and development sector, this does not mean that they are the only actors of this system. This system includes actors such as firms, governments, public research institutions, support companies and other relevant organizations. Therefore this basic sectoral system consists of various actors and numerous linkages.

McKelvey & Orsenigo summarised eight features of systems of pharmaceutical innovation: first of all, the actors and linkages are not simply co-existing, but dynamically interact with each other (McKelvey & Orsenigo 2001). At the same time, new actors are emerging and old actors may exit, therefore linkages are also changing at the same time. For example, in a sector system of innovation, a company may compete with companies in the same system, may also establish long or short term collaboration with other companies, furthermore, it is regulated by a government agency and may be awarded a research grant from an agency, it may also collaborate with a

university on a specific research project etc. The collective of linkages forms the network where the company positioned. One important feature of this system is that it is changing overtime.

McKelvey & Orsenigo further suggested that this set of relations or network is not considered as coherent and efficient (McKelvey & Orsenigo 2001). The previous discussion of policy debates illustrated the conflict of interest of actors within this system. The third feature is that "the nature and the form of these relationships may also look different when looked at from alternative levels of aggregation or scales of analysis" (McKelvey & Orsenigo 2001, P61). Studies which focus on large pharmaceutical companies will require a different analysis to studies which focus on small to medium sized companies, although both large pharmaceutical companies and small to medium sized companies are all considered in the same system of innovation.

The forth feature is that the system of innovation in pharmaceuticals can be defined in different boundaries, as suggested in the previous subsection, e.g. national, sectoral etc., the fifth feature is that the system changes over time which may be caused by external or internal factors (McKelvey & Orsenigo 2001).

The sixth feature is that "evolution and adaptation to (internally generated and exogenous) shocks implies processes of restructuring, division of labour, reconfiguration of complementarities" (McKelvey & Orsenigo 2001, P64). McKelvey and Orsenigo provide the example of molecular biology: "the emergence of a new knowledge base (molecular biology) implied a new "problem", new ways and procedures of learning, a new technological regime. The adaptation to the new knowledge base (technological regime) implied a deep reconfiguration of the system: at the firm level, at the level of the patterns of division of labour and relationships among firms (through the appearance of new specialized biotechnology firms, the emergence of networks of collaborative relations but also through M&A), at the level of market structure" (McKelvey & Orsenigo 2001, P64). The seventh feature suggested is analysis from a systematic and dynamic view. The eighth and final feature is that "within the evolving system, the lack or the weakness of specific

competencies, agents or relations between agents decreases overall performance" (McKelvey & Orsenigo 2001, P65). These eight features described and summarized the actors and linkages of an innovation system.

Another set of elements are knowledge and technology. Knowledge accumulation and diffusion is central to innovation activities and there are three key dimensions of knowledge: accessibility, opportunity and cumulativeness (Malerba 2005). Greater accessibility of knowledge within the sector may lead to a higher level of imitation of product and process (Malerba 2005). The sources of technological opportunity to innovation may come from universities or from advances in equipment or from suppliers and users (Malerba 2005). Cumulativeness was affected by the learning processes, the firm's capability and feedback from the market, and high cumulativeness leads to high "appropriability of innovation" (Malerba 2005). The knowledge base and technology further influenced the boundaries of Sectoral Systems of Innovation, e.g. the development of molecular biology changed the structure of the pharmaceutical and biotechnology industry (Malerba 2005).

Malerba suggested that a sector is composed of organizations and individuals: organizations included firms (e.g. users, producers, and suppliers), non-firms (e.g. universities, governments, financial institutions, trade unions, and technical associations); individuals included consumers, entrepreneurs, and scientists; and the key actors of Sectoral Systems of Innovation are firms (Malerba 2005).

The definition of "institutions" is controversial. There are two types of interpretation: one definition is that institutions include norms, routines, common habits, established practices, rules, laws, standards, and so on (Edquist 1997;Lundvall 1992;Malerba 2005); institutions have also been defined as different players and organizations of the system (Nelson & Rosenberg 1993). In Susan's study *National systems of innovation: complex interdependence in the globe systems*, 'institutions' are interpreted as interlinks of the elements (Susan 1997). In the DTI Comparative

Statistics for the UK, European and US Biotechnology Sectors for the years 2001, 2003 and 2003, they adopted national and Sectoral Systems of Innovation to compare the performance of biotechnology in different countries. However, they interpreted 'institutions' as organizations rather than interlinks. Moreover, many other works do not even interpret this term at all. In the publication of *Innovation Systems: analytical and methodological issues* in 2002 Carlsson et al. avoided using 'institutions'. They interpreted 'systems' as component, relationships and attributes (Carlsson et al. 2002): components are the operating parts of a system, and relationships are the links between components, and attributes are the properties of the components and relationship between them. Therefore, as Edquist suggested, Systems of innovation should be used as a conceptual framework (intermediate theory) rather than a theory (Edquist 2005).

2.1.3.Why adopt Sectoral Systems of Innovation approach?

The Systems of innovation approach has been applied in many different ways: sectoral, national and regional. The DTI report and EU Commission also adopted this approach to conduct comparative analysis of different countries.

Edquist suggestes six advantages to using the systems of innovation framework: this approach "places innovation and learning processes at the centre of focus, adopts a holistic and interdisciplinary perspective, employs historical and evolutionary perspectives, emphasizes interdependence and non-linearity, compasses both product and process innovation, and emphasizes the role of institutions" (Edquist 2005, P185). Drug innovation, from the birth to the development of drugs, is not dependant on one single innovation or several sciences; it is the product of the accumulation of knowledge combined with the long time development of the

education base, industry base, economics and politics, as well as different resources required and interactions of actors of the innovation network. Therefore, System of Innovation approach, which emphasises the historical and evolutionary context of the innovation, is an appropriate conceptual framework for this study.

However, there are also problems with this conceptual framework: first problem is, as discussed above, the different interpretation of 'institutions'. Are they rules, laws and norms? Or are they organization? Moreover, as an intermediate theory, how to define the core elements of the system is another problem (Edquist 1997).

Although there are limitations of systems of innovation, it has been adopted by many researchers. For example, the biotechnology industry was investigated from the perspective of regional (Asheim & Gertler 2005;Cooke 2002), national (Edwards et al. 2006), technological (Bergek et al. 2008) and sectoral systems of innovation (Brusoni & Geuna 2003;McKelvey & Orsenigo 2001). Since globalization has blurred national boundaries, some researchers also adopt an international/ global sectoral perspective. Bartholomew argued that the particular characteristics of national systems of biotechnology innovation "form the basis for complex interdependence within the global system, through international technological cooperation and the cross-border adoption and adaptations of institutional forms and practices" (Bartholomew 1997, P241). Van Rooij et al. studied the foreign technologies imported into Dutch companies from a perspective of international –sectoral systems (Van Rooij et al. 2008), and Miyazaki & Islam also adopted a similar approach to investigate Sectoral Systems of Innovation in nanotechnology (Miyazaki & Islam 2007). A system-evolutionary perspective has also been used to describe the dynamics of the life science sector and its implications on regional innovation policy (Rosiello & Orsenigo 2008).

Malerba suggested four key challenges that are required for a better understanding of the relationship between innovation and the evolution of industries: the analyses of demand, knowledge, networks and co-evolution (Malerba 2006). Considering the pharmaceutical and

biotechnology industry as a Sectoral Systems of Innovation, this study will examine the emergence of new actors in this system of innovation – the drug discovery and development companies established after 1980s, when biotechnology first started to be applied to the drug innovation process. This study will investigate the knowledge, networks and co-evolution of the drug discovery and development subsector from a perspective of Sectoral Systems of Innovation. As discussed in Section 1.3, this study will focused on this subsectors' structure, their knowledge contribution, their networking and collaboration with other actors and how this has changed over time.

2.2. Literature Review

2.2.1 Development of Research Questions

Pisano had observed a trend toward vertical integration of new biotechnology companies from R&D activities to manufacturing and marketing during the 1980s (Pisano 1991). The rationale for integration of manufacturing is mainly "the complexity of process development and scale-up, the problems of protecting intellectual property rights, and regulations which make it costly to switch manufacturers after conducting Stage III clinical trials " (Pisano 1991, P244), and the rationale for integration of distribution is the transaction cost occurred in penetrating a new market (Pisano 1991, P246). Pisano also suggested that the rate of integration of new biotechnology firms is constrained by the availability of capital (Pisano 1991).

However, after 15 years development, other researchers observed a different trend in biotechnology governance. Kollmer and Dowling (Kollmer & Dowling 2004) collected data from a sample of 70 North American biopharmaceutical firms from ReCap, combined with a

questionnaire survey of these companies. They suggested that "being not-fully integrated is not a transitional state, but a sustainable business strategy" (Kollmer & Dowling 2004, P1148).

It is important for biotechnology firms to know when to vertically integrate, when to license and when to collaborate (Pisano 1991). Pisano suggested that the biopharmaceutical companies may adopt different strategies because of their products. He suggested three types of companies: companies adopting novel research methods and tools, companies focusing on novel targets and mechanisms, and companies focusing on novel compounds, treatments and markets (Pisano 2006, P167-172). He analyzed the degree of information asymmetry, the need for investments in specialized assets, the tacitness of the knowhow and the degree to which they held relevant intellectual property (Pisano 2006, P165-166). Pisano suggested that companies developing novel research methods and tools may adopt a strategy of contract service, companies focusing on novel targets and mechanisms may develop long-term collaboration with large pharmaceutical companies, and companies focusing on novel compounds may further their aims by integration (Pisano 2006).

Kollmer and Dowling's findings indicated that licensing is a commercialisation strategy for both fully and not-fully integrated firms: for not fully integrated firms, licensing accounted for 76 per cent of total revenues, and for integrated companies, licensing still contribute 38 per cent of the total revenues (Kollmer & Dowling 2004). This result is consistent with a cross sector study which indicated that firm size is the determinant of licensing (Gambardella, Giuri, & Luzzi 2007): "...licensing has become a well-established commercialisation strategy which is used to fully exploit a company's technology assets"(Kollmer & Dowling 2004, P1148). The main reasons for fully –integrated companies to license out technology are generally strategic misfit and/or low perspective of return (Kollmer & Dowling 2004). Arora & Ceccagnoli found that when effectiveness of patent protection increased, firms are more likely to patent; compared with firms lacking specialized complementary assets, firms that have specialized complementary assets are more reluctant to license (Arora & Ceccagnoli 2006).

Comparing these studies discussed above, there are three major arguments and differences. First of all, whether being not-fully integrated is a sustainable stage of firms as suggested by Kollmer & Dowling, or vertical integration is a major aim of a company's development as suggested by Pisano. Pisano argued that the drug discovery and development companies are started with fragments of an innovation process and business practice, therefore, vertical integration is a major aim of a company's development, from project development to manufacturing and marketing (Pisano 2006). Moreover, the capability of firms and their position within networks also connected with its strategy. Gulati, Nohria, & Zaheer suggested that "an understanding of the consequences of the ubiquitous growth of strategic networks emphasizes that firms are more properly viewed as connected to each other in multiple networks of resource and other flows" (Gulati, Nohria, & Zaheer 2000). What are the major factors influencing the strategy of companies: products and services, stage of life cycle, position within networks, or availability of capital?

The second difference is that Kollmer & Dowling argued that licensing is a well-established strategy of biotechnology firms and contributes greatly to the revenues of the industry; while Pisano argued that the commercialization of patents is in fact impeding flow of information this industry, although the revenues grew very fast, the profit is close to zero. The negative impact of intellectual property is also suggested by other researchers (Murray & Stern 2007).

Thirdly, Pisano argued that (2006) performance of the biopharmaceutical industry did not meet the perspective, mainly because "this sector has indiscriminately borrowed business models, organization strategy and approaches from other high tech industry". While other researchers were focused on a solution of all high tech industries (Gambardella, Giuri, & Luzzi 2007;Hall & Bagchi-Sen 2007).

One important issue concerning the difference in these previous studies is the measurement of performance: in Pisano's study, the major indicator is the cost per new molecular entity (NMEs) by biotech and financial returns. However, as Kollmer & Dowling's study indicated, the patents

should also be considered as an important measurement of R&D performance. Industry structure is also an important issue of performance measuring: since this pharmaceutical and biotechnology sector requires specific knowledge, the number of players is limited by this barrier (Bruno et al. 2008, P43). Bagchi-Sen suggests that the structure of the US biopharmaceutical sector is dominated by a few large and many small firms: the small firms are research focused or act as technology developers and several large firms are now integrated biopharmaceutical companies (Bagchi-Sen 2007a). In a sector with hierarchical structure, large companies played a profound role as dominant competitors. On one hand, these established companies who dominate the market are an obstacle to innovation: based on a survey during 2002-04, 15 per cent of biotechnology innovation companies regarded this factor as highly important barrier to their innovation activities (Cleff et al. 2008). On the other hand, for biotechnology companies, competitors are an important source of learning, 24 per cent of companies regarded competitors as information sources and 34 per cent of companies collaborate with their competitors (Cleff et al. 2008). Another determinant would be R&D intensity: companies with high R&D intensity and low R&D intensity will adopt different strategies (Hall & Bagchi-Sen 2007).

Based on the argument above, there are two research questions concerning the co-evolution of strategy networking and industry structures:

3) Is there a divergence of strategies existing in the drug discovery and development subsector? If so what are the key factors that determine this divergence?

4) How does the divergence of strategy influence the industry structure?

In the next sections further literature will be reviewed, which will provide a broader context for the study.

2.2.2 Structure and dynamics

Earl-Slater has observed that the number of UK biotechnology and pharmaceutical companies has grown from 286 in 1975, 310 in 1980, 326 in 1984, 352 in 1987, and 464 in 1998; with their R&D expenditure increasing from £359 million in 1982 to £1,113 million in 1996; and the value of exports (primary, semi-finished and finished drugs) increasing from £978 million in 1982, to £3,180 million in 1996 while the real value of imports has risen from £375 million in 1982, to an estimated £1,802 million in 1996 (Earl-Slater 1998). This suggests that an important characteristic of the industry is massive growth and R&D intensity, which is similar to the results of this study.

Since this pharmaceutical and biotechnology sector requires specific knowledge, the number of players is limited by the ability to gain access to that knowledge (Bruno, Miedzinski, Reid, & Ruiz Yaniz 2008, P43). Bagchi-Sen suggests that the structure of the US biopharmaceutical sector is dominated by a few large and many small firms: the small firms are research focused or technology developers and several large firms are now integrated biopharmaceutical companies (Bagchi-Sen 2007). This is a central focus of this study, and the UK biopharmaceutical subsector examined in this study showed a similar structure. This structure has an impact on the interactions between biopharmaceutical companies, between companies and universities and between biopharmaceutical and large pharmaceutical companies. In this study, empirical data indicated that the large companies are major knowledge contributors and that they play important roles in networking with other actors of the innovation systems.

The relationship with universities, biotechnology or pharmaceutical or other large companies is essential for small firms to survive and grow (Bagchi-Sen 2007b). This is also an important feature of this sector: universities and public research institutes' basic scientific discoveries can be further developed and turned into new products and new processes (Patel, Paunov, & Arundel 2008).

Moreover, universities and public research institutes train highly skilled employees for this industry (Patel, Paunov, & Arundel 2008). Patel, Paunov, & Arundel suggest there are three diffusion mechanisms of basic biotechnology discoveries: 1) biotechnology firms spin-off from universities and public research institutions, e.g. university researchers establish new companies; 2) universities and public research institutions may form alliances with pharmaceutical and biotechnology companies, e.g. licensing out patents and co-development of products; 3) basic biotechnology discoveries are diffused via employment of highly skilled postgraduate students and researchers (Patel, Paunov, & Arundel 2008).

As discussed in an earlier section, there is an argument about the existence of a 'biotech revolution', because the limited success in increasing the rate and scope of change in productivity or the quality of drugs has been over estimated (Hopkins, Martin, Nightingale, Kraft, & Mahdi 2007). Hopkins et al. argued that biotechnology is "following a well-established incremental pattern of technological change and creative accumulation that builds upon, rather than disrupts, previous drug development heuristics" (Hopkins, Martin, Nightingale, Kraft, & Mahdi 2007). This is supported by the data collected from this study finding that many biopharmaceutical companies also use chemistry as a major technology in drug development.

However, the performance of this sector cannot be explained by any single factor: "performance in knowledge creation is highly correlated with that in commercialization and finance... thus countries with high levels of public and private knowledge creation activities are also countries that excel in terms of patents, start-ups and alliances" (Patel, Paunov, & Arundel 2008, P3). Empirical data indicates that countries' performance in biopharmaceutical development and clinical trials are positively connected with strategic alliances, supply of venture capital and biotechnology patenting (Patel, Paunov, & Arundel 2008). Furthermore, patents and strategic alliances are significantly correlated (Patel, Paunov, & Arundel 2008). Similar results are also indicated by the Biopolis Final Report, which argues that policy makers should adopt an approach focussed on both basic scientific research and commercialization (Enzing et al. 2007).

Industrial dynamics and competition are influenced by many factors, including market structure and patent protection expiry. Magazzini, Pammolli, & Riccaboni investigated the USA, UK, Germany, and France market, and suggest that the consequences of patent expiry have different impacts on innovators and followers: "in systems that rely on market-based competition, original products enjoy premium prices and exclusivity profits under patent protection, and face fierce price competition after patent expiry; and in systems that rely on administered prices, penetration by generic drugs tends to be rather limited" (Magazzini, Pammolli, & Riccaboni 2004, P175). In fact, for the UK drug discovery and development companies, they face both markets: domestic systems that rely on administered prices and foreign systems (e.g. US) that rely on market-based competition. Both markets have impacts on this subsector's structure, knowledge production and networking.

Since the companies of this sector all have specific knowledge and technology, we should ask how the hierarchical structure of the sector influenced knowledge production and the kinds of technology in use. As indentified in this project, both biotechnology and chemical technology are adopted in this sector, which raises several questions: how successful are these technologies in developing new drugs? What technologies have been involved in the alliances between drug innovation companies and big pharmaceutical companies? Why do drug discovery and development companies prefer these technologies?

2.2.3 Globalization and clustering

There is controversy between two contrasting perspectives regarding the geographical clustering of biotech firms: one view is that competences for learning are leveraged from open networks and collaborations, and others argue that, "as intellectual assets are protected by property rights,

knowledge adheres to specific locations mainly as a consequence of scientists' immobility" (Rosiello 2007, P787). In this section, we will first review studies on both sides: start with the global picture and move down to the regional level.

Florida suggested that globalization of innovation is driven in large measure by technology factors (Florida 1997). This trend of globalization of biotechnology innovation is an important feature of both academia and industry research. Cooke investigated the global bioscience research system by adapting a global network analysis, which looked at collaborations between "star" scientists and their institutes in bioregions at a global level, with evidence from analyzing co-publication of bioscientific articles in US and EU SCI cited journals (Cooke 2006). He suggested that the strongest bioregions are in North America, particularly around Boston, San Diego and San Francisco. Sweden and UK are the strongest European research bases. Cooke also identified a hierarchical structure and the main network nodes in the global bioscience research system (Cooke 2006).

From a perspective of industry, many other studies have shown evidence of a geographical concentration of drug innovation. Achilladelis & Antonakis investigated 1,736 new drugs marketed between 1800 and 1990, and suggested that drug innovation was highly concentrated in the USA, UK, Germany, Switzerland and France, which together accounted for 80 per cent of total drug innovations (Achilladelis & Antonakis 2001). The findings also indicated that the development of the drug innovation sector is influenced by globalization, from knowledge generation and commercialization to mergers and acquisitions.

From a regional perspective, Cooke suggests that the biopharmaceutical companies tend to locate in knowledge-driven clusters centred upon universities, research hospitals and research institutes (Cooke 2003). The strong tendency towards geographical concentration of research and related economic activities is a crucial feature of the biotechnology industry (Rosiello & Orsenigo 2008). There are two major types of cluster formation: "spontaneous clusters, that are the result of the

spontaneous co-presence of key factors", and "policy driven clusters, that are triggered by the strong commitment of governmental actors whose willingness was to set the conditions for the cluster creation, either as a response to an industrial crisis or as a deliberate decision to foster the biotech sector" (Chiaroni & Chiesa 2006, P1064). There are different opinions about policy driven clusters. Some researchers argue that policies to promote clusters are not necessary, "except for the "organically" developed clusters...clusters as a policy concept, and particularly in relation to funding, have proven to be inadequate and have led to the creation of artificial clusters with none of the inherent interactions" (Bruno, Miedzinski, Reid, & Ruiz Yaniz 2008, P43). The important clusters of drug discovery and development companies indentified in this study are mainly "organically" developed clusters. Local governments are also important in cluster development.

Economic geography research of science-based clusters is an important area of study (Cooke 2001;Cooke 2004;Cooke 2005a;Cooke 2005b;Feldman & Francis 2003;Howells 2002). Casper argues that although regional technology clusters are an important source of economic development, few successful biotechnology clusters exist (Casper 2007). Casper uses social network analysis to examine the emergence of social networks linking senior managers employed in biotechnology firms in San Diego, Californa, and found that "labor mobility within the region has forged a large network linking managers and firms, while ties linking managers of an early company, Hybritech, formed a network backbone anchoring growth in the region" (Casper 2007, P438). Another study of California biotechnology suggest the positive impact of research universities on nearby firms relates to identifiable market exchange between particular university star scientists and firms (Zucker, Darby, & Armstrong 1998).

In contrast, a study of Cambridge indicated that the University of Cambridge does not dominate the scientific linkages of the area's firms: a large percentage of Cambridge's firms do not derive from its university, and the majority of scientific collaborations are not with the University of Cambridge laboratories, nor do Cambridge scientists dominate the scientific advisory boards of these firms (Casper & Karamanos 2003). Moreover, the majority of scientists within the area's

biotechnology firms appear not to have left the University of Cambridge laboratories to move to industry (Casper & Karamanos 2003). However, Casper & Karamanos's research is about general firms, this may be not true for the biopharmaceutical sector because it is characterized by strong linkages with research institutions.

There are different views of the impact of clustering, some researchers argued that geographic proximity does not influence company performance (Tallman & Phene 2007), while many others found that is very important. Audretsch and Stephan examined how biotech companies and universities were geographically bounded, and they observed that the specific role played by the scientist shaped this link (Audretsch & Stephan 1996). Murray investigated the biotechnology firms and their academic inventors, and suggested that scientist not only contribute human capital but also social capital to firms: scientist' social capital, which shaped by their career path, can be transformed into scientific networks the firm embedded (Murray 2004). Quintana-Garcia & Benavides-Velasco observed that firms located in knowledge driven clusters not only benefit from local upstream alliances with public research institutes, but also attract downstream alliances with foreign companies (Quintana-Garcia & Benavides-Velasco 2006). Furthermore, many studies indicate that venture capital firms which fund biotechnology companies also cluster in the same regions, e.g. between 1988 and 1999, over half of the US biotechnology firms received locally based venture funding (Powell et al. 2002).

Previous studies also indicated that how a company could benefit from clustering and geographic proximity is determined by the companies own attributes. Small firms' R&D activities benefit more from being in particular locations than large firms' R&D activities (Feldman 1994). Spill over of knowledge, from a university, research institute, or industrial corporation, to a start-up company "facilitates the appropriation of knowledge for the individual scientist(s) but not necessarily for the organization creating that new knowledge in the first place" (Audretsch & Stephan 1999, P97). Other factors also influence the clustering impact on companies. Van Geenhuizen & Reyes-Gonzalez found that companies involved in the first stage of the knowledge

chain in new drugs and diagnostics research would benefit from knowledge spillover. In contrast, for service companies, the stage in the knowledge chain does not matter (van Geenhuizen & Reyes-Gonzalez 2007). Moreover, firms embedded in alliance networks that exhibit both high clustering and high reach (short average path lengths to a wide range of firms) will have greater innovative output than firms in networks that do not exhibit these characteristics (Schilling & Phelps 2007). Furthermore, there are increasing returns associated with cluster size, but also "diseconomies of agglomeration play an increasingly important role as clusters evolve" (Folta, Cooper, & Baik 2006, P217).

In short, the previous studies indicated the global competition and collaboration of biopharmaceutical subsector is in fact driven by several clusters which acted as main network nodes in the global bioscience research systems (Cooke 2006). The formation clusters were results of a combination of local factors or driven by policies (Chiaroni & Chiesa 2006). These key factors include collaboration with local research institutes and universities and financial support from local venture capitals. Clustering also attracts foreign companies and large pharmaceutical companies to downstream alliances with these companies. To what extent a company could benefit from clustering is determined by many factors, e.g. the nature of clustering, company size, company's product and service and management experiences. The question raised here is what the key factors are for the formation of clusters of the drug discovery and development sector. Is there any difference between clusters of pharmaceutical and biotechnology companies, and clusters of drug discovery and development companies?

2.2.4 Alliances and networking

The notion of alliances and networks are widely studied in different disciplines, such as economics, corporate strategy, and inter-organizational studies, and different theoretical perspectives and methodologies have been used to "understand the formation, evolution, operation and outcomes of organizational alliances and networks" (de Rond & Bouchikhi 2004;Osborn & Hagedoorn 1997, P261).

Strategic alliances are defined as "voluntary arrangements between firms involving exchange, sharing, or co-development of products, technologies, or services; they can occur as a result of a wide range of motives and goals, take a variety of forms, and occur across vertical and horizontal boundaries"(Gulati 1998, P293). Gulati, Nohria, & Zaheer suggest that a firms' conduct and performance could be better understood by examining the network they embedded (Gulati, Nohria, & Zaheer 2000). There are five key issues relating to alliances identified by Gulati: "the formation of alliances, the choice of governance structure, the dynamic evolution of alliances, the performance of alliances, and the performance consequences for firms entering alliances" (Gulati 1998, P298-309).

Therefore, to better understand the drug discovery and development sector, this study investigated the alliance agreements and the "intangible networking" of the drug discovery and development sector, i.e. co-publishing of scientific papers and patents. As indentified in this study the vertical and horizontal dimensions are both very important features of the drug discovery and development sector.

Many researchers have indicated that the role of alliances has become very important in the drug innovation process; however, Arora and Gambardella argue that companies differed significantly in their ability to benefit from alliances (Arora & Gambardella 1994). Powell studied the networks in the pharmaceutical and biotechnological industry by using a theory of learning from alliances, and suggested that more greater efforts were needed to understand knowledge generating and transfer in these networks (Powell 1998).

From the perspective of large pharmaceutical companies, factors such as new product development, economies of scale, public ownership, and geographic location in a regional technology cluster, are all important factors in forming alliances with biotechnology start-ups (Rothaermel 2002). Rothaermel drew this result from a study on 325 biotechnology firms' 973 alliances formed with large pharmaceutical companies in a 25-year period (Rothaermel 2002). Colombo also observed that those firms which have patents and "developed ready-to use proprietary technological knowledge" will attract more partners to form alliances than firms which do not have patents (Colombo, Grilli, & Piva 2006).

For foreign and domestic companies, the most attractive factors in forming alliances are different (Coombs, Mudambi, & Deeds 2006). Coombs et al. studied 64 US public owned biotechnology companies between 1982 and 1993, and argued that US biotechnology companies' patent portfolio is a determinant for US domestic partners to form alliance, while US biotechnology companies "located in technologically munificent environments are the preferred alliance partner for foreign firms" (Coombs, Mudambi, & Deeds 2006, P422).

Rothaermel observed that the companies acting as buyer benefit more than R&D providers from the alliance (Rothaermel 2001). Rothaermel investigated 889 strategic alliances between 32 US large pharmaceutical companies which acted as buyers and biotechnology companies which acted as R&D providers, and found that "incumbents that focus their network strategy on exploiting complementary assets outperform incumbents that focus on exploring the new technology" (Rothaermel 2001, P687). In the case of biotechnology start-ups, network formation and industry growth are significantly influenced by the development and nurturing of social capital (Walker, Kogut, & Shan 1997).

Based on a study of the Canadian biotechnology industry, Baum and Silverman observed that a firms' alliance capital, in particular, downstream and horizontal alliances, as well as their human capital and intellectual capital are important factors for venture capitals to form ties with

biotechnology companies (Baum & Silverman 2004). Furthermore, substantial boosts in venture capital financed alliance activity, and increased potential of start-up Initial Public Offering (IPOs), will attract more reputable venture capital (Hsu 2006). This is important because companies with successful IPOs are more likely to attract further findings, and this may broaden the gap between companies. Gulati and Higgins found that the nature of ties and uncertainty of the marketplace have contingent impacts upon the alliances (Gulati & Higgins 2003). Based on a case study of new biotechnology firm, they observed that "ties to prominent venture capital firms are particularly beneficial to IPO success during cold markets, while ties to prominent investment banks are particularly beneficial to IPO success during hot markets" (Gulati & Higgins 2003, P127). Based on two case studies, Schweizer also suggested the pressure from capital market led to strategic consolidation of the pharmaceutical and biological industry (Schweizer 2002).

Firm specific uncertainties are also determinants for biotechnology firms to form alliances (Beckman, Haunschild, & Phillips 2004). Lerner and Merges suggest that the reasons that small R&D intensive firms which have novel technologies and seek alliances are that these companies frequently lack the necessary financial support for their research projects, or "lack complementary assets such as sales force and manufacturing know-how, which may take many years to develop" (Lerner & Merges 1998, P126). Lerner and Merges investigated 200 randomly selected alliances from the Recombinant Capital database, and their observation suggest that for the firms which acted as R&D providers in alliances, their loss in prior year before forming alliances often accounted for "one-third of the average firm's shareholder equity and nearly one-half of its cash and equivalent"(Lerner & Merges 1998, P140). This study also systematically collected data from the Recombinant Capital database. Together with data collected from government databases, the findings of this study indicated that continuously high R&D intensity is a more general reason explaining why companies form alliances, regardless of loss or gain in the previous year.

Moreover, the financial conditions of firms which acted as R&D providers have "profound effects on the allocation of control right" of alliance (Lerner & Merges 1998, P153). These control rights

included many aspects, and the most important control rights suggested by Lerner and Merges are the management of clinical trials e.g. decision of drug candidates entering clinical trials and decision of disease indications, design of initial manufacturing process and design of manufacturing process after approval, and the plan of marketing strategy e.g. where firms acted as R&D providers they could have exclusive rights or co-market rights in one or more markets (Lerner & Merges 1998). These control rights have an impact on the development of R&D providers: decisions on clinical trials, e.g. indications and drug candidates, determine the potential returns of new drugs; manufacturing design determines the rights of manufacturing, because drugs approved by FDA only applied to specific facility which manufactured them, and it is expensive and time consuming to undergo another review if another company wants to produce these drugs; marketing and co-marketing rights would give R&D providers the opportunity to established their own sale force and gain experience, which will facilitate their further development (Lerner & Merges 1998).

The number of alliances is positively connected to a firms' rate of new product development, according to Deeds and Hill's study of 132 biotechnology firms (Deeds & Hill 1996). However, this relationship is nonlinear, because each alliance contributes differently to the new product development and there are risk with alliances aimed at gaining access complementary assets; rather the relationship between the number of alliances and the rate of new product development may be an inverted U-shape, which means "at low levels strategic alliances are positively related to new product development, but as the number of alliances increases, the benefits begin to decrease, and at high levels the costs of an additional alliance actually outweigh the benefits" (Deeds & Hill 1996, P42).

Based on their study of 554 biotechnology companies in a 15-year period, Oliver suggests that the number of alliances is connected with firm's life cycle: in particular, a lack of alliances was associated with firm death (Oliver 2001).

There are also arguments about the connections between the number of alliances and R&D stages. Pisano investigated 260 biopharmaceutical projects, and suggested that projects with partners have a higher failure rate than project development internally, because "projects with poorer prospects for reaching the market tend to be licensed to collaborative partners while those with better prospects are commercialized internally" (Pisano 1997, P1). Similarly, Rothaermel & Deeds also observed that as firms and their technology capability grow, they tend to move their product from alliances to internal development (Rothaermel & Deeds 2004). This was also supported by Oliver's observation: the number of alliances increased during "exploration stage of the organizational learning –cycle" and number of alliances reduced during "the exploitation stage" (Oliver 2001, P483). For Dedicated Biotechnology Firms (DFSs), the firm's growth need, their capabilities and their awareness of alliances risk, which are all key factors of alliances formation, change during firm growth (Oliver 2001).

The success of networking is influenced by many factors. Lane & Lubatkin suggest that the similarity of the partners' basic knowledge, lower management formalization, research centralization, compensation practices, and research communities were positively connected to inter organizational learning (Lane & Lubatkin 1998).

Based on observation of 1910 compounds developed by US pharmaceutical and biotechnology firms between 1988 and 2000, Danzon et al. argued that drug candidates developed with partners have a higher rate of success, "at least for the more complex phase 2 and phase 3 trials, particularly if the licensee is a large firm, because experience increases the probability of success for late-stage trials" (Danzon, Nicholson, & Pereira 2005).

There are also arguments about connections between alliance performance and inter-organizations learning routines (experience), which is defined as "stable patterns of interaction among two firms developed and refined in the course of repeated collaborations" (Zollo, Reuer, & Singh 2002, P701). There are three types of alliance experience: partner-specific experiences, which are

obtained by repeated collaborations with the same partner and represent depth of knowledge; technological-specific experience, which are obtained from repeated alliances in the same domain and represent the technological depth; and general experience, which are gained from alliance with multiple partners (Hoang & Rothaermel 2005;Zollo, Reuer, & Singh 2002). Zollo et al. argue that the partner-specific experiences influence alliance performance, while technological-specific experiences and general experiences do not (Zollo, Reuer, & Singh 2002). Hoang and Rothaermel's observation indicate that only general experiences have positive influence on alliance performance and show diminishing returns, while partner-specific experiences have negative influence on alliance performance. However, other researchers argue that for large pharmaceutical companies and small biotechnology firms, pervious alliance experience have a negative effect on their subsequent alliance formation (Roijakkers, Hagedoorn, & Van Kranenburg 2005).

Orsenigo et al (2001) have analyzed the structural evolution of the network of collaborative agreements in pharmaceutical R&D in the last 20 years (Orsenigo, Pammolli, & Riccaboni 2001). They suggested that both the growth of knowledge and the structural evolution of the network have been characterized by fast expansion, proliferation of research trajectories and techniques, and hierarchization: "the cumulative nature of such processes has been imposing different degrees of structural stability at different levels of the hierarchy...major changes in the network structure have occurred in correspondence with the emergence of a new set of transversal technologies" (Orsenigo, Pammolli, & Riccaboni 2001). This study will investigate those same themes in the drug discovery and development sector, exploring how technology is involved in changes in the alliance agreements in the past two decades.

In short, literature on alliances and networking are mainly focused on driving forces of alliances formation, alliances formation, performances and factors influenced alliances. Market uncertainty and firm specific uncertainty are determinants for biotechnology firms to form alliances (Beckman, Haunschild, & Phillips 2004). Firms' intellectual capital, human capital, alliance capital (Baum & Silverman 2004), economies of scale and geographic location (Gulati & Higgins 2003;Rothaermel

2002) are also factors to attract partners. For small companies, their partners include venture capitals, large pharmaceutical companies and other domestic and foreign companies. Number of alliances is connected with firms' rate of drug innovation (Deeds & Hill 1996) and stages of product development (Danzon, Nicholson, & Pereira 2005). To what extent companies could benefit from alliances determined by their competencies (Arora & Gambardella 1994), their role played in alliances (Rothaermel 2001), and financial conditions (Lerner & Merges 1998). This study emphasises the historical perspective of the drug discovery and development sector asking if, as the knowledge and experience accumulates, will the partners in alliances, content of the alliances and number of alliances change as well?

2.2.5 R&D activities

There are both external and internal forces driving innovation. Achilladelis & Antonakis suggest that the driving forces for innovation include scientific and technological advances, market demand, societal needs, government legislation, new raw materials, competition among firms, and the creation of corporate technology traditions; and "the intensities of these driving forces and their synergies varied over time and thus determined the rate of technical change" (Achilladelis & Antonakis 2001, P585). The first and last factors suggested by Achilladelis & Antonakis are internal factors and others are external factors.

As major forces driving innovation, technology advances have important impact on the drug discovery and development sector. A good example is biopharmaceuticals. Biopharmaceuticals are growing very fast in the past decades. "Biopharmaceutical" was defined as "any biology-based therapeutic that structurally mimics compounds found within the body", including recombinant

proteins, monoclonal and polyclonal antibodies, peptides, antisense oligonucleotides, therapeutic genes, and certain therapeutic vaccines (Nagle, Lugo, & Nicita 2003, PS124).

US biopharmaceutical drug candidates are growing at an aggressive rate (16- 30 per cent), faster than the rate of growth observed for traditional "pharmaceuticals" (approximately 4 per cent) (Nagle et al. 2008, P229). About 150 biopharmaceuticals have been approved, and this class of therapeutics generates over $50 billion in sales every year (Redwan 2007). The majority of these products are developed and produced in mammalian cell lines (70 per cent), prokaryotic systems (15 per cent), and yeast (five per cent), respectively (Redwan 2007). However, the cost of discovery and development is also very high. The estimated R&D per each approved biopharmaceutical molecule is as much as $1,318 million (Redwan 2007).

In terms of blockbusters, which refer to drugs with sales of more than $1 billion a year, 3 out of 36 blockbusters (eight per cent) were biological products in 2003, and this had risen to 18 of 101 drugs (18 per cent) in 2006 (Lawrence 2007). Furthermore, eight out of 36 drugs with sales over $2 billion ('super' blockbusters) were biological products (Lawrence 2007). This indicated the increasing importance of biopharmaceuticals.

Nagle et al. investigated US biopharmaceutical pipeline drugs in May 2006, and observed that of 111 biological drug candidates in phase II late stage development, 87 are new molecular entities, and 24 are already approved for other indications; moreover, 25 of the 111 drug candidates have completed phase III trials (Nagle, Nicita, Gerdes, & Schnneichel 2008). This suggests that there more biological drugs on market. Nagle et al. also observed that from 2003 to 2006, the number of drug candidates in phase II or later stages increased by nine per cent (from 102 to 111), while the number of indications increased by 22 per cent (from 156 to 190) (Nagle, Nicita, Gerdes, & Schnneichel 2008).

These 111 biological drug candidates in 2006 were developed for 190 indications associated with 38 disease categories. Cancer is the largest disease category: 43 biopharmaceuticals (39 per cent of pipeline drugs) targeted 83 cancer indications (44 per cent of pipeline indications), which included primary therapy and supportive care for cancer; while in 2003, there were 30 cancer related biopharmaceutical drug candidates (29 per cent of pipeline agents) in phase II or later stage development targeted for 62 cancer indications (40 per cent of pipeline indications) (Nagle, Nicita, Gerdes, & Schnneichel 2008). This suggested that more and more drugs are developed for cancers.

In terms of marketed drugs, most biopharmaceutical blockbuster drugs in 2006 were also cancer or cancer-supporting products, while in the early 1980s blockbusters were mainly protein replacement therapies, e.g. Amgen's Epogen and Neupogen (filgrastim) prescribed for neutropenia (Lawrence 2007).

Immune-mediated inflammatory disorders are the second largest disease category, and more than 20 per cent of drug candidates targeted these inflammatory diseases. Examples include rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, type 1 diabetes mellitus, and multiplesclerosis (Nagle, Nicita, Gerdes, & Schnneichel 2008). Their results were very similar to the results of this study. Nagle also suggested the gap between cancer and other disease targets in the pipeline is widening.

Research output can also be measured by scientific publications and patents (Rodriguez et al. 2007). Deeds, DeCarolis, & Coombs observed that there is a strong positive relationship "between the impact—as measured by citations—of a team's prior research in the academic community and the productivity of that team in a commercial research laboratory" (Deeds, DeCarolis, & Coombs 2000, P212). In the United States, while large firms often produce a larger number of patents per firm, the patenting rate for small firms is typically higher than that for large firms when measured on a per-employee basis (Audretsch 2002). Moreover, the breadth of patent protection significantly affects valuations (Lerner 1994). MacPherson & Boasson investigated the spatial distribution of

patent activity among publicly traded companies in the U.S. pharmaceutical industry and suggest that "patent counts respond positively to the degree of spatially concentrated production (density of competition)" (MacPherson & Boasson 2004, P319).

Grabowski & Vernon have published a large number of studies on the topic of cost and returns. They investigated 100 new drugs launched in the US during the 1970s, and found that the return in R&D for the average new drugs was approximately equal to 9 percent industry cost of capital (Grabowski & Vernon 1990). They also investigated the returns to pharmaceutical research and development in the US (1980 -1984), and their findings indicated that the distribution of sales revenues for new drug was highly sloped, with the top deciles of new drugs accounting for more than half of the total sales (Grabowski & Vernon 2000). One of their later studies on returns for new drug introduced in the 1990s gave a similar conclusion (Grabowski, Vernon, & Dimasi 2002). More recently, Grabowski has suggested that the pharmaceutical industry was experiencing a transition period characterized with higher cost of innovation with fewer new drugs (Grabowski 2004).

Dimasi et al. surveyed 12 US pharmaceutical companies and found that average out-of-pocket costs per approved new chemical entity (NCE) was $ 114 million (dollars value of 1987), and average out-of-pocket costs to the point of marketing approval was $ 231 million (dollars value of 1987) (Dimasi et al. 1991). In their later study, the average out-of-pocket costs per new drug was $ 403 million (dollars value of 2000), and average out-of-pocket costs to the point of marketing approval was $ 802 million (dollars value of 2000) (Dimasi, Hansen, & Grabowski 2003). These results indicate that bringing a drug to market is a very expensive process.

Cohen & Levinthal suggest that a firm's R&D activity not only generate new knowledge, but also contributes to a company's absorptive capacity (Cohen & Levinthal 1990). Absorptive capacity is defined as "the ability of a firm to recognize the value of new, external information, assimilate it, and apply it to commercial ends is critical to its innovative capabilities" and it is "a function of the

firms prior knowledge" (Cohen & Levinthal 1990, P128). Knowledge base and internal R&D structure positively influence a company's absorptive capacity (Zhang, Baden-Fuller, & Mangematin 2007). Small firms mainly focused on discovery; and large firms, focused on both discovery and development (Mc Namara & Baden-Fuller 2007).

Besides internal R&D, outsourcing of R&D is also very important for a company's growth. There are two types of factors influencing the outsourcing of R&D activities: factors which initiate the outsourcing R&D activity, and framing factors, which shape the outsourcing R&D activities; furthermore the framing factors are divided into implementation factors which occurred during the operation of outsourcing R&D, and outcome factors which determine the performance of alliances (Howells, Gagliardi, & Malik 2008).

Howells, Gagliardi, & Malik observed that the major reasons for external outsourcing of R&D are access to necessary expertise which is not available in-house, reducing development time and time to market, and reducing development cost (Howells, Gagliardi, & Malik 2008). Moreover, firms experiencing declines in internal productivity tend to outsource R&D, in particular, acquiring pipeline drugs (Higgins & Rodriguez 2006). The key criteria for compannies selecting R&D partners include research and technical capabilities, ability to get the project done on time and their flexibility (Howells, Gagliardi, & Malik 2008). The barriers for formation of R&D alliances include confidence in a partner's ability, concern about the potential leak of key knowledge/intellectual property, and concern that the partnered research/technology is too central to firm's competitive advantage (Howells, Gagliardi, & Malik 2008).

Studies of company innovation strategies suggest that internal R&D and external knowledge acquisition are complementary activities, because both internal R&D and outsourcing R&D are important path for companies obtain knowledge and technologies (Cassiman & Veugelers 2006). A fast product development rate will enable companies "to gain early cashflow for greater financial

independence, to gain external visibility and legitimacy as soon as possible, to gain early market share, and to increase the likelihood of survival" (Schoonhoven, Eisenhardt, & Lyman 1990, P177).

In short, both internal R&D and outsourcing of R&D contributed to a company's competency and capacity. In the past decades, the drug innovation in the US, in particular, biological drugs innovation, grow very fast in the last decades. At the same time, discovery and development cost are also increased dramatically. How has the British drug discovery and development sector generated knowledge since 1980s? What format of knowledge has it generated? How has networking influenced that knowledge production?

2.2.6 Firm governance and strategy

Dimasi suggests that besides factors such as cost of R&D trends, scientific opportunity, regulations and technology spill over, which have an impact on innovation of all pharmaceutical and biotechnology firms, firm specific factors, such as "individual organizational structures and how effectively a firm reacts to changes in its environment" should also be studied to give a comprehensive view of this industry (Dimasi 2000, P1192).

The large biotechnology companies and new established companies adopted different strategies mainly because they have different development histories, resources and knowledge bases (Senker 1996). Hall & Bagchi-Sen suggests that biotechnology firms along with other more R&D intensive companies tend to adopt research focused strategies such as strengthening their own research capabilities, entering into research collaborations with universities, industry leaders and other biotech firms, and licensing their technology; while less R&D intensive companies tend to adopt

production based strategies such as gaining market access, maintaining connections with customers, and building their research base (Hall & Bagchi-Sen 2007).

As Koza & Lewin suggested, a company's alliances are also part of a company's strategy, and most importantly, they co-evolve with the company's strategy, as well as the institutional, organizational, and competitive environments (Koza & Lewin 1998). However, Koza & Lewin did not provide further evidence for the framework they proposed.

Dyer & Singh suggest four potential sources of inter-organizational competitive advantage: relation-specific assets, knowledge sharing routines, complementary resources and capabilities, and effective governance (Dyer & Singh 1998). The leadership a high technology firm needs is related to who has experience in R&D, but which is separate from the scientific team (Deeds, DeCarolis, & Coombs 2000).The practices of knowledge management vary among firms, because of the different organizational settings, technology domains and new product development (Ding & Peters 2000). Biotechnology start-ups may choose locations to access technologies advances developed by universities and public institutions (Audretsch, Lehmann, & Warning 2005). Furthermore, the prime locations for biotechnology startups would be expanding areas rather than established locations (Deeds, DeCarolis, & Coombs 2000). Arora & Ceccagnoli found that when effectiveness of patent protection increased, firms are more likely to patent; compared with firms lacking specialized complementary assets, firms have specialized complementary assets are more reluctantly to licensing (Arora & Ceccagnoli 2006).

In short, in order to survive and grow, high-tech firms tend to adopt different strategies to access knowledge, develop novel technologies and build competitive advantages. This study will try to provide evidence of the co-evolution of companies' strategy and networking, and the co-evolution of companies' strategy and their position in industry.

2.2.7 Policies and regulations

Innovation in policy making is closely connected to innovation in theory development, as suggested by the Biopolis Final Report. Policy making before the 1990s – first generation policy - was based on the linear model of innovation. The emphasis was on encouraging applicable basic research and knowledge diffusion "along the innovation chain", its primary aim being to "compensate for so called market failures" (Enzing et al. 2007, P21).

Since the 1990s, when "the non-linear model and more interactive nature of innovation processes were recognized", the systematic approach was adopted in policy making, and its primary aim was to compensate for systemic failures, such as "inadequate framework conditions and infrastructure provision, or network and capability failures" (Enzing et al. 2007, P21). The primary activity of second generation policy making is to analyse systematic deficiency, or "bottleneck analyses" (Arnold 2004). Therefore, changes in policy making approach are the result of interactions between actors of innovation systems, i.e. policy makers, academics and firms.

Reiss et al. proposed four areas that should be continuously supported by policies:

1) *The generation and maintenance of a suitable knowledge base for biotechnology and the availability of qualified human resources;*
2) *The transmission of biotechnological knowledge from the sites of its generation to possible loci of application;*
3) *The full integration of biotechnology into economic sectors via the successful introduction of biotechnology-based products into the markets;*

4) *The industrial development of the biotechnology sector including small and medium-sized enterprises and larger firms.*

(Reiss et al. 2005, http://www.isi.fhg.de/t/projekte/innopol-e-rt-policy-bench.htm)

Comparing UK policy between 1994-98 and 2002-05, the four areas proposed by Reiss et al. were all covered, either by generic policy or biotech-specific policies (D'Este, Senker, & Costa 2007).

Another major change is that new actors influenced innovation policy making. Since 1994 regions have been participating in policy-making for biotechnology: between 1994 and 1998, some local governments were active in supporting local university research and economic development, and later between 2002 and 2005, local governments were very active in biotech-policy making, e.g. commercialization of basic research and support SMEs (Enzing et al. 2007, P17). However, funding from the government at the national level accounted for the majority of the total policy-directed grants. Take biotech-specific research funding for example, during the period 2002-2005, there were 539.4 million Euro funds from national governments and 45.9 million Euro funds from regional governments. Another example is biotech-specific commercialization funding of the same period, in which there were 108.1 million Euro from national governments and 2.5 million Euro from regional governments (D'Este, Senker, & Costa 2007). Currently there are two ways to grant funding: funds are granted by government through a competitive and peer-reviewed process, or through the allocation of block grants given to universities and research institutes (D'Este, Senker, & Costa 2007; Enzing et al. 2007).

The funding of basic research has profound impacts on innovation performance. Bruno et al. suggested that the supply side is more important than demand side in biotechnology innovation, i.e. the driving force of biotechnology innovation was research capacity, therefore, it is important to fund the research base of biotechnology and give researchers market advice at the same time (Bruno, Miedzinski, Reid, & Ruiz Yaniz 2008). Patel, Paunov, & Arundel argued that public

expenditures on biotechnology R&D were not directly connected with performance of commercialization and output indicators, but indirectly influence these performance via training highly skilled postgraduates, however, they also admitted the long R&D process was not considered in their research, and analyzing the R&D expenditure and output of the same periods may not map the real picture (Patel, Paunov, & Arundel 2008).

The structure of policy making also has impacts on the performance of innovation systems. The Biopolis Final Report analyzed 18 national policy making systems of 18 European countries (Switzerland, Denmark, Sweden, Finland, Austria, UK, Belgium, the Netherlands, Ireland, Germany, Norway, France, Italy, Spain, Greece, Luxembourg, Portugal and Iceland), and suggested that the countries with "convergent innovation systems, with high interactions amongst a large diversity of actors and concentrated decision making processes with *ex ante* coordination" had better performance than other countries (Enzing, Giessen, Van der Molen, Manicad, Reiss, Lindner, Lacasa, Senker, Rafols, D'Este Cukierman, & Costa 2007, P16).

Since there are more actors involved in the policy making process, it is recommended that the national government of European countries should avoid coordination gaps (Enzing et al. 2007, P17).

> *"...it is highly recommended that national governments close the 'coordination gap'; not only between national departments, but also between national and regional governments and international institutions. This involves co-ordination of simultaneous policy actions addressing the core set of innovation policies such as science, technology and education, as well as a re-direction of policy actions that pursue other primary objectives such as public health and regional development."*

(Enzing et al. 2007, P17)

Moreover, innovation speed and direction are also influenced by public attitudes, e.g. there are public debates on "manipulation of human cells and embryos for pharmaceutical research, and human and animal cloning" (Patel, Paunov, & Arundel 2008, P6). Therefore, the interactions and communications between public, policy makers, researchers and firms are very important to the innovation process. Researchers argue that policy makers should emphasise the risk factors of biotechnology innovation, and improve the "combination of strategic management and scientific knowledge" (Bruno, Miedzinski, Reid, & Ruiz Yaniz 2008, P43). In this study, policy implications will be discussed based on the empirical data collected from the drug discovery and development sector.

2.3 Summary

This chapter started with the two different observations of the biopharmaceutical industry, and generated two research questions that reflect the core elements of the Sectoral Systems of Innovation.

As a highly R&D intensive sector, the drug discovery and development companies' major activities are directly or indirectly related to the competition of knowledge exploration and knowledge acquisition. For example, biopharmaceutical companies tend to cluster in locations near universities, research hospitals and research institutes. The formation of clusters are the result of a combination of local factors or driven by policies (Chiaroni & Chiesa 2006). These key factors include collaboration with local research institutes and universities and financial support from local venture capitalists. Clustering also attracts foreign companies and large pharmaceutical companies to forge downstream alliances with these companies. To what extent a company could benefit from

clustering is determined by many factors, e.g. the nature of clustering, company size, the company's products and services and management experiences. The US and EU pharmaceutical and biotechnology industry has been growing very fast in the past two decades. The structure of the pharmaceutical and biotechnology industry is hierarchical. It is dominated by several well established companies, but there are also a large number of small to medium sized firms. These companies adopted different strategies due to their available resources, knowledge base and histories.

The pharmaceutical and biotechnology industry is characterized by extensive alliances and networking, in particular, networking and alliances are important for small firms to survive and grow. As an R&D intensive industry, internal R&D and R&D outsourcing are both important for companies. Literature on alliances and networking are mainly focused on the driving forces of alliance formation, performance and factors influencing alliances. Market uncertainty and firm specific uncertainty are determinants in biotechnology firms' strategies in forming alliances (Beckman, Haunschild, & Phillips 2004). Number of alliances is connected with firms' rate of drug innovation (Deeds & Hill 1996) and stages of product development (Danzon, Nicholson, & Pereira 2005). To what extent companies could benefit from alliances determined by their competencies (Arora & Gambardella 1994), their role played in alliances (Rothaermel 2001), and financial conditions (Lerner & Merges 1998).

However, from a perspective of Sectoral Systems of Innovation, it is still not clear how alliances change when industry evolves. Considering the pharmaceutical and biotechnology industry as a Sectoral System of Innovation, this study will examine the emergence of new actors in this system of innovation, those being the drug discovery and development companies established after the 1980s, when biotechnology first started to be applied to the drug innovation process. To what extent the emergence of the UK drug discovery and development companies established after the 1980s contributed to the sectoral systems of pharmaceutical and biotechnology innovation, in terms of knowledge production and technology, is the central question. How have these companies'

strategies developed? How do they ally with other actors of this system? Who benefits from the emergence of UK drug discovery and development companies and the networks associated with them?

In response to these questions, this study examines the subsector's structure, the size and age of firms, their clustering and concentration. In addition, it also investigates the knowledge production of the drug discovery and development subsector. It not only examines their R&D expenditures and product pipelines, but also focuses on their small scale contributions i.e. scientific publications and patents. This study also pays attention to the alliances of the drug discovery and development subsector, in particular, the number of alliances, the purpose alliances, technologies, disease indications, and partners. From a perspective of dynamics, this study examines how alliances changed over time. Details of methodology and research design will be discussed in the next chapter.

Chapter Three: Research Design and Methods

3.1. Introduction

This chapter aims to discuss the research design and methods applied in this study. This study began with mapping the UK pharmaceutical and biotechnology industry, where the drug discovery and development sector is embedded, followed by an overview of the drug discovery and development sector.

The main data sets were used to describe and analyse this sector's R&D and alliance activities. There are three groups of indicators that are widely used in analysing science, technology and innovation (STI): R&D expenditures and sales; patent applications, grants and citations; and scientific publications and citations (Smith 2005b). These three groups of indicators will be covered in this study. Considering the accessibility of data sources and availability of data, R&D expenditures and sales, scientific publications and citations, and patent applications will be used as major indicators of innovation. In addition, the less standardized indicators, drugs and pipeline drugs, will also be used as supplementary indicators to measure the output of the drug discovery and development sector. Alliance agreements were used to analyse the collaborations and networking of this sector.

This broad design of methodology was chosen because this study intended to examine the best available indicators for the knowledge produced by this subsector and industry dynamics. The reason for not chose interview company managers is that this study aimed to objectively describe this subsector and measure its output.

This chapter will begin with introducing the data sources of this study: qualitative and quantitative information on the drug discovery and development subsector was collected from various data sources, including government databases, commercial databases, scientific search engines, websites of industry associations, and the websites of individual companies. The next section will introduce the measurement and indicators chosen to describe the sectoral structure, innovation and alliance activities. The following section will discuss the sample selection criteria and the boundaries of this research: how the company list was identified and what data would be included in this study. In the next section, how the research design has been evolved will be presented, from a pilot study to the main research stages. Then methods and tools used in data analysis will be introduced. The limitations of this study will be discussed in the next section, followed by a summary of this chapter.

There were no ethical concerns about commercial confidentiality because data used in this study did not include interview with companies, and all data is publicly available.

3.2. Data Sources

3.2.1. Biotechnology Company Compendium: 2003/2004

BioCommerce Data Ltd. published an industry directory of the biotechnology industry: *Biotechnology Company Compendium 2003/2004 UK* (BioCommerce Data 2003), whose data was mainly collected from a survey of companies. Different from the definition of biotechnology introduced in the Introduction Chapter, the *Biotechnology Company Compendium 2003/2004* adopted a very broad definition of biotechnology, which also included companies focused on traditional chemical technologies.

The main body of the pharmaceutical and biotechnology companies list was identified from this book. Major categories included biomaterial, chip arrays, diagnostic, drug delivery, drug discovery and development, equipment and reagents, non-drug product development, sequencing, software and I.T., and support services.

However, considering its methods and publication date, information from this book was not enough to create a comprehensive list of the pharmaceutical and biotechnology industry to fulfill this study. Therefore, other sources were accessed to complete the industry list.

3.2.2. Websites of Industry Associations

In order to product a comprehensive list of the pharmaceutical and biotechnology companies, two major associations' websites were accessed.

The Bioindustry Association (BIA), which was established in 1989, is a trade association for innovative enterprises in the UK's bioscience sector (www.bioindustry.org). Their websites provided a list of over 300 members, including companies, organizations and public research institutions. This member list provided very valuable information of companies that were not included in the *Biotechnology Company Compendium 2003/2004,* in particular, those small companies established after 2003.

The Association of the British Pharmaceutical Industry (ABPI) is a trade association of companies in the UK producing prescription medicines (www.abpi.org.uk). Their websites provide a list of memberships, which mainly included well established pharmaceutical companies. Their web sites also provided very useful statistics of these integrated pharmaceutical companies.

Based on these data, a preliminary list of pharmaceutical and biotechnology industry was generated, which included all pharmaceutical and biotechnology companies that appearing in these resources. Further resources were accessed to validate the information on these companies.

3.2.3. Company House, London Stock Exchange, Websites of Individual Companies and Internet Archive

Companies on the preliminary list of the pharmaceutical and biotechnology industry were checked and validated on the Company House website (www.companieshouse.gov.uk), the London Stock Exchange website (www.londonstockexchange.com), websites of individual companies and the Internet Archive (www.archive.org).

Company House is an executive agency of the Department for Business, Enterprise and Regulatory Reform (BERR). Their functions include storing company information and making this information available to the public (www.companieshouse.gov.uk).

London Stock Exchange (www.londonstockexchange.com) provides detailed information and news releases on these companies which trade on the main market and alternative investment market (AIM)[4]. This information and related news releases include companies' profiles, trading history and annual reports.

Individual company's website provided information on each company's history, structure, current activities, contacts and archives of their news releases. Individual company's website was not only used to check and validate the basic information, but also provided very valuable information on their drug, pipeline and alliances.

However, there were circumstances in which companies' websites were under maintenance, or removed because of merger and acquisitions. In these cases, the Internet Archive (www.archive.org) was used to retrieve companies' online information. Internet Archive is a non-profit organization, which preserves websites of different periods and provides valuable historical information which is not available at present.

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[4] AIM is the London Stock Exchange's international market for smaller growing companies (www.londonstockexchange.com).

According to the criteria which will be discussed in a later section, a final list of 604 pharmaceutical and biotechnology companies were identified after validating the preliminary list and a list of 81 drug discovery and development companies was also generated. These companies' basic information were recorded and analysed. After identifying this list of drug discovery and development companies, details of these companies' activities, e.g. R&D expenditure and income, marketed drugs and pipeline drugs, scientific publications, patent publications and alliances agreements, were collected from several different databases.

3.2.4. R&D Scoreboard Published by UK Government

R&D Scoreboard is an annual UK government publication of top companies investing in R&D. It was firstly published in the 1990s by the Department of Trade and Industry (DTI). After the DTI was spilt on 28 June 2007 into the Department for Business, Enterprise and Regulatory Reform (BERR) and the Department for Innovation, Universities and Skills (DIUS), the R&D Scoreboard 2007 was co-published by DIUS and BERR.

The R&D Scoreboard series publications provide information on top UK companies R&D input and output: their R&D investment and income, which were collected from the audited annual reports and accounts of companies. This data was also accessible online (www.innovation.gov.uk). The data collection and analysis procedure of R&D Scoreboard series publications followed the *Frascati Manual* published by the OECD (OECD 2002). The *Frascati Manual* was first published in 1963 and aims to provide a guideline for practicing surveys of R&D, and the current version is the sixth edition published in 2002 (OECD 2002).

The limitation of the R&D Scoreboard series publications was that they did not provide information on small companies, and these small companies R&D information was also difficult to obtain from other sources. Therefore companies' R&D expenditure and income analysis of this study were focused on major drug discovery and development companies.

3.2.5. Recombinant Capital Database

Information on alliance, drugs on the market and pipeline drugs was partly obtained from companies' websites, and partly obtained from the Recombinant Capital (Recap) database. Recap is a consulting firm established in 1988 and based in San Francisco, providing a comprehensive archives of pharmaceutical and biotechnology alliances agreements (www.recap.com). All the pharmaceutical and biotechnology agreement held by the U.S. Securities and Exchange Commission (SEC) are available in Recap's database. Their other resources include biotechnology and pharmaceutical company press releases, company presentations made at investment conferences and other public meetings. Each agreement gives information on the R&D provider, client, country of companies, technology, alliance stage, indication and size.

The Recap database also provided information on pipeline drugs, in particular, drug candidates in clinical trials.

The limitation of the Recap database was that as a US based database, their information about the UK pharmaceutical and biotechnology industry was not comprehensive, therefore, data on alliances, drugs and pipeline drugs was also obtained from each company's website. Data from both sources were triangulated with each other.

3.2.6. Database of Science Citation Index Expanded

The drug discovery and development sector's scientific publication and citation data were collected from the Science Citation Index (SCI) Expanded published by Thomson Reuters (http://isiwebofknowledge.com). SCI Expanded coved 6934 scientific journals published world wide and tracked back to 1900. Only research articles, reviews and letters were studied in this project, this is because research articles and reviews are usually peer reviewed (Lopez-Illescas, de Moya-Anegon, & Moed 2008;Moed 2008). Although letters may include peer reviewed letters and normal correspondence (Lopez-Illescas, de Moya-Anegon, & Moed 2008), they were considered in this research because letters are an important contribution from companies. Publications from 1982 (the year of first paper published by any company identified in this study) to 2006 were included. Citation data were expanded to 2008, which allowed the papers published in 2005 and 2006 to be fully cited and calculated.

3.2.7. Europe's Network of Patent Databases (esp@cenet)

The data on patent publication analysed in this study were obtained from the European Patent Office (EPO) website, which provides a database (esp@cenet) of comprehensive patent publications from the 19th century to date. The online database esp@cenet (http://gb.espacenet.com) not only provides patent information on European countries, but also

documents at a worldwide level. The limitation of esp@cenet database was that abstracts were not available for some of the patent publications.

3.3. Measurements and Indicators

In order to answer the research questions proposed at the beginning of this thesis, this study will measure and describe the industry and sectoral structure, R&D activities and alliances activities.

Considering the accessibility of data sources and availability of data, R&D expenditures and sales, scientific publications and citations, and patent applications will be used as major indicators of innovation. The main reason for their wide use is that these indicators are able to capture small scale changes in science, technology and innovation (Smith 2005b). In addition, the less standardized, but very important indicator- drugs on the market and pipeline drugs, which refer to the new product underdevelopment, will also be used as a supplementary indicator to measure the output of drug discovery and development sector.

In this section, indicators and measurements used in this study will be introduced and how these indicators were reviewed and used by other researchers will also be discussed. The coverage of indicators includes industry structure, R&D investment, scientific publications, patent publications, and alliances. Moreover, the advantage and limitations of these indicators and measurements will also be addressed.

3.3.1. Industry and sectoral background

To provide a background on how the drug discovery and development subsector evolved, the pharmaceutical and biotechnology industry where the drug discovery and development subsector is embedded were described first, followed by an introduction of the structure of the drug discovery and development subsector. The background discussion was used to facilitate an understanding of the dynamics and evolution of the drug discovery and development subsector.

As discussed in the literature review chapter, companies' locations, ages, sizes, products and services are all important factors, which have a combined impact on the industry and subsector. Therefore, information on 604 pharmaceutical and biotechnology companies' size, location, age, products and services was collected and analysed. Furthermore, similar information on 81 companies which focused on drug discovery and development were analysed.

3.3.2. R&D investment, sale and R&D intensity

Three economic measurements of R&D were used in this study: R&D investment, sales and R&D intensity. According to the DTI, the "R&D investment" in these publications is defined as "the cash investment which is funded by the companies themselves: excludes R&D undertaken under contract for customers such as governments or other companies; and also excludes the companies' share of any associated company or joint venture R&D investment" (DTI 2002;DTI 2003;DTI 2004;DTI 2005;DTI 2006b). "Sales" is defined as the "total (operating) income" (DTI 2002;DTI

2003;DTI 2004;DTI 2005;DTI 2006b). R&D intensity is defined as the ratio of expenditures by a firm on research and development to the firm's sales (Smith 2005b).

R&D expenditure as a measurement was firstly available in the 1950s, and it is still one of the most popular innovation indicators (Kleinknecht, Van Montfort, & Brouwer 2002). The advantages of using R&D expenditure as an innovation measurement were that it could be collected and compared across time, countries and industries (Kleinknecht, Van Montfort, & Brouwer 2002;Smith 2005b). The disadvantages are that "standard R&D surveys tend to severely underestimate the small scale and often informal R&D activities in smaller firms" (Kleinknecht, Van Montfort, & Brouwer 2002, P111), which is also a limitation of this study.

The DTI started to use R&D intensity as an innovation indicator since its 2001 R&D Scoreboard. R&D intensity or R&D input/output ratios have been used to categorise countries, sectors and organizations, e.g. an industry with a high ratio is normally classified as a high technology industry (5 per cent), and an industry with a low ratio (<1 per cent) is regarded as a low technology industry (Smith 2005b). Many studies have observed that there are regular patterns in the distribution of R&D intensity within any given industry, therefore to use R&D intensity to classify industries is problematic, because a high tech industry may also contain low R&D intensity firms (Cohen & Klepper 1992;Hughes 1988). Based on this characteristic intra-industry distribution of R&D intensity, this study classified the firms into different groups according to their R&D intensity, and made efforts to describe these different groups.

3.3.3. Scientific publications

The number of publications was used in this study to evaluate the productivity of the UK drug discovery and development subsector. The focus of company research was investigated by counting keyword frequency. The country of authors was studied to figure out the UK's partners in co-publishing. Countries of authors were analysed to indentify the most competitive region of the industry in terms of publishing.

In addition, the source of publications and references was investigated to map the publishing pattern of the drug discovery and development subsector, and how their research has influenced other publications. The indicators used to measure the publication source and citing source were similar, both including the subject of journal, country of journal and the number of publications or references.

In this study, the popular indicator Journal Impact factor was not used. The reason for this is that Journal Impact factor was calculated on a three yearly basis. However, the coverage of this research is 25 years. Therefore it is not very accurate to describe the impact of a journal over this long time period. Moreover, Journal Impact factor could only evaluate the impact of certain journals; it does not necessarily correlate with the impact of an individual article published in that journal.

In order to measure the impact of companies' publications, total counts of citations and the *h*-index were adopted in this project. The presumption is that "a paper must have a certain quality in order to have an impact on the scientific community" (Okubo 1997, p.25).

The *h*-index was proposed by Hirsh in 2005, and it is defined "as the number of papers with citation number >*h*" (Hirsch 2005,p.16569). It was quickly adopted by many researchers and the *Web of knowledge* started to used the *h*-index in their citation report (Bornmann, Mutz, & Daniel 2008). The *h*-index was firstly used to measure the output of individual scientists, but was later used to evaluate "departments, institutions, or laboratories. The importance of the *h*-index can be

further enhanced when it is properly calibrated for the size of the group" (Kinney 2007p.17943). In this study counts of citations and the *h*-index were used to evaluate the cumulative impact of the UK drug discovery and development companies' publications.

It is important to note that these two indicators measured the cumulative impact of a company's publications. This factor should be taken into account because companies with a longer history may benefit from this measurement (Hirsch 2005). Moreover, these two indicators generally overlook the most influential publications (Hirsch 2005). For example, the total number of citation of Avidex and Crusade Laboratories were 362 and 361 respectively, however, the most citied paper of Avidex had been cited 46 times, while that of Crusade Laboratories had been cited 197 times. Similarly, the *h*-index also overlooks the high-end of companies' publications, e.g. the *h*-index of Oxxon and Pharmagene were both 9, however, the most citied paper of Pharmagene had been cited 68 times, while that of Oxxon had been cited 221 times.

To solve the first problem, average citations per publication and average citations per year were adopted to evaluate the quality and impact of a company's research. In addition, the total citations of the most cited papers were counted in order to compare the high-end of a company's publications.

Although the SCI citation database has been widely used by scholars, there are several limitations affecting the results of this study: firstly, it does not count citations in book and conference proceedings (Meho & Yang 2007). Secondly, it has citing errors "such as homonyms, synonyms, and inconsistency in the use of initials and in the spelling of non-English names (many of these errors, however, come from the primary documents themselves rather than being the result of faulty ISI indexing)"(Meho & Yang 2007,p.2105). In this study, because of the second limitation, 3444 out of 79878 (4.9 per cent) references were discarded. Thirdly, self-citations were not eliminated from the citation analysis. Hirsch argues that the impact of self-citations on *h*-index is smaller than on the total counts of citations (Hirsch 2005). In this study, self-citations were

tolerated and considered. It is also important to note that some document types are cited more often than others, e.g. reviews are usually cited more often than research articles (Hirsch 2005). Moreover, some research fields have higher citation rates than other fields (Seglen 1997).

3.3.4. Patent publications

Two types of patent information could be used to describe the innovation activity of drug discovery and development firms: patent publications and granted patents. Patents are an indicator used to measure science and technology output. There are four principle knowledge indicators used by the OECD: R&D investment, employment of engineers and technical personnel, patents and international balance of payments for technology, and among these indicators, patents most directly measure knowledge output (OECD 1996). Publications of patents are applications under provisional protection, and could be easily browsed in the patent office database. There are two advantages of analyzing patent data, firstly they are available over a range of countries and years, and they contain details of knowledge formation, i.e. information on technology class, information on inventor and country of inventor (Hall 2008). Secondly, patents that cite other patents and non-patent documents provide information on knowledge diffusion (Hall 2008).

Pavitt suggests that there are three sources of biases in granted patent counts (Pavitt 1988), and these biases are also applicable to patent publications. These three biases are on three different levels: country level, sector level and firm level. Firstly, there are different economic costs and benefits of patenting in different countries, e.g. time of examination, size of market and subject matter coverage (Pavitt 1988). For example, the United States Patent and Trademark Office (USPTO) processed patent applications faster than the European Patent Office (EPO) and Japan

Patent Office (JPO) (van Pottelsberghe & Francois 2006). Secondly, for different technologies and sectors, the importance of patents as protection against imitation is different (Pavitt 1988). Thirdly, the different strategies for innovation among firms also vary, e.g. filling innovation under different names (Pavitt 1988).

Compared with analyzing granted patents, there are three advantages to analyzing patent publications. First of all, it is easier to access patent publications than granted patents via the European Patent Office database. Second, the time lag between application and patent publication is 18 months; this is much shorter than the 48 months from application to granting patents. The patent publication database will therefore provide more current information about firms' innovation activity. Third, the patent publications database will provide more comprehensive information on firms' research fields, because it includes all outputs with commercial potential, regardless of their originality.

Compared with granted patent data, one disadvantage of using patent publications is that these patent publications were subjected to further examination which leads to further differentiation. Firstly, the substantive examination rates may vary. For USPTO, applicants do not need to send requests for substantive examination, while the EPO and JPO need a separate request. The examination rate of USPTO is 100 per cent, the examination rate of EPO is 87 per cent and only 54 per cent for JPO (van Pottelsberghe & Francois 2006). Second, as discussed earlier, the rates of granting are also different between different offices. Therefore, the counts of patent publications are greater than the count of granted patents, while the general quality of patent publications is lower than granted patents.

In short, both granted patents and patent publications have pros and cons as indicators. The patent publications were chosen as indicators because they were easier to collect and the information was more up to date. For each patent publication, the patent title, abstract, patent number, publication

date, inventors, applicants, European classification number and countries of inventors and applicants were collected.

3.3.5. Alliances activities

As discussed in the literature review chapter, collaborations and networking have been broadly studied by many researchers, and alliance agreements have been widely used in innovation studies (Arora & Gambardella 1994;Colombo 2003;Deeds & Hill 1999;Gerard et al. 2001;Hynes & Mollenkopf 2008;Jeffrey & Maurizio 2005;Jones 1996;Lerner, Shane, & Tsai 2003;Reuer, Arino, & Mellewigt 2006;Smith 2005a;Staropoli 1998;Stuart, Ozdemir, & Ding 2007). In response to our research questions, agreements signed by drug discovery and development companies were collected, and details were recorded and analyzed, including signees, country of signees, date of agreements signed, disease indications, technologies, and stages of product development.

The limitation of using alliance agreements was that it is difficult to know the status of collaboration. Moreover, it is also difficult to evaluate the performance of alliances.

3.3.6. Drugs on the market and in development

The marketed drugs and drugs in the development pipeline are very important indicators of the productivity of the pharmaceutical and biotechnology industry. Different from scientific publications and patent publications, which capture the small scale changes in science and

technology development, drugs and pipeline drugs are product innovations or potential product innovations. In particular, drugs and pipeline drugs in late stages have important implications to the innovation systems (Nagle, Nicita, Gerdes, & Schnneichel 2008;Nagle, Lugo, & Nicita 2003).

However, because of the expensive and time consuming process of drug discovery and development, the majority of drug discovery and development companies investigated in this study do not have drugs on market. Although most of them have pipeline drugs, they may license these entities to other companies for royalties, or sell them for cash. In these cases, these companies' capacity may be underestimated. On the other hand, a company having many pipeline drugs may not only represent its internal R&D capacity, but also many other competencies, e.g. its financial capacity if they acquired pipelines externally, and its experience of managing product development. Moreover, unlike scientific publications and patent publications which are available for public access, many companies are not willing to disclose detail of their pipeline drugs on their websites, and it is often hard to find out the stage of clinical development of if a product candidate has ceased development.

Although drugs in development have many limitations as indicators to measure and compare individual firms, in this study they still provided very useful information on the innovation activities of the whole subsector, e.g. the technology in use, disease indications, and stages of development. Drugs and pipeline drugs were analyzed in the background chapter to facilitate the understanding this subsector.

3.4. Selection Criteria

This section will discuss the sample selection criteria and the boundaries of this research: how the companies list was identified and what data would be included in this study.

3.4.1. Company selection

UK Pharmaceutical and Biotechnology Company

1) They must be a pharmaceutical or biotechnology (human medical related) companies
2) Based in the UK (UK origin firms, foreign subsidiaries, new firm formed after merging with/acquired by other companies)
3) Provide at least one of the following products or services: biomaterial, chip arrays, diagnostic, drug delivery, drug discovery and development, equipment and reagents, non-drug product development, sequencing, software and I.T., and support service.

Drug discovery and Development Company

1) Company's major activities / initial aims were drug discovery and development. Drug delivery, vaccine, antibody humanization and compound library were included. Companies which did not have clear product pipelines were included. However, their main activity should be in-house drug discovery or development.
2) Companies only focusing on contact services were excluded from this study, e.g. Aeres biomedical, which provides antibody humanization service to other companies involved in product development

3) Based in the UK (UK origin firms, foreign subsidiaries, new firm formed after merging with/acquired by other companies).UK subsidiaries focusing on activities other than research were excluded. However, for UK research subsidiaries of foreign companies, they may be involved in research activities other than drug discovery and development.

4) Established after 1977: after the creation of the first biotechnology firm –Genentech (United States). Data collected in this project covered until 01/01/2007. Therefore, company name and corporate structure referred to the company status on 01/01/2007.

Categorizations of Drug discovery and Development Companies

1) Group one: pure UK companies -- UK firms not involved in overseas expansion or acquisition (these companies may be involved in local merger and acquisitions)
2) Group two: UK companies with foreign branches or which acquired foreign companies
3) Group three: UK firms which were acquired by foreign small to medium sized companies
4) Group four: UK firms which were acquired by large pharmaceutical companies
5) Group five: Foreign subsidiaries in the UK

Record of Company details

1) Location:
    i. For firms in group one and two, locations were where the headquarters were located.
    ii. For firms of group three and four, locations were where the original business was located.

iii. For firms of group five, locations were main UK research sites.

2) Year of founded:

i. For firms which was spun out from other firms, the year of founding was the year of forming the new business

ii. For firms which changed their names or were acquired by other firms, year of founding was that of the old business.

iii. For firms merged with or acquired by other firms, year founded was the founding year of the oldest business.

3) Ownership refers to company ownership status in 2006.

4) Country: for group two companies, countries of foreign branches were collected. For groups three, four and five, countries of foreign parent company were collected.

3.4.2. R&D expenditure

1) For UK companies which had foreign branches or acquired foreign companies, their R&D expenditure and sale were the figure of the UK headquarter.

2) For foreign companies which have UK subsidiaries – their R&D expenditure and sale figure was for the UK subsidiaries.

3.4.3. Scientific publications

1) At least one author was from a British company that had been identified as belonging to the drug discovery and development subsector (this included its domestic subsidiaries, laboratories, and UK merger and acquisition). Because companies' name may be abbreviated when appearing in addresses, possible abbreviations were searched. Results were compared with companies' domestic addresses (and old domestic addresses if there were any), to eliminate any company with a similar name. This research was focused on UK companies and their publications, therefore these companies' foreign subsidiaries were not considered[5].
2) Scientific papers published before 01/01/2007.
3) If the company was formed by acquisition and merger of several companies, the number of SCI papers is the sum of papers published by all UK companies / branches. (These 'old' companies which counted should be drug discovery and development companies and fulfil the basic criteria)
4) SCI Publications types: articles, letters and reviews.

3.4.4. Patent publications

1) Patents were counted only if one of the applicants/inventors was an employee of a UK branch or headquarter.
2) Patents published before 01/01/2007.
3) Patent publications data were collected from the database at worldwide level. The same patents which were published in different countries were counted as ONE patent publication.

[5] Papers co-published by UK companies and their foreign subsidiaries were included in this study.

4) Patents which belong to the same patent family, i.e. similar but slightly different patents (different patent number), were counted as individual patents in this study.

5) If the company was formed by acquisition and merger of several companies the number of patents is the sum of patents published by all UK companies / branches. (These 'old' companies which counted should be drug discovery and development companies and fulfil the basic criteria)

3.4.5. Marketed drugs and drugs candidates

1) Only clearly described product pipelines were recorded. Therefore, total number may be underestimated.

2) For groups one, three and four, data may be missing after acquisition (underestimated). For group two companies, it is very difficult to identify where product are being developed, therefore, data may include several products developed overseas (overestimated). For group five companies, data was only available for a few companies.

3.4.6. Alliance agreements

1) Data covered the period from 01/01/1983 (first agreement in database) to 01/01/2007

2) For group one companies, data may be missing due to the size of companies. For group two companies, data may include several alliances signed by overseas subsidiaries (overestimated). For group three and four companies, data may be missing after

acquisition (underestimated). For group five companies, data was only available for a few companies which were managed separately from their parent companies.

3.5. Research Stages

3.5.1. Pilot study

Based on the criteria discussed in previous sections, information on 128 drug discovery and development companies was collected and evaluated. There were very limited data on foreign companies' UK subsidiaries (group five). Data of companies which were acquired by foreign companies or by large pharmaceutical companies before 2004 were also largely unavailable (small fraction of group three and four).

Therefore, from a pragmatic point of view, the companies list was further narrowed down. The redefined company list included pure UK origin companies (group one), UK origin companies with foreign branches or acquired foreign companies (group two), and UK origin companies which were acquired by foreign companies or by large pharmaceutical companies between 01/01/2004 and 01/01/2007[6] (i.e. a fraction of group three and four).

The rationale for including 'UK origin companies which were acquired by foreign companies or by large pharmaceutical companies between 2004 and 2006' was that: there is a time lag between patent applications and publications, scientific paper submission and acceptance, announcement of acquisition and completion of acquisition. The measurements of this study were still in effect

[6] This is cconsisted with the time scale of alliances data, SCI publication data and patent publication data.

within this three years window. Therefore, in practice, these companies could be roughly viewed as group one or two companies.

Another pilot study was conducted to investigate problems that may occur in data collection and analysis. Take patent publication for example. 30 firms were randomly selected and their patent information was collected from the European Patent Office online database. In total data on 561 patents was collected in the pilot study, and collated into an Excel datasheet. The first major problem was duplicate publications. In this study, patent publications data was collected from databases at worldwide level, therefore, one discovery or invention may have been published in different countries. The esp@cenet database provides a results list which eliminated duplicates in the first 500 search results, and after testing, in most cases, the results list were ready to use. However, patents which belonged to the same patent family, i.e. similar but slightly different patents, were counted as individual patents in this study, and could not be eliminated from the results. The second issue was that patent co-applicants or co-inventors were firms which both investigated in this study, therefore a patent may be counted twice. When searching patent applicants or inventors, these types of patents were identified to avoid putting them in the datasheet twice. Finally, the pilot study datasheet was designed and improved after preliminary analysis: the final version of the datasheet consisted of patent title, abstract, patent number, publication date, inventors, applicants, European classification number and countries of inventors and applicants.

Similarly, pilot studies were also conducted for the other data sets to identify and solve problems that may occur in practice.

3.5.2. Main research stages

Based on the pilot study, during the main research stages, several software and tools were used to facilitate the data processing.

Data on publications and references were downloaded to a Microsoft Access database using bibliometric analysis software SITKIS (Schildt 2002), and analysed in SITKIS and Statistical Package for the Social Sciences (SPSS). Citation data were collected from SCI Expanded, which provides citation reports for a group of publications. The SCI Expanded citation report for each company's publications were collected and entered into Microsoft Excel spreadsheets. Query results for each company's publication in SCI Expanded Advanced Search were compared with publication data from each company to ensure the Citation Report included, and only included, the publications that fulfilled the criteria of this study.

Based on the datasheet designed in the pilot study, a database of the patent publication information of the UK drug discovery and development firms was created. In total 2,827 patent publications from 81 British drug discovery and development firms between 1982 and 2006 were filed in the Microsoft Excel spreadsheets and analyzed. Patent analysis included year of publication, type of invention/discovery, countries of inventor/applicants, and research collaboration with other companies and institutes. Similarly, data on alliances agreements, marketed drugs and pipeline drugs, and R&D expenditures/sales were also recorded and analysed in Microsoft Excel spreadsheets.

Data of alliances agreements were further imported to SocioMetrica VisuaLyzer 2.0 (Medical Decision Logic 2007). SocioMetrica VisuaLyzer 2.0 then transferred alliance agreements into graphically displayed networks, which illustrate how the drug discovery and development companies allied with other actors of the innovation systems.

3.6. Limitations of the Methods Used

As discussed in previous sections, there are three limitations of this research, briefly speaking limitation of data sources, measurements and indicators, and research practice. Firstly, for the secondary data collected from the established databases, these databases have limitations in collecting, storing and distributing data. For examples, the Recap database is biased in collecting information on UK companies, the DTI innovation database is biased on collecting information of small companies, and the SCI Expanded is biased in collecting citation data from books and conference proceedings. Secondly, as discussed earlier, each measurement and indicator has limitations, e.g. alliance performance and consequent impact could not be evaluated from agreements, and commercial potential could not be precisely evaluate from patent publications. There are also time lags between submission and acceptance of scientific papers, and applications and the publication of patents. Thirdly, the limitations of research practice include availability of data, and the need to balance cost and effectiveness.

Despite these limitations, there are several advantages of this study. Firstly, the data collected covered various sources, including government databases, scientific databases, commercial databases, industry associations and companies' websites. Secondly, data covered various aspects of the drug discovery and development subsector's R&D expenditure, drugs and pipeline drugs, scientific publications, patent publications, and their alliance agreements. Thirdly, according to the DTI R&D Scoreboard, the major actors in the UK drug discovery and development sectors were included in this study. Finally, this study also analyzed the background to the pharmaceutical and biotechnology industry, where the drug discovery and development subsector is embedded. This background analysis, together with the historical review of the industry, will facilitate the understanding of the drug discovery and development subsector.

In short, this chapter provides details of research design, data collection, criteria of company selection, the conduct of research and data analysis. The following chapter will present the background to the pharmaceutical and biotechnology industry in general, and to the drug discovery and development subsector in particular.

Chapter Four: Background

This chapter aims to provide a background of drug discovery and development subsector: the pharmaceutical and biotechnology industry this subsector embedded, the nature of drug discovery and development subsector, the product produced and in development by these companies, and their R&D expenditures and sales. This chapter will plot this group of companies and provide a basic understanding of this study.

The first section will focus on mapping the current British pharmaceutical and biotechnology industry, providing details about their activities, ages, and locations. This section will present an industrial background to the drug discovery and development subsector.

The second section will provide an overview of the drug discovery and development subsector, more precisely, the drug discovery and development companies which were established after 1980s– when the biotechnological era began. This group of companies is the focus of this project: their activities of knowledge generation, knowledge transfer and knowledge diffusion will be discussed in the next three chapters. This section will pay attention to the extent of clustering and the age profile of the industry.

The third section will provided account of marketed drugs and drugs in development of this subsector. These indicators provide very useful information on the R&D activities of the whole subsector, e.g. the technology in use, disease indications, and stages of development.

Other R&D indicators concerned in this chapter are R&D expenditure and R&D intensity. In the fourth section, the pattern of R&D expenditure and R&D intensity will be discussed. There will be a summary at the end of this chapter.

4.1. Overview of the British Pharmaceutical and Biotechnology Industry

In this project, 604 pharmaceutical and biotechnology companies have been investigated. Based on UK market share information (year 2004) published by the Association of the British Pharmaceutical Industry (ABPI), these companies were categorized into two groups: large pharmaceutical companies (25, 4 per cent), and medium to small sized firms (579, 96 per cent).

4.1.1. Large pharmaceutical companies

The 25 largest pharmaceutical companies accounted only for 4 per cent of total number of companies studied, however, their product sale was £ 7.9 billion, accounting for 66.8 per cent of the UK total market share in 2004 (Table 4) (ABPI 2008). Their primary care sales were £ 6.2 billion in total, accounting for 68.1 per cent of the primary care market, and their hospital sales were £ 1.8 billion, accounting for 62.7 per cent of the hospital care market. Pfizer had the largest share of primary care and total market share in the UK, and Roche had the largest share of hospital sales.

Twelve out of these 25 companies were American companies (48 per cent); three were German companies (12 per cent); and two (eight per cent) were from UK, France, Switzerland, Denmark and Japan respectively.

Table 4 Market share of the 25 large pharmaceutical companies

(ABPI 2008)

Ranking	Corporation	Country of origin	Total market sales £m	% share of total market
1	Pfizer	USA	1273	10.7
2	GlaxoSmithKline	UK	1065	9.0
3	Sanofi Aventis	France	755	6.4
4	Wyeth	USA	619	5.2
5	Astrazeneca	UK	591	5.0
6	Novartis	Switzerland	450	3.8
7	Roche	Switzerland	399	3.4
8	Merck Sharp & Dohme	USA	330	2.8
9	Lilly	USA	319	2.7
10	Johnson & Johnson	USA	284	2.4
11	Boehringer Ingelheim	Germany	241	2.0
12	Novo Nordisk	Denmark	183	1.5
13	Abbott	USA	174	1.5
14	Schering Plough	USA	153	1.3
15	Bayer	Germany	117	1.0
16	Bristol-Myers Squibb	USA	116	1.0
17	Astellas Pharma	Japan	110	0.9
18	Ivax	USA	108	0.9
19	Servier	France	105	0.9
20	Schering Ag	Germany	100	0.8
21	Mundi International	USA	93	0.8
22	Procter & Gamble	USA	91	0.8
23	Eisai	Japan	90	0.8
24	Baxter	USA	88	0.7
25	Leo Pharma	Denmark	76	0.6

The American companies' total UK market sale was £ 3,648 million, which accounted for 30.8 per cent of total UK market sales, followed by British companies (£ 1,656 million, 14 per cent), French companies (£ 860 million, 7.3 per cent), Swiss companies (£ 849 million, 7.2 per cent), Germany companies (£ 458 million, 3.8 per cent), Danish companies (£ 259 million, 2.1 per cent) and Japanese companies (£ 200 million, 1.7 per cent).

The UK primary care market demonstrated the same pattern. The American companies' UK primary care market sales were £ 2,850 million, which accounted for 31.4 per cent of UK primary care market sale, followed by British companies (£ 1,387 million, 15.3 per cent), French companies (£ 684 million, 7.5 per cent), Swiss companies (£ 526 million, 5.8 per cent), German companies (£ 327 million, 3.6 per cent), Danish companies (£ 226 million, 2.5 per cent) and Japanese companies (£ 178 million, 2.0 per cent).

The UK hospital market showed a different pattern, where Swiss companies performed second best to the American companies. The American companies' UK hospital market sales were £ 797 million, which accounted for 28.6 per cent of UK hospital market sales, followed by Swiss companies (£ 322 million, 11.5 per cent), British companies (£ 269 million, 9.7 per cent), French companies (£ 176 million, 6.3 per cent), German companies (£ 132million, 4.6 per cent), Danish companies (£ 33 million, 1.2 per cent) and Japanese companies (£ 22 million, 0.8 per cent).

In short, the largest pharmaceutical companies accounted for two thirds of total UK market sales, and large American companies, in particular, accounted for almost one third of the total UK market sales.

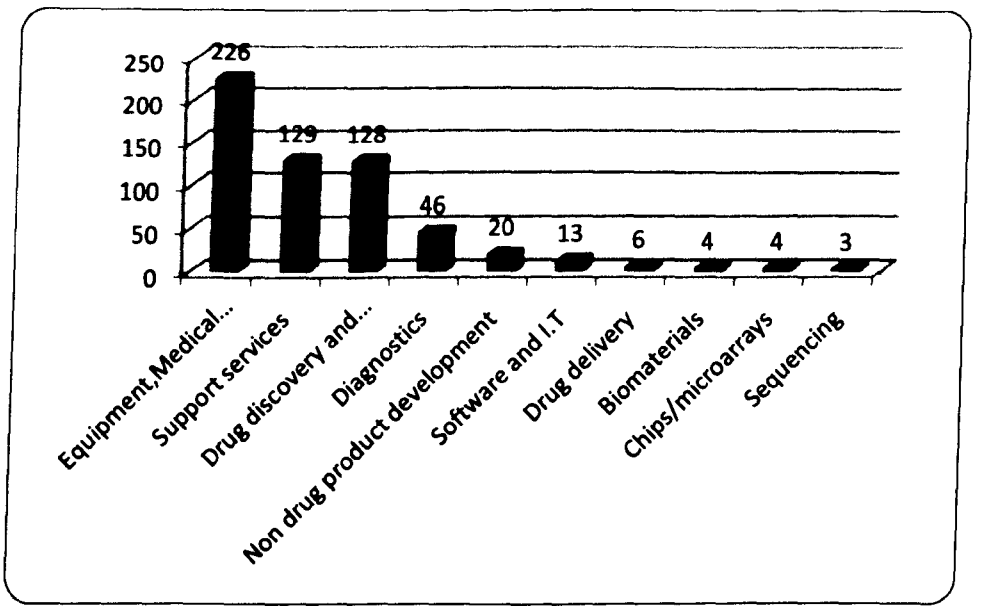
4.1.2. Small to medium sized firms

Products and services

In number, small to medium sized companies (579) accounted for 96 per cent of the industry. They were categorized into 10 groups according to their major products or services (based on the classification system developed by BioCommerce 2003/2004): these were biomaterial; chip arrays; diagnostic; drug delivery; drug discovery and development; equipment and reagents; non-drug product development; sequencing; software; and I.T. and support services.

As shown in Chart 1, the equipment and reagents sector had the largest number of small to medium sized companies (226, 39 per cent), followed by the support services sector(129, 22 per cent), the drug discovery and development sector (128, 22 per cent), the diagnostics sector (46, 8 per cent), non-drug product development (20, per cent), software and I.T. (13, two per cent), drug delivery(6, one per cent), biomaterial(4, 0.7 per cent), chip arrays (4, 0.7 per cent) and sequencing (3, 0.5 per cent).

Chart 1 Number of companies in each sector



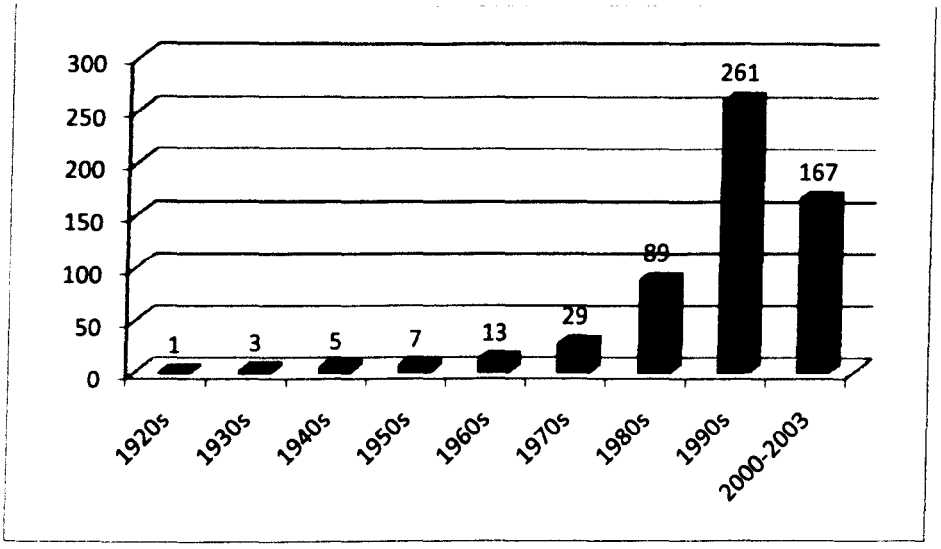
A series of reports on the biotechnology industry were published by the DTI. They aimed to compare the performance of the biotechnological sector in different countries. They adopted a slightly different classification systems and definitions from this project (large pharmaceutical companies, equipment and reagents companies were excluded from their study). However, after converting data to the DTI's definition, their results were similar to this research.

In their report, there were 382 UK companies in 2003 and 350 companies in 2004, whose "primary commercial activity depends on the application of biological organisms, systems or processes, or on the provision of specialist services to facilitate the understanding thereof" (DTI 2006a, P19). Excluding the equipment and reagents companies, the number of companies studied in this project was 353, which was similar to the DTI's results.

Year founded

Depending on the purpose of one's research, there are two ways to analyse the number of companies founded in each period. The first method is to collect historical information on the industry, and to compare the number of companies founded in different periods or different areas. However, it is very difficult to collect data on companies which are out of business. The second method, which was adopted in this project, is to collect information on existing companies from specified periods, and to map the industry by age groups.

Chart 2 Number of companies in each age group

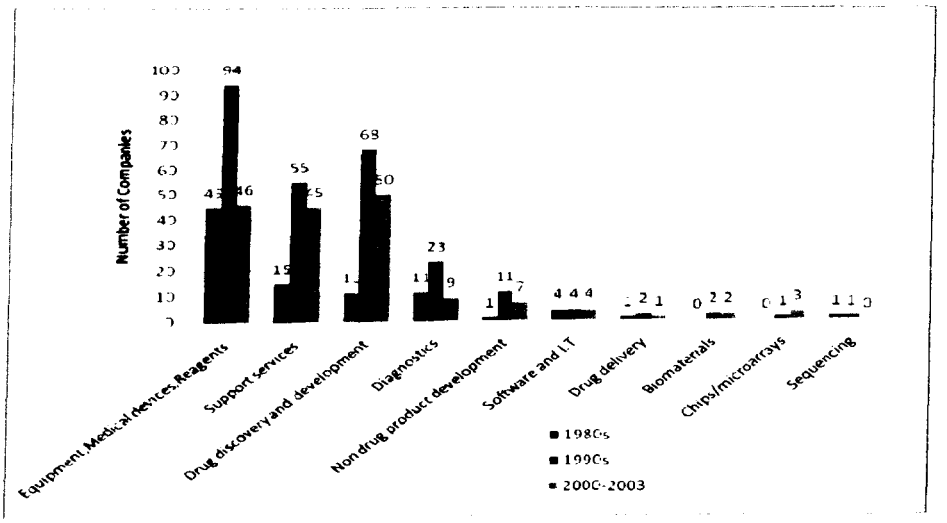


As shown in Chart 2, 261 out of 575 (data of four companies were not available) small to medium sized companies (45 per cent) were founded during the 1990s. 29 per cent of the companies were founded 2000. The total number of companies founded after 1980 was 517, accounting for 90 per cent of all the small to medium sized firms.

In the DTI's statistics, the age range was split into 5 groups: 0-2 years, 3-5 years, 6-10 years, 11-15 years ad over 15 years. In 2003, 22 per cent of companies were aged between 0-2 years, 26 per cent were aged between 3-5 year, 24 per cent were aged between 6-10 years, 12 per cent were aged between 11-15 years, and 16 per cent were aged over 15 years (DTI 2006a). Based on the DTI's methods, 20 per cent of companies studied in this project were aged between 0-2 years, 27 per cent of companies were aged between 3-5 year, 21 per cent of companies were aged between 6-10 years, 11 per cent of companies were aged between 11-15 years, and 21 per cent of companies were aged over 15 years. Compared with the DTI's statistics, the results were very similar and both indicated that there were fewer companies in the age group of 11-15 years than other groups.

Companies founded before the 1980s only accounted for 10 per cent of the total number of the whole industry. They were mainly equipment/device/reagents companies (41, 71 per cent), and support companies (11, 19 per cent). As shown in Chart 3, the equipment and reagents sector accounted for the largest percentage of the small to medium sized companies which were established during the 1980s and 1990s. From the 1980s until now, the numbers of surviving drug discovery and development companies and support services companies has been growing faster than other sectors. During 2000-2003, the number of new drug discovery and development companies was more than new companies of other sectors, followed closely by equipment and reagents, and support services.

Chart 3 A comparison of companies founded in the 1980s, 1990s and 2000-2003



One explanation for the fast growing number of these two sectors is that investors have been more and more interested in these two types of companies because both of them are working on the core products of the pharmaceutical and biotechnology industry. Drug discovery and development companies have their own product pipelines, which may lead to new drugs or intermediates; support services companies, of which the majority are contract research and clinical trial companies, are also indirectly involved in drug discovery and development. The large number of

equipment and reagents companies is not surprising: it is partially due to their close collaboration with the large pharmaceutical companies, which provide a steady income stream.

Locations

There were 470 small to medium sized pharmaceutical and biotechnology companies located in England, 76 companies in Scotland, 26 in Wales and 7 in Northern Ireland. As shown in Table 5, Cambridgeshire (79, 17 per cent), London (39, eight per cent), Oxfordshire (37, eight per cent), Berkshire (29, five per cent) and Surrey (28, five per cent) have the largest number of companies. Cambridgeshire, in particular, had twice as many companies as London. The areas which had more than 20 pharmaceutical and biotechnological companies were all in southern England. As shown in Table 6, Glasgow (13, 17 per cent), Dundee (10, 13 per cent) and Edinburgh (7, nine per cent) have the largest number of companies in Scotland. Cardiff (3, 12 per cent), Deeside (3, 12 per cent) and Swansea (3, 12 per cent) have the largest number of companies in Wales.

Table 5 Number of companies in each County (England)

Area	Num. of com.	Area	Num. of com.	Area	Num. of com.	Area	Num. of com.
Cambridgeshire	79	Lancashire	12	Leicestershire	6	Norfolk	2
London	39	West Sussex	12	Merseyside	5	South Yorkshire	2
Oxfordshire	37	West Yorkshire	10	Nottinghamshire	5	Cornwall	1
Berkshire	29	Greater Manchester	9	Dorset	5	Cumbria	1
Surrey	28	Middlesex	9	North Yorkshire	4	East Yorkshire	1
Buckinghamshire	24	West Midlands	9	Worcestershire	4	Shropshire	1
Hampshire	22	Gloustershire	8	Durham	3	Somerset	1
Cheshire	19	Wiltshire	8	Staffordshire	3	Warwickshire	1
Hertfordshire	17	Bedfordshire	7	Derbyshire	2	Northampshire	1
Essex	13	Suffolk	7	Devon	2		
Kent	13	Tyne and Wear	7	East Sussex	2		

Table 6 Number of companies in each county (Scotland)

Area	Number of Companies	Area	Number of Companies	Area	Number of Companies
Glasgow	13	Livingston	2	East Lothian	1
Dundee	10	Paisley	2	Galashiels	1
Edinburgh	7	Penicuik	2	Inchinnan	1
Bellshill	5	Troon	2	Inverbervie	1
Aberdeen	4	Arbroath	1	Irvine	1
Roslin	4	Auchermuchty	1	Oban	1
Perth	3	Ayr	1	Tranent	1
Stirling	3	Buckhaven	1	Uddingston	1
East Kilbride	2	Cupar	1	Walkerburn	1
Inverness	2	Dalkeith	1		

The biotechnology cluster research conducted by DTI in 1999 provided a different number of companies (Table 7); however, it demonstrated a similar pattern as the one above. They also suggested several factors which encourage cluster development: such as a strong science base, an entrepreneurial culture, growing company base, the ability to attract key staff, good premises and infrastructure, the availability of finance, business support service and large companies, skilled work force, effective networking and supportive policy environment (DTI 1999).

Table 7 Biotechnology company and research strength in areas visited

(DTI 1999: 15)

Area	No. of companies	Premier research and regulatory institutes	Top funded Universities bioscience
Cambridge	Approx. 150	LMB, Sanger, Babraham, EBI	Cambridge
Oxfordshire	Approx. 50	IMMM, Human Genetic Center	Oxford
London	Approx. 50	MCA, EMEA	UCL, IC, UMDS, School of Tropical Hygiene
Southeast (Surrey, Sussex, Kent)	50-100		Sussex
Central Scotland	Approx. 50	Roslin Institute	Edinburgh, Glasgow, Dundee

As mentioned before, southern England is very important for the pharmaceutical and biotechnology industry because of the high concentration and large number of companies. As shown in Table 8, over 60 per cent of companies in Cambridgeshire, London, Oxfordshire, Surrey, Buckinghamshire and Hampshire employed fewer than 50 staff; while over 40 per cent of companies in Berkshire employed more than 50 staff.

Table 8 Size of Companies in Different Areas

	>10	10--50	51--100	101--500	Over 500	Total
Cambridgeshire	23	38	6	6	2	75
London	13	17	3	4	1	38
Oxfordshire	7	16	5	5	1	34
Berkshire	4	12	3	7	2	28
Surrey	6	17	2	2	0	27
Buckinghamshire	5	12	2	3	2	24
Hampshire	4	10	2	4	0	20

Cambridgeshire has the largest number of small to medium sized equipment and reagents firms, support services firms, drug discovery and development firms, diagnostics firms and non drug development firms. In Cambridgeshire, Buckinghamshire, Berkshire, Herefordshire, and Hampshire, the largest sector of the local pharmaceutical and biotechnological industry was equipment and reagents, while in London and Oxfordshire, the drug discovery and development sector was the largest sector (Table 9). As shown in table 9, Cambridgeshire and London, which have the largest number of drug discovery and development companies, also have the largest number of support services companies. This may indicate that local supply sector and discovery/ development sector collaborate closely with each other.

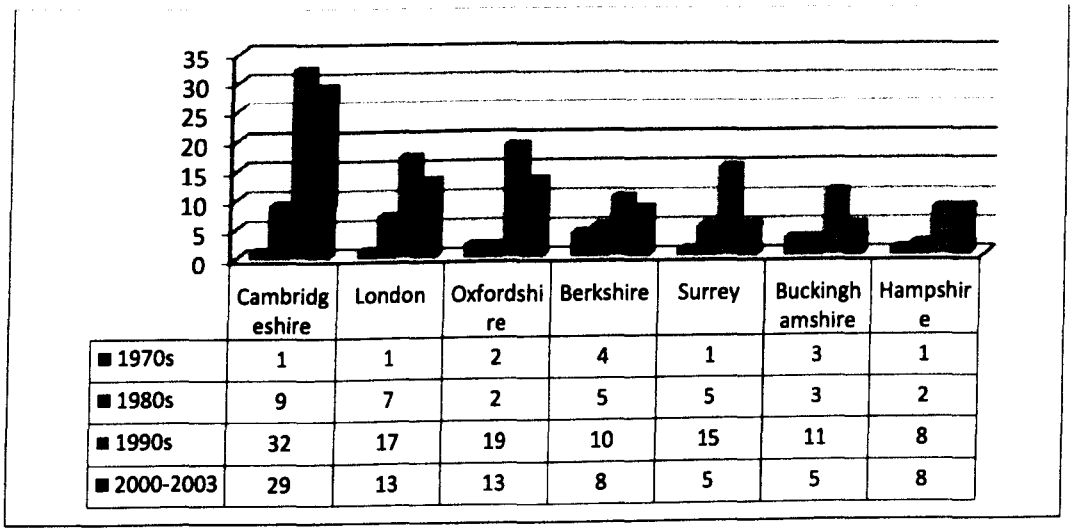
Table 9 Products and services in each area

	Equipment, Medical devices, Reagents	Support services	Drug discovery and development	Diagnostics	Non drug product development	Total
Cambridgeshire	25	18	24	5	2	74
London	8	8	19	1	0	36
Oxfordshire	10	5	18	2	0	35
Berkshire	13	6	8	1	0	28
Surrey	8	8	4	4	2	26
Buckinghamshire	14	5	2	1	0	22
Hampshire	11	6	1	3	0	21

Table 10 Company age groups of each area

	1920s	1930s	1940s	1950s	1960s	1970s	1980s	1990s	2000-2003	Total
Cambridgeshire	0	0	1	1	4	1	9	32	29	77
London	0	1	0	0	0	1	7	17	13	39
Oxfordshire	0	0	0	0	1	2	2	19	13	37
Berkshire	1	0	0	0	1	4	5	10	8	29
Surrey	0	0	0	0	1	1	5	15	5	27
Buckinghamshire	0	0	0	2	0	3	3	11	5	24
Hampshire	0	1	0	0	0	1	2	8	8	20

Chart 4 Company age group of each area



As discussed earlier, ten per cent of the small to medium sized companies were established before the 1980s. These companies were mainly located in Cambridgeshire, Berkshire, and Buckinghamshire (Table 10). Companies established after the 1980s were mainly located in Cambridgeshire, London and Oxfordshire (Table 10 and Chart 4). This was connected with the phenomenon discussed before, that a large number of drug discovery and development companies were emerging after the 1980s in Cambridgeshire, London and Oxfordshire.

Cooke conducted a study of biotechnology clustering in 2001. He identified that Cambridgeshire, Oxfordshire and Surrey were the three major biotechnology clustering centers in England (Cooker, 2001), which is different from Cambridgeshire, Oxfordshire and London identified in this study. There are two main reasons for this difference: first, Cooke's data were focused on the biotechnology sector rather the pharmaceutical and biotechnology industry as in this study. Second, Cooke's data was collected before 2000. After the year 2000, as shown in table 8, more firms were established in London than in Surrey. Spending on biotechnology related research in London is estimated to be £300 million per annum, which is the largest in the UK (DTI 2003).

Size of companies

At the beginning of this chapter, market capitalisation used to distinguish the size of companies, which easily categorized the pharmaceutical and biotechnological companies into two groups. However, share value on market is normally used for large public companies for which financial information are easy to obtain. To further discuss the size of smaller private companies, another measurement will be used: number of staff, which was collected by *Biotechnology Company Compendium 2003/2004*.

As shown in Chart 5, 25 per cent of total companies employed fewer than 10 staff, 47 per cent of companies employed 10 to 50 staff, 11 per cent of companies employed 51 to 100 staff, 14 per cent of companies employed 101 to 500 staff, and 3 per cent of companies employed more than 500 staff. For the largest four sectors (equipment and reagents, support services, drug discovery and development, and diagnostic companies), '10-50 staff' was the largest size group.

Chart 5 Number of companies in each size group

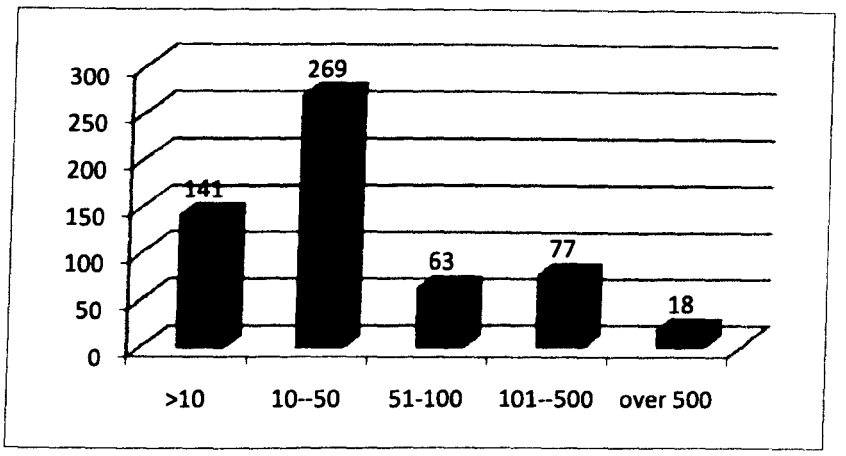
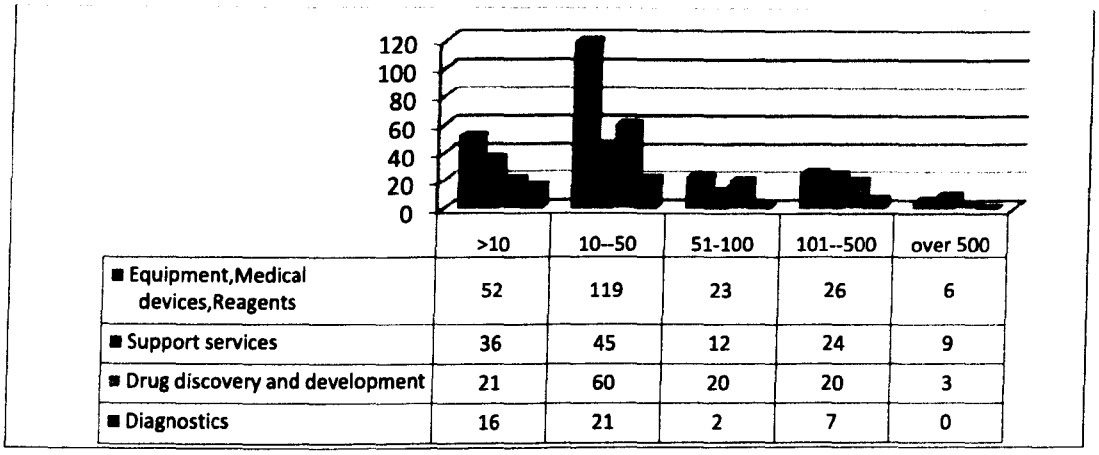


Table 11 Product and services of each size group

	>10	10--50	51-100	101--500	over 500
Equipment, medical devices and reagents	52	119	23	26	6
Support services	36	45	12	24	9
Drug discovery and development	21	60	20	20	3
Diagnostics	16	21	2	7	0
Non drug product development	5	11	4	0	0
Software and I.T	5	6	1	1	0
Drug delivery	1	2	0	0	0
Biomaterials	3	1	0	0	0
Chips/microarrays	2	1	0	0	0
Sequencing	0	2	0	0	0

As shown in Table 11 and Chart 6, firms employing fewer than 10 staff were mainly equipment and reagents, and support services companies; firms employing 10-100 staff were mainly equipment and reagents, and drug discovery and development companies; companies employing 101 to 500 staff were mainly equipment and reagents, and support services companies; and companies employing over 500 staff were mainly support companies, which provide contract research of clinical trials.

Chart 6 Product and services of each size group



	>10	10--50	51-100	101--500	over 500
Equipment,Medical devices,Reagents	52	119	23	26	6
Support services	36	45	12	24	9
Drug discovery and development	21	60	20	20	3
Diagnostics	16	21	2	7	0

There are 128 drug discovery and development companies in the UK, accounting for 22 per cent of all small to medium sized companies. From the 1980s until now, the numbers of surviving drug discovery and development companies have been growing faster than other sectors. During 2000-2003, the number of new drug discovery and development companies was more than other sectors. Cambridge has the largest number of drug discovery and development firms compared with other areas. In London and Oxford, the drug discovery and development sector is the largest sector of the local pharmaceutical and biotechnology industry. 65 per cent of the drug discovery and development companies employed fewer than 50 staff. However, in the size group of 50-100 staff, the drug discovery and development sector accounted for the largest percentage compared with other sectors. Based on this background, the next section will describe a picture of the drug

discovery and development companies established after 1980 – when the biotechnological era began. In particular, the study will focus on companies of UK origin.

4.2. British drug discovery and development companies established during the modern biotechnology era

The companies, which are directly involved in drug discovery and development, can be categorized into two groups; companies of UK origin, and UK subsidiaries owned by foreign companies or large pharmaceutical companies. Because the information on the foreign subsidiaries is always integrated with foreign parent company and other subsidiaries, it is very difficult to study them individually. Although they could be preliminarily identified as R&D sites, it is difficult to identify whether they are directly involved in drug discovery and development or other research activities. Therefore, this project will focus on drug discovery and development companies of UK origin. This section will discuss the age distribution, clustering and products produced by this sector. The next three chapters will continue to discuss how this sector has been involved in knowledge generation, transfer and diffusion.

4.2.1. Location

Of the 81 British origin companies, Cambridgeshire (21, 26 per cent), London (15, 18 per cent) and Oxfordshire (11, 14 per cent) had the largest number of drug discovery and development companies. In other words, 58 per cent companies were in these three areas.

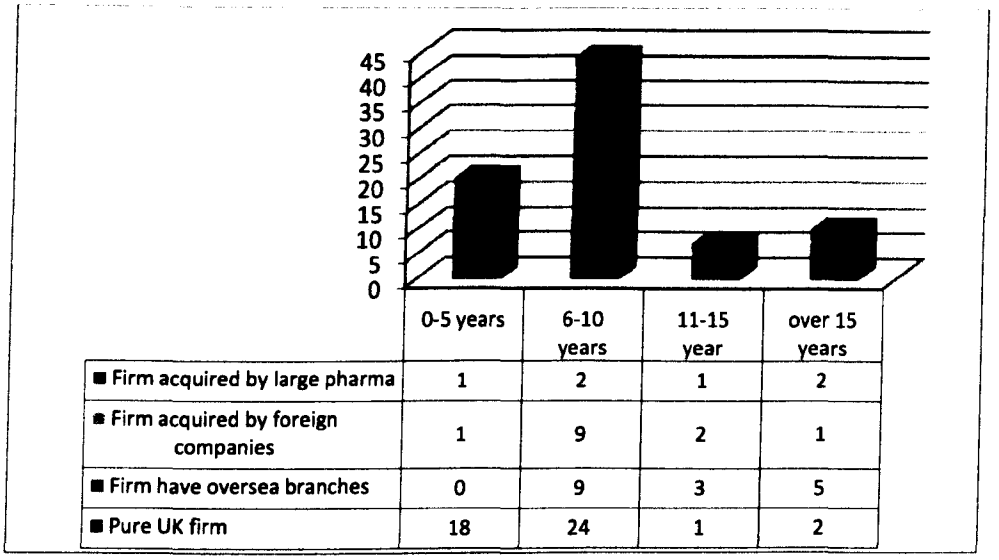
As of 2006, 17 drug discovery and development companies had established their branches oversea- four originally from Cambridge (24 per cent) and London (24 per cent) respectively.

From 2003 to 2006, 19 companies had been acquired by foreign companies and big pharmaceutical companies. Five of them were in Cambridge (26 per cent), and three in Oxford (16 per cent), London (16 per cent) and Berkshire (16 per cent) respectively. Of the six companies which had been acquired by big pharmaceutical companies, two were in Cambridge and Oxford respectively.

4.2.2. Year of establishment

As of 2006, 20 of the 81 drug discovery and development companies had been established for up to five years (26 per cent), 44 companies (54 per cent) were in the six to ten year age group, seven companies (eight per cent) in the 11-15 year group, and ten companies (12 per cent) had been established for more than 15 years (Chart 7).

Chart 7 Age groups of drug discovery and development companies

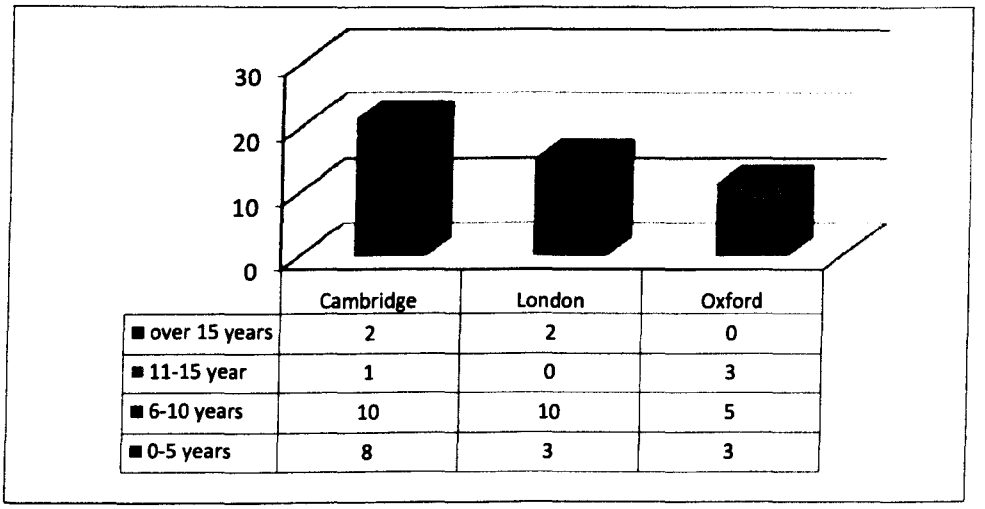


	0-5 years	6-10 years	11-15 year	over 15 years
Firm acquired by large pharma	1	2	1	2
Firm acquired by foreign companies	1	9	2	1
Firm have oversea branches	0	9	3	5
Pure UK firm	18	24	1	2

17 out of 19 companies which had been acquired by foreign companies or large pharmaceutical companies were established more than five years ago. All of the companies which had established foreign branches had been established more than five years ago; with five of them (29 per cent) had been established more than 15 years. This suggests that firms that survive and mature either establish operations outside the UK or are acquired. Only a small minority of firms retain a pure UK focus.

In Cambridge, London and Oxford, the largest age group is 6-10 years. In total, 70 per cent of companies in these three areas had been established for more than five years (Chart 8).

Chart 8 Locations and age group of companies



	Cambridge	London	Oxford
over 15 years	2	2	0
11-15 year	1	0	3
6-10 years	10	10	5
0-5 years	8	3	3

Chart 9 Locations of companies established over 15 years

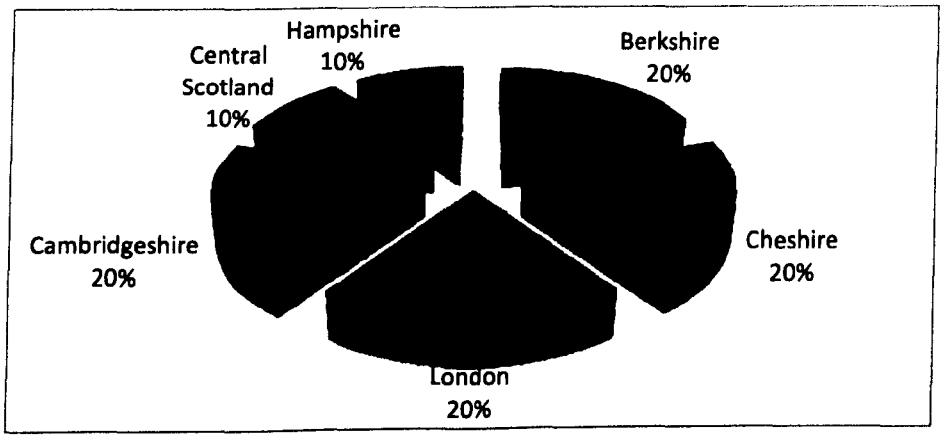
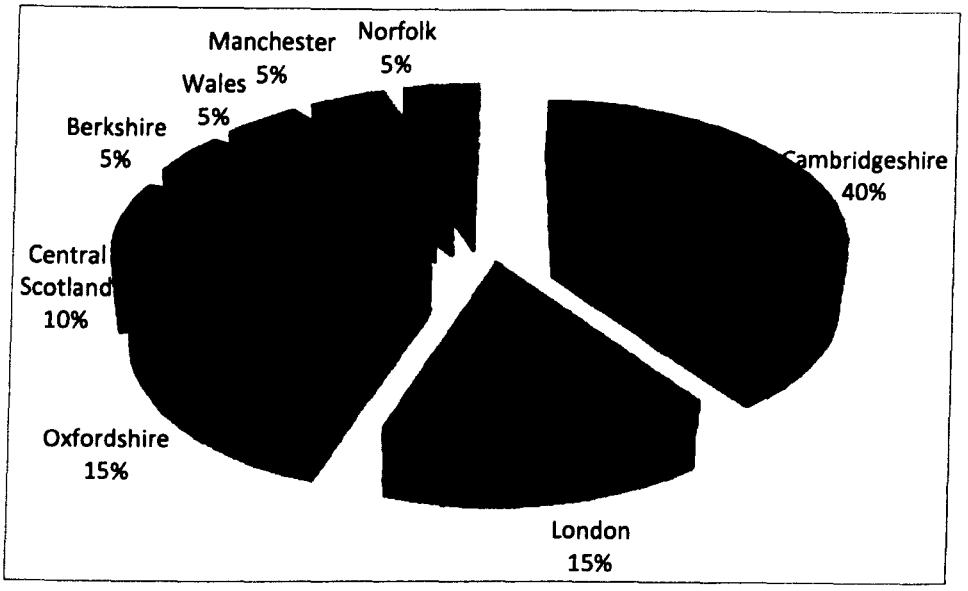


Chart 10 New established companies in each area (0-5 years)



Drug discovery and development companies aged over 15 years were located in Cambridgeshire (20 per cent), London (20 per cent), Cheshire (20 per cent), Berkshire (20 per cent), Hampshire (10 per cent) and Central Scotland (10 per cent) (Chart 9). Compared with this relatively even spread the pattern, the new established companies (0-5years) demonstrated characteristics of clustering (Chart 10). 40 percent of new companies were located in Cambridge. 70 per cent of the new established companies were located in Cambridge, London and Oxford.

In short, because drug discovery and development is a long-term orientated procedure, these companies were inclining to launch near where there existed a strong science base and well developed support services, to ensure their sustained development. The clustering of research institutes, research-based companies and support companies, will lead to close collaboration among them, and this will further facilitate the knowledge generation, transfer and diffusion process.

4.3. Drugs on the Market and in Development

4.3.1.Overview

The data of marketed drugs and drugs in the development pipeline was collected from the Recombinant Capital (www.recap.com) database and company press releases. The difference between marketed drugs and drugs in the development pipeline is that marketed drugs are approved by authorities and drugs in the development pipeline are drug candidates in clinical trials. 355 marketed drugs and drugs candidates from 63 companies were recorded and analysed. Product information on the other 18 companies was not available, because the information of product pipelines was not disclosed or the development programmes were still in the early preparatory stage.

The data of marketed drugs and drugs candidateswas cumulative information: these pipelines also included candidate compounds which failed to enter the next clinical stage and product development programs which have been terminated due to other reasons, e.g. financial reasons.

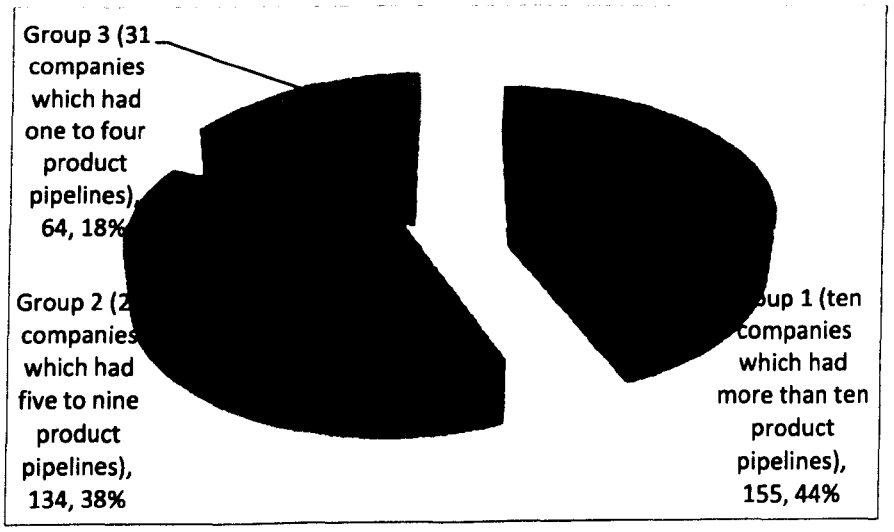
For drug candidates which have more than one potential indication, there may have been parallel development programmes. The same candidate compound which was developed to treat several diseases was recorded as one drug or one pipeline drugin this study. Around one tenth of the drug candidates had more than one indication.

The average number of marketed drugs and drugs candidatesof these 63 companies was 5.6. Ten companies had more than ten products. This highly productive group had 155 marketed drugs and drugs candidates, which accounted for 44 per cent of total number (Chart 11). The next group is

companies which had five to nine marketed drugs and drugs candidates. These 22 companies had 134 marketed drugs and drugs candidates, and accounted for 38 per cent of the total. The third group of companies had one to four marketed drugs and drugs candidates. These 31 companies had 64 marketed drugs and drugs candidates, and accounted for 18 per cent of the total.

This highly hierarchical structure of output not only resulted from the intensive R&D investment by the top companies, but also was a result of merger and acquisition (see Chapter Seven).

Chart 11Number of marketed drugs /drugs candidates of each group



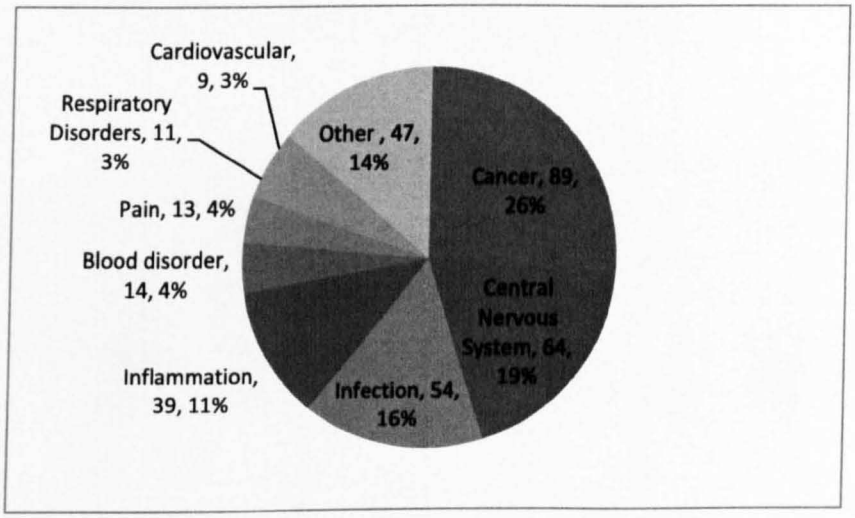
4.3.2.Indications

The major indications of marketed drugs and drugs candidates were cancer, central nervous system diseases, infection, inflammatory diseases, blood disorders, pain, respiratory disorders and

cardiovascular diseases (Chart 12). Other indications included metabolic disorders, gastrointestinal diseases, kidney disease, bone, cocaine addiction, etc.

Cancers were the most important indications, 89 drugs and pipeline drugs were discovered and developed to treat cancers, and accounted for 26 per cent of total number of product pipelines. There were 64 drugs and pipeline drugs (19 per cent) with the potential to treat central nervous system diseases, 54 were for infection (16 per cent) and 39 drugs (11 per cent) for immune-mediated inflammatory diseases. The marketed drugs and drugs candidates for these four major indications accounted for 72 per cent of total products. These four indications were also the major areas of alliances (see Chapter Seven).

Chart 12 Indications of marketed drugs and drug candidates (percentage)



4.3.3. Stages of product pipelines

The stages of product pipelines were mainly concentrated at lead and preclinical stages. There were 69 drug candidates in lead stage, which accounted for 21 per cent of total products (Chart 13 & 14). The largest group is drug candidates in preclinical stages, 94 candidates accounted for 29 per cent of the total. 47 drug candidates, (14 per cent) were in Phase I, 58 (18 per cent) were in Phase II and 23 (seven per cent) were in Phase III. One per cent of drugs were waiting approval and ten per cent (give number) were approved. Late stage development was mainly conducted by large drug discovery and development companies, e.g. Shire Pharmaceutical accounted for 31 per cent of drug candidates in Phase III. One possible reason for the concentration of the early stages of development was that small to medium sized companies were young and generally had insufficient resources to move beyond Phase I.

Chart 13 Stages of drugs candidates (2006)

(Accumulated data on all historic products)

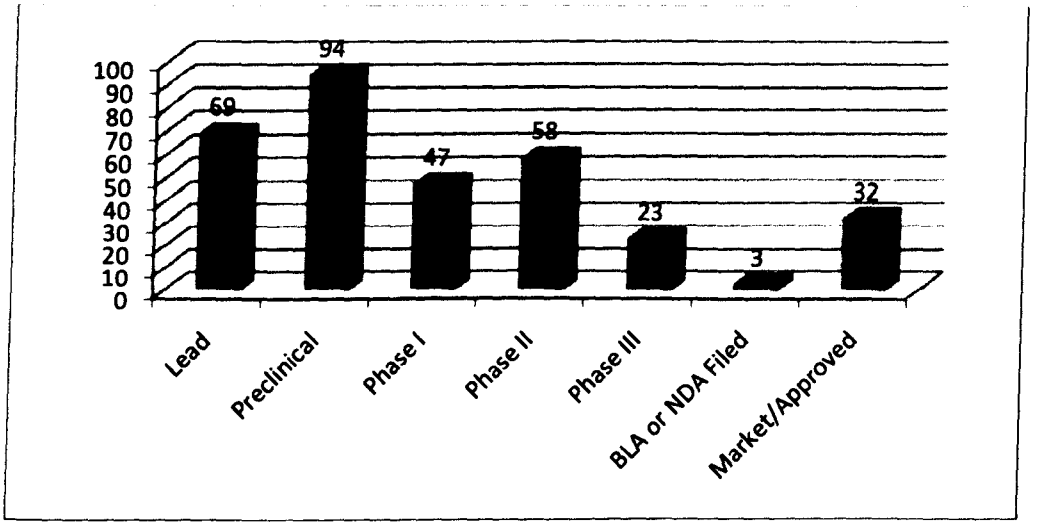
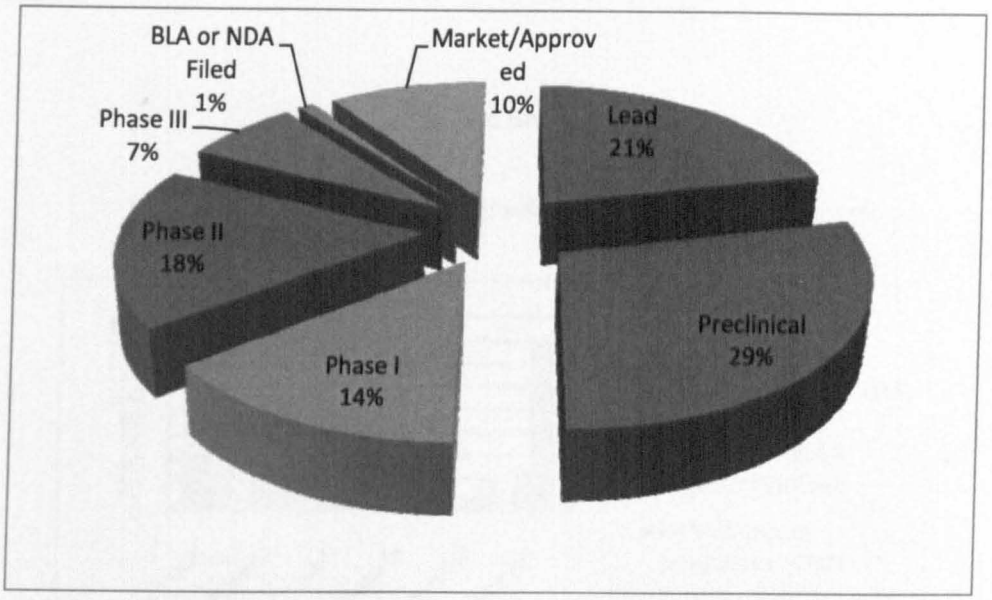


Chart 14 Stages of marketed drugs and drugs candidates (percentage)



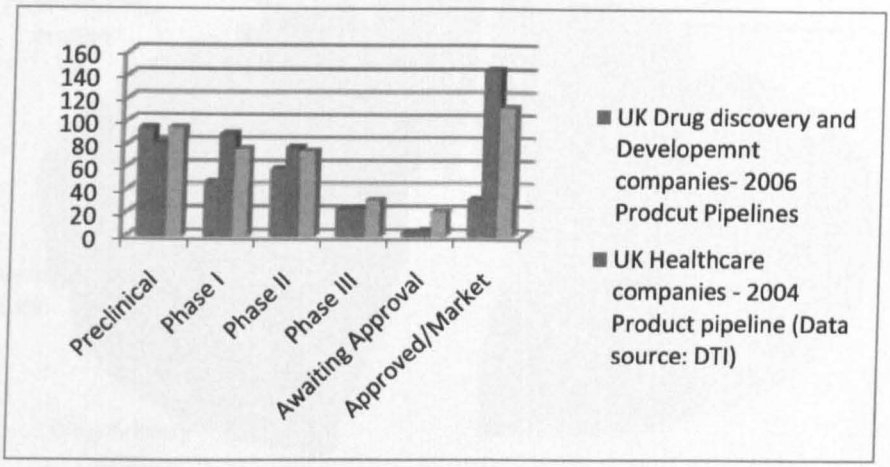
DTI's 2003/2004 report on the UK biotechnology sectors also collected stage information[7]. The DTI's report studied 350 companies, including service and technology providers. Because the methodologies were different, these two studies could be only roughly compared (Chart 15). The result of comparison indicated that the drug discovery and development subsector played a very important role in preclinical, Phase I, Phase II and Phase III development. However, their approved drugs and marketed drugs only accounted for a small fraction of the whole healthcare industry. This is mainly because many drug candidates development is moved to larger pharmaceutical companies which are able to continue the expensive and time-consuming process of late stage development. Therefore, R&D activity of a drug discovery and development company should be measured by a range of indicators, which could give a more comprehensive view of their activity

[7] Comparative Statistics for the UK, European and US Biotechnology Sectors –Analysis Years 2003 & 2004

and productivity, e.g. in the next two chapters, scientific publication and patents data will be discussed.

Chart 15 Stages of drug development

Drug discovery and development subsector vs. healthcare industry

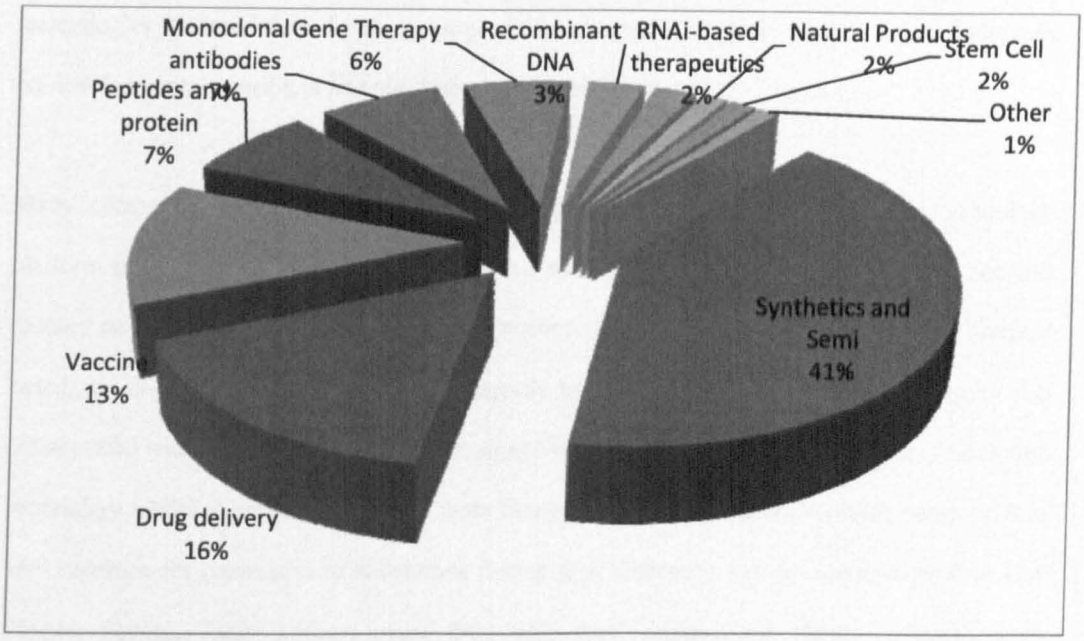


4.3.4.Technologies

The technologies used in discovering and developing drugs included synthetics, semi synthetics, drug delivery, vaccine, peptides and protein, monoclonal antibodies, gene therapy, recombinant DNA, RNAi-based therapeutic, natural products, and stem cell. 142 drug candidates were synthesized or semi synthesized (i.e. based on chemistry), and this accounting for 41 per cent of all drug candidates. Drug delivery and vaccine accounted for 16 per cent and 13 per cent respectively. Major technologies which were used to discover and develop biological therapeutics included peptides and proteins (seven per cent), monoclonal antibodies (seven per cent), gene therapy (six

per cent) and recombinant DNA (three per cent) – these accounted for a total of 23 per cent. Based on the study of agreements, these technologies were also major areas concerned in alliances.

Chart 16 Technologies of marketed drugs and drugs candidates



50 per cent of the technologies used by drug candidates in lead and preclinical phase were using chemical technology, 37 per cent were biotechnology, seven per cent were drug delivery and six per cent were other technology, such as natural products. In phase I and phase II, the chemical technology accounted for 40 per cent, biotechnology accounted for 39 per cent, and drug delivery increased to 17 per cent. In phase III, chemical technology accounted for 48 per cent, biotechnology dropped to 22 per cent, and drug delivery increased to 26 per cent. Among the approved and marketed drugs, chemical technology only accounted for 16 per cent, 22 per cent were biotechnology, and drug delivery increased to 62 per cent. Biotechnology mainly appeared in the early stage development. The approved and marketed drug delivery products were mainly developed by Vectura and Skyepharma.

4.3.5.Formation of product pipelines

Drug discovery and development is a long term process and involves many actors and different technologies. To build their development portfolio, companies may rely on their original research, co-development, licensing in and out, and acquisitions.

Many companies began to build their product pipelines by exploring their own technology platform and expertise. For example, Oxagen is a company that was established in 1997, and was focused on identifying drug targets through genetics. In 2003, it began to build its own pipelines based on G-protein coupled receptors program to treat inflammatory disease. Oxagen also collaborated with other companies: Oxagen signed agreements with DanioLabs to use DanioLabs' proprietary model to screen compounds from Oxagen's G-protein coupled receptor program. It is very common for companies to collaborate during drug discovery and development process (see Chapter Seven). Their partners come from both local regions and abroad, included large pharmaceutical companies, universities, public institutes, and small to medium sized companies.

Licensing in and out is also very important for the drug discovery and development process. Cyclacel's drug candidate CYC 381 was in-licensed from the American company Lorus Therapeutics, and Lorus will receive an upfront fee, milestones and royalties on product sales. Similarly, it is also very common for drug discovery and development companies to license out their patents.

Acquisition is another way to expand a product pipeline. For example, Antisoma's drug candidate AS1411 was in clinical trials to treat cancers. It was originally developed by Dr Paula Bates, Dr John Trent and Prof. Donald Miller at the University of Alabama and then at the University of Louisville, and formally named AGRO100. AGRO100 entered clinical trials in Aptamera Inc.,

which was founded by these three researchers. Then it became one of Antisoma's product pipelines when Aptamera were acquired by Antisoma in February 2005, and renamed as AS1411.

The building of product pipelines is therefore based on the accumulation of science and technology. Various actors have contributed to the knowledge generation, transfer and diffusion process.

4.4. R&D investment

According to the Department for Innovation, Universities and Skills' 2006 report, the pharmaceutical and biotechnology industry was the largest investor in R&D compared with any other industry, and the top two were large pharmaceutical companies: GlaxoSmithKline and AstraZeneca. 83 per cent of total UK R&D investment was conducted by the top 100 companies[8]. 20 out of the top 100 UK R&D investors were pharmaceutical and biotechnology companies and five of these 20 companies were from the drug discovery and development subsector described here: Shire, Cambridge Antibody, Acambis, Vernalis and SkyePharma.

To picture the activities of this subsector's R&D, investment and sale information were collected from database of Department for Innovation, Universities and Skills (www.innovation.gov.uk). Information from 35 drug discovery and development companies was collected from this database. Information of the two largest pharmaceutical R&D inventors GlaxoSmithKline and AstraZeneca was also recorded and used as benchmarks.

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[8] http://www.innovation.gov.uk/rd_scoreboard/default.asp?p=3

4.4.1.R&D investment (1995 -2006)

The pharmaceutical and biotechnology industry is the largest R&D Investor. The total investment of "the top 15 companies of R&D investment" of this industry grew fast between 1995 and 2006 (Chart 17). The investment in 2006 was double the investment in 1998. The average annual investment growth rate was 8 per cent between 1995 and 2006.

Between 1995 and 1998, R&D investment increased steadily, followed by a dramatic increase between 1998 and 2002. Between 2002 and 2003, the R&D investment dropped back slightly, then increased steadily until 2006. Between 1995 and 1998, the average annual investment growth rate was 7 per cent. During the fast growing period 1998 and 2002, average annual investment growth rate was 16 per cent. Between 2002 and 2006, the average annual investment growth rate dropped to 2 per cent.

Chart 17 Total R&D investment of the top 15 UK pharmaceutical and biotechnology companies (£M)

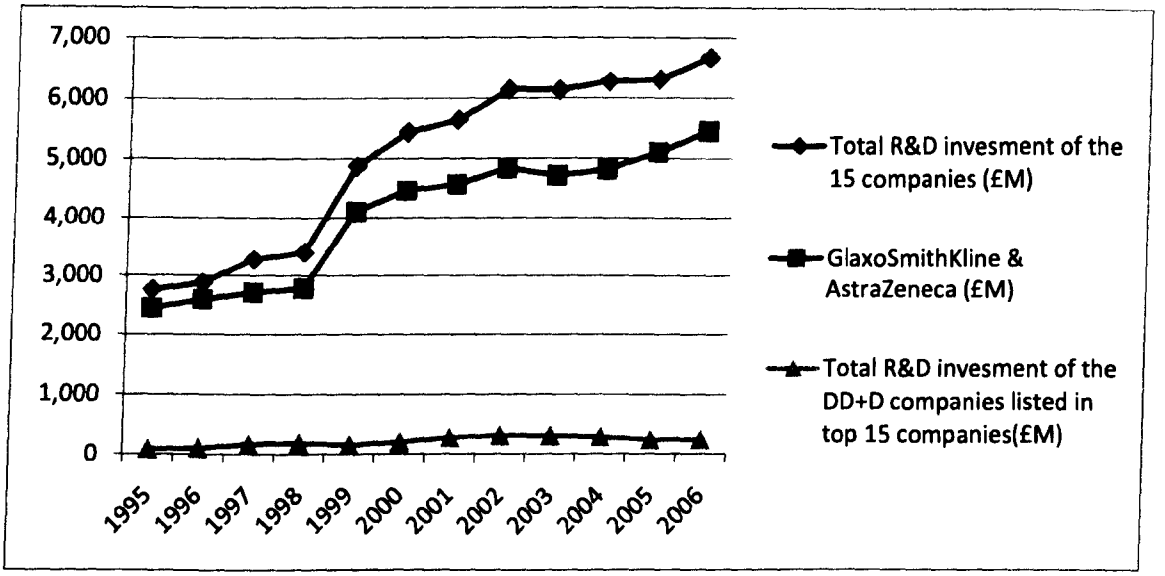
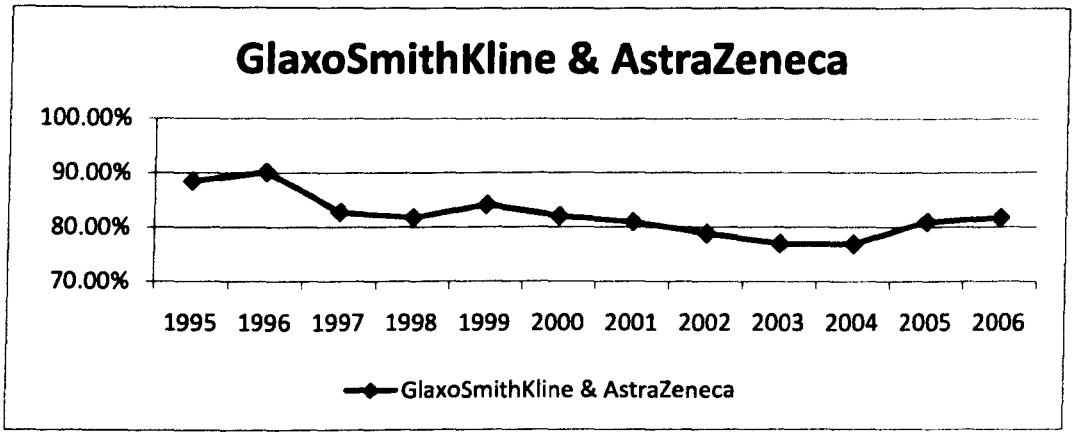


Chart 18 GlaxoSmithKline & AstraZeneca

(Total investment of the top 15 companies is 100 per cent)



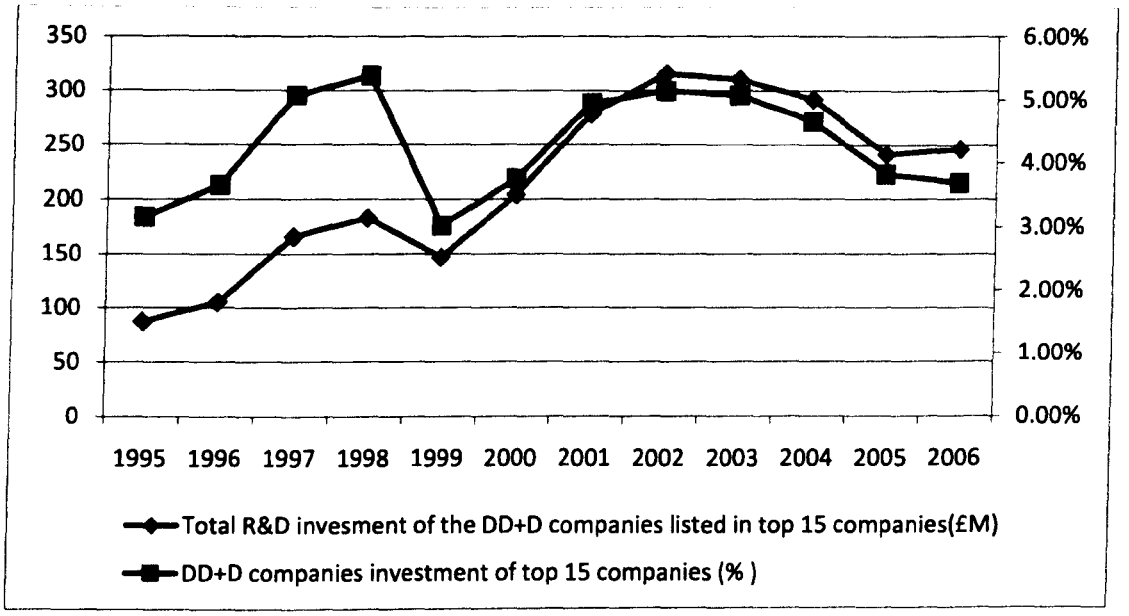
The R&D investment of the pharmaceutical and biotechnology industry were dominated by GlaxoSmithKline and AstraZeneca[9] (Chart 17 & 18). As the largest R&D investors in the UK, they accounted for 90 per cent of total R&D investment of the "top 15 UK pharmaceutical and biotechnology companies invested in R&D" in 1996 and this number was 82 per cent in 2006.

Although the drug discovery and development companies listed in the "top 15 UK pharmaceutical and biotechnology companies invested in R&D", only accounted for less than 6 per cent of the total 15 companies' investment, this group of companies on average spent 215 million pounds in R&D every year (Chart 19). The continuously heavy R&D investment produced large number of patents and drug candidates.

[9] GlaxoSmithKline's investment between 1995 and 1999 were calculated by adding up investment of Glaxo Wellcome and SmithKline Beecham. AstraZeneca's investment between 1995 and 1997 were calculated by adding up investment of Zeneca and Astra Pharmaceuticals.

Chart 19 Top drug discovery and development companies of R&D investment

(Total investment of the top 15 companies is 100 per cent)



The drug discovery and development companies listed in the "top 15 UK pharmaceutical and biotechnology companies invested in R&D" are a group of the most successful companies of this subsector. 1999 and 2002 were two important years of R&D investments. In 1999, the total investment of this group of companies declined by 20 per cent, around 36 million pounds. The company's highest rank in R&D investment was 10, which was the least performance between 1995 and 2006, and four companies entered the top 15 (Chart 20 & 21). However, the whole industry R&D experienced a dramatic increase by 43 per cent in 1999. This was mainly contributed by AstraZeneca. It is important to notice that Shire ranked 4th in R&D investment of the UK pharmaceutical and biotechnology industry, and 17th of R&D investment of all UK companies. This indicated that this subsector is highly R&D intensive, and building R&D advantage is an important strategy of this industry.

Chart 20 Drug discovery and development company's highest rank in R&D investment

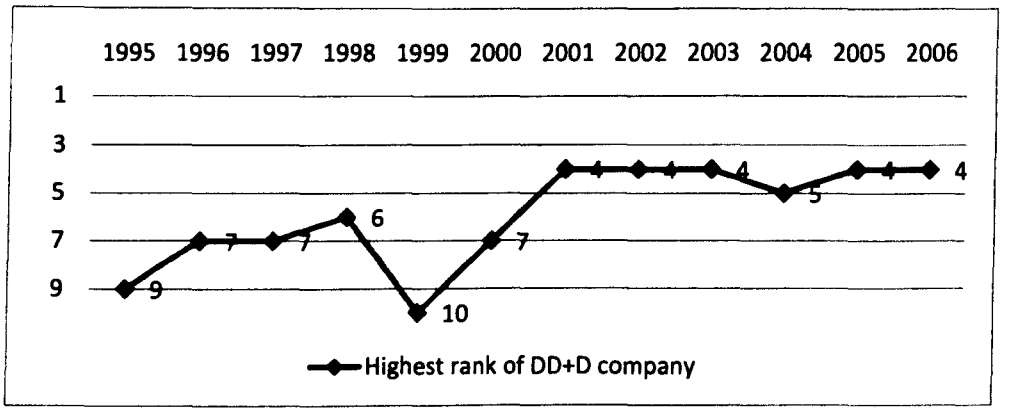
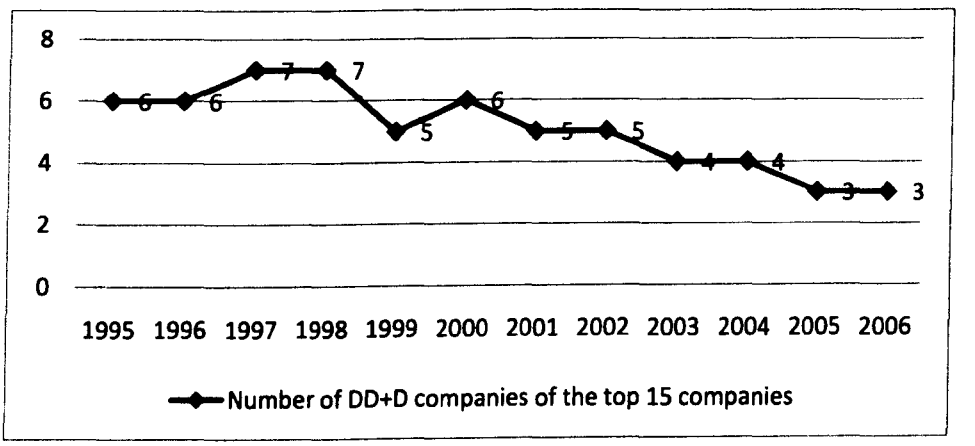


Chart 21Number of drug discovery and development companies listed in the top 15 companies in R&D investment



The number of drug discovery and development companies listed in the top 15 did not increase since 2000(Chart 21). This was mainly due to the expanding and the consolidation of this industry. The highest rank of companies maintained at fourth and fifth after 2000.

Year 2002 was another turning point. The R&D investments of this group of companies increased in 2000 and then decreased since 2003. This was mainly due to the merger and acquisition within

this industry. Oxford Glycosciences, the third largest R&D investment company within the drug discovery and development subsector in 2002, were acquired by Celltech in 2003. However, the total R&D investment of Celltech in 2003 did not increase compared with the total investment of Oxford Glycosciences and Celltech in 2002. Celltech, the second largest R&D investment company of the drug discovery and development subsector in 2004, was later acquired by the Belgium company UCB, and changed its name to Celltech R&D in 2005. The R&D investment of Celltech dropped from 95.7 million pounds in 2002 to 52.6 million pounds in 2006.

Powderject, the fourth largest R&D investment company of the drug discovery and development subsector in 2002, was acquired by the American company Chiron in 2003. The R&D investment of Powderject, was later added to Chiron's R&D investment, but did not show in this indicator. Similarly, Cambridge Antibody Technology, the second largest R&D investment company of the drug discovery and development subsector in 2005, was acquired by AstraZeneca in 2006, and its R&D investment was added to AstraZeneca.

The historic record of R&D investment of this subsector suggests that although this subsector had several successful stories, the whole subsector was still immature. Companies survived from R&D investment shortage in 1999, experienced consolidation within the subsector and a short time growth. Then their output was harvested by large pharmaceutical companies via acquisition.

4.4.2.R&D Intensity

R&D intensity is defined as the ratio of expenditures by a firm on research and development to the firm's sales[10]. The pharmaceutical and biotechnology industry is an R&D intensive industry, and the drug discovery and development subsector is characterized by exceptionally high R&D intensity.

According to the Department for Innovation, Universities and Skills' 2006 report, the R&D intensity of the UK top 850 R&D investment companies was 1.8 per cent. The R&D intensity of the UK top 114 pharmaceutical and biotechnology companies was 15.2 per cent, and the median was 31.6 per cent. The average R&D intensity of the top 15 pharmaceutical and biotechnology companies was 36 per cent in 2006.

The average R&D intensity of the UK top 29 drug discovery and development companies was 1321 per cent in 2006, and this large number was due to several low sale companies. The median value of R&D intensity of these 29 companies was 141 per cent. Only one company's R&D intensity was lower than the 15.2 per cent average of the industry. Only 5 out of 29 companies' R&D intensity was lower than 40 per cent.

4.5. Summary

This chapter discussed the pharmaceutical and biotechnological industry and introduces the context where the drug discovery and development sector is positioned. The UK pharmaceutical and biotechnology industry is dominated by a few large international companies. The largest pharmaceutical companies accounted for two thirds of total UK market sales, and large American

[10] http://economics.about.com/od/economicsglossary/g/randin.htm

companies, in particular, accounted for almost one third of the total UK market sales, followed by the large British biotech companies, which accounted for 14 per cent of the total UK market sales. Therefore, the drug discovery and development companies are positioned in an industry with fierce competition from both foreign and domestic large pharmaceutical companies.

Through analyzing a set of descriptive data, i.e. locations, number of staff, products and services, and company ages, a picture of small to medium sized companies of the UK biotechnology industry was mapped. This chapter found that the growth of the UK biotechnology industry, in terms of number of firms, was due to certain products and services in the sector: equipment and reagents, drug discovery and development, and support services. These companies were mainly located in southern England, and most were established after 1990. From the 1980s until now, the numbers of surviving drug discovery and development companies and support services companies has been growing faster than other sectors. The data on the UK pharmaceutical and biotechnology industry collected in this study is similar in results to that of DTI's report of the UK pharmaceutical and biotechnology industry. This thesis also suggested a similar pattern to the DTI's report, in terms of products and services, age group and locations.

One finding is that Cambridgeshire and London not only have the largest number of drug discovery and development companies, but also have the largest support service companies. This may indicate that the local supply sector and discovery/ development sector collaborate closely with each other. Interestingly, companies which are clustering in Cambridge and London are also the active players of global connection, in terms of international expansion and acquisition. Firms that survive and mature either establish operations outside the UK or acquired foreign companies. Only a small minority of firms retain a pure UK focus. The main reason for this is the importance of international markets, in particular, the need to have an operational base in the US.

Newly established pharmaceutical and biotechnology companies indicated more concentrated pattern in locations such as Cambridgeshire, London and Oxfordshire. The result of clustering is

different from Cooke's research (Cooke, 2001) which suggested that Cambridgeshire, Oxfordshire and Surrey were the clusters of newly established biotechnology companies. The main reason for the difference is that this thesis extended the research time window, and obtained more information on newly established companies. After the year 2000, more firms were established in London than in Surrey. Spending on biotechnology related research in London is estimated to be £300 million per annum, which is the largest in the UK (DTI 2003).

The new findings of this chapter are about the product pipelines of the drug discovery and development subsector, which has not been studied by other researchers before. There are several important features of the product pipelines of this subsector. Firstly, the drug discovery and development subsector has played a very important role in constructing product pipelines, in particular, in the early stages of drug discovery and development. The output of drug candidates was concentrated in well established firms. Late stage product development was also controlled by a small number of companies. Secondly, the major indications of marketed drugs and drugs candidates were cancer and central nervous system diseases, followed by infection and immune-mediated inflammatory diseases. These results are similar to the findings of alliances studies in Chapter Seven. Thirdly, chemical technologies, e.g. synthetics and semi-synthetics dominated the technologies in use for the creation of products, followed by biologicals (vaccine, peptides and protein, monoclonal antibodies, gene therapy and recombinant DNA). Biologicals were mainly in early stage development. One important finding was that although chemical technologies were the most important technology in lead, preclinical, phase I, phase II, and phase III, drug delivery technologies were the most important technologies among approved and marketed drugs. These drug delivery products were mainly developed by two companies: Vectura and Skyepharma. Moreover, companies may rely on different sources of knowledge to build their development portfolio, e.g. their own original research, co-development with other companies or institutes, licensing in and out, and acquisitions. The pipeline indications are similar to the large pharmaceutical companies, which also suggested the influence of large pharmaceutical companies on this sector, as the most important clients and investors.

There are several findings of R&D investment: firstly, the pharmaceutical and biotechnology industry invested heavily in R&D. The pharmaceutical and biotechnology industry is the UK's largest R&D investor. GlaxoSmithKline and AstraZeneca dominated over 80 per cent of all R&D investments in the pharmaceutical and biotechnology industry. The drug discovery and development subsector only accounted for a small fraction of total R&D investment. However, compared with other companies of the pharmaceutical and biotechnology industry, this subsector is highly R&D intensive. Secondly, the product pipelines and R&D investment of the UK drug discovery and development companies are hierarchically distributed among firms. The top drug discovery and development companies ranked very high in terms of R&D investments of the pharmaceutical and biotechnology industry. The heavy investment of this subsector produced a large number of patents and drug candidates.

The exceptionally intensive investment was a risk for the long term business development. Many companies invested more than 80 per cent of their sales into R&D. This continuous, exceptionally intensive investment produced large numbers of patents and drug candidates, but also produced high risks for long term business development. Exceptionally high R&D intensity could be a possibly explain why some of the most productive companies were easily harvested by large pharmaceutical companies and other foreign companies.

Policy implications

This subsector was highly influenced by other actors in the system, e.g. large pharmaceutical companies (indication) and support subsector (clustering). As shown in this chapter, this subsector is very R&D intensive. R&D investment is the driving force of development, but also a restraint of many companies. Both well established firms and young small firms in the drug discovery and development subsector face intense competition from local clusters of firms and international rivals.

In Europe INNOVA Workpackage Nine, Cleff et al. suggested that the most important financial barrier for innovation is that lack of finance support, and the next two most important financial barriers are high innovation cost and economics risk (Cleff et al. 2008). 45 per cent of the biotechnology firms are influenced by shortage of finance support, 28 per cent of companies have problems of innovation because of high cost and 22 per cent of companies have problems with predicting and handling innovation uncertainties and risk (Cleff et al. 2008). For small startups, their major problems are how to survive in local clusters while attracting investors to finance their product pipelines. For large and well established firms the major problems are how to quickly develop and market new products while minimizing the financial risk.

The main challenge for policy is how to support small companies which will help in creating a large number of jobs, and at the same time how to support established companies which will help enforce the leading status of UK drug discovery and development.

Chapter Five: Knowledge Generation: Scientific Publications

5.1. Introduction

Publication and citation analysis has been widely used by scholars to measure innovation performance (Cordero 1990). This chapter aims to analyse and discuss the knowledge generation of the drug discovery and development subsector using bibliometric data. As discussed in the Chapter Three, scientific publications and citations were examined to describe this subsector's contribution to knowledge generation.

The first section will focus on analysing the drug discovery and development subsector's publications of articles, reviews and letters. In addition to examine productivity, subject of publications, location of authors, source of publications and sources of references are also analysed, giving more details about their regional performance and global cooperation. The second section will analyse citations, paying attention to the impact of scientific research. The final sections will discuss and summarise the findings of the bibliometric study.

5.2. SCI Publications

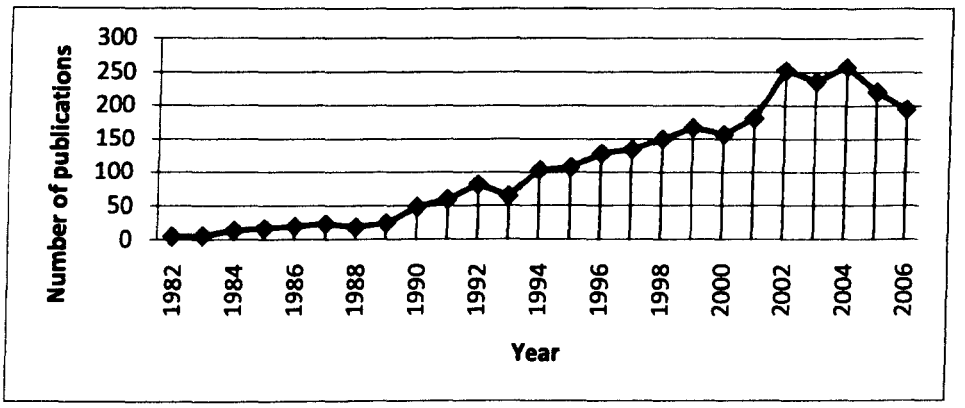
5.2.1.Productivity

In this study, 2663 SCI papers published by 81 British origin companies between 1982 and 2006 were collected and analysed. The first publication collected in this project was dated 1982.

In the 25 years between 1982 and 2006, 106.52 papers were published each year on average. As shown in Chart 22, only four papers were published in 1982. During the 1980s, the number of publications grew slowly, but steadily. Although the number of publications declined in 1993, overall it grew faster in the 1990s than in the 1980s. After 2000, the number of publications saw a dramatic accelerating growth, followed by turbulence in 2003 and 2004, then continuously declined from 2005 to 2006. The number of papers published in 2006 was only slightly higher than the number of papers published in 2001.

One explanation for this decline is that since 2000 this industry experienced consolidation and restructuring, and some companies which had published large number of papers almost went out business, e.g. PPL. Another reason is that some of the most productive companies slowed down their rate of publications, e.g. Xenova, published 13 papers in 2002, 10 papers in 2003, and 18 papers in 2004, but only published 4 papers in 2005 and 3 papers in 2006 after being acquired by Celtic Pharma Development (BERMUDA) in 2005. It therefore appears that industry structure and stability have a significant impact on publications output. The companies' strategy was also an important factor, which may lead firms to switch from publications to other activities.

Chart 22 Scientific publications between 1982 and 2006



Webster studied UK biomedical publications between 1989 and 2000. 355,188 articles, reviews and notes published in biomedical journals were generated from Research Output Database[11] (Webster 2005). UK authors published 24,141 papers in 1989 to 33,972 in 2000, at an average growth rate of 2.3 per cent each year (Webster 2005). Roughly comparing Webster's research with this project yields an interesting result: although drug discovery and development companies' publications only accounted for as little as 0.1 per cent of the total UK biomedical papers in 1989, and 0.5 per cent in 2000, the average annual growth rate was as high as 18.4 per cent[12]. It suggested that the publishing ability of this subsector was improved significantly, and this subsector played an increasing role in biomedical knowledge production.

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[11] The Research Output Database yield more publications than SCI in Webster's research, this mainly due to the searching and selecting criteria (Webster 2005).

[12] The formula used in this project to calculate average annual growth rate is $\alpha = \left(\sqrt[(Y_t - Y_0)]{\frac{N_t}{N_0}} - 1 \right) \times 100$,
N is number of publications, and Y is year. This formula is different from the Webster's. If using this formula, the average annual growth rate of UK biomedical publications would be 3.2 per cent, higher than 2.3 per cent in Webster's research.

The average publication per company was 32.8. The companies' performances were very different: the largest number of individual company' publication was as many as 794 papers, while some companies did not publish any. Therefore companies were grouped according to the number of their publications (this group is different from group in chapter eight). As shown in Chart 23, three drug discovery and development companies (four per cent) published more than 100 papers between 1982 and 2006 (Group one), and their publications accounted for over half of total publications; nine companies (11 per cent) published less than 100, but more than 50 papers (Group two), and their publications accounted for around one quarter of total publications; 25 companies (31 per cent) published less than 50, but more than ten papers (Group three), and their publications accounted for one fifth of total publications; 30 companies (37 per cent) published no more than ten papers (Group four), and their publications accounted for less than one twentieth of total publications; and 14 companies (17 per cent) did not publish any article, review or letter (Group five). Comparing this with the data on biotechnology cluster of Scandinavia – Medicon Valley, where 63 out of 109 companies (58 per cent) had published paper (Coenen, Moodysson, & Asheim 2004), the British drug discovery and development companies appear to be more active in publishing.

It is notable that 15 per cent of companies published around three fourths of total publications output. Celltech[13], which was at the top of the hierarchy, published the largest number of papers of all companies: 794 papers, which accounted for 30 per cent of the total. Vernalis[14] (formerly

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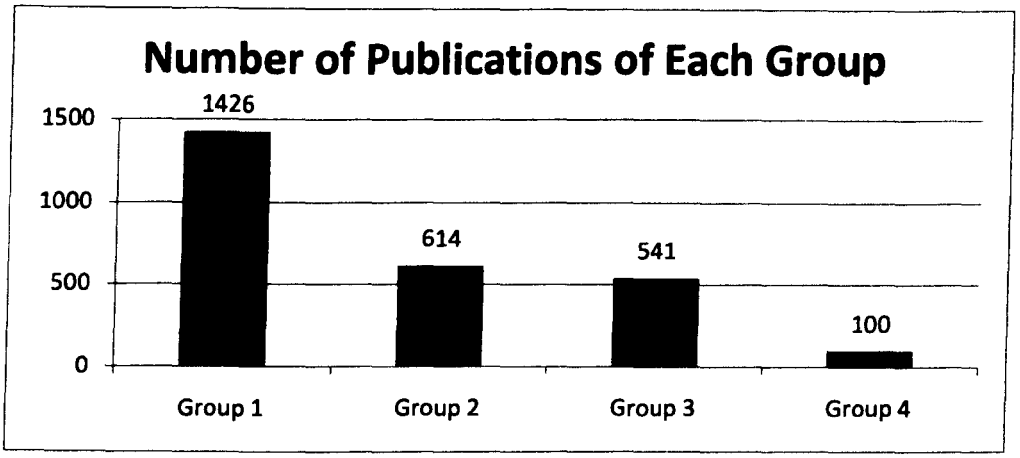
[13] In 1999, Celltech acquired Chiroscience (UK) and then merged with Medeva (UK); in 2000, Celltech acquried Cistron Biotechnology (USA) and in 2003, Celltech acquired Oxford Glycosciences (UK). Celltech was acquired by UCB (Belgium) in 2005. Data presented here included papers published by Celltech and other three British origin companies Chiroscience, Medeva and Oxford Glycosciences.

[14] In 2003, Vernalis mergered with British Biotech (UK), which merged with RiboTargets (UK) earlier in 2003; then Vernalis acquired Ionix Pharmaceuticals (UK) and Cita NeuroPharmaceuticals (Canada) in 2005. Data presented here included papers published by Vernalis, British Biotech, RiboTargets and Ionix Pharmaceuticals. It is important to notice that over 70 per cent papers published by this group were published by British Biotech.

British Biotech) published the second largest number of papers: 451 papers, which accounted for 17 percent of all publications. Therefore just two firms accounted for nearly half of all publications.

Chart 23 Publications of Different Group



To evaluate the productivity of the drug discovery and development subsector, results from another study were compared with this research. McMillan and Hamilton investigated the bibliometric data of US pharmaceutical companies between 1981 and 1993, and found that the average number of publications per company was 2653 papers (McMillan & Hamilton 2000). These companies included some of the largest pharmaceutical companies in the word, Abbott Laboratories, American Home Products Corporation, Bristol-Myers Squibb Corporation, Johnson & Johnson, Eli Lilly and Company, Merck & Co., Inc., Pfizer Inc., Schering–Plough Corporation, Smithkline Beecham Group PLC, Syntex Corporation, the Upjohn, and Warner–Lambert. The reason they chose this period was that "it was one of the industry's most profitable (period) and pharmaceuticals were one of the most profitable industries in the US overall" (McMillan & Hamilton 2000,p.467). During the same period, Celltech [15], a newly established British biotechnology company, published 298 papers between 1982 and 1993 (all types of scientific

[15] Different from footnote 4, only Celltech were considered here.

publication are considered in order to be consistent with McMillan & Hamilton's study), representing 11 per cent of the average number of papers published by these well-established US pharmaceutical companies.

Based on another study, between 1996 and 2000, the top two British Universities in publishing biotechnology paper were the University of Cambridge and the University of Oxford. The average publication (articles, notes and reviews) per year between 1996 and 2000 were both 536 (Patel 2003a). The top three British companies in publishing biotechnology papers were Glaxo Wellcome Plc, Smithkline Beecham Plc and Astrazeneca. Their average publications (articles, notes and reviews) per year between 1996 and 2000 were 72, 53 and 47 respectively (Patel 2003a). The most productive drug discovery and development company, Celltech, on average published 50 papers per year between 1996 and 2000. This number was only one tenth of the University of Cambridge and University of Oxford, but is similar to a large pharmaceutical company. This result indicated the strong research contribution of the biotechnology sector. One possible reason for this was the close connection between the drug discovery and development subsector and public institutions, with a significant number of papers involving academic co-publishing.

In terms of publication number, a small group of the most productive companies published the majority of papers. They played a very important role in contributing to the output of the drug discovery and development subsector. One reason for this phenomenon was that Celltech was established in 1980, and British Biotech (now part of Vernalis) was established in 1986, therefore accumulating publications during their long period of operation. However, this single reason could not explain why these two companies were far more productive than other companies established in the 1980s. Many other factors may also influence the number of publications: company strategy, product and service, and connections with public research institutions.

Interestingly, 14 out of the top 15 most productive companies had been involved in mergers and acquisitions, and 13 out of these 14 companies had been involved in international merger and

acquisitions before 2006. The connection between productivity and merger and acquisition activity will be discussed in the Alliances Chapter.

5.2.2. Subject of Publications

From the database of 2663 publications, 10855 keywords were generated. After analysing the frequency of keywords in the database, 30 keywords which appeared most frequently were listed in Table 12.

Cancer, immune diseases and immune mediated inflammation, and infectious diseases were studied most. Important research areas included protein expression and purification, cells, monoclonal antibodies, molecular structure and binding, gene cloning and expression, and drug design. It is notable that most of these terms are associated with biotechnology and molecular biology rather than synthetic chemistry. Therefore, the major subjects included genetics, oncology, immunology and immune mediated inflammation, infection, molecular biology and biochemistry.

Webster's research on overall UK and world biomedical publications suggested that the sub-fields with the most number of papers published by UK authors were infectious diseases, genetics, endocrinology and oncology; and the worldwide research had the same trend (Webster 2005). Because the molecular biology and biochemistry publications were categorized into other sub-fields in Webster's biomedical classification, the results indicated that the biotechnology companies have very similar research fields when compared to public institutions, and further suggested their roles as "key 'makers' as well as 'takers' of local and global (knowledge) spillovers" (Cooke 2006).

In other words, the drug discovery and development subsector followed a similar research direction as public institutes, and played the roles of both learner and inventors at the same time.

Table 12 Keywords frequency in scientific publications

Keyword	Count	Keyword	Count
EXPRESSION	282	GENE	68
PROTEIN	164	TUMOR-NECROSIS-FACTOR	65
CELLS	141	THERAPY	55
MONOCLONAL-ANTIBODY	119	ANTIGEN	54
ACTIVATION	108	IMMUNIZATION	53
IDENTIFICATION	101	PURIFICATION	52
CRYSTAL-STRUCTURE	99	ANTIBODY	49
CANCER	93	DRUG DESIGN	49
MICE	93	CLONING	48
ESCHERICHIA-COLI	91	DESIGN	45
IN-VITRO	91	IMMUNOTHERAPY	45
BINDING	90	RESPONSES	45
IN-VIVO	84	T-CELLS	43
INHIBITORS	73	MATRIX METALLOPROTEINASES	42
RECEPTOR	72	INFECTION	41

5.2.3.Location of Authors

Authors in 47 countries and regions co-published papers with the UK drug discovery and development subsector. The total number of papers co-published with authors from foreign countries was 1271, accounted for 47.8 per cent of total publications. It indicated a close connection between the UK drug discovery and development subsector and researchers in foreign countries. In particular, US authors contributed to 21 per cent of total publications; followed by authors from Germany, Netherlands, France and Switzerland (Table 13). These countries all contributed two to three per cent of total publications. This study revealed similar results as

Webster's research, with the UK's leading partner in publication being the US, followed by EU countries (Webster 2005).

Table 13 Countries of Co-authors

	Number of co-publishing papers	Percentage of total publications
US	561	21.1
GERMANY	81	3.0
NETHERLANDS	72	2.7
FRANCE	69	2.6
SWITZERLAND	54	2.0
ITALY	52	2.0
AUSTRALIA	46	1.7
CANADA	44	1.7
SPAIN	32	1.2
BELGIUM	29	1.1
JAPAN	25	0.9
DENMARK	21	0.8
NEW ZEALAND	20	0.8
IRELAND	18	0.7
AUSTRIA	15	0.6

Based on bibliometric analysis of the top ten journals contained in the SCI database, the overall picture of bioscience research showed a similar result: the US dominated the research publication collaboration with UK (Cooke 2006). Cooke argued that the five US "metacentres" were at the top of the co-publishing hierarchy, they were Boston, Cambridge (US), New York, San Francisco and San Diego; London, Cambridge (UK) and Stockholm were at the next level; followed by Oxford, Lund and Uppsala (Cooke 2006). In his study, London, Cambridge and Oxford were the "metacentres" of co-publishing within the UK. The results of earlier chapter have showed that London, Cambridge and Oxford have the largest number of drug discovery and development companies. The clustering in these three places is a possible reason for the attracting foreign researchers to co-publish papers with the local drug discovery and development subsector.

The study of UK authors also showed a concentration of publishing in southeast England. In this study, each author's address was taken as one count of contribution.[16] Within the UK, 90 per cent of the authors' addresses were located in England, nine per cent in Scotland, and only one per cent in Wales (Chart 24). In England, 20 per cent of addresses were from Cambridge and Oxford respectively, and 19 per cent were from London, giving a total of nearly 60 per cent for these three areas (Chart 25).

Chart 24 Number of authors contributed to publications (UK)

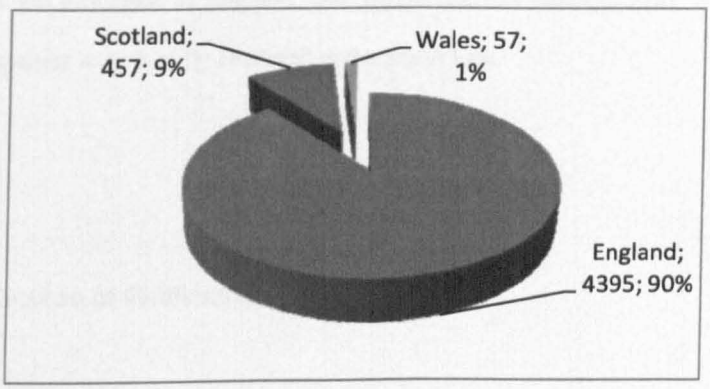
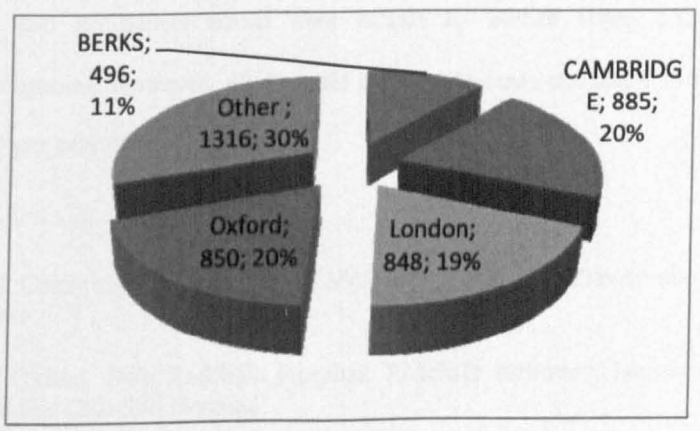


Chart 25 Contributions of different region in England



[16] Suppose co-authors contributed equally in publishing.

However, the pattern of industry publication is different from the publications of public research institutes. In Webster's study, public research institutes and Universities in London published 36 per cent of UK total biomedical publications, Cambridge and Oxford published around 5 per cent each (Webster 2005) giving a total of 45 percent for these three areas. The difference was probably due to the large number of leading research institute in London. There are four leading public research institutes in Cambridge[17] and five leading public research institutes in Oxford[18], but only in London West and West Central area, the number of public institutes is as many as 14[19] (Webster 2005). However, both Webster's research and this study indicate that the publishing was highly concentrated in the Southeast of England. One reason for this concentration was that the most productive companies were heavily clustered in the South East.

5.2.4.Source of Publications

The 2663 articles, reviews and letters were published in 718 journals. 670 out of 718 journals published less than ten papers which were written by British origin drug discovery and development companies. However, 48 journals (seven per cent) published 1104 papers, which accounted for 41 per cent of total publications.

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[17] University of Cambridge, Laboratory of Molecular Biology, Addenbrooke's Hospital and Babraham Institute

[18] University of Oxford, John Radcliffe Hospital, Radcliffe Infirmary, laboratories of Medical Research Council and Churchill Hospital

[19] University College London, London School of Hygiene and Tropical Medicine, Imperial Cancer Research Fund, Institute of Child Health, King's College, Institute of Neurology, Great Ormond Street Hospital, National Hospital of Neurology and Neurosurgery, Birkbeck College, Hammersmith Hospital/Royal Postgraduate Medical School, St Mary's Hospital, Charing Cross Hospital, University College and Middlesex School of Medicine, and Imperial College of Science, Technology and Medicine.

The top ten journals which published most of the drug discovery and development subsector's papers were *Bioorganic & Medicinal Chemistry Letters* (78, 2.9 per cent), *VACCINE*(53, 2.0 per cent), *Journal of Biological Chemistry* (52, 2.0 per cent), *Tetrahedron Letters* (47, 1.8 per cent), *The Journal of Immunology* (41, 1.5 per cent), *Biochemical Journal* (37, 1.4 per cent), *Journal of Medicinal Chemistry* (37, 1.4 per cent), *Cancer Research* (35, 1.3 per cent), *British Journal of Cancer* (31, 1.2 per cent) *and British Journal of Pharmacology* (31, 1.2 per cent).

As shown in Table 14, eight of the top 15 journals which published most of the subsector's papers are chemistry or biochemistry related. The focus of the other six journals included vaccine, immunology, biology, pharmacology and cancer. One of these covered all scientific disciplines (*Nature*). Therefore, in terms of subjects of journals, chemistry and biochemistry slightly outweighed the biotechnological research. Given the keyword findings, this suggests that the majority of publications were focused on molecular biology and biotechnology, but were published in chemistry and biochemistry journals. This provides a useful insight into the type of knowledge produced by these firms.

Table 14 Publications on Each Journal (Top 15)

Journal	Subject	Country	Articles	Total Cites	Number of papers (this study)
Bioorganic & Medicinal Chemistry Letters	Interface of chemistry and biology	ENGLAND	1264	16692	78
VACCINE	Vaccines and vaccination	ENGLAND	928	15193	53
Journal of Biological Chemistry	Biochemistry and molecular biology	UNITED STATES	4336	410903	52
Tetrahedron Letters	Organic chemistry	ENGLAND	1989	68926	47
The Journal of Immunology	Immunology	UNITED STATES	1846	117464	41
Biochemical Journal	Biochemistry and cellular and molecular biology	ENGLAND	529	47296	37
Journal of Medicinal Chemistry	Chemical-biological relationships, mainly the bond between molecular structure and biological activity	UNITED STATES	864	38868	37
Cancer Research	Cancer	UNITED STATES	1493	112911	35

British Journal of Cancer	Cancer	ENGLAND	541	28295	31
British Journal of Pharmacology	General pharmacology	ENGLAND	379	22441	31
Journal of Molecular Biology	Organisms or their components at the molecular level	UNITED STATES	981	64356	29
Drug Discovery Today	Drug discovery associated technologies, the management, commercial and regulatory issues	ENGLAND	129	4122	27
Journal of Computer-Aided Molecular Design	Chemistry and Materials Science	NETHERLANDS	50	2437	27
NATURE	All disciplines of science	ENGLAND	962	390690	27
Nucleic Acids Research	Physical, chemical, biochemical and biological aspects of nucleic acids and proteins involved in nucleic acid	ENGLAND	943	74972	26

According to the ISI Journal Citation Reports 2006, of the 15 journals, *Journal of Biological Chemistry*, *Tetrahedron Letters* and *The Journal of Immunology* published the largest total number of publications in 2006.

Nine out of the 15 journals are British Journals, five are American journals, and one is a Netherlands' journal. This indicates that the drug discovery and development subsector are more inclined to publish in British Journals.

5.2.5.Source of References

By analysing the pattern of citing reference and the source of references it is possible to understand the role of the drug discovery and development subsector played in knowledge flow. It will also map how the subsector's research has been influenced by existing research.

The 2663 papers citied 67434 references in total. The top three references are Laemmli's (1970) paper '*Cleavage of structural proteins during the assembly of the head of bacteriophage T4*' which was cited 98 times, Nobel Prize Winner Sanger's (1977) paper '*DNA sequencing with chain-terminating inhibitors*' which was cited 52 times, and Berman's (2000) paper '*The Protein Data Bank*' Which was cited 44 times.

These 67434 references were published in 8171 different journals or books. Table 15 lists the journals which were citied most. These top 15 out of 8171 journals (0.2 per cent) accounted for 40 per cent of total citations. The top 81 journals (one per cent) accounted for 76 per cent of total citations. Therefore, this citation pattern was highly hierarchical. Although these publications were cited widely, there were a small group of journals which have much greater impact than the rest of the journals. In other words, the one per cent most cited journals were the major knowledge base of the drug discovery and development subsector.

Table 15 Most cited Journals (Top 15)

Journal	Country	Time of citation
P NATL ACAD SCI USA	UNITED STATES	3552
J BIOL CHEM	UNITED STATES	3507
NATURE	ENGLAND	3225
SCIENCE	UNITED STATES	2226
J IMMUNOL	UNITED STATES	2075
CANCER RES	UNITED STATES	1606
CELL	UNITED STATES	1587
J MED CHEM	UNITED STATES	1519
J MOL BIOL	UNITED STATES	1459
BIOCHEMISTRY-US	UNITED STATES	1336
J EXP MED	UNITED STATES	1095
J VIROL	UNITED STATES	1063
J AM CHEM SOC	UNITED STATES	1001
NUCLEIC ACIDS RES	ENGLAND	978
EMBO J	UNITED STATES	812

Further investigation showed interesting a result: 13 out of the 15 top journals were American. As discussed earlier, when publishing their work, the drug discovery and development companies were inclined to choose British journals, followed by American journals. However, their references are mainly from American journals. Although this may not directly indicated a knowledge flow from American to the UK, because these journals are very internationalized, this phenomenon did suggest the positive impact of American academic publication upon British drug discovery and development research. This is perhaps unsurprising given the very large scale of US academic research in this area, but highlights the key role public research plays as the foundation for commercial research.

In short, the pattern of citing references was very hierarchical and the publications were heavily influenced by American journals. This result suggested that American academic publications are very important to the UK drug discovery and development subsector's research.

5.3. Citations

5.3.1. Counts of citations

The 2663 papers were cited 89,992 times since first published: each paper was citied 33.8 times on average. If compared with the average citation to UK biotechnology publications - 4.8 citations per item in 1995/1996, and 5.2 in 1999/2000 (Calvert, Senker, & Schenk 2003), the average number of citations per firm's publication was far above average[20]. Although the high number of citations was

[20] Calvert, Senker, & Schenk's research included publications of plant biotechnology, animal biotechnology, environment biotechnology, bioprocessing, diagnostics and therapeutics, platform biotechnology, and cell factory.

partly due to the higher citation rates of biomedical publications than other research areas, e.g. plant science (Kinney 2007,p.17943), and partly due to the long time accumulation of citations, the average number of citations per firm's publication were still far greater. As discussed later, one possible reason for the significant citation rate was that this subsector was the first mover in many research fields, and therefore their papers were highly cited.

The top ten of the 81 companies' publications accounted for 85.6 per cent of the total citations. This also presented a hierarchical pattern. As shown in Table 16 and 17, Celltech, Vernalis, and Cambridge Antibody's publications were ranked highest in terms of total counts of citations: each having 31682 (35.2 per cent) ,21082 (23.4 per cent) and 6773 (7.5 per cent) citations respectively. Citations to publications of these three companies accounted for 66.2 per cent of total citations. The Pearson correlation test was conducted to examine if there was a significant correlation between total number of publications and total number of citations ($r=0.985$, $p<0.01$) and showed that the number of publications and total number of citations were statistically significantly correlated. This is a very strong correlation, which suggests that the most productive companies were also the most influential companies in publication.

Moreover, Celltech, Vernalis, and Cambridge Antibody also had the largest number of average citation per year: 1173, 958, and 356 citations per year respectively. The results of total citations and average citation per year suggests that Celltech, Vernalis, and Cambridge Antibody not only had a strong cumulative impact on research, but also continuously influenced the research field since they started to publish papers. In other words they are very significant producers of scientific knowledge.

Table 16 Publication and Citations (Top 10 companies)

company name	Number of Publication	Sum of the Times Cited	Average Citations per Item	Average Citations per Year	h-index	Most citied paper
Celltech Group plc (Acquired Chiroscience in 1999;merged with Medeva in 1999; acquried Cistron Biotechnology US in 2000; acquired Oxford Glycosciences in 2003; acquried by UCB Belgium in 2005)	794	31682	39.9	1173.4	88	689
Vernalis (formally known as Vanguard Medica;acquired by British Biotech and name change to Vernalis in 2003; British Biotech merged with RiboTargets in 2003; acquired Ionix Pharmaceuticals in 2005; acquired Cita NeuroPharmaceuticals Canada in 2005)	451	21072	46.7	957.9	78	995
Cambridge Antibody (Acquried Aptein US in 1998; Acquired by AstraZeneca in 2006)	91	6773	74.4	356.5	28	939
Xenova (acquired KS Biomedix in 2003; acquired Cantab Pharmaceuticals in 2001; acquired by Celtic Pharma Development BERMUDA in 2005)	181	4531	25.0	206.0	37	384
PPL Therapeutics plc (Acquired by QED in 2004)	55	3837	69.8	274.1	21	1450
Astex Therapeutics (merged with metaGen Germany in 2003)	64	2288	35.8	286	24	259
Oxford BioMedica plc	81	2214	27.3	147.6	25	142
Oxagen	66	1664	25.2	151.3	22	201
Cyclacel Ltd (founded in the UK, headquarter in US, primary research facility is located in The UK)	78	1644	21.1	149.5	23	116
Acambis (1992-1999 Peptide Therapeutics; acquired OraVax US and changed name in 1999)	51	1281	25.6	98.5	18	169

Cambridge Antibody, PPL therapeutic and Vernalis had the highest average citation per publications: 74.4, 69.8 and 46.7 citations per publication respectively. The results suggest that these three companies' publicationa were of the highest quality. In terms of the most cited papers, these three companies all had papers cited over 900 times (Gearing & Newman 1993;Mccafferty et al. 1990;Wilmut et al. 1997). PPL Therapeutics' famous paper about Dolly the sheep -"*Viable offspring derived from fetal and adult mammalian cells*", which was published in *Nature* in 1997, has been cited 1450 times. Cambridge Antibody's original research *"Phage Antibodies - Filamentous Phage Displaying Antibody Variable Domains"*, which was also published in *Nature* but seven years earlier, was cited 939 times. British Biotech's (acquired by Vernalis) review paper *"Circulating Adhesion Molecules in Disease"*, which was published in *Immunology Today* in 1993, was cited 995 times. It is important to notice that these three papers had been published for over

ten years, even over 15 years; therefore their impact on biotechnology research showed a cumulative effect.

Table 17 Ranking of Companies by Different Citation Indicators

Rank	Number of Publication	Sum of the Times Cited	Average Citations per Item	Average Citations per Year	h-index	Most citied paper
1	Celltech	Celltech	Cambridge Antibody	Celltech	Celltech	PPL Therapeutics
2	Vernalis	Vernalis	PPL Therapeutics	Vernalis	Vernalis	Vernalis
3	Xenova	Cambridge Antibody	Vernalis	Cambridge Antibody	Xenova	Cambridge Antibody
4	Cambridge Antibody	Xenova	SR Pharma	Astex Therapeutics	Cambridge Antibody	Celltech
5	Oxford BioMedica	PPL Therapeutics	Oxxon	PPL Therapeutics	Oxford BioMedica	Xenova
6	Cyclacel	Astex Therapeutics	Celltech	Xenova	Astex Therapeutics	Protherics
7	Vectura	Oxford BioMedica	KuDOS Pharmaceuticals	Oxagen	Cyclacel	Astex Therapeutics
8	Oxagen	Oxagen	Crusade Laboratories	Cyclacel	Oxagen	Oxxon
9	Astex Therapeutics	Cyclacel	Astex Therapeutics	Oxford BioMedica	PPL Therapeutics	SR Pharma
10	Amarin	Acambis	CeNes Pharmaceuticals	KuDOS Pharmaceuticals	Amarin	Oxagen

5.3.2.h-index

The average *h*-index was 8.8, Maximum was 88, minimum was 0, Standard deviation was 14.3, and median was 4. This result suggests a hierarchical pattern of publication output with a small number of top firms producing the large majority of citations: *h*-indices for a few companies were very high, and for the majority of companies were relatively low. This result is consistent with the results obtained by other indicators.

The Pearson correlation test was conducted to examine if there was a significant correlation between total number of publications and *h*-index ($r=0.926$, $p<0.01$). This is a very strong correlation, i.e. the number of publications and *h*-index were statistically significantly correlated. In other words, the most productive companies normally had the highest h-index. As discussed earlier, the total number of citations was also statistically significantly correlated with the total number of publications, therefore, the impact of companies' publications correlated with its number of publications.

However, as a new indicator emerging since 2005, there are many discussions about applying the *h*-index to analysing output of organizations and universities. It should be adjusted before analysing different subjects to account for varying norms, and should be interpreted carefully. Unfortunately there is not enough data to benchmark this industry at present. Kinney compared American Universities' output by using an adjusted *h*-index. This method was based on observation of when "evaluating sets of publications greater than several hundred, the *h*-index vs. the size of the set (*N*) is characterized by an approximately universal growth rate" (Kinney 2007,p.17943). However, because the paper concerning methodology adopted by Kinney is still in press, details are not available at this stage. Therefore, further study is needed to investigate this issue.

Table 18 *h*-index for UK Drug Discovery and Development Companies

h-index	Minimum	Maximum	Mean	Standard deviation	Median
Value	0	88	8.84	14.28	4

5.4 Discussion and Summary

In this chapter, three aspects of SCI publications have been addressed: productivity and impact of companies' research, regional performance and global cooperation, and knowledge flow.

There are several major findings in this chapter. First of all, the drug discovery and development subsector is a major producer of knowledge. It is clear that the output of these companies is highly innovative and important, as seen by the high h-factors and number of citations.

Roughly comparing Webster's research (Webster 2005) with this project yields an interesting result: although drug discovery and development companies' publications only accounted for a small fraction of total UK biomedical papers (including publications of universities and research institutes), the publishing ability of this subsector has improved significantly, and this subsector played an increasing role in biomedical knowledge production.

If compared with the biotechnology sector of other countries, such as the biotechnology cluster of Scandinavia – Medicon Valley for example (Coenen, Moodysson, & Asheim 2004), the British drug discovery and development companies appear to be more active in publishing.

If comparing with well established pharmaceutical companies, the successful drug discovery and development companies published as many as large British pharmaceutical companies (Patel 2003). Drug discovery and development companies are also active in publishing compared with well established US pharmaceutical companies (McMillan & Hamilton 2000).

An important finding is that this subsector's publications and citations data indicates a very hierarchical structure: a few companies dominated the publications produced by the subsector, in terms of both quantity and impact. One possible reason is that many of these high-end companies were established in the 1980s and so may be the first movers in their fields, which enables them to accumulate larger numbers of publications and citations, as well as research experience. Although the total output of this subsector only accounted for a small proportion of all UK biomedical publications, the growth rate of publications and the impact of publications are far above average. An important finding was that the impact of the leading companies' publications was strongly correlated with its number of publications. This also supports the idea that the leading firms are very important producers of knowledge.

Secondly, this subsector was highly geographically concentrated in terms of knowledge production and international networks. The pattern of industry publication is different from the publications of public research institutes. In Webster's study, public research institutes and Universities in London published 36 per cent of UK total biomedical publications, Cambridge and Oxford published around 5 per cent each (Webster 2005). In the drug discovery and development sector 20 per cent of addresses were from Cambridge and Oxford respectively, and 19 per cent were from London, giving a total of nearly 60 per cent for these three areas.

This subsector collaborated widely with other countries in publishing: the US dominated in co-publishing within this subsector, followed by EU countries. Within the UK, Cambridge, Oxford and London were active centres in publishing. Total publishing and co-publishing were both highly concentrated in the Southeast of England, which was correlated with company clustering in these three places. Publication was even more concentrated than the number of companies in these areas.

Thirdly, whilst the papers were published across a wide range of journals, they were concentrated in a small group of journals. If compared with the average citation to UK biotechnology publications (Calvert, Senker, & Schenk 2003), the number of citations per firm's publication was

far above average. Furthermore, although a wide range of journals were cited, the references in these publications also presented a pattern of concentration. Interestingly, the major journals publishing these papers were mainly British, but the major journals these papers cited were mainly American. These results suggest the impact of American institutions upon this subsector's research. Together with results of co-publishing, research in the US strongly influenced the UK drug discovery and development companies in a direct way through co-publishing and in an indirect way through citation.

Finally, this subsector published in both biological and chemical knowledge, but with a greater emphasis on molecular biology and biotechnology. It followed a similar research route and direction as the public institutes, and has produced very significant papers. Therefore it played the roles of both learner and inventor at the same time.

Implications for policy:

This chapter indicated that companies' capability of publishing is enhanced by learning from networking; therefore policies could aim at encouraging the collaboration between companies, universities and public institutes, for example, this could be achieved by enhancing the mobility of highly skilled researchers and postgraduates, and encourage collaboration between researchers and industry. Furthermore, the networking between different actors in scientific publications would also facilitate the commercialization of scientific discoveries.

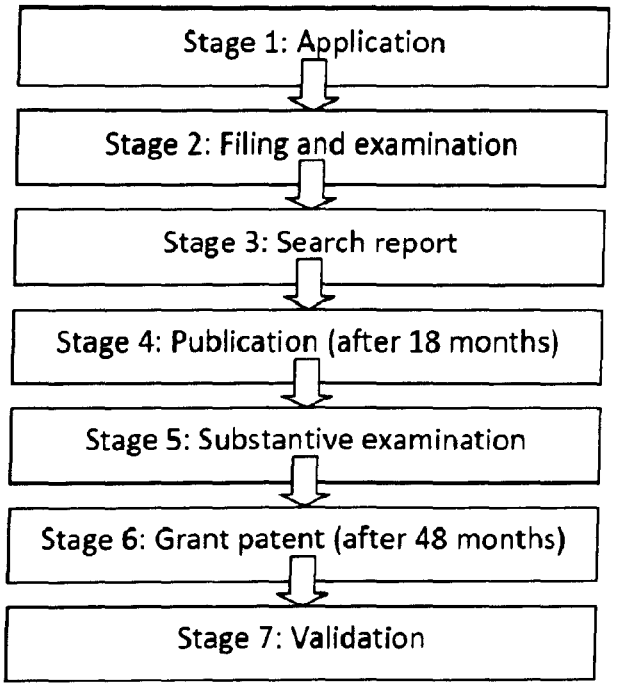
Chapter Six: Knowledge Production: Patents Publications

6.1. Introduction

This chapter will continue to discuss the R&D output of the UK drug discovery and development subsector. This chapter will focus on the publication of patents by firms in the drug discovery and development subsector, one of the firm's intangible assets. Patents are defined by the European patent office as "a legal title granting its holder the right to prevent third parties from commercially exploiting an invention without authorization"(The European Patent Office 2008).

A normal European patent grant procedure has seven steps: first, the inventors should send an application to the European patent office. This application consists of a grant request, a description of the invention, claims and an abstract. The application will be examined and filed after the patent office receives it. Then a search report which contains a list of all relevant documents will be generated and sent to the inventor. After 18 months, the patent application will be published together with the search report. At this stage, the application is protected by provisional protection. If the inventor decides to pursue the application, a substantive examination will be carried out. Then the Patent Office will decide on whether to grant the patent, and, if so, it takes effect on the date of publication. It normally takes 48 months from application to patent grant. The final step is validation in each state belonging to the European Union (Figure 4).

Figure 4 The European patent grant procedure



From the perspective of a biotechnology and pharmaceutical company, patents, trademarks, copyrights and trade secrets constitute a companies' intellectual property, and this has an impact on almost every aspect of a company's business, i.e. revenues, management, alliances, market awareness, and financing (Schneider 2002).

As an industry focusing on innovation, there are two types of output: product innovation and process innovation. This chapter will examine both product innovation e.g. new therapeutics and devices, and process innovation, e.g. fermentation and separation. The main aim of this chapter is to describe the innovation activities of drug discovery and development firms by analyzing patents publications. In this chapter, patent analysis included year of publication, type of invention/discovery, countries of inventor/applicants, and research alliance with other companies and institutes.

There are four sections in this chapter: the first section will describe how the drug discovery and development subsector performed in patenting. The second section will focus on patent content and types. In the third section, co-patenting between British and foreign inventors will be analyzed. The final section will be the discussion and conclusion.

6.2. Productivity

6.2.1. Growth of patent publications

From a view of the UK pharmaceutical and biotechnology industry, two UK-based large Pharmaceutical firms are amongst the world leaders in a number of fields of biotechnology, whether measured by volume or by impact of patenting: GlaxoSmithKline and AstraZeneca (Patel 2003b, p29). However, since late 1990s, other institutions and specialized biotechnology company have started to a play more important role (Patel 2003b).

In this study, 2827 patents from 81 companies have been collected. The earliest patent date was 1982, which was granted to the first British biopharmaceutical firm: Celltech.

The number of patents published has grown dramatically from 1982 to 2006 (Chart 26&27). (It is important to note that the year in the chart is the publication date and there is an 18 month time lag between application and publication). There are three leaps: the first in 1997, the second in 2001/2002, and the third in 2006. From 1982 to 1996, the number of patents published each year, grew slowly and steadily. In 1997, patent numbers increased by 61 per cent compared with 1998, and then in 2001 and 2002, patent numbers increased by 56 per cent and 39 percent compared with previous years. 2006, in particular, saw an output of published patents that was equivalent to one

fifth of all the patents published since 1982. The number of published patents increased 75 per cent compared with the previous year, 2005. It is also important to notice that before the dramatic increase in 2001/2002, and 2006, there were three years 'preparation' periods: the line between 1997 and 2000, and the line between 2002 and 2005 were flat or slightly 'U' shape.

Thumm investigated patent applications of 103 European biotechnology companies (103 biotechnology firms in several European countries, including 22 Dutch, 28 German, 20 British,19 Spanish, 10 Italian, and 4 others), and found that the number of European patenting applications grew 4 per cent between 1991 and 1997 (Thumm 2001), and the UK led the growth. Compare with Thumm's research, the growth rate of the British drug discovery and development subsector's worldwide patenting application, which was obtained from this study, was much higher: 29 per cent every year between 1991 and 1997. Although Thumm focused on European patents application, and this research included worldwide patent information, the performance of this subsector was still far above the average of the European biotechnology industry between 1991 and 1997. One possible reason is that many biotech firms only supply services, reagents etc. – whereas the drug discovery and development forms are focused heavily on products and have a much greater likelihood to patent.

Another interesting trend was found in this study: comparing the total patents in each five-year period (Chart 27), the numbers of patent publications were twice as many as previous five-year period, i.e. between 1987-1991 firms published twice as many patents as periods between 1982-1996, similarly, 1992-1996 firms published twice as many patents as 1987-1991, 1997-2001 published twice as many patents as 1992-1996, and 2002-2006 published twice as many patents as 1997-2001. This is a dramatic increase and an important trend in the subsector. As discussed in Literature Review Chapter, number of patents is an important factor to attract financial support (Baum & Silverman 2004); therefore, one possible reason for the dramatic increase was that companies published more patents in order to attract potential partners.

Chart 26 Patents published vs. SCI paper published (1982-2006)

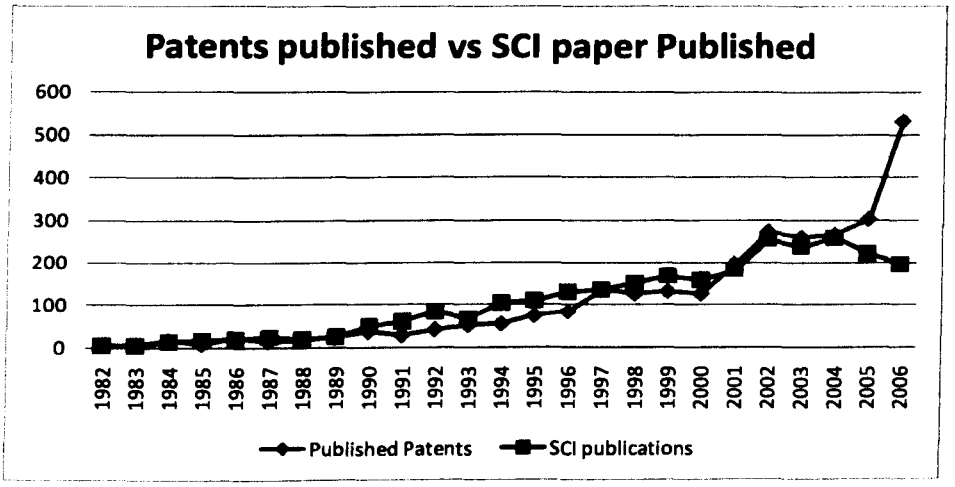
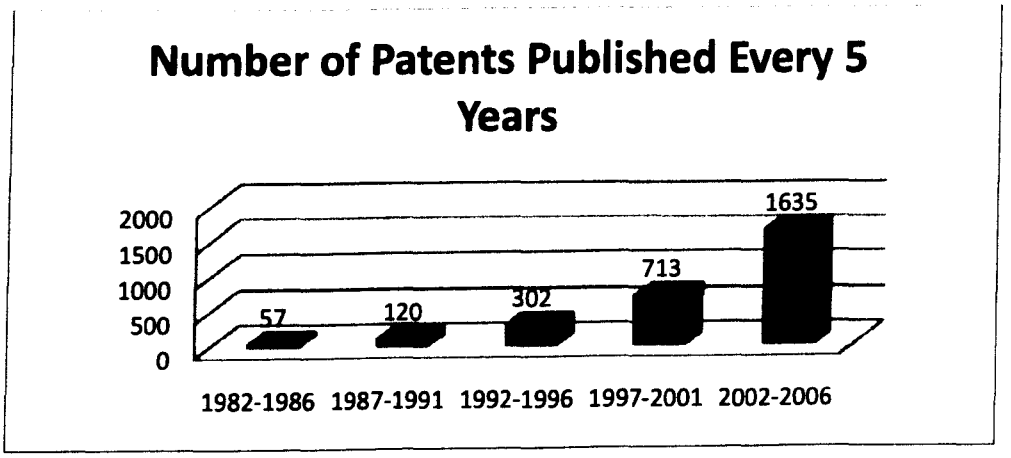


Chart 27 Number of patents published every 5 years



All the results above suggested that the UK drug discovery and development subsector grew fast in patenting, and played an important role in the EU biotechnology and pharmaceutical industry.

There are several reasons for the fast growth of patent publications. Firstly, this growth was partly driven by the overall growth of the patenting activity of the UK pharmaceutical and biotechnology industry: between 1986 and 1990, 313 biotechnology patents invented by UK companies were granted by USPTO, and between 1996 and 2000, there were 1164 patents granted by USPTO (Patel 2003b). The number of UK patents granted in the US also showed a fourfold increase, which was similar to the trend of patents granted worldwide to the drug discovery and development subsector. The fast growth of the UK drug discovery and development subsector in patenting was also partly driven by the global trend of patenting in this industry. From 1980 to 2003, the number of patents on therapeutically active compounds at USPTO grew very fast, in particular, between 2000 and 2003 (Hopkins et al. 2007). Another driving force would be the fast growth of US pharmaceutical and biotechnology. The US was the largest partner of the UK drug discovery and development subsector (see Chapter Seven), and the total number of genetic engineering and pharmaceuticals patents granted to US institutes and companies between 1982 and 1998 were as many as 13982 (Gittelman 2006).

Comparing the patent publications with SCI publications between 1982 and 2006 (Chart 26), highlights three features. First, between 1989 and 2000, the patent publications and the SCI publications followed similar trends, but SCI publications were slightly greater than patent publications in most years. Second, between 2001 and 2004, the patent publications and the SCI publications still followed similar trends, but patent publications were slightly more than SCI publications. Third, from 2005 to 2006, the number of patent publications grew dramatically while the number of SCI publications decreased dramatically. This suggests that the drug discovery and development subsector have been paying more attention to patent publications rather than scientific publications since 2001. One explanation is that the increasing number of patents, both grant patents and patents publications, will provide potential opportunities for companies to generate income by licensing out, contract service and research alliances, promote market awareness, attract

and motivate expertises, and further attract more investment (Schneider 2002). This correlates with the busting of the biotech bubble after 2001, when many companies encountered financial problems, and an increased number of patents would increase the likelihood of attracting investment.

Table 19 Number of Publications in 2005 and 2006 (Top firms)

Company Name	Patents Published in 2005	Patents Published in 2006	Net Increase	Total Number of Published Patent 1981-2006
Astex Therapeutics [21]	5	39	34	58
Vernalis [22]	23	45	22	306
Avidex Ltd [23]	5	23	18	41
Vectura [24]	24	40	16	210
Oxford BioMedica [25]	5	19	14	108
Domantis Ltd	8	21	13	43
KuDOS Pharmaceuticals [26]	5	18	13	40
Cambridge Antibody[27]	9	18	9	71

[21] Astex Therapeutics merged with metaGen (Germany) in 2003.

[22] In 2003, Vernalis mergered with British Biotech (UK), which merged with RiboTargets (UK) earlier in 2003; then Vernalis acquired Ionix Pharmaceuticals (UK) and Cita NeuroPharmaceuticals (Canada) in 2005. Data presented here included papers published by Vernalis, British Biotech, RiboTargets and Ionix Pharmaceuticals.

[23] Avidex Ltd was acquired by Medigene (Gemany) in 2006.

[24] Vecture acquired Innovata (UK) in 2006; Innovata was formed in July 2005 when ML Laboratories PLC (UK) acquired Quadrant (UK).

[25] Oxford BioMedica acquired Oxxon Therapeutics (UK) in 2007 (Oxxon Therapeutics was recorded separately)

[26] KuDOS Pharmaceuticals Ltd was acquired by AstraZeneca (UK/Sweden) in 2005.

[27] Cambridge Antibody acquired Aptein (US) in 1998 was acquired by AstraZeneca (UK/Sweden) in 2006.

Further investigations into the years 2005 and 2006, found that the increased number of publications had several features. First of all, the whole subsector contributed to the increasing number of publications. 50 of the 81 firms (62 per cent) published more in 2006 than in 2005, seven (nine per cent) published the same number, nine (11 per cent) of the firms in 2006 did not publish as many patents as in 2005, and 15 (18 per cent) firm did not publish any patents in 2005 and 2006. Secondly, a small number of companies' contributions accounted for the majority of the increase. Eight (ten per cent) firms contributed 61 per cent of the 2005/2006 increase in number of publications (Table 19). Thirdly, the top performing firm in 2005 and 2006 was Celltech[28], which had 44 patents published in 2005 and 51 in 2006, did not contribute much to the increase. The net increase number was only seven, which ranked 12th in terms of net increase of patents. This was mainly due to the recent acquisition of Celltech by UCB.

6.2.2 Distribution of output

The average number of patents published by each company between 1982 and 2006 was 34.9. Five (six per cent) of the 81 companies published more than 100 patents (group one), 34 (42 per cent) companies published more than ten but less than 100 patents (group two), and 42 (52 per cent) companies published ten or less patents, including six companies which did not published any patents before 2007 (group three) (Chart 28).

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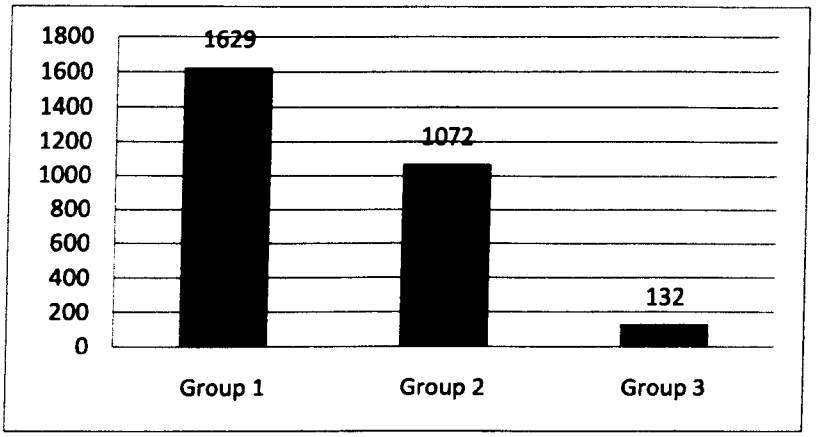
[28] In 1999, Celltech acquired Chiroscience (UK) and then merged with Medeva (UK); in 2000, Celltech acquried Cistron Biotechnology (USA) and in 2003, Celltech acquired Oxford Glycosciences (UK). Celltech was acquired by UCB (Belgium) in 2005. Data presented here included papers published by Celltech and other three British origin companies Chiroscience, Medeva and Oxford Glycosciences.

Chart 28 Patents published by Each Group



Five (six per cent) of the best performance firms contributed 57.6 per cent of the total patent publications. Celltech, from 1982 to 2006, had published 879 patents, which accounted for 31.1 per cent of the total patent publications, and Vernalis[29] had published 306 patents (10.8 per cent). According to Patel's research, SmithKline Beecham Plc, which has the largest number of patents, was granted 629 US patents between 1986 and 2000, while Celltech, published 579 patents between 1986 and 2000. The performance of Celltech's patents is very significant. According to Patel, in terms of UK inventing patents granted by USPTO between 1996 and 2000, Celltech ranked fifth in the UK biotechnology and pharmaceutical industry, next to AstraZeneca, the Medical Research Council, SmithKline Beecham Plc and Unilever Plc, and British Biotechnology [30] ranked 11th. This result indicates that the drug discovery and development subsector, in particular the top companies, played very important roles in patenting, with levels of activity comparable to large pharmaceutical companies. This is remarkable given their difference in size.

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[29] In 2003, Vernalis merged with British Biotech (UK), which merged with RiboTargets (UK) earlier in 2003; then Vernalis acquired Ionix Pharmaceuticals (UK) and Cita NeuroPharmaceuticals (Canada) in 2005. Data presented here included papers published by Vernalis, British Biotech, RiboTargets and Ionix Pharmaceuticals. It is important to notice that over 70% papers published by this group were published by British Biotech.

[30] In 2003, British Biotech (UK) merged with RiboTargets (UK), later merged with Vernalis in the same year.

34 companies of group two contributed to 38 per cent of total patents publications. Similar as SCI publications, the performance of patent publications was dominated by several outstanding companies. The main reasons for this were that these companies, e.g. Celltech and Vernalis/British biotech, have been established a long time, and experienced many mergers and acquisitions, which enable these companies to accumulate large numbers of patents and research experiences.

It should be noted that the continuously growing trends of the whole drug discovery and development subsector, and the outstanding performance of several top firms in patent publications, were two possible reasons for attracting acquirers. Since 2000, many top performing firms with large numbers of patents publications have been acquired by foreign companies, in particular, large pharmaceutical companies. For example, the top company Celltech, was acquired by UCB for £1.5 billion in May 2004. Similarly, Cambridge Antibody Technology was acquired by AstraZeneca for £702 million in May 2006.

6.3. Content and Classification of Patent Publications

6.3.1. Content of Patent Publications

Considering the extremely large amount information contained in patent abstracts and descriptions, this study adopted a novel method in analysing patent content. This method was used to obtain preliminary results of patent content analysis, and still needs to be improved in future studies. This method was based on keyword analysis. There were two sources of keywords. The first set of keywords was identified from the results of previous research of alliances and company technology. The second set of keywords was identified from patent abstracts. Patent abstracts were imported into software *Hermetic Word Frequency Counter* to identify frequently appearing keywords in

patent abstracts. Then all of the keywords were categorized into different groups and browsed in patent abstracts. The 'find' function of Excel was used to identify the frequency of keywords. The advantage of this simple step is that no matter how many times a keyword appeared in an abstract, each keyword was only counted once for that abstract.

The frequency of how often these keywords occurred in the abstracts reflected the activities and focus of these firms. This method, combined with a European patent classification analysis will describe the innovation activities of the drug discovery and development firms.

There were several limitations of this method: first of all, abstracts of 447 patents (16 per cent) were not available in the database. Secondly, as stated earlier, this study included many similar inventions/discoveries which belonged to the same patent family, in particular, these patents were about compounds rather than method/procedure, therefore the frequency of keywords may be slightly biased. Although this method still needs improving, it did provide valuable preliminary results.

The keywords which appeared most were categorized into three groups. The first group described the patent, which included compound, composition, formula, method, process, treatment, device, and reagent (Table 20).

Table 20 Keyword (Group 1)

Keyword	Frequency
Compound	776
Treatment	725
Formula	660
Method	571
Composition	245
Process	203
Device	67
Reagent	50

The results of the first group of keywords (Table 20) indicated that the largest category of patents were related to compounds/ compositions and their formula, followed by patents describing new method/process, which in many cases were linked to the new compounds. The third largest category was devices and reagents. The top three categories are all about products or drug candidates.

The second group was about technology, which included both biological related technology and chemical related technology, e.g. gene, genome, sequence, virus, vector, nucleotide, peptide, polypeptide, protein, antigen, antibody, immune, herb, polynucleotide, mutation, vaccine, hormone, stem cell, drug delivery, toxin, generics, micro array, recombinant, monoclonal, synthetic, screening, natural, etc (Table 21).

Table 21 Keyword (Group 2)

Keyword	Frequency	Keyword	Frequency	Keyword	Frequency
Peptide/protein	696	Delivery	84	Mutation	25
Gene/ genome/	558	Vaccine	80	Toxin	25
Antibody	280	Natural	79	Hormone	18
Vector	200	Screening	48	Stem cell	11
Recombinant	150	Monoclonal	44	Array	5
Virus	112	Synthetic	41	Generic	5
Polynucleotide/ nucleotide	109	Library	31	Herb	3

The results of technology/product keywords research (Table 21) indicate that the peptide/ protein were the most popular area in patents, and in many this type of patents, relevant gene/polynucleotide/ nucleotide were also patented. Antibody was another product group which was preferred by these firms. Other products described in these patents included synthetics, vaccines, toxins, hormone, natural compounds, and small numbers of stem cell and generics. The patented technologies also include screening and libraries. The biological technologies accounted

for the majority of patent publications, while chemical technologies such as synthetics, screening, library etc. only accounted for a small fraction.

The third group was about indications, which included cancer, central nervous system, neural, arthritis, pain, respiratory disorders, cardiovascular, inflammatory, infection, antibiotics, antiviral, obesity, auto immune, gastrointestinal, antibacterial (Table 22).

Table 22 Keyword (Group 3)

Keyword	Frenquency	Keyword	Frenquency
Immun(e)	344	Cardiovascular	28
Inflammatory	197	Obesity	22
Cancer	136	Gastrointestinal	22
Infection	60	Respiratory	21
Nervous / neuro	51	Brain	13
Pain	44	Leukaemia	7
Antibacterial	34	Antiviral	5

One fourth of the patents had described possible indication of a compound. As shown in Table 22, large groups of indications included immune disorders and immune mediated inflammatory diseases, cancer, Infection, and nervous system diseases. Small groups of indications included pain, cardiovascular, obesity, gastrointestinal disorders and respiratory disorders. This result was similar to the results of SCI publication: cancer, immune disorders and immune mediated inflammatory diseases, and infectious disease were the major subject of SCI publications.

In short, based on the three sets of key words, the patent publications are mainly about therapeutics which developed with biological technology, in particular therapeutics treating cancer, immune disorders and immune mediated inflammation, and infection.

6.3.2. Classification of Patent Publications

The European patent classification system (ECLA) was built on the International patent classification (IPC). There are nine categories: A stands for human necessities, B for performing operations and transporting, C for chemistry and metallurgy, D for textile and paper, E for fixed constructions, F for mechanical engineering, lighting, heating, weapons, blasting engines or pumps, G for physics, H for electricity, and Y for general tagging of new technological development. The patent publications of drug discovery and development subsector were mostly classified as A and C, and a small number of publications were classified as B, G and Y. The classification system is very complex, and an example will be cited here to explain it.

Celltech published a pharmaceutical product for antineoplastic therapy in 1990 with foreign inventors. Its publication number was WO9001950, and it was classified as A61K39/395 and C07K16/24B. It belongs to two different categories. This is very common in publication classification. For the first classification: A61K39/395, A stands for human necessities, 61 stands for medical and veterinary science and hygiene, K stands for preparation for medical, dental, or toilet purposes, 39 stands for medicinal preparations containing antigens or antibodies, 395 stands for antibodies, immunoglobulins and immune serum. There are further categories as A61K39/395A, A61K39/395B, A61K39/395C, A61K39/395D, A61K39/395E, A61K39/395S stands for their source, for example A61K39/395C stands for "against materials from animals". There are further subcategories for A61K39/395C: e.g. A61K39/395C3 stands for against tumour tissues, cells and antigens. Similarly, for C07K16/24B, C stands for chemistry and metallurgy, 07 stands for organic chemistry, K stands for peptides, 16 stands for immunoglobulins, e.g. monoclonal or polyclonal antibodies, 24 stands for against cytokines, lymphokines or interferons,

and B stands for tumour Necrosis factors. According to this classification system, each patent publication could be classified to one or more categories. However, this system was very complicated, e.g. the 2316 publications which had European classification numbers could be classified into over 1300 categories. Therefore, in this project, a simplified system was used (Table 23 & Appendix 2).

Table 23 Product innovation and process innovation

Innovation type	Classification	EU classification code	Description	Number
Product innovation	Biological molecule	C07K	Peptides	716
		C12N	Micro-organisms or enzymes; compositions thereof	488
	Chemical molecule	C07D	Heterocyclic compounds	645
		C07C	Acyclic or carbocyclic compounds	194
		C07J	Steroids	26
		C07H	Sugars; derivatives thereof	34
		C07F	Acyclic, carbocyclic or heterocyclic compounds containing elements other than carbon, hydrogen, halogen, oxygen, nitrogen, sulphur, selenium or tellurium	31
	Device	A61M	Devices for introducing media into, or onto, the body	72
Process innovation	Preparation and process	A61K	Preparations for medical, dental, or toilet purposes	642
		C40B	Combinational chemistry; libraries	35
		C12P	Fermentation or enzymes-using processes to synthesize a desired chemical compound or composition or to separated optical isomers from a racemic mixture	52
	Measurement and analysis	G01N	Investigating or analysing materials by deterring their chemical or physical properties	170
		C12Q	Measuring or testing processes involving enzymes or micro-organisms	77

From Table 23 & Appendix 2, several categories had large numbers of publications. For product innovation, there were 716 patent publications about peptides and 488 about micro-organisms and enzymes. 645 patent publications were about heterocyclic compounds and 194 about acyclic or carbocyclic compounds. Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as part of the

ring. They may be either simple aromatic rings or non-aromatic rings. Some examples are pyridine (C5H5N), pyrimidine (C4H4N2) and dioxane (C4H8O2). Acyclic compounds are organic compounds have open chain structure and do not form a ring. Carbocyclic compounds are compounds with a homocyclic ring in which all the ring atoms are carbon, for example, benzene. Micro-organisms, enzymes and the majority of peptides are biological molecules. Heterocyclic, acyclic and carbocyclic compounds are all chemical molecules. This distribution is similar to the results obtained from previous keyword methods, that patent publications were favoured biologicals to chemicals. For process innovation, there were 642 publications about preparations for medical and dental, and 170 publications about analysis of compounds' chemical and physical properties.

According to the European Patent Classification system, "Peptides" (C07K) and "Heterocyclic compounds" (C07D) were the largest two sub categories of "Organic chemistry" (C07), and they accounted for 49 per cent and 44 per cent of C07 respectively. Furthermore, "Peptides having more than 20 amino acids; gastrins; somatostatins; melanotropins; derivatives thereof" (C07K14) and "Immunoglobulins, e.g. monoclonal or polyclonal antibodies" (C07K16) were major groups of "Peptides" (C07K).

"Medicinal preparations containing organic active ingredients" (A61K31) was the largest sub category of "Preparations for medical, dental, or toilet purposes" (A61K), and it accounted almost for half of the total patents published in this category.

"Inhalators" (A61M11) was the largest sub category of "Devices for introducing media into, or onto, the body" (A61M), and it accounted for 89 per cent of the total patents published in this category. 77 per cent of "Combinational Chemistry" (C40) patents were about "Libraries" (C40B40). Inhalators are the most important categories of drug delivery, and libraries are the most important categories of combinational chemistry.

The largest sub category of "Biochemistry; microbiology; enzymology; mutation or genetic engineering" (C12), is "Micro-organisms or enzymes" (C12N), whose largest sub group was "Mutation or genetic engineering" (C12N15). C12N15 accounted for 74 per cent of C12N. Other researchers also investigated C12N patents. The growth of British biotechnology companies in C12N patenting was around averagely 12 per cent every year between 1985 and 1997 (Thumm 2001). Compared with this research, although the number of C12N patenting accounted for less than 2 per cent of the total British C12N patenting from Thumm's research, the average growth rate was higher, around 16 per cent every year between 1985 and 1997. This indicated that although the drug discovery and development subsector published slightly fewer patents on C12 compared to other biotechnology sectors, e.g. agriculture and food science, this sector's publication increased faster than average for the biotechnology industry.

Immunoglobulin (C07K16) and genetic engineering products (C12N15) (Appendix 3) were two of the most important publication fields, in terms of both number of patent publications and significance. Publications of these two categories had several sub-categories. For immunoglobulin (319 patent publications), over two thirds of patent publications were about antibodies obtained from animals or humans, in particular from tumour cells. These patents were focusing on antibodies against cytokine, lymphokine, and interferon (100 patent publications), and antibodies against receptors, cell surface antigens, and cell surface determinants (107 patent publications). There were also 60 patents of hybrid immunoglobulin. Antibodies have been a major focus of the products developed by Celltech and other parts of the UK industry (e.g. CAT) – the same is also true of the cytokines.

For genetic engineering products (331 patent publications), 93 patent publications were concerned with viral vectors adapted for animal cell hosts (i.e. gene therapy). 58 patent publications were about extracting or separating nucleic acids from biological samples, isolating an individual clone

by screening libraries and cDNA synthesis. There were also 52 patent publications about using DNA or RNA fragments to produce fusion proteins, for use in MAbs and similar products

Another important application of the European patent classification was to analyse the innovation activities of the drug discovery and development firms in different periods. This method was used to describe the dynamics of technology in use. Four categories of patents were selected and analysed to picture the output of this subsector: peptides (C07K), heterocyclic compounds (C07D), device for drug delivery (A61M) and combinational chemistry products (e.g. libraries) (C40B).

From 1982 to 2006, the published patents on peptides have been increasing dramatically (Chart 29). There were two leaps of peptide patent publications in 2001/2002 and 2006, with several year flat-line "preparation periods". This trend was very similar as the total patent publications. Another similarity between total number of published patents and peptide patents was that, the number of peptide patents published also doubled every five years (Chart 30), which suggests that this category grew very fast between 1982 and 2006. As the largest sub category, the growth in number of peptide patents was also represented by the trend of total growth of published patents. However, in terms of the percentage of the four selected categories (Chart 31), the peptide patents showed an unsteady decrease between 1987 and 1996. The next ten years, the percentage of peptide patents begin to increase, and reached its peak in 2001, then followed by a steady decrease. Although in terms of 5-year periods, the percentages of peptide patents were kept at around 50 per cent of the four sub category between 1992 and 2006 (Chart 32), the weight of peptide patents actually decreased after 2001. One reason was the increase of patent publications on heterocyclic compounds after 2001.

Chart 29 Patents (C07K & C07D) Published between 1982 and 2006

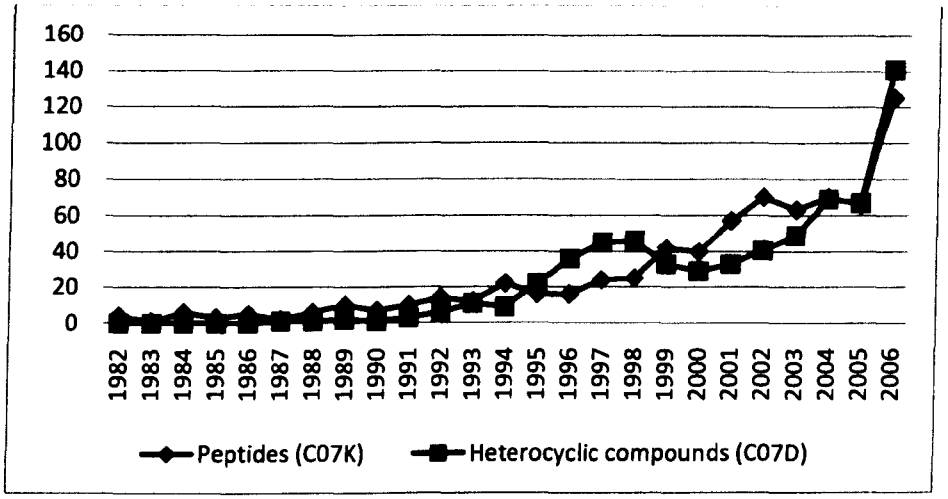
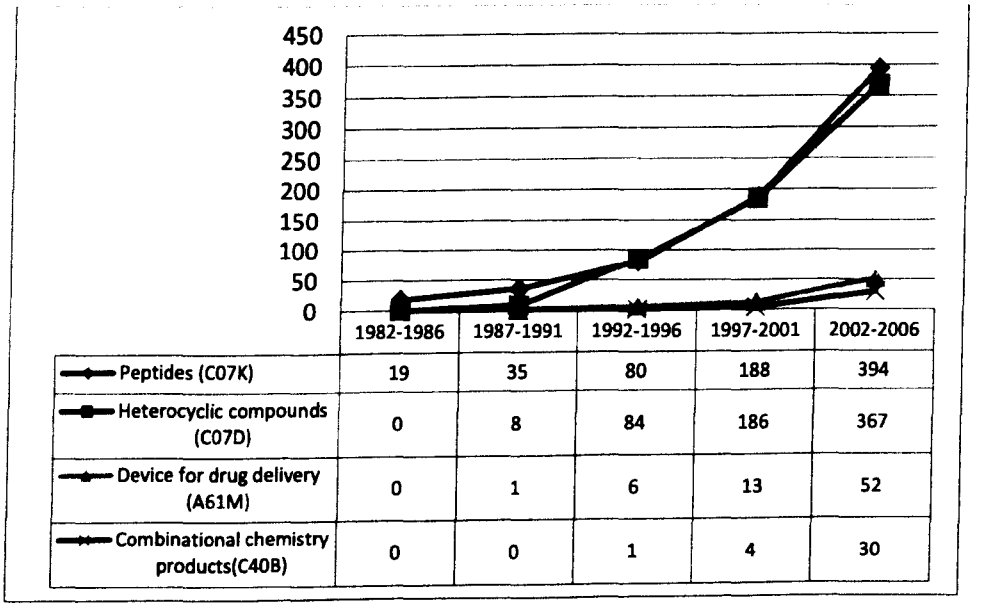


Chart 30 Four Categories of Patents Published Every Five-Years



	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006
Peptides (C07K)	19	35	80	188	394
Heterocyclic compounds (C07D)	0	8	84	186	367
Device for drug delivery (A61M)	0	1	6	13	52
Combinational chemistry products(C40B)	0	0	1	4	30

Chart 31 Four Categories of Patents Published between 1982 and 2006 (%)

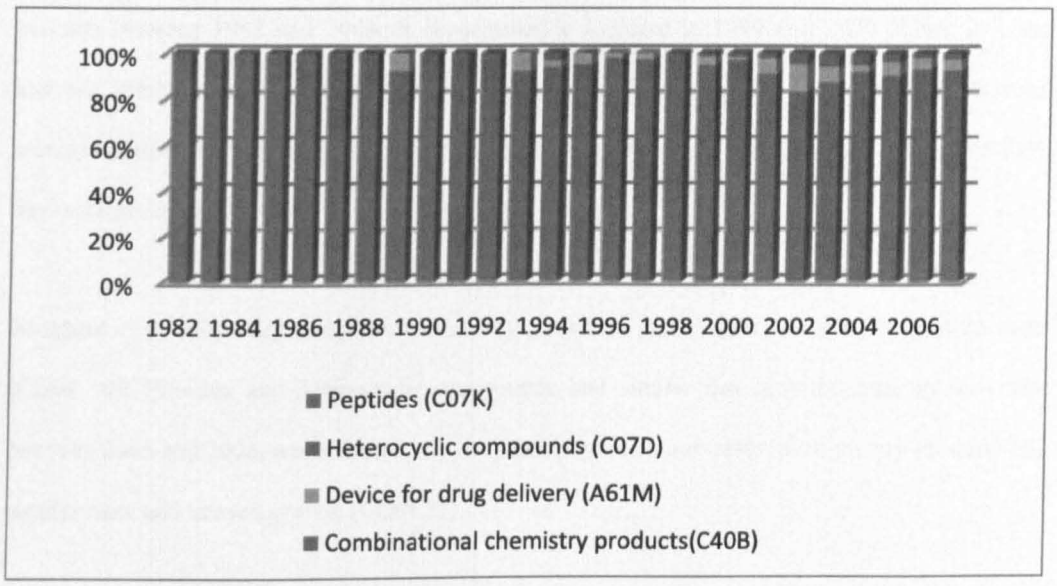
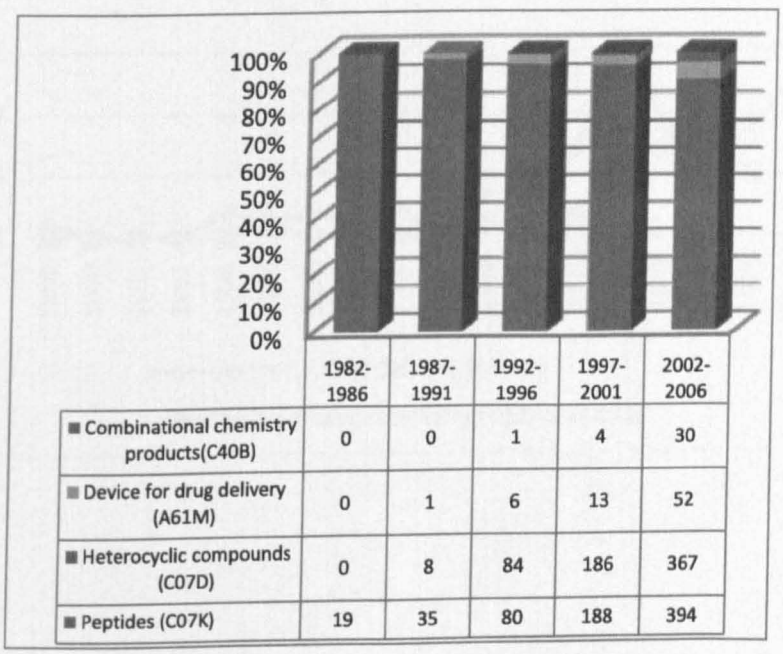


Chart 32 Four Categories of patents published every five years (%)

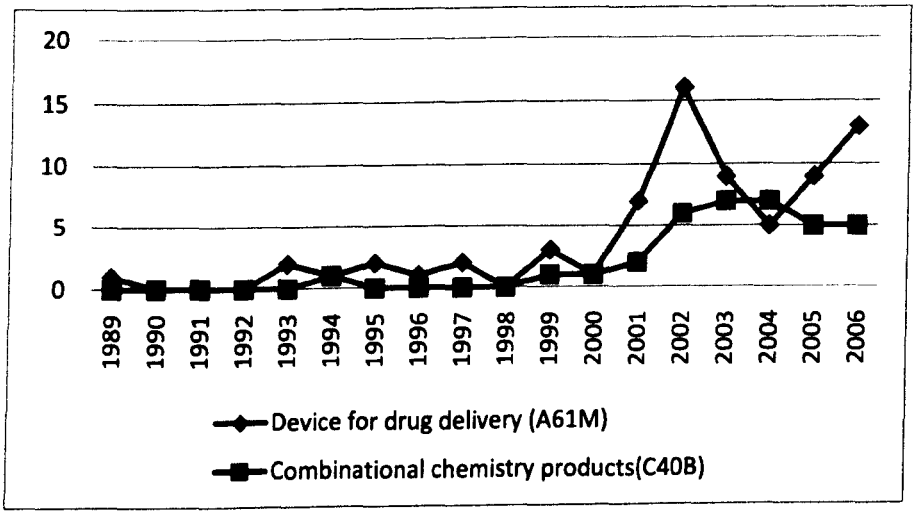


	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006
Combinational chemistry products(C40B)	0	0	1	4	30
Device for drug delivery (A61M)	0	1	6	13	52
Heterocyclic compounds (C07D)	0	8	84	186	367
Peptides (C07K)	19	35	80	188	394

The growth of patent publications on heterocyclic compounds has not been steady over the past 25 year. The first patent of heterocyclic compounds was published 5 years later than the first patent of peptide (the chemical molecule patents published before 1986 were focusing on sugar and steroids). In terms of number of published patents, heterocyclic compound patents showed an uneven increase between 1982 and 2006. It experienced a decrease in 1999 and 2000 (Chart 29), and increase afterwards. From Chart 32, the percentage of heterocyclic compound patents were increase dramatically in the second five- year period (1986-1991), then kept still in the next three five-year periods (1992-2006).

Numbers of all four categories showed a steady growth in each 5-year period in the past 25 years (Chart 30). Peptides and heterocyclic compounds had similar fast growth trend, in particular between 2005 and 2006, while devices for drug delivery and combinational chemistry products had similar slow and uneven growth (Chart 33).

Chart 33 Patents (A61M & C40B) Published between 1989 and 2006



An important reason for uneven growth of device was that three fourths of device patent publications were contributed by ML lab and its subsidiaries[31]. Their company strategy and research activities had a significant impact on the number of patent publications on devices. Similarly, the patent publications on libraries were dominated by two companies: Domantis Ltd[32] (43 per cent) and Cambridge Antibody Technology [33] (37 per cent). The overall number of patent publications on libraries increased dramatically after 2001, and this was mainly because of the founding of Domantis Ltd in 2000. In other words, because only a few companies were involved in patent publications on devices and libraries, and these two areas were dominated by even fewer companies, the total numbers of patent publications were much less than that of peptides and Heterocyclic compounds. Their numbers were also influenced by one or two companies' activities.

6.4. Patent Co-publishing

6.4.1. Country of patent co-publishing

401 out of 2827 patents in this study (14 per cent) were published in collaboration with foreign companies and institutes: 59 were co-published by more than two different countries. There were 32 countries involved in patent co-publishing, and major countries included US, Australia, Germany, Switzerland, France, Finland, China, Italy, Belgium and Netherlands (Table 24). The United States, in particular, has the largest number of patent co-publishing with British companies.

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[31] ML Lab Plc merged with Quadrant in 2005, and changed its name to Innovata Plc. Innovata Biomed was a subsidiary of ML Lab. In 2007, Innovata Plc was acquired by Vectura Group plc.

[32] Domantis Limited was acquired by GlaxoSmithKline in 2007

[33] Cambridge Antibody Technology was acquired by AstraZeneca in 2006

This patent co-publishing involved cooperation with universities and companies. These countries were located in four economic regions: Europe, North American, Asia Pacific, and Africa (Table 25). Europe has the largest number of patent co-publishing with British companies, 209 publications, which accounted for 43.9 per cent of the total co-publications; followed by North America, which has 167 co-publications with British companies, accounted for 35.1 per cent of the total co-publication. Rest of the world accounted for 21.0 per cent.

Table 24 Countries of patent co-publishing

COUNTRY NAME	COUNTRY CODE	NUMBER OF CO-PATENTS	COUNTRY NAME	COUNTRY CODE	NUMBER OF CO-PATENTS
USA	US	162	Canada	CA	5
Australia	AU	37	Czech Republic	CZ	5
Germany	DE	30	Israel	IL	5
Switzerland	CH	28	Republic of Korea	KR	5
Finland	FI	26	Norway	NO	5
China	CN	25	South Africa	ZA	4
France	FR	22	Greece	GR	3
Belgium	BE	16	Ireland	IE	3
Italy	IT	16	Spain	ES	2
Netherlands	NL	13	Hungary	HU	2
Sweden	SE	13	Latvia	LV	2
Austria	AT	12	India	IN	1
Japan	JP	9	Lithuania	LT	1
New Zealand	NZ	8	Poland	PL	1
Denmark	DK	7	Portugal	PT	1
Gambia	GM	6	Ukraine	UA	1

Table 25 Regions of co-publishing

Region	Countries	NUMBER OF CO-PATENTS	Percentage
Europe	Germany, Switzerland, Finland, France, Belgium, Italy, Netherlands, Sweden, Austria, Denmark, Czech Republic, Norway, Greece, Ireland, Spain, Hungary, Latvia, Lithuania, Poland, Portugal, Ukraine	209	43.9%
North America	USA, Canada	167	35.1%
Asia Pacific	Australia, China, Japan, New Zealand, Israel, Republic of Korea, India	90	18.9%
Africa	Gambia, South Africa	10	2.1%

If compared with results from networking alliances (Chapter Seven) (Chart 34 & 35), these two studies show both similarities and differences. Several countries that have strong research connections with British drug discovery and development firms are also major co-applicants/ inventors, e.g. US, Germany and Switzerland. However, there were exceptions. Finland and China, which did not show strong connection in research alliances according to firms' press releases, published over twenty separate patents. While Japan and Canada, which showed relatively strong connections with British firms, published only 9 and 5 patents. The number of co-publishing patents with scientists from Gambia was the highest of African countries, and they were mainly about malaria vaccines.

The main reason for this was the difference of alliance purposes. For example, Japan showed very strong connections with the UK drug discovery and development subsector, however, the number of co-patenting publications was very small. One possible reason is that Japanese companies involved in alliances were large pharmaceutical companies; the agreements signed with Japanese companies were focused on licensing in, licensing out and acquisitions, rather than co-patenting. Another example is Switzerland which also showed strong connections with this subsector, however, many agreements signed with Swiss companies were about manufacture and supply. Therefore the number of co-patents did not connect with the number alliances.

Chart 34 Number of co-patenting by country

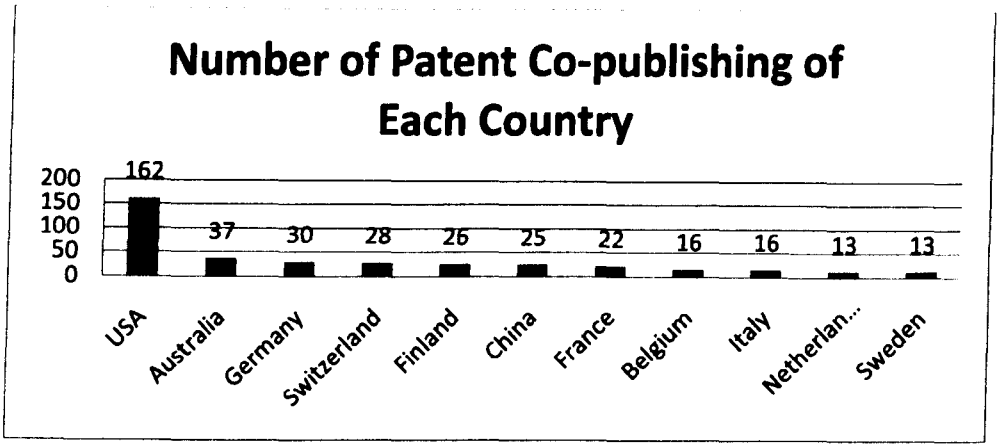
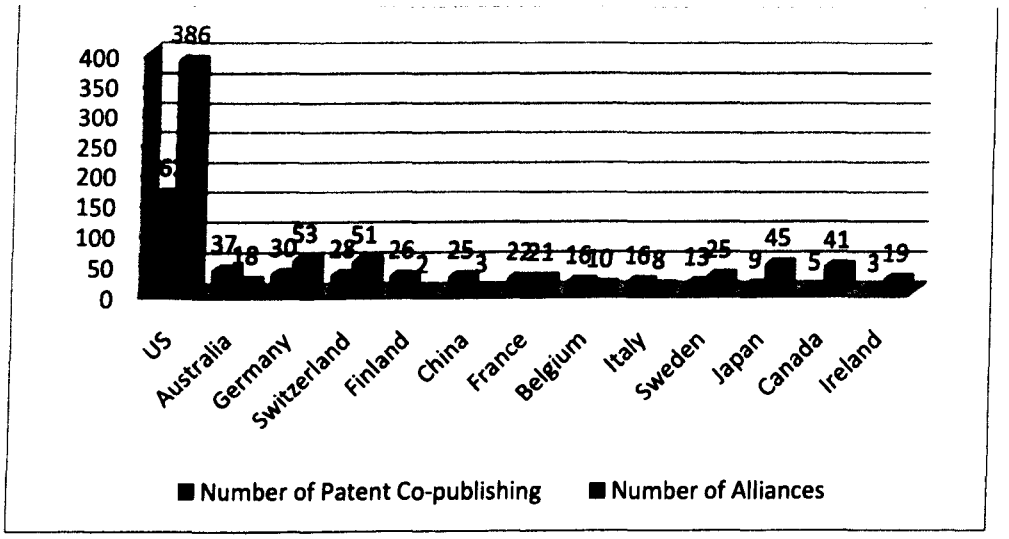


Chart 35 Country of alliances compared with country of co-publishing

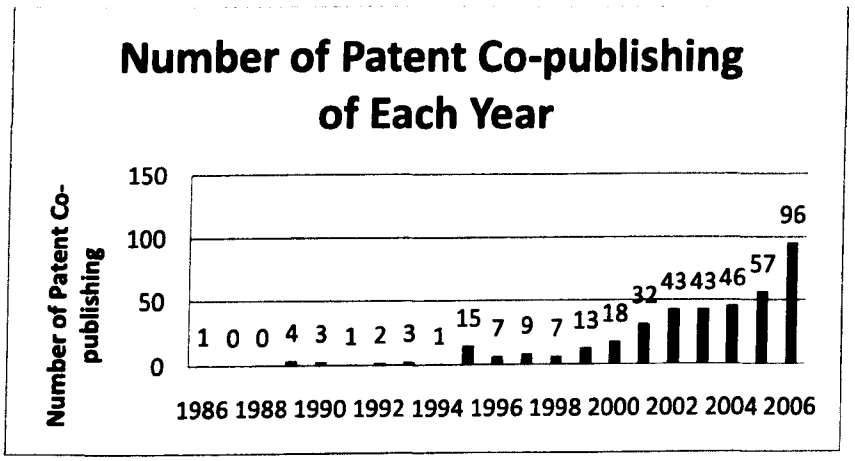


6.4.2. Counts of patent co-publications

The drug discovery and development subsector started co-publishing patents in 1986, but the real increase was from 1995, and then dropped down in 1996 and increased from 1999. 79 per cent of

patent co-publications were published after 2000 (Chart 36). Before 2001, the number of co-publications with an inventor from a foreign country was less than 20 in each year. In 2001, the number of co-publications increased by 78 per cent compared with the number in 2000. The other increase is in 2006, which increased 68 per cent compared with the number of 2005. This trend was similar to the total patent publications (Chart 37 & 38). However, the percentage of publishing patents with foreign inventors was no more than 21 per cent. Therefore, the overall increase of patent publications was mainly due to UK firms, rather than to co-publishing patents with foreign countries.

Chart 36 Number of co-patenting of each year



Ahrweiler, Gilbert, & Pyka investigated the UK and German based biotechnology based-industry, and suggested that international network formation increased between 1990 and 2000 (Ahrweiler, Gilbert, & Pyka 2006). This result was based on granted co-patents, and they further suggested that the UK firms have a higher proportion of co-patenting than German firms (Ahrweiler, Gilbert, & Pyka 2006).

Chart 37 Patents Co-published with Foreign Inventors

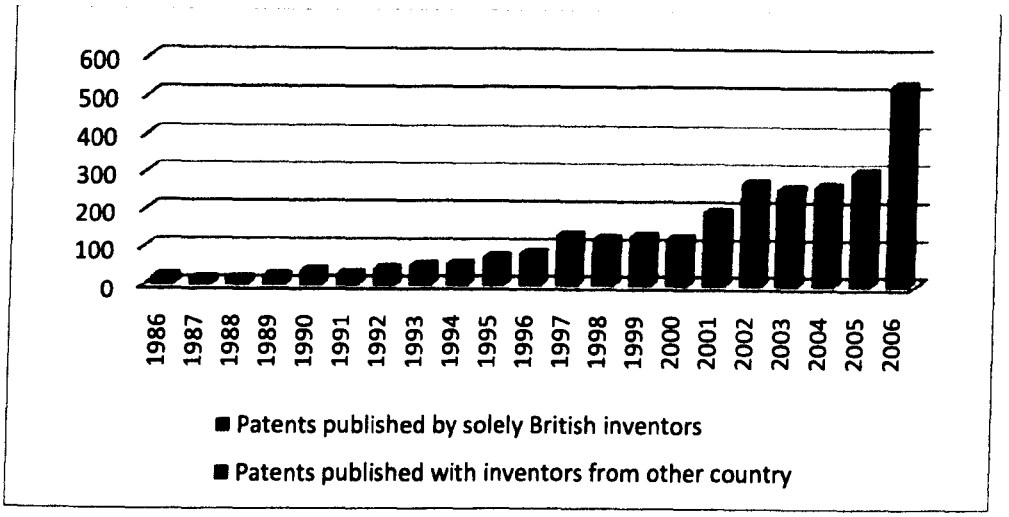


Chart 38 Patents co-published with foreign inventors (%)

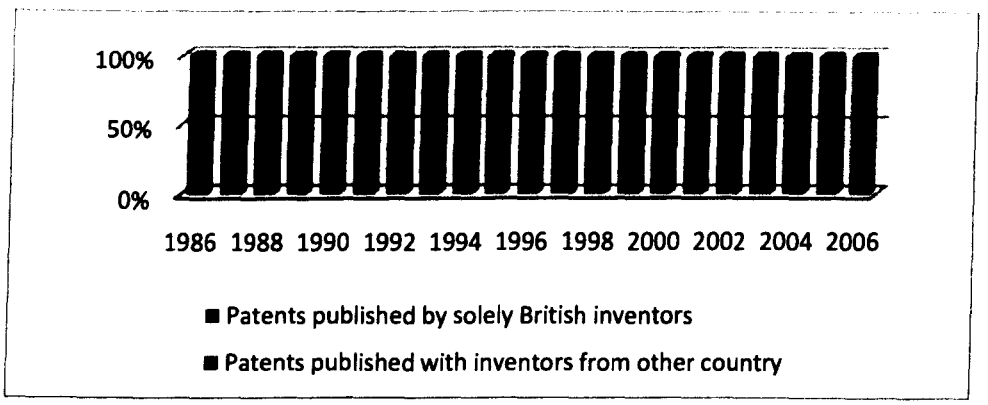


Table 26 Types of patent co-publications

Innovation type	Classes	EU classification	Description	Number of publications	Total
Product	Biological molecule	C07K	Peptides	124	196
		C12N	Micro-organisms or enzymes; compositions thereof	72	
	Chemical	C07D	Heterocyclic compounds	57	95
		C07J	Steroids	12	
		C07C	Acyclic or carbocyclic compounds	8	
		C07F	Acyclic, carbocyclic or heterocyclic	5	

innovation	molecule		compounds containing elements other than carbon, hydrogen, halogen, oxygen, nitrogen, sulphur, selenium or tellurium		
		C07H	Sugars; derivatives thereof	12	
		C08B	Polysaccharides; derivatives thereof	1	
	Devices	B05B	Spraying apparatus; atomising apparatus; nozzles	0	10
		A61M	Devices for introducing media into, or onto, the body	10	
Process innovation	Preparations and processes	A61K	Preparations for medical, dental, or toilet purposes	111	129
		C12P	Fermentation or enzymes-using processes to synthesize a desired chemical compound or composition or to separated optical isomers from a racemic mixture	5	
		C12R	Processes using micro-organisms	1	
		C40B	Combinational chemistry; libraries	11	
		B01D	Separation	1	
	Measuring and analysing	C12Q	Measuring or testing processes involving enzymes or micro-organisms	3	18
		G01N	Investigating or analysing materials by deterring their chemical or physical properties	15	
	other	Y01N	Nanotechnology: Nanobiotechnology; nanotechnology for materials and surface science	1	1

6.4.3. Contents of co-publishing patents

According to the European patent classification codes, two thirds of the co-patenting publications were focused on product innovation, and one third on process innovation (Table 26). There were three types of product innovation: macro molecules, small molecules and devices. In co-patenting, 65 per cent of the product innovations were biological molecules, 32 per cent were chemical molecules, and only 3 per cent were devices. 87 per cent of the process innovations were focused on preparations and processes, 12 per cent were on measurement and analysis. Therefore, the main field of co-publishing patents with foreign inventors focused on biological molecules. This suggests that patenting publications and co-patenting were both more active in biological research than chemical research.

6.5. Summary

In this chapter, three aspects of patent publications have been addressed: the productivity of the drug discovery and development subsector in terms of patent publications, patents co-publishing with other countries, and the contents of patents.

There are four major findings of this chapter. First of all, this subsector played an important role in patent publication. The number of patent publications grew fast in the past 25 years. Before 2005, patent publications presented a similar trend as SCI publications. However, after 2005, the number of patent publications increased dramatically, while the number of SCI publications began to fall. The increase of patent publications was contributed by the whole subsector rather than a few companies. One possible reason was that in order to attract investment, many small to medium-sized companies paid more attention to patents publications rather than scientific publications. Another possible reason is competition, as MacPherson & Boasson argued, the number of patents are positively correlated with the density of competition (MacPherson & Boasson 2004, P319).

Secondly, similar to the pattern of SCI publications, the patent publications pattern also indicated a hierarchical structure. A small number of companies published the majority of patents. The top company, Celltech, even published as many patents as many large pharmaceutical companies. This high output of patents was mainly the result of the large amount of R&D investment of this subsector (DTI 2006a). 2004/2005 R&D investment of Shire Pharmaceutical and Celltech were £112 million and £106 million. They ranked fifth and sixth among the UK biotechnology and pharmaceutical industry, following GlaxoSmithKline (£2839 million), AstraZeneca (£1981 million), Pfizer (£597 million) and Eli Lilly (£147 million).

Thirdly, knowledge formation was also enhanced by networking with foreign countries. In particular, after 2000, the amount of patent co-publishing increased dramatically and co-publications were focused on both product and process innovation. American companies and institutes have been the largest partner in co-patenting. Comparing data on alliances (next chapter) with data of co-publications, several countries which have strong research connections with the British drug discovery and development firms are also the major co-applicants/ inventors, e.g. US, Germany and Switzerland. However, this is not always the case. The largest region of co-publishing patents was Europe, followed by North America. Compared with German companies, the UK firms have a higher proportion of co-patenting than German firms (Ahrweiler, Gilbert, & Pyka 2006).

Finally, major indication groups included immune disorders, inflammatory diseases, cancer, infection, and nervous system diseases, which is similar as the results obtained from SCI publication study. Overall, patent publications of biological compounds are more than that of chemical compounds. For individual technologies, patents of peptides and heterocyclic compounds grew very fast, while devices for drug delivery and combinational chemistry products were slow and steady. Unlike patent publications of peptides and heterocyclic compounds, which were contributed by a large number of companies, patent publications of devices and libraries were contributed by a few companies. These latter two areas were dominated by even fewer companies, and the total number of patent publications was much less than that of peptides and heterocyclic compounds. Their numbers were mainly influenced by one or two companies' activities.

In short, in terms of counts of patent publications, the output of the UK drug discovery and development subsector was very remarkable. Furthermore, these outputs indicated a hierarchical structure: a few successful companies, which have been established for a long time, have large amounts of R&D investment, and accumulated large numbers of patent publications, and thus dominated the patent publications. The fast growing numbers of patent publications between 1982 and 2006 suggested that these companies were very successful in knowledge output, in particular,

research and development on biological compounds and small molecules. This was partly driven by the large domestic R&D investment, global trend of industry development and networking with other fast growing countries.

Implications for policy:

Patel argued that UK firms have great potential to commercialize biotechnology discoveries, and its performance is influenced by factors such as "availability of venture capital and the continuing supply of well trained scientists and engineers from the UK science system, both of which have the potential to be greatly influenced by government policies" (Patel 2003b, P4).

Based on the data of both scientific publications and patents publications, the accumulation of knowledge is also very important to a firm's patenting. As Malerba suggested, knowledge accumulation and diffusion is central to innovation activities and cumulativeness was affected by the learning process, the firm's capability and feedback from the market, and high cumulativeness leads to high appropriability of innovation (Malerba 2005). Therefore, policies could also aim at enhancing networking and advisories of market. Enhancing networking and advisories of market would help companies commercialize their knowledge (e.g. licensing out) and get funds for their further development.

Chapter Seven: Alliances

7.1. Introduction

As reviewed in Chapter two, the notion of alliances and networks are widely studied in different disciplines, such as economics, corporate strategy, and inter-organizational field, and different theoretical perspectives and methodologies have been used to "understand the formation, evolution, operation and outcomes of organizational alliances and networks" (de Rond & Bouchikhi 2004;Osborn & Hagedoorn 1997, P261).

This chapter aims to describe the alliance activities of the UK drug discovery and development firms by analyzing agreements signed with other companies. This chapter also aims to find out why drug discovery and development companies are networked with other companies and what roles they play in networking? Moreover, how these companies networked during different periods and to what extent they networked? What technologies and disease indications were involved in these alliances? These questions are essential to answer the issue whether the British drug discovery and development subsector benefited from policies which aimed to promote the biotechnology and pharmaceutical industry.

In this chapter alliance agreements signed by drug discovery and development companies will be analyzed. 943 alliance agreements dated from 1983 to 2006 were collected. As discussed in the Methodology Chapter, data were collected from Recombinant Capital database and companies' websites. The Recombinant Capital database was also use by other researchers (Lerner & Merges 1998). According to types of signees, there are two types of agreements: agreements signed within the drug discovery and development section, or agreements signed between drug discovery and development companies and other pharmaceutical and biotechnological companies. This classification is used to describe the roles the drug discovery and development subsector played in the pharmaceutical and biotechnology industry. According to country of signees, there are two types of agreements: agreements signed with British companies, and agreements signed with foreign companies. This classification is used to describe the roles the drug discovery and development subsector played in international knowledge flow.

The first section will describe an overview of alliances between 1983 and 2006, and further details of these alliances will be analyzed in later sections, including geographical networking, purpose of alliances, disease indications, technology and stage of alliance, followed by discussion of key features of alliances in different periods. The final section is the summary and conclusion.

7.2. Overview of Networking

The networking of UK drug discovery and development companies has been changing dramatically in the past decades. During the 1980s, shortly after the UK first generation biotechnology firms were born, they established connections with the pharmaceutical and biotechnology industries from other countries: 32 agreements in total during 1980s. The data

presented in this study were data of the UK first generation companies which was still in operation in 2006. Therefore, the real number of agreements was actually underestimated. As shown in Chart 39, the yellow dot in the middle represent the British drug discovery and development subsector established during 1980s. Other dots represented the domestic and foreign partners of this subsector. Lines represented the alliance agreements signed between these drug discovery and development companies and their partners. The largest group as partners during the 1980s was US pharmaceutical and biotechnological industries, in particular, the US large pharmaceutical companies (Chart 39). During the 1980s 19 agreements (59 per cent) were signed with US companies. The drug discovery and development subsector also established a few connections with European and domestic large pharmaceutical companies, and other biotechnology and pharmaceutical companies from Europe and the rest of the world.

In the 1990s, the UK first generation firms established wider connections with other companies. US companies were still the largest group of partners. However, these companies cooperated more with the US small to medium sized biotechnology and pharmaceutical companies, rather than with large pharmaceutical companies. The emerging British drug discovery and development companies also rapidly established collaborations with US and EU companies. These companies which were founded after 1990 not only allied foreign and local companies, but also with their domestic competitors: the first UK generation drug discovery and development companies. The rapid growth of second generation firms changed the structure of the network (Chart 40).

Chart 39 Networking of the UK biotechnology subsector during the 1980s

(Powered by VisuaLyzer 2.0)

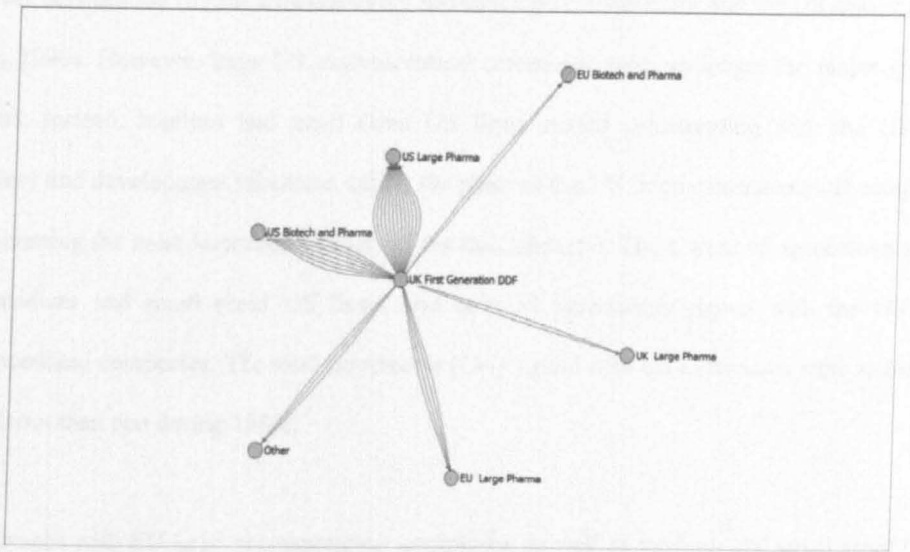
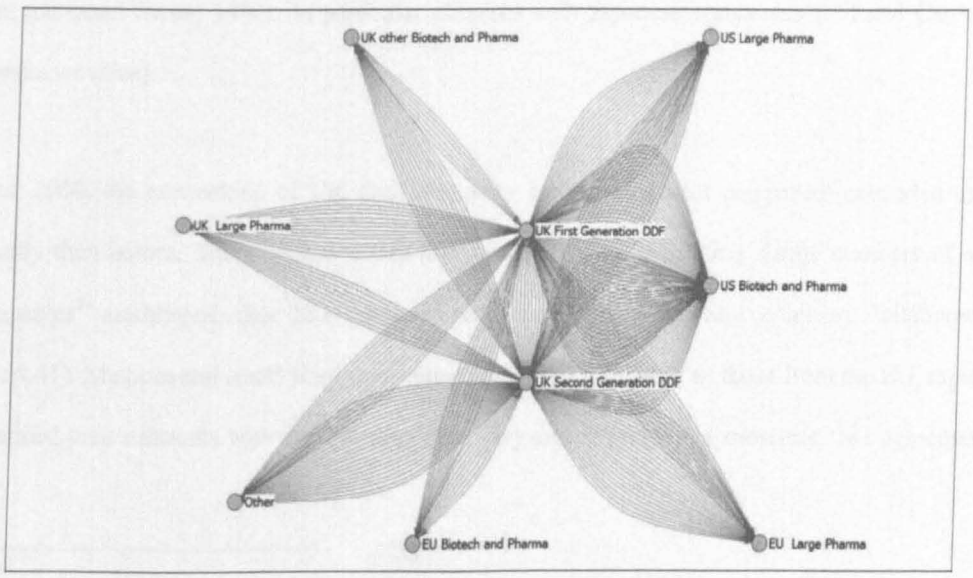


Chart 40 Networking of the UK biotechnology subsector during the 1990s

(Powered by VisuaLyzer 2.0)



Both first generation and second generation firms played important roles in networking. There were 290 agreements signed in total during the 1990s. Besides small scale collaboration between first and second generation firms, many local support companies also joined the network. The alliances between the British drug discovery and development subsector and the US also expanded during 1990s. However, large US pharmaceutical companies were no longer the major group of partners, instead, medium and small sized US firms started collaborating with the UK drug discovery and development subsector, taking the place of the US large pharmaceutical companies, and becoming the most important partners of the this subsector. There were 95 agreements signed with medium and small sized US firms, and only 39 agreements signed with the US large pharmaceutical companies. The total agreements (134) signed with US companies were as many as seven times than that during 1980s.

The alliances with EU large pharmaceutical companies, as well as medium and small sized firms, also increased to 54 agreements: as many as nine times than that during 1980s. The top three countries were Germany (12 agreements), Switzerland (nine), and France (seven). The collaboration with the UK pharmaceutical companies was also expanding, but less than collaboration with the US and the EU. Connections with companies in other geographic regions also increased during 1990s, in particular alliances with Japanese companies (15) and Canadian companies (five).

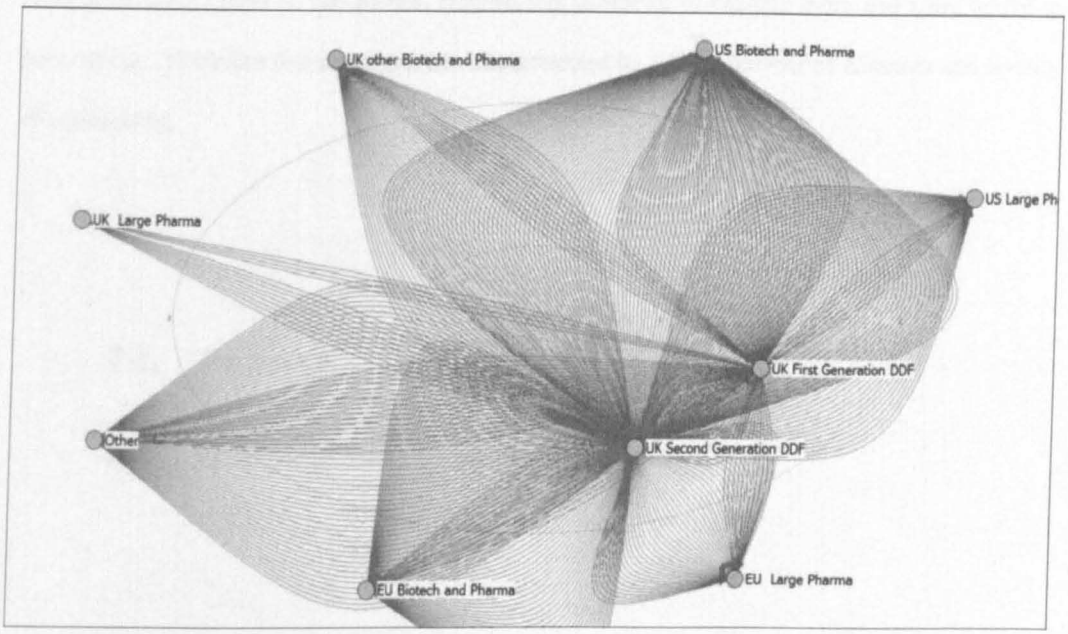
After 2000, the networking of UK drug discovery and development companies expanded more quickly than before. The alliances within this subsector were increasing. Large numbers of new companies[34] established after 2000 attracted more foreign and domestic company collaborators (Chart 41). Medium and small sized companies from the US, as well as those from the EU, rapidly expanded their networks with the UK drug discovery and development subsector. 181 agreements

[34] The UK drug discovery and development companies established after 2000 are also part of second generation firms.

were signed with medium and small sized companies from the US, and 91 agreements were signed with medium and small sized companies from EU.

Chart 41 Networking of the UK biotechnology subsector after 2000

(Powered by VisualLyzer 2.0)



Large pharmaceutical companies from the US, EU, Asia and UK all played important roles in collaborations. However, the number of UK partners was less than that of the US and the EU. The increasing number of alliances from areas other the EU and the US, were mainly the results of connections with Japan, Australia and Canada. The top three EU countries which signed agreements with this subsector were Switzerland (27 agreements), Germany (24 agreements) and Belgium (nine agreements).

In short, the path of networking of UK drug discovery and development subsector began with collaborating with US companies, in particular large pharmaceutical companies, and then moved on to collaborate with small and medium sized companies from the US and the EU. One possible

reason for this was that in the last decade, the UK companies moved from research and development providers (R&D provider) to clients or co-developers. These worldwide alliances between small to medium sized companies also indicated a trend towards the division of labour in research and development in this subsector.

The growth of the drug discovery and development subsector, in terms of both size of individual companies and number of companies, enabled this subsector to become more and more active in networking. Therefore this subsector was characterized by a large number of alliances and density of networking.

7.3. Partners

7.3.1. North American companies

Since the start of the industry, US firms have been the most important partners for the UK drug discovery and development subsector in terms of number of alliances. US firms have been involved in 41 per cent of all alliances (386 agreements); this is even higher than the 38 per cent of local alliances (355 agreements). In total, United States and Canada have been involved in 45 per cent of all alliances. The main reason for this is the leading role and the sheer size of the North American industry since 1980s. One important motivation for drug discovery and development subsector to form alliances with US companies was to access the technology advances.

In the 1980s, 59 per cent of agreements were signed between the UK drug discovery and development subsector and the US companies. On most occasions they acted as R&D buyers. However, in the 1990s, the percentage of US partners dropped to 46 per cent. Large American

pharmaceutical companies were still major buyers; however, a significant number of American companies became R&D providers in British-American alliances: 87 British companies were R&D providers and 47 US companies were R&D providers in British-American alliances during 1990s. Three companies were very active in sourcing R&D in American: they were Shire Pharmaceutical (five agreements), Cambridge Antibody (four agreements), and Celltech (including smaller UK firms that were acquired by Celltech such as Chiroscience, Medeva, and Oxford GlycoSciences, in total 18 agreements). These drug discovery and development companies accumulated knowledge and experience through alliances.

After 2000, the percentage of British-American alliances decreased to 37 per cent. UK companies became more active in acquiring American companies, which would enable them to enter the North American market and to expand their products portfolio. The total number of agreements acquiring or purchasing assets of the US companies was 20 after 2000. For example, Shire Pharmaceutical, had acquired three US companies and subsidiaries of one US company before 2000, and after 2000, Shire Pharmaceutical acquired another three US companies and one Canadian company. In 1997 Shire Pharmaceutical acquired drug delivery company Pharmavene, which is key for drugs CARBATROL and ADDERALL XR, and marketing company Richwood Pharmaceutical Company to enter US market. In 1999, Shire Pharmaceutical acquired the German, French and Italian sales and marketing subsidiaries of Fuisz Technologies Ltd, and merged with American company Roberts Pharmaceutical Corporation to build market cap. In 2001, Shire acquired Canadian company BioChem Pharma to build market cap. In 2002, Atlantic Pharmaceutical was acquired by Shire, and turned into a principle manufacturing site of its US operation. In 2005 and 2007, shire acquired Transkaryotic Therapies Inc and New River Pharmaceuticals Inc respectively for their technology platform and pipelines (www.shire.com).

7.3.2. Domestic and European Companies

UK drug discovery and development companies became increasingly active in networking within both local companies and companies from other European countries after 1990.

Firstly, connections were strengthened among UK companies, in particular, within the drug discovery and development subsector. For the British-British alliances identified in the study, the percentage grew from 16 per cent in 1980s to 22 per cent of total alliances number in 1990s, and increased to 23 per cent after 2000. The alliances among British companies, in particular the internal connections within the drug discovery and development subsector, was actually strengthened. However, the total number of British-British alliances only accounted for a small fraction of the total alliances. Mergers and acquisitions within the subsector after 2000 also led to consolidation of this industry: large drug discovery and development firms were formed after 2000, e.g. Celltech and Cambridge Antibody, although many of them were later acquired by large pharmaceutical companies.

Secondly, companies from other European countries also became more active in networking with the UK drug discovery and development subsector after 1990s. Most of these companies were large pharmaceutical companies from Switzerland (e.g. Novartis), Germany (e.g. Bayer) and France (e.g. Rhone-Poulenc Rorer). After 2000, large pharmaceutical companies from Belgium (e.g. UCB) and Ireland (e.g. Elan) also became important clients of the UK drug discovery and development firms. Their major interest was research collaboration, licensing, and acquisition, and this will be discussed in details in later sections.

Companies from Switzerland and Germany also acted as service providers: German companies were mainly focused on research collaboration and licensing, and Swiss companies were mainly

suppliers and manufactures to UK firms. The number of alliances with Belgium companies was very small; however, one third of these alliances were about acquisitions, e.g. Celltech was acquired by UCB in 2004, Inpharmatica and Prostrakan's French subsidiary ProSkelia were both acquired by Galapagos NV in 2006. This trend was partly driven by the motivation of European biotechnology and pharmaceutical industry to access technologies and markets.

7.3.3. Asia and Pacific companies

Companies from Japan, in particular large pharmaceutical companies, had allied with the UK drug discovery and development subsector since the 1980s. They mainly acted as buyers and were interested in research development and licensing. Companies from Australia also became more important partners after 2000 (16 agreements). They were not only buyers but also R&D providers. There were also partners from other countries of this area after 2000, e.g. China, India, Singapore and Korea. However, their alliances only accounted for less than two per cent of the total.

Why did these companies ally more with foreign companies than local companies? Learning knowledge from alliances, gaining access to complementary assets and novel technologies and building technology advantages could be the main reasons they allied with foreign companies, in particular, US companies. Based on research on the UK genomic firms, Cooke observed that the British companies are more innovative in partnering with US and Asian firms (Cooke 2006). He suggested that "firms have no desire to conduct R&D with local competitors because they already know its likely content due to 'open science' and localized knowledge spillovers among firms competing in highly specific local niches" (Cooke 2006, P1274).

7.4. Purposes of Alliances

7.4.1. Licensing, research and clinical development

The major purpose of alliances was licensing in and licensing out: 34 per cent of total alliances in the 1980s were concerned with licensing; later this number grew to 57 per cent in the 1990s, and 64 per cent after 2000. The main reason for this was that intellectual capital accumulated since 1990s attracted many partners to form alliances with the UK drug discovery and development companies (Coombs, Mudambi, & Deeds 2006;Hsu 2006).

Although the number of alliances concerned with research and development has grown steadily since the 1980s, the growth rates were slower than that of licensing. As a consequence, 50 per cent of total alliances in the 1980s were concerned with clinical development. This number decreased to 39 per cent in 1990s, and fell further to 22 per cent after 2000. The percentage of alliances concerned with research has been stable at one fifth since 1980s.

This fast growth in licensing, steady growth of research and slower growth in development may suggest that many UK drug discovery and development companies start discovery and development internally. These companies which began exploring new product pipelines, due to the constraint of financial support, they licensed out products with poorer prospects in early stages rather than continued to development stage (as mentioned in the Literature Review Chapter). This also indicated their relative maturity in early stage product discovery and development.

7.4.2. Acquisition, Asset purchases, Joint Venture and Equity Investment

In the 1980s, acquisitions were very rare, and later in 1990s, there were 22 acquisitions, and since 2000, 70 acquisitions have been recorded including ten brand acquisitions. Similarly, the number of asset purchases also grew fast, from 18 cases in 1990s, to 46 cases after 2000. At the same time, the growth of numbers in joint venture slowed down.

One possible reason for the fast growing number of acquisitions, as suggested by Walsh, was that the acquisitions were more attractive and less risky than normal collaborations if companies wanted to develop products internally (Walsh 2002). Other possible motives for acquisitions included moving away from R&D weakness by accessing technology and expertise, i.e. large pharmaceutical companies acquired biopharmaceutical companies, and to achieve market presence, i.e. UK drug discovery and development companies acquired US biopharmaceutical companies (Walsh 2002). One example was in 1997 Shire Pharmaceuticals acquired specialty sales and marketing company Richwood Pharmaceutical Company to enter the US market. In 1999, Shire Pharmaceutical acquired the German, French and Italian sales and marketing subsidiaries of Fuisz Technologies Ltd to enter major European markets.

As discussed earlier in this chapter, merger and acquisitions have a very important impact on the structure of this industry. Since the 1990s, merger and acquisitions enabled several drug discovery and development companies to go into the top biopharmaceutical companies of Europe, such as Celltech and Shire Pharmaceutical. On the other hand, large scale merger and acquisitions after 2000 also lead to dramatic changes in the subsector structure.

After 2000, drug discovery and development companies acted as buyers in 55 per cent of acquisitions and asset purchases, including acquisitions and assets purchases within the drug discovery and development subsector (Table 27). Drug discovery and development companies were mainly focused on buying domestically or from North American. 24 per cent of total acquisitions and asset purchases were UK drug discovery and development companies buying North American companies, and European companies only accounted for six per cent. 25 per cent of total acquisitions and asset purchases were UK drug discovery and development companies buying domestically, divided into 18 per cent buying within drug discovery and development subsector, and seven per cent buying out of this subsector.

North American companies were also a major buying force in acquiring UK drug discovery and development subsector, accounted for 22 per cent of total acquisitions and asset purchases, which is slightly less than the UK drug discovery and development companies purchasing from North American (Table 28). 12 per cent of total acquisitions and asset purchases were European companies acquiring UK drug discovery and development companies, which is twice as much as the UK drug discovery and development companies buying from Europe.

There are three types of domestic buyers: buyers within the drug discovery and development subsector were the largest buyers, and accounted for 18 per cent of total acquisitions and asset purchases. This is the determinant of subsector structure change and dynamics. Buyer companies out of this subsector accounted for eight per cent of total acquisitions and asset purchases, including large pharmaceutical companies such as GSK and AstraZeneca.

Although the number of acquisitions by large pharmaceutical companies (including large pharmaceutical companies from other country) was less than that of other companies, the large pharmaceutical companies actually conducted the largest acquisitions in this subsector: they 'harvest' the well established companies, in particular, those most successful companies, of the drug discovery and development sector.

Table 27 Acquisitions/asset purchases of other companies

Categories	Region		Number	Percentage Of all A/A
Acquisitions/assets purchases of foreign companies	North American	US	22	24%
		Canada	6	
	Europe	Germany	3	6%
		Switzerland	2	
		Sweden	1	
		Spain	1	
Acquisitions/assets purchases within UK drug discovery and development subsector	UK		21	18%
Acquisitions/assets purchases of other UK companies			8	7%

Table 28 Acquisitions/asset purchases by other companies[35]

Categories	Region		Number	Percentage Of all A/A
Acquisitions/assets purchases by foreign companies	North American	US	21	22%
		Canada	5	
	Europe	Belgium	3	12%
		Ireland	3	
		Sweden	3	
		Switzerland	3	
		Netherlands	1	
		Germany	1	
	Other	Australia	1	3%
		Japan	1	
		India	1	
Acquisitions/assets purchases by UK large pharmaceutical companies	UK		4	3%
Acquisitions/assets purchases by other UK companies			6	5%

[35] Total number was slightly different from simply adding up because some company belong to more than one country, e.g. AstraZeneca was a UK-Sweden company.

7.5. Disease indications and Technologies

Alliances were mainly focused on cancer and central nervous system diseases, as well as infection, inflammation and pain. Cancer was the major indications of alliances. In the 1990s, there were 27 alliances focused on cancer, accounted for nine per cent of total alliances during 1990s (Table 29). After 2000, this number grew to 92 alliances, accounted for 15 per cent of total alliances after 2000. No alliance focused on the central nervous system in the 1980s. There were 22 alliances concerned with the central nervous system diseases in the 1990s accounting for eight per cent of total alliances during 1990s. This number increased to 75 after 2000, which accounted for 12 per cent of alliances during this period. Treatment for infection, inflammation and pain were other concerns of the alliances, which have grown fast in the last decades. In the 1990s, there were 16 agreements focused on infection; after 2000, this number grew to 42. In the 1990s, there were 16 and 13 alliances on inflammation and pain respectively; after 2000, these numbers grew to 31 and 35.

Table 29 Indications of Alliances

Indications	1990s		After 2000	
	Number of alliances	Percentage	Number of alliances	Percentage
Cancer	27	9	92	15
Central Nervous System Disease	22	8	75	12
Infection	16	6	42	7
Inflammatory disease	16	6	31	5
Pain	13	4	35	6

Alliances slowly expanded on researching cardiovascular diseases, respiratory, genito-urinary, autoimmune, blood and haematopoietic factors, gastrointestinal, kidney disease and wound care. Records of other indications also presented an increase trend in the number of alliances; however,

they were still on a smaller scale. These indications included cardiovascular diseases, respiratory, genito-urinary, autoimmune, blood and haematopoietic factors, gastrointestinal, kidney disease and wound care. For example, cardiovascular diseases were major indications in the 1980s: there were five alliances concerned with cardiovascular diseases (16 per cent), more than cancer and infections. In the 1990s, there were 11 alliances and the percentage dropped to four per cent and after 2000, the number of alliances focused on cardiovascular diseases were 13, and only accounted for two per cent of the total number. The alliances concerning diagnostics, ophthalmic, dermatologic, metabolic disorders, and obesity were relatively less active in the last decades.

7.6. Technologies

Both chemical and biological technologies have been involved in alliances. The number of alliances involving synthetics, screening, drug delivery, rational drug design, monoclonals, bioinformatics, gene expression, vaccines and proteomics, grew very fast since 1990s. Technologies related to chemistry were very popular in alliances, e.g. synthetics, screening and rational drug design after 2000. In the 1980s, the total number of alliances focusing on synthetics, screening and rational drug design was five. However, in the 1990s, the number of alliances concerning synthetics, screening and rational drug design increased to 39, 27 and 14 respectively, and after 2000, there were 123, 87 and 45 alliances respectively (Table 30). This made synthetics and screening the most popular technology in alliances, accounting for 20 per cent and 14 per cent of total alliances after 2000.

Table 30 Technologies most in use in alliances during 2000 and their use during 1990s[36]

Technologies Involved in Alliances		1990s			After 2000		
		Number of alliances	Percentage	Total	Number of alliances	Percentage	Total
Chemistry	Synthetics	39	13	69 (24 per cent)	123	20	184 (30 per cent)
	Screening	27	9		87	14	
	Rational drug design	14	5		45	7	
Biotechnology	Monoclonal	31	11	65 (22 per cent)	69	11	205 (33 per cent)
	Bioinformatics	2	1		47	8	
	Gene expression	22	8		44	7	
	Proteomics	7	2		42	7	
	Vaccines	16	6		40	6	

Biological technologies, such as monoclonal, bioinformatics, gene expression and proteomics, also became more important in alliances during last decades. The number of alliances concerning monoclonals grew from 31 in the 1990s to 69 after 2000. There were only two cases of use of bioinformatics before 2000; however, this number was 47 after 2000. This made the bioinformatics the fastest expanding technology in alliances. Gene expression, vaccines and proteomics also have shown a fast growing trend since the 1990s. Although each individual biological technology did not dominated after 2000, the total percentage of biological technologies increased, i.e. monoclonal, bioinformatics, gene expression, proteomics and vaccines, accounted for 33 per cent of total alliance after 2000. This percentage was more than the 30 per cent of alliances using chemical technologies, which suggests that although both chemical and biological technologies are very important in alliances, overall biological technologies were expanding faster than chemical technologies in alliances since 1990s.

Technologies such as peptides, gene sequencing and cell therapy were also expanding in use in alliances. There were only four agreements concerned about peptides during 1990s, after 2000, this

[36] The total number of alliances using chemical and biological technologies was less than adding up individual technologies, because an alliance may involve more than one technology. Also there are small amount of alliances involve in using both chemical and biological technologies.

number increased to 26. Alliances about gene sequencing were ten during 1990s and 13 after 2000. There was only one agreement about cell therapy before 2000, and after 2000, there were 11 agreements.

Apart from the popular technologies discussed above, there were also many technologies less in use in alliances, such as natural products, separation, immunoassay, immunoglobulin and transcription factors. One reason for this was that these technologies were very mature, and companies could use these technologies without partnership.

7.7. Stage of drug discovery and development

Alliances were signed at an early stage of discovery in 1980s. During 1980s, except for one alliance which was signed after the drug was approved, all others were signed at discovery (5, 16 per cent), lead molecule (5, 16 per cent) and formulation stages (5, 16 per cent)[37]. None of them had entered the preclinical or clinical stage. This indicates that in the1980s, drug discovery and development companies, such as Celltech, were focusing on early stage drug discovery. This also suggests that this subsector was still immature.

In the 1990s the stages of alliances extended to all eight stages, from discovery, lead molecule, formulation, to preclinical, phase I , phase II, phase III, BLA/NDA filed and approved stages. There largest groups were alliances signed at discovery and formulation stages, accounting for 22 per cent and 14 per cent of the total respectively. Alliances signed at preclinical and later stages accounted for 27 per cent (Table 31). Although there were only a few alliances signed at phase III,

[37] Some data were not available, therefore the total percentage were less than 100 per cent.

this still indicated that the drug discovery and development subsector started to enter into late stages of drug development.

Table 31 Stage of drug discovery and development in alliances

Stage of signing agreements	1980s		1990s		After 2000	
	Number of Agreements	Percentage	Number of Agreements	Percentage	Number of Agreements	Percentage
Discovery	5	16	65	22	193	31
Lead Molecule	5	16	14	5	29	5
Formulation	5	16	42	14	32	5
Preclinical	0	-	22	8	23	4
Phase I	0	-	14	5	22	4
Phase II	0	-	12	4	29	5
Phase III	0	-	9	3	21	3
BLA/NDA filed	0	-	2	1	6	1
Approved	1	3	16	6	34	5

After 2000, the numbers of alliances increased in all stages except the formulation. Since the 1990 the drug discovery and development subsector was involved in all stages of drug discovery and development, and this subsector kept active in networking after 2000. The agreements concerning with discovery grew very fast, from 65 agreements (22 per cent) in the 1990s to 193 agreements (31 per cent) after 2000. The number of alliances signed at lead molecule grew steady, from 14 agreements (five per cent) in 1990s to 29 agreements (five per cent) after 2000. On the other hand the number of alliances signed at formulation stage decreased after 2000 (Table 31). There are 42 agreements (14 per cent) signed at lead molecule stage during the 1990s, this number dropped to 32 (five per cent) after 2000. The number of agreements signed at preclinical stage increased from 22 in 1990s to 23 after 2000, while the percentage dropped from eight per cent of total alliances during 1990s to four per cent after 2000. The overall number of agreements signed at discovery, lead molecule, formulation and preclinical stages grew steady and dominated the total number of agreements.

The numbers of alliances signed at phase I, phase II, and phase III increased steady after 2000. The number of agreements signed at phase I grew from 14 (five per cent) during 1990s to 22 (four per cent) after 2000. The number of agreements signed at phase II grew from 12 (four per cent) during 1990s to 29 (five per cent) after 2000, and the number of agreements signed at phase III grew from nine during 1990s (three per cent) to 21 after 2000 (three per cent). The overall percentage of agreements signed at phase I, phase II, and phase III kept at 12 per cent since 1990s.

7.8. Alliance activity in different periods

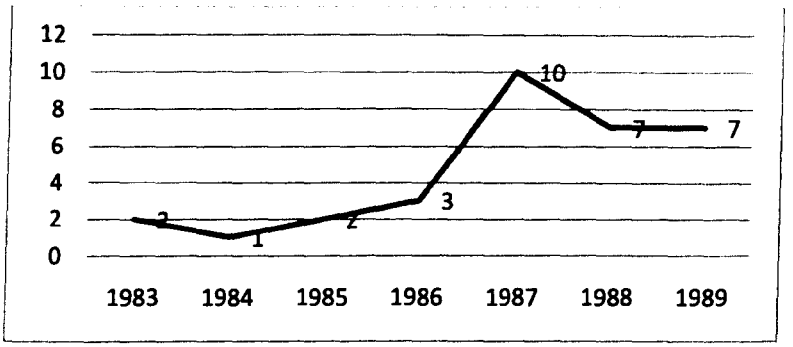
One of the most notable features of this data is that alliance activities had different characteristics during different time periods: not only has the number of alliances fluctuated over time, but also the purpose, technologies and disease indications have changed. This section will describe the alliances from a perspective of dynamics.

7.8.1. 1980s

Small scale alliances focused mainly on R&D providing during the 1980s. During the 1980s the number of alliances created by the UK drug discovery and development subsector was no more than ten each year (Chart 42). There were only eight firms involved in alliances. Two of them were major participants: Celltech involved in 15 agreements, accounted for 47 per cent of all alliances in the 1980s, and Vernalis involved in seven agreements, accounted for 20 per cent. Other important

firms included Shire Pharmaceutical, Xenova, Amarin, Controlled Therapeutics, Chiroscience (acquired by Celltech in 1999) and Cantab Pharmaceuticals (acquired by Xenova in 2001). These six companies accounted for 33 per cent of all alliances.

Chart 42 Agreements signed during 1980s



Another important feature during 1980s was that in most of the 32 alliances (with only two exceptions) the UK drug discovery and development firms played the role of R&D provider rather than purchaser. Their partners were mainly from the US: 19 agreements (59 per cent) were signed with US companies. The majority of these clients were large pharmaceutical companies, which included Lilly, SmithKline, Abbott, Baxter, Pifzer, Roche and DuPont. The major fields of research varied, including drug delivery, monoclonals, recombinant DNA and synthetics. Major indications were cardiovascular diseases and cancer. 72 per cent of agreements were about research, development and license.

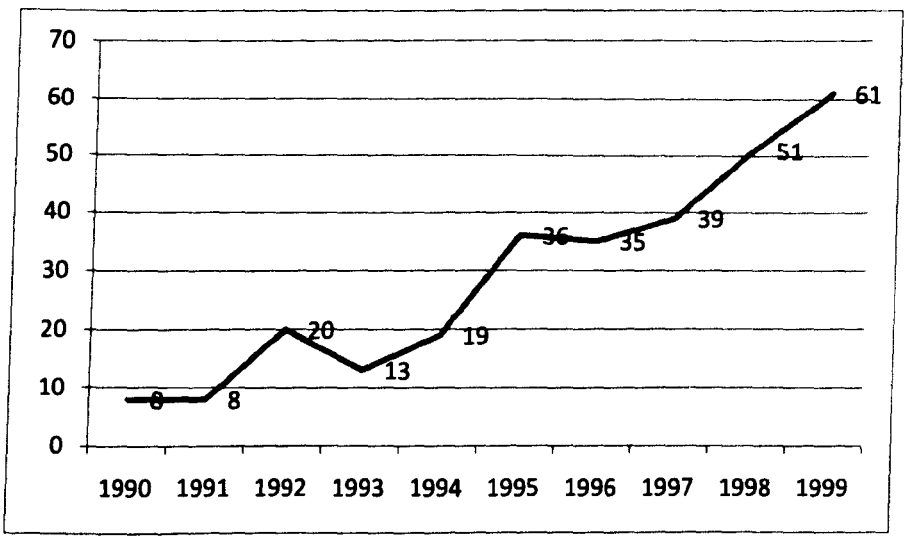
7.8.2. 1990s

Alliances grew steadily during the 1990s. Although there was a slight decrease in terms of agreements in 1993 and 1996 (Chart 43), the overall trend was a growth: from eight agreements in 1990 to 61 agreements in 1999. The main reason for the growth was that the newly established

drug discovery and development firms started networking. The new important players included Acambis, Cambridge Antibody, Medeva, Oxford BioMedica, Oxford GlycoSciences, and Pharmagene. They signed 165 agreements in total, which accounted for 57 per cent of total agreements signed during the 1990s.

Celltech was still the most active player in networking, not only because it was involved directly in 14 per cent of the total number of alliances during the 1990s, but also because of two mergers and acquisitions in 1999, which made Celltech the largest biotechnology company in Europe. One merge was between Chiroscience and Celltech to form Celltech Chiroscience plc in June 1999, and the other was when Celltech Chiroscience plc acquired Medeva Plc in November 1999. Another important acquisition also happened in the same year when Shire Pharmaceutical acquired Robert Pharmaceutical, a US company, for one billion US dollar in stock. These signs indicated that the UK drug discovery and development firms were not only active R&D providers, but also active buyers, and collaboration within the UK discovery and development subsector was becoming more and more common. This further suggests increasing maturity of these companies during 1990s.

Chart 43 Agreements signed during 1990s



One direct result of the growing intra-sector alliances was that the percentage with foreign companies, in particular, US companies, decreased. The number of agreements signed with US companies increased from 19 during 1980s to 134 during 1990s. But the percentage of alliances with US companies decreased: 59 per cent of total alliances during the 1980s, compared with 46 per cent during the 1990s.

Major collaboration fields not only included synthetics, monoclonals, recombinant DNA and drug delivery, but also expanded to gene expression, gene therapy, proteomics, peptides, vaccines, bioinformatics, combinational chemistry, screening, rational drug design, and natural products.

Cancer, central nervous system diseases and anti-inflammatory diseases became the most important indications of alliances during 1990s, compared with cardiovascular diseases and cancer during 1980s. Other disease major indications included autoimmune, cardiovascular, dermatologic, gastrointestinal, infection, metabolic disorders, pain, respiratory disorders, and wound care. There was also a small number of research alliances on blood & hematopoietic factors, gynecological/genito-Urinary, kidney disease, ophthalmics and obesity.

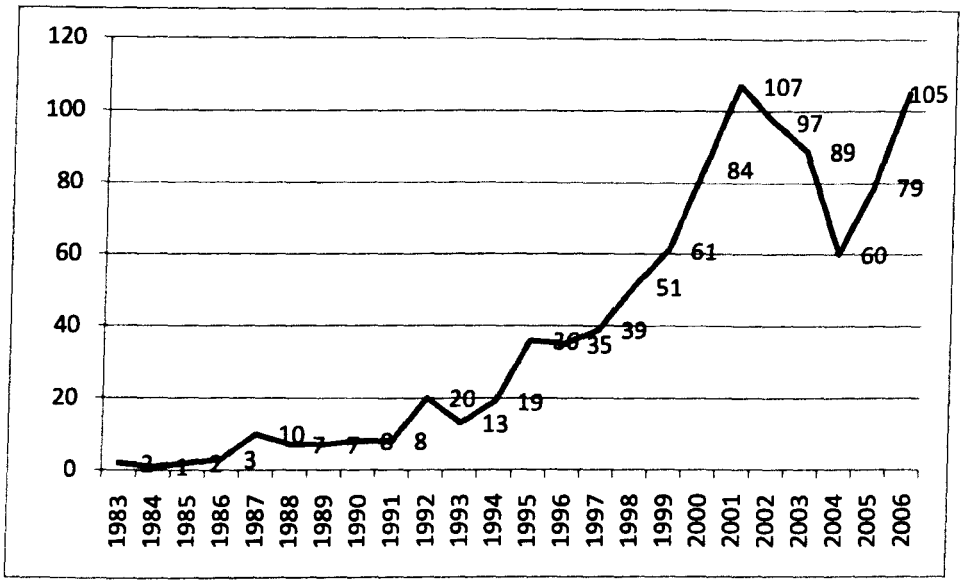
Each alliance may have several purposes, for example, one agreement many included both co-development and license. During the 1990s, 73 per cent agreements were about research, development, and licensing; this is similar as the level of 72 per cent agreements about research, development, and license during 1980s.

7.8.3. After 2000

There was a dramatic increase in the total number of alliances, together with large scale mergers and acquisitions since 1999. However, by 2002 this trend was broken when the alliance number

decreased for three years: the number of alliances in 2004 was 56 per cent as many as that in 2001. Then in 2005 and 2006, the number of alliances started growing rapidly again (Chart 44). The agreements signed in 2006 were only two fewer than that of 2001.

Chart 44 Agreements signed between 1983 and 2006

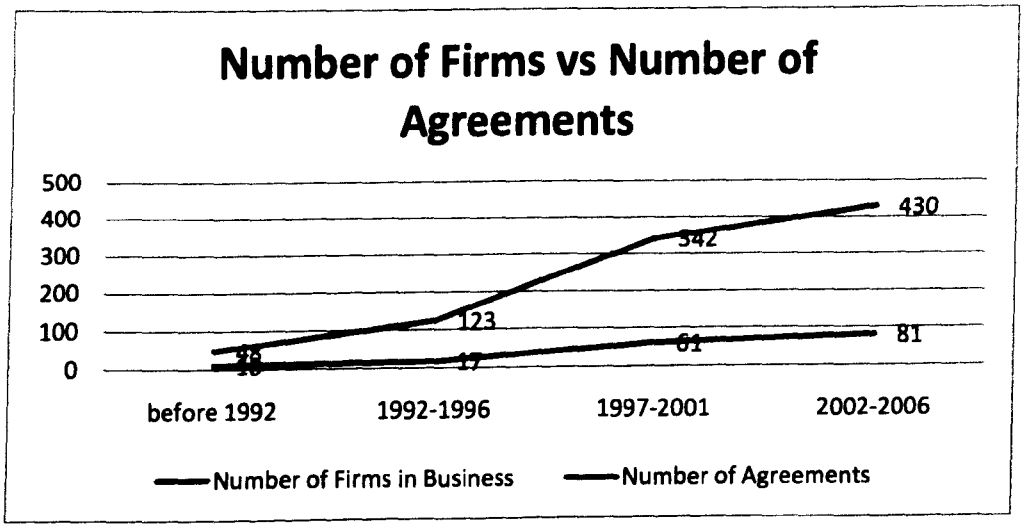


However, the decrease in numbers in 2002/2004 did not indicate inactive networking; rather this indicated an important consolidation of this subsector, because there were large scale mergers and acquisitions which replaced the normal co-research and co-development (Table 32). Besides consolidation within the UK biotechnology sector, this industry consolidation also included foreign companies, in particular large pharmaceutical companies, from North America, Europe, and Asia. The overall increase pattern of alliances was not only because of the growing number of firms (Chart 45). The growing size of firms, which accumulated large number patents and experience, is an important factor attracting partners.

Table 32 Selection of Acquisitions (Over £100 million)

Date	UK DD+D company which has been acquired	Company which acquired UK DD+D company	Value
May 2006	Cambridge Antibody Technology	AstraZeneca (UK-Sweden)	£702million
July 2005	Arakis Limited	Sosei Co. Ltd (JAPAN)	£106.5 million
May 2004	Celltech	UCB (Belgium)	£1.53 billion
May 2003	PowderJect	Chiron (US)	£542 million

Chart 45 Number of Firms vs Number of Agreements



Other research on European biopharmaceutical industry between 1980 and 2000 also showed intensive and increasing networking (Ahrweiler, Gilbert, & Pyka 2006). Ahrweiler suggested that

"networks persist as the main structuring principle of the biotech industry despite firms changing their components, attachment strategies and structural properties. For example, in the UK and German biopharmaceutical industries, collaborative activity can be observed as a permanent feature" (Ahrweiler, Gilbert, & Pyka 2006).

Similar as 1990s, cancer, central nervous system diseases, and inflammatory diseases were still the main indications of alliances. 15 per cent of all alliances after 2000 were about cancer treatment. Infections also became a major indication after 2000. The major technologies concerned in agreements were synthetics, screening and drug delivery, followed by monoclonals, gene expression and bioinformatics. The technology involved in alliances also expended to cell therapy. Both biological and chemical technologies increased in use in the alliances after 2000; however, biological technologies grew faster than chemical technologies.

7.9. Summary

In this chapter, alliances of the drug discovery and development subsector have been reviewed and discussed. Previous researches indicated that the motivation of drug discovery and development companies to form alliances included learning from alliances, gaining access to complementary assets and novel technologies; reducing cost, market uncertainty and firm specific uncertainty; and building competitive advantages.

This project found that the evolution of networking of the UK drug discovery and development subsector began with collaborating with US companies, in particular large pharmaceutical companies, and then moved to collaborate with small and medium sized companies from the US

and the EU. The role which drug discovery and development firms played in alliances since the 1980s moved from solely R&D providers to buyers, reflecting the continuous growth and development of the drug development subsector since the 1980s. They have been generating, learning and diffusing knowledge through networking, and this has enabled their development and strength.

As Senker suggested, the histories, resources and capacity of companies determined its strategy (Senker 1996). Companies with more R&D capacity are inclined to choose a research oriented strategy, and gain returns mainly from licensing out and contracting, while companies with more experience of downstream development are inclined to choose licensing in and marketing. The fast growth in licensing, steady growth of research and slower growth in development may suggest that many UK drug discovery and development companies have started discovery and development internally. Although these companies have been exploring new product pipelines, due to the constraint of financial support, they licensed out products in early stages rather than continued to development stage. This also indicated their relative maturity in early stage product discovery and development. Their maturity in early stage product discovery could be the main reason why many companies which were developing platform technologies and early stage products were acquired by large pharmaceutical companies.

Form a perspective of the drug discovery and development subsector, these companies learnt from networking, and the growth of the subsector accompanied the increase of networking, in terms of both sheer numbers and density. The tradition of networking in this subsector enables accumulation of alliance experiences and further facilitates the performance of alliances. In the next two chapters, data on alliances and data from other chapters will be integrated and discussed.

Implications for policy:

The continuously exceptional intensive investment of the drug discovery and development sector produced large numbers of patents and drug candidates, but these patents and compound candidates need to be rapidly converted into successful products, otherwise these companies would be affected by financial problems and acquired by large pharmaceutical companies. This raises important questions about the long-term benefit of the industry to the UK economy, as it would appear that the benefits of the very successful knowledge production of these firms do not remain in the UK. Although the connections of this subsector with the domestic industry have been expanding, it still only accounts for a small fraction of the total alliances. It therefore appears that foreign countries are benefitting significantly from the activities of the UK drug discovery and development industry. Policies should respond to the "harvest" of successful UK knowledge and firms by foreign companies or large international pharmaceutical companies, and enable the healthy growth of the UK drug discovery and development sector.

Chapter Eight: Integration of Data

Considering the pharmaceutical and biotechnology industry as a Sectoral Systems of Innovation, this study investigated the emergence of new actors in this system of innovation – the drug discovery and development companies established after the 1980s, when biotechnology first started to be applied to the drug innovation process. Malerba suggests four key challenges that are required for a better understanding of the relationship between innovation and the evolution of industries: the analyses of demand, knowledge, networks and co-evolution (Malerba 2006). This study investigated the knowledge base, technology domain and networks of UK the drug discovery and development companies. Using the conceptual framework of Sectoral Systems of Innovation, four issues were examined in this study:

1) The drug discovery and development subsector's structure, the size and age of firms, their clustering and concentration;
2) The knowledge contribution of the drugs discovery and development subsector and how this has developed over time;
3) Their networking and collaboration with other actors and how this has changed over time;
4) The development of different company strategies.

From a historical and industry dynamics perspective, this study aimed to understand the co-evolution of knowledge and network, and to stress the policy implications of these developments.

This study began with a historical introduction of the drug discovery and development activities of the pharmaceutical and biotechnology industry, and how policy and regulations were used to shape this sector. This historical background was mainly focused on the period before the emergence of the focal companies, followed by a discussion of the contemporary pharmaceutical and biotechnology industry. Within this context, the focal subsectors' nature, technology domain, knowledge contribution, and networking were studied from a perspective of dynamics.

This chapter will first look at the structure, clustering and concentration of the drug discovery and development subsector. Then it will discuss knowledge production and networking, and its impact on the wider pharmaceutical and biotechnology industry. Finally it will categorize the 81 companies according to their operations and activities and further analyze strategies, alliances and knowledge production. The third section is a preparation for answering research questions in the conclusion chapter.

8.1. Mapping the drug discovery and development subsector

8.1.1. Clustering, concentration and globalization

One important feature of the UK drug discovery and development subsector was its hierarchical structure comprised of a few mature firms and a large number of young small firms: 80 per cent of companies have been established for less than ten years and 63 per cent of companies employed

less than 50 staff. This is similar to Bagchi-Sen's study on US biopharmaceutical industry (Bagchi-Sen 2007).

The UK pharmaceutical and biotechnology industry is clustered in the southeast of England, with the drug discovery and development subsector located mainly in Cambridge, London and Oxford. However, the larger drug discovery and development companies who survived and matured, either established operations outside the UK or were acquired, in particular by foreign pharmaceutical companies or large international pharmaceutical companies. Only a minority of firms retained a sole UK focus. This suggests that it is difficult to survive in a global industry with a purely national focus. The main reason for this is the importance of international markets, in particular, the need to have an operational base in the US.

Based on the analysis of scientific publications, this subsector was highly geographically concentrated in terms of knowledge generation. Within the UK, Cambridge, Oxford and London were active centres in publishing. Total publishing and co-publishing were both highly concentrated in the Southeast of England, which was correlated with company clustering in these three places. Publication was even more concentrated than the number of companies in these areas, suggesting the most productive firms were mainly in this area.

Analysis of scientific publications also highlighted the heavy international networking of this sector. These forms collaborated widely with other countries, with the US and EU dominating co-publishing within this subsector. The result of citation analysis also indicated an important impact of American institutions upon this subsector's research. Together with results from co-publishing, research in the US strongly influenced the UK drug discovery and development companies in a direct way through co-publishing and an indirect way through citation. Therefore, basic knowledge, as measured by publications output, was generated within a global network, but UK based authors were geographically concentrated.

In contrast to the global network of the co-publication of scientific papers, patents were mainly published by UK inventors. There were only 14 per cent of patents co-published with inventors from other countries, mainly in the EU, with the majority of patents published by local inventors. However, the analysis of alliances agreements indicated that licensing was globalized. In other words, patenting mainly happened locally, but commercialization was globalized.

In short, this subsector shows a hierarchical structure in term of being dominated by a small number of very productive firms and these companies were highly clustered in Cambridge, London and Oxford. Basic knowledge production, which was generated through global cooperation, was also concentrated in these areas. However, patenting mainly happened locally, while commercialization was globalized.

8.1.2. R&D outputs

Another feature of this subsector was that companies were very R&D active. The top drug discovery and development companies ranked very high in terms of R&D investments. Compared with other companies of the pharmaceutical and biotechnology industry, this sector is very R&D intensive. Many companies invested more than 80 per cent of their sales in R&D. This exceptional intensive investment was a risk for the long term business development of this group of firms, as it made them vulnerable to acquisition from larger companies wishing to access new knowledge. In this sense, these highly productive firms can be thought of as 'knowledge rich', but had not managed to get commercial benefit from this due to the long time required for product development.

The drug discovery and development subsector is a major producer of knowledge, with the subsector's publications and citations data indicating a high level of productivity and a very hierarchical structure; a few companies dominated the publications produced by the subsector, in terms of both quantity and impact. One possible reason is that many of these high-end companies were established in the 1980s and may be the first movers in their fields, which enable them to accumulate larger numbers of publications and citations, as well as research experience. It is clear that the output of these companies is highly innovative and important, as seen by the high h-factors and number of citations. Although the total output of this subsector only accounted for a small proportion of all UK biomedical publications, the growth rate and impact of publications were far above average. An important finding was that the impact of the leading companies' publication was strongly correlated with its number of publications. This also supports the idea that the leading firms are very important producers of knowledge, both in terms of quality and quantity.

Similar to the pattern of SCI publications, the patent publications pattern also indicated a hierarchical structure, with a small number of companies publishing the majority of patents. The top company, Celltech, published as many patent as many large pharmaceutical companies. This high output of patents was mainly the result of the large amount of R&D investment of this sector.

The drug discovery and development sector has played a very important role in constructing product pipelines, in particular, in the early stages of drug discovery and development. The output of drug candidates was concentrated in well established firms, with late stage product development controlled by a handful of companies.

It is also important to notice that this industry has a large number of young small companies, and they only have limited scientific publications, patents and product pipelines. Considering most firms examined in this study have already formed product pipelines, therefore, for these young small firms, to survive and continue their product development is more difficult, because their

portfolios are less attractive to venture capitals and large pharmaceutical companies (Baum & Silverman 2004).

8.2. Networking and Collaboration

8.2.1. The dynamics of networking and collaboration

Alliance activities had different characteristics during different time periods: not only has the technologies changed over time, but also the number of alliances, purpose, disease indications have changed. This section will describe the alliances from a perspective of dynamics.

Small scale alliances focused mainly on R&D contracting occurred during the 1980s. Their partners were mainly from the US. Major indications were cardiovascular diseases and cancer.

Alliances number grew steadily during the 1990s, in particular collaboration within the UK discovery and development sector became more and more common, but the major partners were from the US and the EU. UK drug discovery and development firms were not only active R&D providers, but also became active buyers both from the foreign countries and internally. Cancer, central nervous system diseases and anti-inflammatory diseases became the most important indications of alliances during the 1990s.

There were dramatic increases in the total numbers of alliances, together with large scale mergers and acquisitions since 1999. Cancer, central nervous system diseases, and inflammatory diseases were still the main indications of alliances.

The purpose of alliances changed over time. 50 per cent of total alliances in the 1980s were concerned with clinical development. This number decreased to 39 per cent in 1990s, and fell further to 22 per cent after 2000. The percentage of alliances concerned with research has been stable at one fifth since 1980s. A major growth area of alliances was licensing: from 34 per cent of total alliances in the 1980s, increasing to 57 per cent in the 1990s, and to 64 per cent after 2000: this was partly due to the dramatic growth of patents. This fast growth in licensing, steady growth of research and slower growth in development suggested that many UK drug discovery and development companies started discovery and development internally, as shown by their product pipelines.

It is important to notice that, although the alliances between the drug discovery and development subsector and domestic companies grew rapidly since 1990s, the number of these alliances only accounted for a small fraction of the total number. The subsector's partners were mainly from the US and the EU. Therefore, much of the knowledge produced by this sector was going abroad through commercial licensing and M&As.

The co-evolution of knowledge production and networking were due to many factors, one major reason was the growing size of this subsector, which accumulated large number of patents and experience in drug development. This was an important factor in attracting partners. These are all features of the industry maturing.

8.2.2. Nodes of network

The three major disease categories of scientific publication and patents were similar: cancer, immune and immune mediated inflammation, and inflection. Scientific papers and patents were both published on biological and chemical knowledge, but with a greater emphasis on molecular biology and biotechnology. When compared with other studies of the research focus of public institutes (Webster 2005), this sector followed a similar research route and directions to the public sector. Considering the clustering of this subsector and global cooperation in scientific publications, these firms focused on learning and producing knowledge at the same time: learning from public institutions globally and locally, and producing large number of scientific papers and patents.

The three major disease categories of marketed drugs and pipeline drugs were cancer, central nervous system disease and infection. This result was similar to the analysis of alliances agreements. It is not supervising because over 70 per cent of alliances were concerned with licensing, research collaboration, and co-development.

The major difference between indications of product pipelines and alliances, and indications of scientific publications and patents publications, was the fraction of central nervous system diseases: this was very significant in product pipelines and alliances. Therefore, there were two patterns of focus in this subsector: it had a shared knowledge and technology domain with universities and public institutions in publishing scientific papers and patents; while the subsector's drugs and pipeline products had a similar focuses to their partners in the pharmaceutical and biotechnology industry.

The findings of this study suggested that there were different focuses on basic knowledge production and product development, and this was mainly due to their interaction with their partners. The focuses of knowledge production of this subsector were changed when partners changed.

In other words, this subsector worked as a node of the network of knowledge production, connecting both academic institutions and the established pharmaceutical industry. These firms served as both knowledge producers in their own right, but also as intermediaries in transferring knowledge from academia to the pharmaceutical industry.

This result therefore give indirect evidence of the impact of technology push and market drive (Walsh, Niosi, & Mustar 1995). This subsector basic research and knowledge transfer might be "pushed" by technological advances of academic institution. Their product development might further "push" their partner's product development and also learn from partners. On the other hand, their product development might also be "driven" by the demand of alliances partners and the wider market. From this perspective it is easier to understand why there has been more emphasis and success for chemistry based products, as these are a better fit with the dominant technology of the mainstream pharmaceutical industry.

8.3. Companies performance

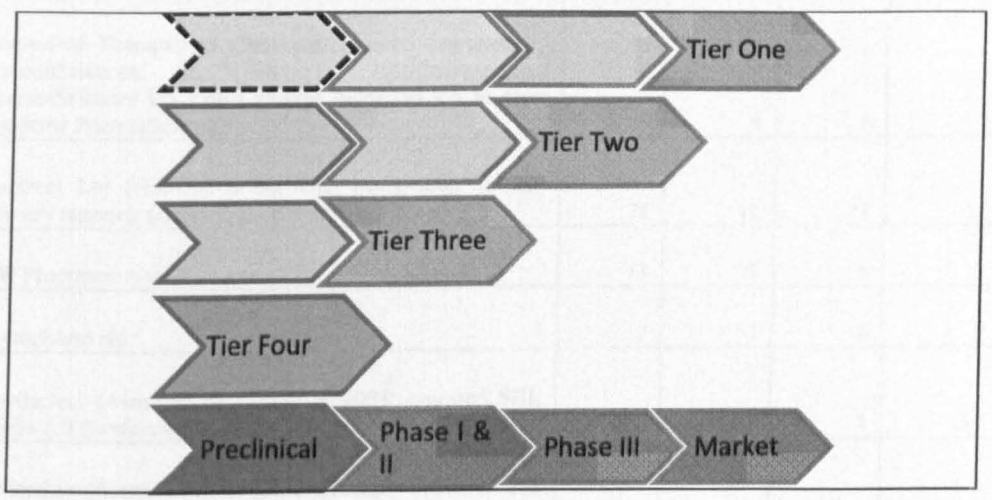
8.3.1. Tiers of companies

Based on the development stages of their product pipelines, the 81 companies were categorized into four tiers. The rational of this categorisation is based on the milestones of the drug discovery and development process. The major hurdles of drug discovery and development process are whether a compound could enter Phase I/II clinical trials, whether a compound could enter Phase III/IV phase trials and whether a compound has reached the market. A compound entering Phase I/II clinical trials indicates that it can be test in human: healthy volunteers in Phase I and a small

group of patients in Phase II (Walsh 2003). A compound yielding positive results could enter Phases III clinical trials, the latter involves 1000-3000 patients and require strong financial support for the clinical trials. After clinical trials, only a small number of compounds reach the market. The resources required to reach Phase I/II are relatively modest. In contrast Phase III trials requires heavy investment and a high level of expertise. Lunching a drug on the market also requires further investment in marketing, regulatory affairs and distribution.

Companies were therefore categorized into four tiers according to their most advanced programme (Figure 5).

Figure 5 Operations of Companies



1) Tier One - partially integrated biopharmaceutical companies: there are 16 companies in this tier, and the major character of these companies is that they all have products on the market. These companies included Acambis, Alliance pharma, Ark Therapertics, Cambridge Antibody, Celltech, Controlled Therapeutics, Cyclacel, GW pharmaceuticals, Phytopharm, PowderJect, ProStrakan, Protherics, Shire Pharmaceuticals, SkyePharma, Vectura, and Vernalis (Table 33).

Table 33 Tier One Companies

Company name	SCI	Patents	Pipelines	Alliance	Year founded
Acambis (1992-1999 Peptide Therapeutics; acquired OraVax US and changed name in 1999, acquired by Sanofi Pasteur in 2008)	51	9	14	31	1992
Alliance Pharma plc	0	0	2	17	1996
Ark Therapeutics (Eurogene Limited acquired the Oy Quattrogene Limited FINLAND in January 2001)	10	32	3	8	1997
Cambridge Antibody (Acquired by AstraZeneca in 2006; ACQUIRED Aptein US in 1998)	91	71	8	57	1990
Celltech Group plc (acquried by UCB Belgium in 2005; Acquired Chiroscience in 1999;merged with Medeva in 1999; acquried Cistron Biotechnology US in 2000; acquired Oxford Glycosciences in 2003)	794	879	19	157	1980
Controlled Therapeutics (Scotland) Limited (acquired by PharmaSciences, Inc US in 1993;Merger of PharmaSciences US with Cytokine Networks US to form Cytokine PharmaSciences in 1999)	7	4	0	2	1986
Cyclacel Ltd (founded in the UK, headquarter in US, primary research facility is located in The UK)	78	91	11	12	1996
GW Pharmaceuticals	13	7	5	1	1998
Phytopharm plc	7	35	6	7	1990
PowderJect (Acquired by Chiron in 2003; acquired SBL vaccin AB Sweden in 2001)	16	1	3	19	1993
ProStrakan (formed after merger of Strakan <Scotland>and Proskelia<France> in 2004)	7	18	1	16	1995
Protherics PLC (formed from the merger of Proteus International Plc <UK>and Therapeutic Antibodies Inc.<US>in 1999, acquired by BTG in 2008)	47	9	4	20	1987
Shire Pharmaceuticals Group plc	19	4	18	66	1986
SkyePharma (acquired Jago Pharma Switzerland in 1996; acquried DepoTech US in 1998; acquired Hyal Pharmaceutical Canada in 1999; acquired RTP Canada in 2002)	0	1	17	18	1996
Vectura(Acquired Innovata in 2006; Innovata was formed in July 2005 when ML Laboratories PLC acquired Quadrant)	68	210	22	20	1987

Vernalis (acquired by British Biotech and name change to Vernalis in 2003; British Biotech merged with RiboTargets in 2003; acquired Ionix Pharmaceuticals in 2005; acquired Cita NeuroPharmaceuticals Canada in 2005)	451	306	10	79	1986

2) Tier Two - Late stage development companies: there are nine companies in this Tier, and the major character of these companies is that they have at least one drug development programme in phase III, but they do not have any drugs on the market (Table 34).

Table 34 Tier Two companies

Company name	SCI	Patents	Pipelines	Alliance	Year of founded
Xenova (acquired by Celtic Pharma Development BERMUDA in 2005; acquired KS Biomedix in 2003; acquired Cantab Pharmaceuticals in 2001)	181	136	20	42	1992
Oxford BioMedica plc (acquired Oxxon Therapeutics in 2007 -- Oxxon Therapeutics was recorded seperately)	81	108	12	16	1995
Alizyme	2	16	4	4	1995
CeNes Pharmaceuticals (mergered with Core Group plc in 1999; acquired Cambridge NeuroScience US in 2000;acquired Excyte in 2000; acquried Management Dynamics Cambridge in 2001;acquired TheraSci in 2003; acquired by Paion AG in 2008)	16	32	9	42	1997
NeuTec (acquired by Novartis Pharma AG Switzerland in 2006)	12	20	2	1	1997
Plethora Solutions	1	2	0	5	2003
Summit plc (VASTox changed name to Summit plc in 2007; VASTox acquired MNL pharma in 2006;acquired DanioLabs Ltd and Dextra Laboratories Ltd in 2007)	3	13	5	6	2001
Antisoma plc (acquired Aptamera US in 2005)	32	21	6	14	1988
Amarin (Acquired Laxdale Scotland in 2004)	60	32	7	45	1989

3) Tier Three - Early stage development firms: there are 24 companies in this Tier, and the major character of these companies is that they have at least one compound in clinical trials, but they don't have compounds in phase III (Table 35).

Table 35 Tier Three companies

Company name	SCI	Patents	Pipelines	Alliance	Year of founded
Adprotech Ltd (ACQUIRED BY Inflazyme Canada in 2004)	20	17	1	6	1997
Arakis Limited (acquired by Sosei Japan in 2005)	1	50	1	9	2000
Argenta (2004 - Argenta Discovery and Etiologics <FOUNDED IN 2002>merge)	19	16	7	20	2000
Arrow Therapeutics Ltd (acquired by AstraZeneca in February 2007)	18	21	6	8	1998
Astex Therapeutics (merged with metaGen Germany in 2003)	64	58	8	18	1999
Cambridge Biotechnology (acquired by Biovitrum AB Sweden in 2005)	0	9	2	1	2001
Chroma Therapeutics	2	16	5	1	2000
Hunter-Fleming Ltd (acquired Aegis in 2000; joint venture to form Trident Pharmaceuticals Inc US with Advent International in 2006; acquired by Newron Pharmaceuticals S.p.A. Itlay in 2008)	2	9	5	1	1999
KuDOS Pharmaceuticals Ltd (acquired by AstraZeneca in 2005)	29	40	3	4	1997
Lipoxen Technologies Ltd	9	20	14	4	2000
Microscience Ltd (Acquired by Emergent Europe US in 2005)	18	31	2	4	1997

NovaBiotics Ltd	0	1	4	0	2004
Onyvax Limited	15	10	6	4	1998
Oxagen	66	20	3	17	1997
Oxxon Therapeutics (Oxxon Pharmaccines Ltd)	10	20	1	2	1999
Pharmagene (acquired by Asterand US 2006)	21	26	0	29	1996
PowderMed (formed in 2004 as a spin-off from PowderJect acquired by Chiron in 2003, then acquired by Pfizer in 2006)	2	4	6	4	2004
PPL Therapeutics plc (Acquired by QED in 2004)	55	41	5	8	1994
ReGen (acuqired Sciencom in 2006; acquired Guildford Clinical Pharmacology Unit Limited in 2004)	5	9	1	0	1998
ReNeuron (Acquired AmCyte US in 2007)	34	15	5	11	1997
Spirogen Ltd	3	22	6	1	2000
SR Pharma (formed Silence Therapeutics AG after acquired by Atugen AG, Germany in 2005)	6	1	7	4	1999
Trigen (In 2005 Trigen Holdings plc and ProCorde GmbH merged to form Trigen Holdings AG)	3	31	5	2	1997
Xention Discovery Ltd	3	11	4	1	2002

4) Tier Four - Early stage firms: there are 32 companies in this tier, and the major character of these companies is that they have a drug discovery programme, but they do not have any compounds in clinical trials (Table 36).

Table 36 Tier Four companies

Company name	SCI	Patents	Pipelines	Alliance	YEAR FOUNDED
Amura (Amura / Proteom 05/06 Merger to form Amura Holdings)	17	20	1	5	1996
Aquapharm Bio-Discovery Ltd	0	2	2	0	2000
Avidex Ltd (acquired by Medigene, Gemany in 2006)	26	41	1	12	1999
Biotica Technology Ltd	26	24	4	3	1997
Cambridge Microbial Technologies Ltd (CMT)	0	1	0	0	1999
Crusade Laboratories Ltd	10	5	0	0	2000
Curidium (Cielo / Curidium 06/06 Acq. for equity to form Curidium Medica)	0	3	0	1	2001
De Novo Pharmaceuticals	40	10	0	10	2000
Discerna Ltd	1	3	0	0	2001
Domainex (merged with NCE Discovery Ltd in 2007)	1	0	0	0	2001
Domantis Ltd (Acquired by GSK in 2007)	6	43	1	10	2002
Drug Discovery Ltd (DDL)	0	0	0	2	1998
Endocrine Pharmaceuticals Ltd	0	2	1	0	1995
GeneMedix (acquired by Reliance Life Sciences Pvt Ltd India in 2007; set subs in Ireland and China)	0	6	0	7	1997
Glycoform Ltd	0	0	2	1	2002
Haptogen Ltd (acquired by Wyeth in 2007)	4	4	1	3	2002
Inpharmatica Ltd (acquired by Biofocus DPI of Galapagos, Netherlands in 2006; acquired ArQule (UK) Limited in 2003)	43	45	1	30	1998
Isogenica Ltd	2	3	0	11	2001
Lamellar Therapeutics Ltd	0	3	0	0	1999
Lectus Therapeutics (Acquired NeuroServe in 2006)	0	0	1	1	2003

Lorantis (acquried by celldex US in 2005)	14	43	0	3	1998
Muscagen Ltd	0	3	0	0	2001
NeuroTargets Ltd (joint venture between Bristol University and ANGLE)	1	4	1	1	1999
Novacta Biosystems Ltd	3	1	5	0	2001
Oxford Genome Sciences (UK) Ltd (Changed its Name to Oxford BioTherapeutics in Dec 2008)	1	1	0	5	2004
Phico Therapeutics Ltd	4	1	0	0	2000
Piramed (acquired by roach in 2008)	1	2	2	1	2003
Prolysis	3	2	2	4	1999
Sareum	3	0	5	10	2003
Scottish Biomedical	7	1	7	2	1999
Senexis Ltd	2	3	4	2	2001
TheRyte Ltd	1	8	1	0	1997

Summarizing the four tables above (Table 33-36), there are three indicators that can be used to describe and compare these four tiers: company age, R&D output and alliances (Table 37, 38 & chart 46).

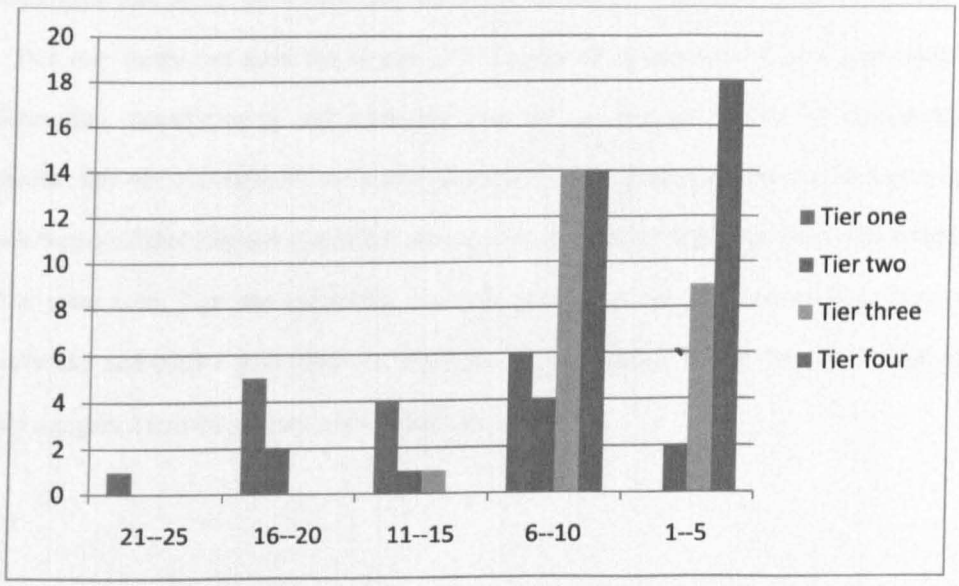
Table 37 R&D Output and Alliances Agreements of Each Tier

	SCI publications		Patents		Pipelines		Alliance Agreements	
	Total	Average	Total	Average	Total	Average	Total	Average
Tier One	1659	103.7	1677	104.8	143	8.9	530	33.1
Tier Two	388	43.1	380	42.2	65	7.2	175	19.4
Tier Three	405	16.9	498	20.8	107	4.4	159	6.6
Tier Four	216	6.8	284	8.9	42	1.3	124	3.9

Table 38 Age Groups and Alliances with Top 50 Pharmaceutical Companies

	NO. of firms	average age	Total NO. of allian ces	average agree-ments	M & A	Licens-ing	average licensing	Collabora -tion	average collabora -tion	Manufact -uring	Market -ing
Tier one	16	14.06	92	5.75	4	58	3.63	22	1.38	5	8
Tier two	9	9.78	37	4.11	1	27	3.00	3	0.33	1	4
Tier three	24	6.12	46	1.92	3	34	1.42	16	0.67	1	1
Tier four	32	5.12	25	0.78	1	23	0.72	8	0.25	0	0

Chart 46 Age group of companies



One important feature of Tier one companies is that they started operating before 1998, with the earliest in business being Celltech, which was established in 1980. Tier two companies have an average ten years of age. In contrast, Tier three six years in business and Tier four, five years. As the first entrants of the industry, Tier one companies have accumulated greater numbers of SCI publications, patents, pipelines and alliance agreements than other tiers.

Further investigation into the alliance agreements signed with the large pharmaceutical companies reveals that each tier has different characteristics. The major purposes of alliance agreements signed with Top 50 pharmaceutical companies are concerned with licensing, collaboration, M&A, manufacturing and marketing, with licensing being the most important purpose of agreements.

Companies of Tier one are very active in all areas of alliances with top pharmaceutical companies: the total number and average number of agreements signed by Tier one companies are more than the other tiers. One reason may be that the average age of a Tier one company is 14 years, which is much greater than that of other tiers. Because of the number of agreements accumulated over time, the Tier one companies have the largest total number of agreements of each type (licensing, collaboration, manufacturing and marketing), as well as average number of agreements. In particular, this tier of companies has higher numbers of M&A with top pharmaceutical companies, which suggested that Tier one companies are acquisition targets of large pharmaceutical companies. At the same time, Tier one companies also rely heavily on top pharmaceutical companies to manufacture and market their products. Therefore the companies in Tier one can be seen to be highly integrated into the pharmaceutical industry.

Companies of Tier two are very active in licensing. Although these companies do not have products on the market, they have a few agreements concerning future manufacturing and marketing. They have relatively high levels of licensing, but low levels of research collaboration with big pharmaceutical companies. This indicated that Tier two companies, which have the potential for product sales have adopted a more independent strategy than Tier one and Tier three companies.

Different from Tier two companies, companies of Tier three are more active in research collaboration with big pharmaceutical companies and less active in licensing. One interesting finding is that there are companies of Tier three established more than 10 years that did not continue downstream development. One explanation could be that these companies are focusing on licensing out rather than vertical integration, however, the data collected in this study indicated that the another possible reason is that these companies are acquired by big pharmaceutical companies or other biopharmaceutical companies, and this prevented them from further developing products.

Companies of Tier four are less active than the other three groups. The main reason is likely their young age.

8.3.2 Insight into Tier One companies

As shown above, the Tier one companies are the only group of companies which have products on the market, and they contributed the majority of SCI publications, patent publications and product pipelines. In other words, Tier one companies are the most successful companies of the drug discovery and development sector, therefore it is necessary to investigate this tier in more detail.

Based on data from this project, the Tier one companies could be roughly categorized into two groups. The major criteria used are R&D investment, R&D intensity, R&D output and income. The rationale of this categorisation is that drug discovery and development is a long and expensive process with high risk, therefore R&D investment and R&D intensity indicate the commitment of a company to innovation, and it is also connected to its ability to raise capital. R&D output refers to SCI publications, patents publications and product pipelines, and it directly measures the company

performance and R&D productivity. Income refers to the commercialization of a company's products and services; it also includes the licensing fee and contract service.

These most successful companies have been categorised into two groups (four companies were excluded from categorisation because data were unavailable due to M&A): Companies with high R&D investment, high R&D intensity, high R&D output and income are categorized into Group A; companies with high R&D investment, high R&D income, but relatively low R&D intensity are categorized into Group B.

Group A: there are seven firms in this group, and they are characterized by heavy R&D investment, high R&D intensity, and very productive output in terms of patents and product pipelines. They are research orientated and the most innovative companies. Their income was ranked top of the drug discovery and development sector, and several of these firms had significant sales. Their R&D intensity was over 54 per cent, with most of these companies' R&D intensity being over 100 per cent.

This group included companies such as Celltech, Vectura, Phytopharm, ProStrakan, Ark Therapeutics, GW Pharmaceuticals and Vernalis. Five of these companies have more than 30 patents, four of these companies' R&D investment is over 10 million pounds each year. For example, Celltech, which is the top company of this group, has 879 patents, an average R&D investment per year of 56 million pounds, average income of 60 million pounds and R&D intensity of 93 per cent. Another typical company of Group A is Vectura: it has 68 scientific publications, 210 patent publications, average R&D investment per year of 5.9 million pounds, average income of 4.2 million pounds and R&D intensity as high as 112 per cent.

Interestingly, companies of Group A are very active in mergers and acquisitions. Five out of seven companies were involved in at least once merger or acquisition since 2000. Again using Vectura as

an example, it acquired Innovata in 2006, and Innovata was originally formed in July 2005 when ML Laboratories acquired Quadrant.

Group B: Group B consists of five firms (SkyePharma, Shire Pharmaceuticals, Protherics, Acambis and Alliance Pharma) and is characterized by heavy R&D investment and a large number of products in development. These companies' income is also ranked top of the subsector, however, their R&D intensity is below 45 per cent, and their patent publications are less than group A. Their major focus is on marketing. Examples of this group are Shire Pharmaceutical and SkyePharma. These companies mainly act as technology and product acquirers. They are less innovative than Group A companies but more commercially focused: these companies invested between £1 million and £131 million each year, and income generated is between £20 million and £780 million, however, none of them has more than 10 patents. Take Shire Pharmaceutical for example: it has only 19 scientific publications and four patent publications, however, its average R&D investment per year is as high as 131 million pounds, its average income is 781 million pounds and R&D intensity is 17 per cent.

The different R&D investment patterns of these two groups are mainly a reflection of companies' strategy, which is in part determined by resources. Hall & Bagchi-Sen suggest that more R&D intensive companies tend to adopt research focused strategies such as a means of strengthening their own research capabilities, entering into research collaborations with universities, industry leaders and other biotech firms, and licensing their technology; while less R&D intensive companies tend to adopt production based strategies such as gaining market access, maintaining connections with customers, and building a research base (Hall & Bagchi-Sen 2007).

Further investigation into Group A and Group B companies indicates that they have different strategies, and this provided evidence for Hall & Bagchi-Sen's arguments. The first group of companies played a key role in knowledge generation and knowledge transfer. Their output accounted for the majority of the subsector's patents and product pipelines: three companies had

more than ten products in development and more than 200 patents. The Group B companies did not generate as large a number of patents as those of Group A: none of them had more than 10 patents developed in house. However, their large number of drugs in development was partly from their original development, and partly through acquisitions. Their R&D intensity was below 45 per cent, but the average sale per company per year was around 200 million pounds and their focus was marketing.

As Pisano (2006) has suggested, drug discovery and development companies are started with fragments of an innovation process and business practice, therefore, vertical integration is a major aim of a company's development: from project development to manufacturing and marketing. The different strategies of Group A and Group B companies indicate different routes of integration. Based on the data from this project, the first and second group companies all achieved a certain level of integration, however, there are two routes of integration: research orientated (Group A) and business orientated (Group B). The key determinant of vertical integration strategy is the availability of financing (Pisano 2006). For the Group A companies, they could generate cash flow from licensing and contract service. For Group B companies, they may generate income from value added downstream in development and marketing, alternatively, they can license in patents from other companies and then license out. The routes they choose are mainly determined by the resources and competencies of companies. The methods they use to generate cash flow may be hybrid.

As Pisano suggests, because the number of successful companies is too small and the time of the company development still relatively short , and because different types of technology and product pipelines have different risks and potential (Pisano 2006), it is therefore difficult to identify the best strategy for the whole industry. The next section will discuss how strategy development connects with companies' technology and products.

8.3.3. Convergence of technology: Chemical and biotech

As discussed in the previous data chapters, the drug discovery and development companies adopt both new biotechnology and traditional chemical technologies. Scientific papers and patents were both published on biological and chemical knowledge, but with a greater emphasis on molecular biology and biotechnology. The technologies that formed the basis of company product pipelines were also focused on both biology and chemistry, but with a greater emphasis on chemical technologies, and the biological technologies were mainly applied in the early stages. However, it should be noted that the technological focus of alliances moved from chemical technology during the 1990s, to biotechnology and biologicals after 2000. Previous chapters suggested that very few biotechnology products entered the final stages of development in this subsector's pipelines: either because they had high failure rates or had been acquired/ licensed out in late stage. The data from early stage pipelines and alliances suggests that this may change in the future, with a greater number of biological drugs coming through the industry pipeline.

Another finding from the data was that the pipelines of companies in Tier one and Tier two are mainly focused on small molecules and drug delivery, which means the most successful companies did not focus on biologicals. Although the large number of small molecule related companies may be the results of the development of genomics, the large proportion of chemicals indicated the cooperation of this sector with large pharmaceutical companies is mainly focused on chemicals. Since large pharmaceutical companies were the largest partners of this sector most Tier one and Tier two companies had at least one alliance agreement with large pharmaceutical company. The average alliance agreements with large pharmaceutical companies of Tier one and Tier two companies was as many as 5.8 and 4, and the major purposes were licensing and research. Celltech together with the companies it acquired (Chiroscience, Medeva and Oxford Glycosciences), has signed 26 major agreements with over 18 large pharmaceutical companies since 1984 (Table 39).

These agreements covered licensing, research, manufacture, supply, asset purchases, and acquisitions. These close connections with large pharmaceutical companies suggested that this sector has been influenced by their partners in the choice of technology and products. Tier three companies are also very active in licensing, take Astex Therapeutics for example, since 2000, it had licensing deals with Sanofi-Aventis, Schering, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, GSK, and had research deals with Johnson & Johnson, AstraZeneca and Sanofi-Aventis.

Table 39 Major agreements signed between Celltech and large pharmaceutical companies

Company history	Year	Large pharmaceutical company	Content
Celltech Acquried by UCB (Belgium) in 2005; acquired Chiroscience in 1999; merged with Medeva in 1999; acquried Cistron Biotechnology (US) in 2000; acquired Oxford Glycosciences in 2003	1986	Lilly	Supply
	1988	Pfizer	License
	1990	Boehringer Ingelheim	License
	1991	Roche	License
	1992	GSK	Asset purchase, license
		Johnson	Research
	1993	Roche	Supply
	1994	Astra	Supply
		Bristol-Myers Squibb	Manufacture
		Merck	Asset purchase, license
		GSK	License
	1995	Zeneca	License, supply
		Elan	License
		Wyeth	Asset purchase, supply
		Upjohn	Research
		Janssen	License
	1997	Schering-Plough	License
	1998	Bristol-Myers Squibb	License
		Zeneca	License
		Pfizer	License
	1999	Merck	License
	2000	Bayer	License
		GSK	License
	2001	Johnson	License
	2002	Amgen	License
	2005	UCB	Acquisition

Moreover, the choice of technology and products had further impact on the company's strategy. Pisano (2006) suggests that biopharmaceutical companies may adopt different strategies because of their products. He suggested three types of companies: companies adopting novel research methods and tools, companies focusing on novel targets and mechanisms, and companies focusing on novel compounds, treatments and markets (Pisano 2006, P167-172). He analyzed the degree of information asymmetry, the need for investments in specialized assets, the tacitness of the knowhow and the degree to which they have relevant intellectual property (Pisano 2006, P165-166). He suggests that companies developing novel research methods and tools may adopt a strategy of contract service, companies focusing on novel targets and mechanisms may develop long-term collaborations with large pharmaceutical companies, and companies focusing on novel compounds may further integrate (Pisano 2006).

However, the data of this project indicated a rather different picture. Most companies discussed in this project can be categorized as companies focusing on novel compounds. As showed in the previous section, these companies are not only moving towards integration, but also have forged long-term collaboration with large pharmaceutical companies, and provided contract service. Take the agreements of Celltech in Table 38 for example. The first Initial Public Offering year of Celltech was 1993. Before 1995, shortly after it became public, Celltech's agreements were regarding contract research, licensing, supply, manufacturing and assets purchase. It depended on the contract research and licensing agreements with large pharmaceutical companies to generate cash flow to fund further research, while relying on the expertise and facilities of large pharmaceutical companies to conduct downstream activities, i.e. manufacturing. At the same time, they also prepared the firms for further integration through the purchase of necessary assets. After 1995, and before the acquisitions by UCB in 2005, Celltech's agreements with large pharmaceutical companies were mainly about licensing.

Therefore, the strategy of cooperation with large pharmaceutical companies has changed over time, and the major factors are not the innovation focus, but available financing, knowledge

accumulation and maturity of the company. Again take Celltech as an example, it had 15 alliance agreements and 109 patent publications during the 1980s, and it had 90 alliance agreements and 502 patent publications during the 1990s.

To conclude, as a company gains enough financing, expertise and experiences overtime, its strategies also change according to their resources and competencies. At the same time, it will rely less on its large pharmaceutical partners and forge connections with other actors.

In short, Pisano's (2006) argument is generally support by data collected from this project; however, empirically there were some important differences, most notably the companies which move towards vertical integration also have forged long term collaboration with large pharmaceutical companies, and licensing is still very important for their income. There are three main reasons to explain this: first, the returns on drug development are highly skewed - downstream products will gain much more return than upstream products. A company wanting to gain a large proportion of return needs to conduct late stage development and marketing. However, the late stage development is time-consuming, costly and risky. Therefore, second, the company needs to generate income from various resources to finance drug development: R&D contracts and licensing. Third, companies that do not have experience in late stage development and marketing may need long term cooperation with other companies, in particular, large companies with complementary assets and funding to co-develop new drugs. Because these companies are dependent on large companies' funding, these three types of strategies are all more or less influenced by the behavior of large companies. Companies focusing on novel compounds may further conduct integration, as with the cases of companies in Group A and Group B, however, the processes are also influenced by other factors. In short, companies' strategies are also determined by network position and stage of company's life cycle.

Based on the empirical data of this chapter, the next chapter will theoretically interpret the development of strategy, and its co-evolution with industry structure.

Chapter Nine: Discussion, Conclusion and Policy Implication

The three main focuses of a sectoral systems framework are knowledge and technological domain, actors and networks, and institutions (Malerba 2005). In the previous chapters, data of knowledge production, technological domain, actors and networking have been investigated and analysed, and the institutions (policy and regulations) were also discussed (Introduction chapter and literature review chapter). This chapter will try to answer the research questions raised in the literature review chapters by looking at the findings using a theoretically interpreting based on the core concept of the sectoral systems framework - co-evolution.

There are two issues to be addressed in this section: a) the co-evolution of strategy and networking, which covered two research questions: Is there a divergence of strategies existing in the drug discovery and development subsector? If so, what are the key factors which determine the divergence of strategy? The second issue is b) the co-evolution of industry structure and strategies, which also covered two research questions: From a perspective of industry, to what are extent the drug discovery and development companies integrated into the traditional pharmaceutical industry and how do divergent technological strategies influence industry structure?

The third section of this chapter is about regulation and policy and will focus on discussing this issue from the perspective of co-evolution, and further elaborate the policy issues raised in this project.

9.1. Co-evolution of networking and technological strategy

As discussed in the literature review chapter, there were different opinions on the shaping of the strategies of biopharmaceutical companies. Pisano had observed a trend towards vertical integration of new biotechnology companies from R&D activities to manufacturing and marketing during the 1980s and suggested that the ultimate strategy for biopharmaceutical companies was vertical integration along the lines of traditional large pharmaceutical companies (Pisano 1991). However, after the application of molecular genetics and recombinant DNA technology, the small biotech start-ups played an important role in innovation, and the large pharmaceutical firms that began to enter the field had to develop new strategies (Galambos & Sturchio 1998). Galambos & Sturchio's research raised the question of strategy development: is the supply of contract service a long term strategy or a temporary strategy? Will these companies continue to a create technology and collaborate with large pharmaceutical companies to finish the clinical and regulatory development processes? Their research indicated that the contracting service is a long term strategy, and biotech-pharmaceutical collaboration will likely remain for a long time, and the large pharmaceutical companies still dominate the innovation process (Galambos & Sturchio 1998b). However, since ten years has passed since Galambos & Sturchio published their paper, there are now companies that are divergent from a sole focus on R&D research or partnership with other companies. As discussed in section 8.3.2, companies may adopt multiple strategies rather than solely contracting R&D or long-term partnership. Kollmer and Dowling (Kollmer & Dowling 2004) suggested that "being not-fully integrated is not a transitional state, but a sustainable business strategy" (Kollmer & Dowling 2004, P1148) and their findings indicated that licensing is a commercialisation strategy for both fully and not-fully integrated firms.

In this study, the divergence of companies' strategy was also observed. As shown in the previous chapter, companies of different tiers have adopted different strategies. The stage of a company's

development is an important factor for the selection of strategy, e.g. different companies with different product pipeline stages have different strategies. For example, the Tier three companies, which have compounds in clinical phase I/II but not in phase III, are mainly focusing on research collaboration with large pharmaceutical companies, while Tier two companies, which already have compounds in phases III, are mainly focusing on licensing out to large pharmaceutical companies. For some Tier one companies, which have a clear "evolving path" from Tier four to Tier Three, Tier two then Tier one, their strategies have been changing overtime. This is also closely connected to their product development stages.

Furthermore, companies which have similar development stages may also have a different combination of strategies. The typical examples are Tier one companies which have been in operation for a long time and already have products on the market. There are generally two types of strategies adopted by Tier one companies: research orientated (Group A) and business orientated (Group B). Another interesting finding is that strategies of both Group A and Group B companies were influenced by their previous strategies and the accumulation process of experience and competency. For example, a typical research orientated company, like Celltech, uses a main strategy of expanding its patent portfolio and licensing out patents while conducting in-house R&D. Further, its previous M&A targets are also mainly research orientated companies. While a typical business orientated company, like Shire pharmaceutical, has a main strategy of licensing in and marketing, and its previous M&A targets are mainly companies which could help it expand its market. For both types of companies, their accumulated or acquired experience and competency were also important factors for strategy making.

Another important factor which influenced the divergence of strategies was the financial condition of companies. There are two sets of evidence relating to this: first of all, companies that wanted to "push" their product into higher clinical stages needed much more funding than it previously, therefore, strategy development of each tier of firms was partly determined by their financial cap. Moreover, the R&D intensity of different companies, which was determined by its nature of

business, further influenced the company's strategy, in particular, the M&A decisions. Companies with high R&D intensity are more active in M&A with large pharmaceutical companies.

There is a notable factor connected to those discussed above – networking. Companies continuously collaborate with other actors during their development: selling knowledge while acquired funding, experience and competencies. Although networking can be seen as a part of a company's strategy, networking also has a profound impact on a company's overall strategy because it involved other actors of the innovation system, in particular, those large pharmaceutical companies which have more control and power over alliance agreements.

There are two perspectives on firm's strategy development connected to networking: one is from capability and learning (Koput, Smith-Doerr, & Powell 1997), which focuses on how firm strategy changes while the firm develops in competition. Another perspective is from risk management, which focuses on how firms minimise the innovation risk by networking (Hopkins & Nightingale 2006).

Learning from networking, in particular, from networking with large pharmaceutical companies, is an important factor influencing a company's strategy making. This is different from the driving factor of financing need and push factor of knowledge accumulation, rather this is an external factor, because this process involves interactions with other actors. Powell, Koput, Smith-Doerr and Owen-Smith suggested that a model of industry evolution could be understood as a learning race from networking, moreover, there are limits to a firm's learning from networking because there is a decrease of return to the networking (Powell, Koput, Smith-Doerr and Owen-Smith, 1999).

Another perspective on the strategic alliances of drug discovery and development companies is risk management. Companies adopt different strategies to minimise the risk of innovation and secure cash flow and investment via networking.

> *"Given the diversity of types of risk, ways of managing them, and differing organizational capabilities, certain organizational structures based on configurations of firms, markets, government bodies and NGOs will be better able to transform and transfer specific types of risk than others. Consequently, firms that can position themselves within these networks and can cost-effectively disaggregate and disappropriate some of the uncertain or undesirable consequences of innovation onto third parties (that are better able to manage these risks) can potentially be at a competitive advantage."*

(Hopkins & Nightingale 2006, P361)

Both perspectives of minimising risk and gaining competency have an emphasis on how to create competitive advantages within the network with other parties. As shown in this study, the alliance contents, purpose and partners changed significantly overtime. The changing positions of companies within evolving networks and the accumulation of experience further influence the development of company strategy. Gulati, Nohria, & Zaheer have suggested that "an understanding of the consequences of the ubiquitous growth of strategic networks emphasizes that firms are more properly viewed as connected to each other in multiple networks of resource and other flows" (Gulati, Nohria, & Zaheer 2000). In particular. there are two important dimensions of biopharmaceutical company alliances: the number of alliances and internationalization.

Koput etc. suggested that "older and larger firms have deeper and more extensive portfolios of collaboration" (Koput, Smith-Doerr, & Powell 1997, P251). This result is supported by the data

collected in this project. However, based on the analysis of Tier one companies, this thesis further suggested the speed of firm growth is faster than the speed of its network expansion. The indicator used is the ratio of number of patents publications and number of alliance agreements. One possible reason is that the companies move from R&D cooperation to in-house development when they have enough funds to conduct their own research, therefore, the number of alliance agreements may decrease while the patents number may increase. Another reason might be that firms are less dependent on acquiring certain recourses from networking when they have accumulated a certain level of experience, however, these companies may rely on networking if they need new resources.

Moreover, the position within networks also connected with a company's technological strategy. Companies need networks to access resources and manage risk, because they do not have the capability to handle certain risks and uncertainties themselves. However, this brings pressure to develop products that 'fit' with their partners, in particular, large pharmaceutical companies. This is supported by findings of this study (As discussed in 8.2). There were different focuses on basic knowledge production and product development, and this was mainly due to their interaction with their partners. The focuses of knowledge production of this subsector were changed when partners changed. Many companies started as biologically focused companies, and then moved to both chemical and biological focus after cooperating with large pharmaceutical companies. In other words, this subsector worked as a node of the network of knowledge production, connecting both academic institutions and the established pharmaceutical industry. As discussed in 8.2.2 these firms served as both knowledge producers in their own right, but also as intermediaries in transferring knowledge from academia to the pharmaceutical industry. This result was also indirect evidence of the impact of technology push and market drive (Walsh, Niosi, & Mustar 1995). This subsector's basic research and knowledge transfer might be "pushed" by technological advances of academic institution. Their product development might further "push" their partner's product development and also they might learn from partners. On the other hand, their product development might also be "driven" by the demand of alliance partners and the wider market.

From this perspective it is easier to understand why there has been more emphasis and success for chemistry based products, as these are a better fit with the dominant technology of the mainstream pharmaceutical industry. This finding also supports the conceptualization of actors and networking in the Sectoral Systems of innovation: the actors and linkages are not simply co-existing, but dynamically interact with each other (McKelvey & Orsenigo 2001).

To summarize, the divergence of strategies could be explained by the levels of financing ability, experience, competency of different tiers, and their positions within the network. For individual companies, it is important for biotechnology firms to know when to vertically integrate, when to license and when to collaborate (Pisano 1991).

9.2. Co-evolution of industry structure and strategy

Many researchers have argued that the reality of the drug discovery and development sector has not met the promise of biotechnology (Hopkins, Martin, Nightingale, Kraft, & Mahdi 2007;Pisano 2006). Pisano (2006) suggested that the main problem was the result of industry structure and strategies, as well as outside factors such as government policies, regulations and capital market:

> *"whereas the effective development application of the technology requires integration, the business of biotech is driven by specialization and fragmentation; whereas the uncertainty and novelty of the science requires rapid diffusion of 'high fidelity' information, the business strategies of biotech firms impede information flow; whereas the science requires long-term cumulative learning, the biotech firms face market pressure to optimize short-term perceptions of value"*

(Pisano 2006, P159).

One important issue concerning the difference is the measurement of performance: in Pisano's study, the major indicator is the cost per new molecular entity (NMEs) by biotech, as well as financial returns. However, as Kollmer & Dowling's study indicated, patents should also be considered as an important measurement of R&D performance. It is also important to notice that Pisano's study of the biotechnology industry indicated that the emphasis on intellectual property actually impeded the activity of networking; moreover, the industry structure does not deal very well with risk management, learning and integration (Pisano 2006). In this project, patents are considered an important part of the performance of this sector, since most companies do not have products on the market.

Orsenigo et al (2001) have analyzed the structural evolution of the network of collaborative agreements in pharmaceutical R&D in the last 20 years (Orsenigo, Pammolli, & Riccaboni 2001). They suggest that both the growth of knowledge and the structural evolution of the network have been characterized by fast expansion, proliferation of research trajectories and techniques, and hierarchization (Orsenigo, Pammolli, & Riccaboni 2001). Their argument is supported by the findings of this study, the fast growing numbers of patents and alliance agreements are concentrated in a small group of companies. During the early 1980s, the sector only consisted of a few companies and the industry structure was simple, and company strategy was largely based on R&D contracting. While many new companies entered this industry, product pipelines were growing, networking was expanding, the older companies appear to have repositioned themselves within the industry: with experience accumulating and capacity growing, a few successful companies and a large number of young companies formed the hierarchical structure (as discussed in chapter four) of this industry. The established companies adopted different strategies to the young firms during this period of expansion and transition.

The first divergence of strategy is mainly determined by stage of companies' life cycle: mature firms adopted different strategies from young firms. At the same time, collaborating with large pharmaceutical companies and exposure to international competition and collaboration also required that companies adjust their strategy from time to time. For the established companies, the second divergence of strategy was determined by many factors including the company's development history, resources and knowledge bases (Senker 1996). Companies with more R&D capacity are inclined to choose a research oriented strategy, and gain return mainly from licensing out and contracting, while companies with more experience of downstream development are inclined to choose licensing in and marketing.

As discussed earlier, a significant proportion of companies in Group A have been acquired by large pharmaceutical companies in the past few years and so the structure of this sector is changing again: there are less companies on the top of the pyramid. Although companies may face less competition within this sector, however, both established companies and young companies will face competition from large pharmaceutical companies which have acquired new innovation competency and retain development capacity. From the perspective of the drug discovery and development industry, the data from the project supports Galambos & Sturchio's research: biotech-pharmaceutical collaboration will likely remain for a long time, (discussion of Celltech in 8.3.2) and large pharmaceutical companies will continue to dominate the innovation process. However, from the view of individual companies in Tier one, the argument that contracting service is a long term strategy may not be supported. Contracting service was the major business in the early stage for many companies, however, for the most successful companies, although contacting services may still exist, companies' focus may move to in house R&D. Many companies are moving from developers to buyers, e.g. Shire Pharmaceutical discussed in Chapter seven. Although small companies may survive from solely contracting service, considering the return of drug discovery and development is highly skewed, many companies are driven to conduct downstream drug discovery and development.

Therefore, there are a group of companies which have been largely integrated into pharmaceutical sector (some companies of Tier one), a group of companies specialized in order to avoid direct competition with established players (some companies of Tier three) Another group of companies chose a more independent route as they started to sell (license) knowledge to other companies as a key element of their commercialisation strategy while continuing to conduct in-house R&D. Since many companies of the last type have been established more than ten years, this would fit with them reaching a 'ceiling' on their activities due to difficulties in raising the large amount of finance required to move into late stage clinical trials. In other words, it might be seen as an important shift in strategy from being fully integrated companies to being suppliers of early stage product candidates. This fits with broader changes in the strategies of large pharmaceutical companies who are increasingly interested in filing their empty pipelines. Therefore, the divergence of companies' strategy may form part of a more general 'vertical disintegration' of the pharmaceutical and biotechnology R&D function.

Since the returns on drug discovery and development are highly skewed, is it the case that biotechnology firms are become more traditional as the biotechnology interorganizational field matures and consolidates as suggested by some researchers? In other words, is it more beneficial for biotechnology companies' survival if they adopt the strategies of traditional pharmaceutical companies?

The findings from this project suggest that firms with a more traditional strategy are less likely to be acquired by large pharmaceutical companies, because the R&D intensity is lower, and the company is less dependent on partners' funding. Moreover, these companies also have better performance according to research (Patel, Arundel, & Hopkins 2008). The top companies of the pharmaceutical and biotechnology industry were identified by correlation of three variables. If considering the links between R&D expenditure and patent applications, SkyePharma, Shire Pharmaceuticals, AstraZeneca and GlaxoSmithKline have the highest ratio of performance measurement. Comparing the patent applications and economic performance it is clear that

AstraZeneca and GlaxoSmithKline have the highest ratios. The third link in consideration is R&D expenditure and profits where Acambis, AstraZeneca and GlaxoSmithKline have the highest ratios (Patel, Arundel, & Hopkins 2008). Interestingly, except big pharmaceutical companies (AstraZeneca and GlaxoSmithKline), Skyepharma, Shire Pharmaceuticals and Acambis are all Group B of Tier one identified in this thesis. This suggests that biopharmaceutical companies which have lower R&D intensities have higher survival rates.

The differences of R&D intensity are important in understanding the merger and acquisitions record since 2000, where exceptional intensive R&D investment could be a possible reason to explain why the output of Tier one, Group A was easily harvested by large pharmaceutical companies and other foreign companies. Due to five years of high R&D intensity, more than ten firms of Group A experienced M&A, and four of them were acquired by large pharmaceutical companies. The exceptional intensive investment was therefore a risk for the long term business development of these firms. Temporary shortage of R&D funding would cause problems for the whole company. The continuously exceptional intensive investment of the firms produced a large number of patents and drug candidates, but unless this was rapidly converted into successful products the companies were vulnerable to acquisition.

While the strategy of transforming the business into a more traditional company model is a way to minimize innovation risk, however, a question is raised: will firms lose innovation advantages at the same time? If so, will the risk to innovation impede the further development of this innovation intensive industry? Or will the industry be more flexible and adopt technology innovation from learning?

9.3. Policy

9.3.1. Questions for policy

One important feature of the UK drug discovery and development sector is that this sector is highly internationalized: it could not survive if it collaborates solely with local companies. There are many reasons for collaboration, and national strength is one of the most important external factors. The national strengths of the UK biotechnology industry include biopharmaceuticals, clinical trials, venture capital, strategic alliances, revenue per employee, and biotech publications (Patel 2008). Amongst the key ingredients of UK success, the most important factors are a pre-existing strong pharmaceuticals sector, effective capital markets and knowledge base (McMeekin & Green 2002b;Van Reenen 2004). These factors played a very important role in decisions of strategic alliances and facilitate the development of this sector. However, how these advantages can be effectively transferred into productivity and at the same time retained in the UK are important issues for policy raised in this thesis.

Both well established firms and young small firms in the drug discovery and development subsector face intense competition from local clusters of firms and international rivals. For small startups, their major problems are how to survive in local clusters while attracting investors to finance their product pipelines. For large and well established firms their major problems are how to quickly develop and market new products while minimizing the financial risk. These large and well established firms are, by far the most important, in terms of their intellectual capital, alliances and market presence. These companies (mainly from Group A and B) dominate the output of this subsector, and this sector's output is far greater than the average of the European industry.

It is therefore worth asking if policy should be focused on supporting these larger biotech firms and trying to secure their leading role in biopharmaceutical research in Europe? Furthermore, if these larger firms are supported, will this further concentrate the industry in the Southeast of England? This may broaden the difference in knowledge production between clusters and other areas. Therefore, how should policy be designed to avoid underutilization of technologies developed by universities and public research institutions outside the Southeast?

On the other hand, should policy be focused on supporting the creation of small start-ups with the aim of creating the next generation of larger successful companies? If so, should policy pay more attention to supporting small start-ups in areas other than the established clusters with the aim of building other successful 'bioregions'?

Moreover, is it realistic to construct an integrated policy framework and to promote the companies at different stages of their life cycles? If so, should policy be designed to enhance the performance at the sector level, industry level, or national level? What is required is recognition of the need for a policy response that recognises the different groups of companies and the different stages of a company life cycle.

As addressed previously, much of the knowledge produced by this subsector is going abroad, as illustrated by the pattern of licensing and commercialization. Furthermore, the acquisition of major Group A companies such as Celltech raises important questions about the long-term benefit of the industry to the UK economy, as it would appear that the benefits of the very successful knowledge production of these firms does not remain in the UK. Although the connections of this subsector with the domestic pharmaceutical industry have been expanding, it still only accounted for a small fraction of total alliances. It therefore appears that foreign countries are benefitting significantly from the activities of the UK drug discovery and development industry.

How should policy respond to the "harvest" of successful UK firms by foreign companies or large international pharmaceutical companies? Is it possible to prevent this subsector from being absorbed by foreign industry? To solve the problems outlined above should policy start by aiming to strengthen domestic networking or begin with enhancing companies' competitiveness through financial support?

9.3.2 Future studies

From a methodological perspective, further studies could benchmark the new indicators used in the citation analysis and compare these to companies' performance. Further analysis of the co-publishing of scientific papers and patents could give more information on networking and collaboration. Attention may also be paid to the analysis of citations of scientific publications in patents, to better understand how and to what extent scientific improvements are transformed into technology innovation in this industry. Similarly, studies of how patent publications cite other patents would facilitate the understanding of knowledge diffusion. Moreover, interviews with company managers could provide subjective information of firms' innovation strategies and help validate the findings of this study concerning the relationship between innovation, knowledge production and company strategy.

From an industry perspective, future studies may pay more attention to the convergence between the biotechnology sector and the pharmaceutical industry, since the biotechnology industry is heavily involved in discovering, developing and producing chemical drugs. Moreover, further studies could also address the impact of globalization on the dynamics of this subsector, e.g. the net benefit of industry from networking and knowledge sharing in the global economy.

Appendix 1 R&D investment of the top 35 companies (2002-2006)

(Data source: DTI)

Company	2006 R&D (£M)	2005 R&D (£M)	2004 R&D (£M)	2003 R&D (£M)	2002 R&D (£M)	Total R&D 2002-2006 (£M)
Shire	154.4	146.71	107.78	128.38	119.34	656.61
Celltech R&D	52.6	90.1	59.7	48.6	31.5	282.50
Vernalis	38.89	26.49	21.42	31.28	23.47	141.55
Acambis	37	34.5	28.9	19.9	16.3	136.60
SkyePharma	31.6	26	27.96	25.06	15.07	125.69
Celtic Pharma	4.36	14.28	15.07	17.66	15.37	66.74
Alizyme	18.33	15.75	6.27	11.4	9.69	61.44
GW Pharmaceuticals	13.1	10.28	13.94	12.68	10.75	60.75
Oxford Biomedica	19.52	9.33	9.19	10.77	10.83	59.64
ProStrakan	10.7	22.43	10.26	5.12	9.26	57.77
Astex Therapeutics	14.69	12.59	11.38	8.67	6.64	53.97
Innovata	8.26	10.37	12.9	10.91	10.85	53.29
Ark Therapeutics	13.02	13.94	9.15	5.37	5.02	46.50
Phytopharm	6.54	6.86	6.35	7.23	6	32.98
Renovo	11.32	7.72	6.12	4.2	3.4	32.76
Antisoma	14.94	6.19	0	1.2	9.73	32.06
Protherics	13.98	6.75	4.58	3.67	1.59	30.57
Arakis	10.35	9	6.39	3.09	1.29	30.12
Vectura	8.03	5.73	5.87	3.84	-	23.47
CeNeS Pharmaceuticals	7.28	4.89	3.48	2.94	3.54	22.13
Amarin	8.41	4.25	1.78	2.78	3.86	21.08
Chroma Therapeutics	8.3	6.69	4.44	0.83	0.69	20.95
Lorantis	4.42	4.53	3.86	3.75	2.69	19.25
ReNeuron	4.37	4.3	2.4	2.11	3.21	16.39
NeuTec Pharma	2.68	5.14	3.29	2.97	1.86	15.94
SR Pharma	3.19	1.66	1.7	3.01	2.46	12.02
Plethora Solutions	5.4	4.55	1.81	-	-	11.76
GeneMedix	2.33	2.21	3.23	2.01	0.78	10.56
Cambridge Biotechnology	2.29	2.88	2.37	0.97	0.11	8.62
Biotica Technology	2.29	1.71	1.25	0.91	0.73	6.89

Alliance Pharma	1.94	2.22	0.86	0.49	-	5.51
Vastox (now Summit)	2.94	1.03	0.27	-	-	4.24
ReGen Therapeutics	0.83	0.75	0.46	0.33	0.58	2.95
Sareum	1.11	0.7	-	-	-	1.81
Lipoxen	1.72	-	-	-	-	1.72
Total R&D (£M)	541.13	522.53	394.43	382.13	326.61	2166.83

Appendix 2 European Classification and publications

A Human necessities				
A01 Agriculture; forestry; animal husbandry; hunting; raping; fishing	A01K New breeds of animals			32
	A01N Preservation of bodies of humans or animals or plants or parts thereof; biocides, e.g. as disinfectants, as pesticides, as herbicides			4
A23 Foods or food stuffs, their preparation or treatment	A23L Foods or food stuffs, their preparation or treatment			7
A61 Medical or veterinary science; hygiene	A61B Diagnosis; surgery; Identification			2
	A61F Filters implantable into blood vessels; prostheses; orthopaedic, nursing or contraceptive devices; fomentation; treatment or protection of eyes or ears; bandages, dressings or absorbent pads; first-aid kits			3
	A61H Physical therapy apparatus			1
	A61J Devices or methods specially adapted for bring pharmaceutical products into particular physical or administering forms; devices for administering medicines orally			5
	A 61 K Preparations for medical, dental, or toilet purposes	A61K8 Cosmetic or similar toilet preparations	2	642
		A61K9 Medicinal preparations characterised by special physical form	89	
		A61K31 Medicinal preparations containing organic active ingredients	315	
		A61K33 Medicinal preparations containing inorganic active ingredients	7	
		A61K35 Medicinal preparations containing material or reaction products thereof with undetermined constitution	16	
		A61K36 Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, e.g. traditional herbal medicines	2	

		A61K38 Medicinal preparations containing peptides	75	
		A61K39 Medicinal preparations containing antigens or antibodies	83	
		A61K41 Medicinal preparations obtained by treating materials with wave energy or particle radiation	4	
		A61K45 Medicinal preparations containing active ingredients not provided for in groups A61K31 to A61K41	35	
		A61K47 Medicinal preparations characterised by non-active ingredients used	110	
		A61K48 Medicinal preparations containing generic material which is inserted into cells of the living body to treat genetic diseases; gene therapy	25	
		A61K49 Preparations for testing in vivo	16	
		A61K51 Preparations containing radioactive substances for use in therapy or testing in vivo	31	
	A61L Methods or apparatus for sterilising materials or objects in general; disinfection, sterilisation, or deodorisation of air, chemical aspects of bandages, dressings, absorbent pads, or surgical articles; material for bandages, dressings, absorbent pads, or surgical articles			10
	A61M Devices for introducing media into, or onto, the body	A61M1 Suction or pumping devices for medical purposes; devices for carrying-off, for treatment of, or for carrying-over, body-liquids; drainage systems	4	72
		A61M11 Sprayers or atomisers specially adapted for therapeutic purposes	2	
		A61M15 Inhalators	64	
		A61M16 Devices for influencing the respiratory system of patients by gas treatment	1	
		A61M35 Devices for allying media, e.g. remedies, on the human body; into human body by diffusion through the skin	2	
		A61M39 Tubes, tube connectors, tube couplings, valves, access sites or the like, specially adapted for medical use	2	
	A61Q Use of cosmetics or similar toilet preparations			2
B Performing operations; transporting				

B01 Physical or chemical processes or apparatus in general	B01D Separation	8
	B01J Chemical or physical processes, e.g. catalysis, colloid chemistry; their relevant apparatus	4
	B01L Chemical or Physical laboratory apparatus for general use	3
B05 Spraying or atomising in general	B05B Spraying apparatus; atomising apparatus; nozzles	3
B28 Working cement, clay, or stone	B28B Methods or machines specially adapted for the product of tubular articles	1
B29 Working of plastics	B29C Injection moulding; i.e. blowing a perform or parison to a desired shape within a mould; apparatus there of	2
B65 Conveying; packing; storing; handling thin or filamentary material	B65B Machines, apparatus or devices for, or methods of, packaging articles or materials; unpacking	2
	B65D Containers for storage or transport of articles or materials; accessories, closures, or fittings therefore; packaging elements, packages	3
B67 Liquid handling	B67B Hand or power-operated devices for opening closed containers	1
	B67C Funnels	1
C Chemistry; Metallurgy		
C07 Organic chemistry	C07B General methods of organic chemistry; apparatus thereof	9
	C07C Acyclic or carbocyclic compounds	194
	C07D Heterocyclic compounds	645
	C07F	31

	Acyclic, carbocyclic or heterocyclic compounds containing elements other than carbon, hydrogen, halogen, oxygen, nitrogen, sulphur, selenium or tellurium			
	C07H Sugars; derivatives thereof			34
	C07J Steroids			26
	C07K Peptides	C07K1 General methods for the preparation of peptides	31	716
		C07K2 Peptides of undefined number of amino acids; derivatives thereof	1	
		C07K5 Peptides containing up to four amino acids in a full defined sequence; derivatives thereof	42	
		C07K7 Peptides having 5 to 20 amino acids in a full defined sequence; derivatives thereof	14	
		C07K9 Peptides having up to 20 amino acids, containing saccharids radicals and having a fully defined sequence; derivatives thereof	2	
		C07K14 Peptides having more than 20 amino acids; gastrins; somatostatins; melanotropins; derivatives thereof	395	
		C07K16 Immunoglobulins, e.g. monoclonal or polyclonal antibodies	319	
		C07K17 Carrier-bound or immobilised peptides	1	
		C07K19 Hybrid peptides	8	
C08 Organic macromolecular compounds; their preparation or chemical working-up; compositions based thereon	C08B Polysaccharides; derivatives thereof			10
	C08F Macromolecular compounds obtained by reactions only involving carbon-to-carbon unsaturated bounds			4
	C08G Macromolecular compounds obtained otherwise than by reactions only involving carbon-to-carbon unsaturated bounds			6
	C08J Processes of treating or compounds macromolecular substances			2
	C08L Compositions of macromolecular compounds			4
C09 Coating, adhesives	C09D Coating compositions based on macromolecular compounds obtained by reactions forming a carboxylic ester link in the main chain			2
	C09J Adhesives; adhesive processes in general			2
C11	C11B			1

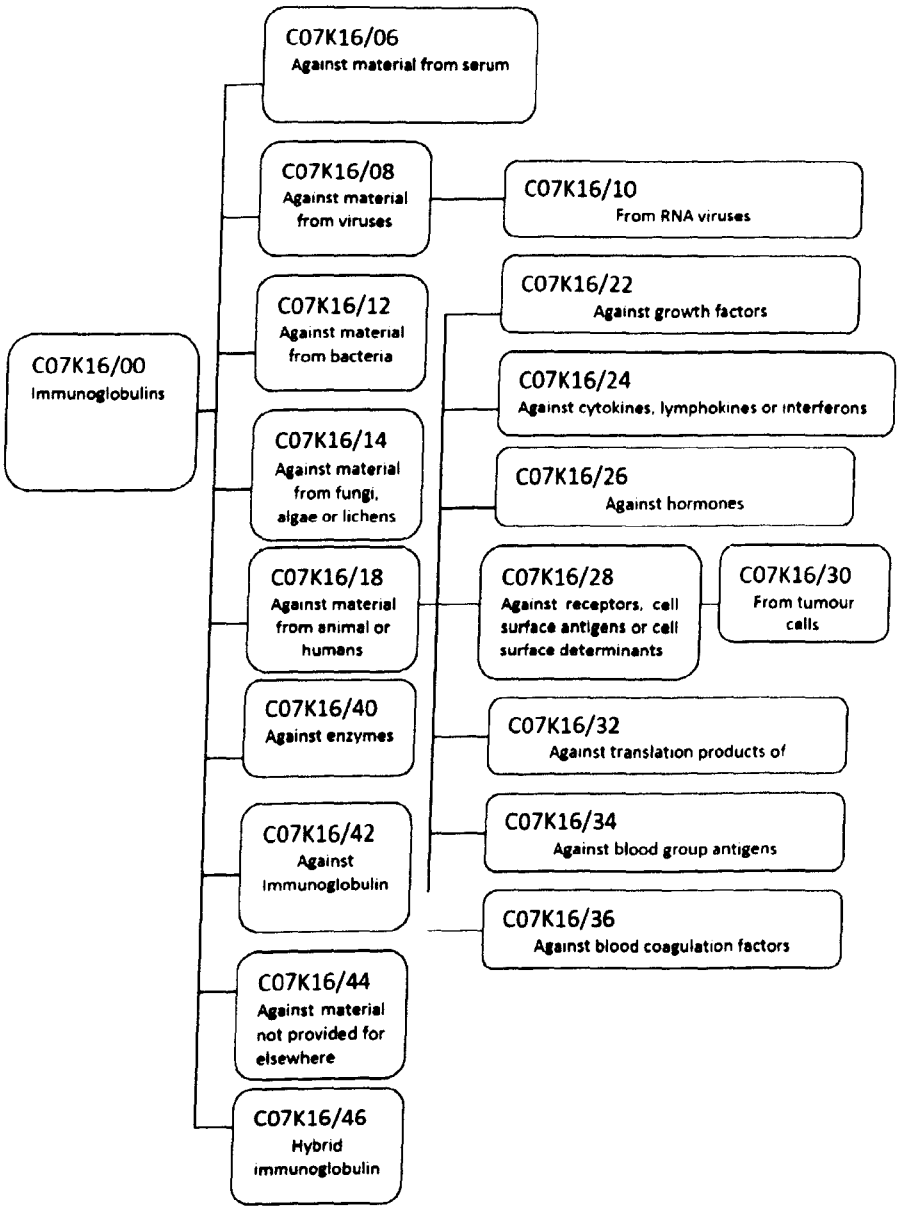
Animal and vegetable oil, fats	Essential oils; perfumes				
C12 Biochemistry; beer; spirits; wine; vinegar; microbiology; enzymology; mutation or genetic engineering	C12M Apparatus for enzymology or microbiology				13
	C12N Micro-organisms or enzymes; compositions thereof	C12N1 Micro-organisms; compositions there of		11	488
		C12N5 Undifferentiated human, animal or plan cells, e.g. cell lines; tissues; cultivation or maintenance thereof; culture media therefore		34	
		C12N7 Viruses; bacteriophages; compositions thereof; preparation or purification thereof		19	
		C12N9 Enzymes; proenzymes; compositions thereof		175	
		C12N15 Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; use of hosts therefor		331	
	C12P Fermentation or enzymes-using processes to synthesize a desired chemical compound or composition or to separated optical isomers from a racemic mixture				52
	C12Q Measuring or testing processes involving enzymes or micro-organisms				77
	C12R Processes using micro-organisms				11
C13 Sugar or starch industry	C13K Glucose				1
C40 Combinational chemistry	C40B Combinational chemistry; libraries	C40B30 Methods of screening libraries		11	35
		C40B40 Libraries per se, e.g. arrays, mixtures		27	
G Physics					
G01 Measuring	G01F Measuring volume; volume flow; mass flow or liquid level; metering by volume				5
	G01N Investigating or analysing materials by deterring their chemical or physical properties				170
	G01P Measuring linear or angular speed, acceleration, deceleration, or shock; indicating presence, absence, or direction, of movement				1
G06 Computing;	G06F Electrical digital data processing				9

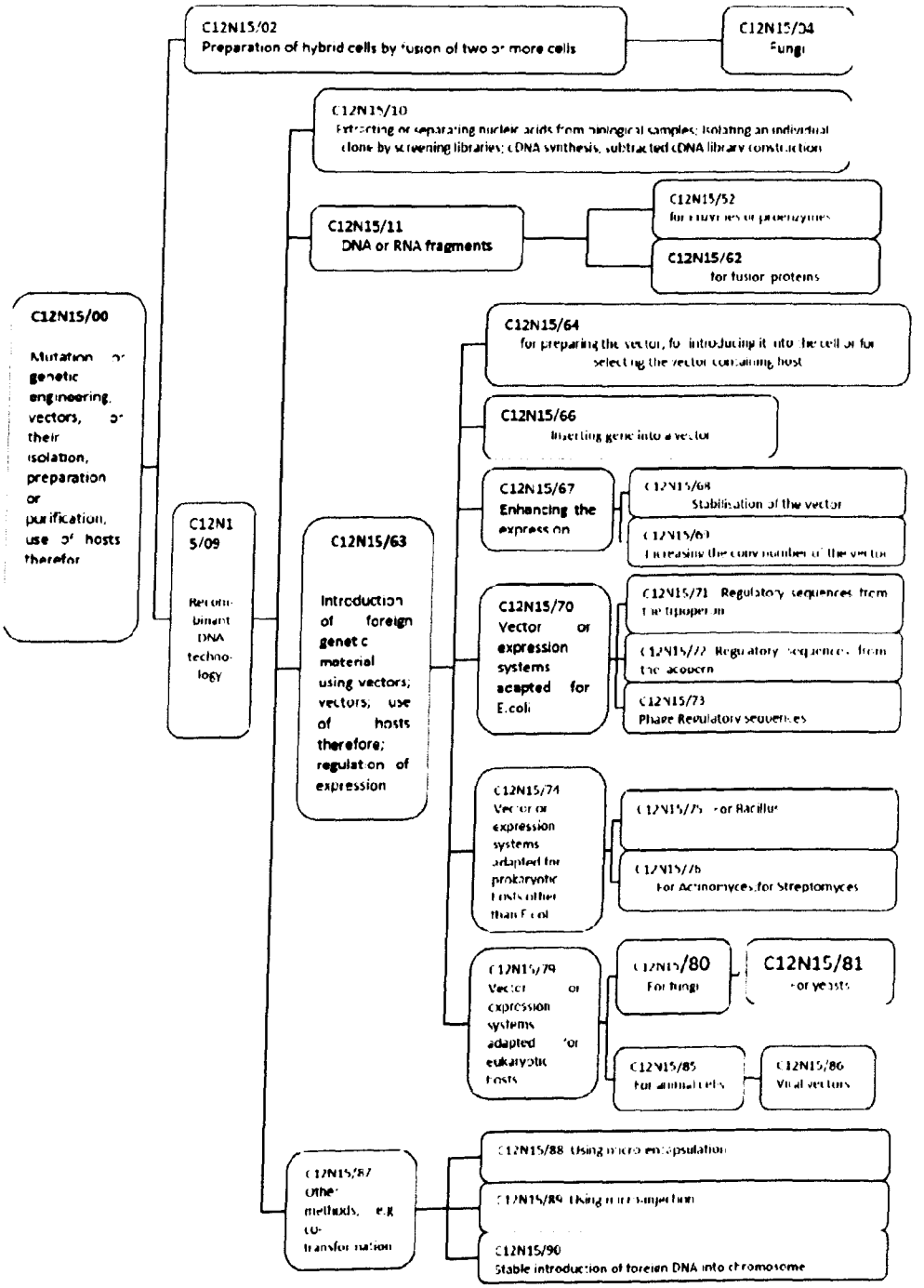
calculating; counting	G06M Counting mechanisms			6
	G06T Image data processing or generation			2
G07 Checking-devices	G07C Digital computers in which all the computation is effected mechanically			1
Y General tagging of new technological developments				
Y01 Broad technical fields characterised by dimensional aspects	Y01N Nanotechnology	Y01N2 Nanobiotechnology	9	13
		Y01N6 Nanotechnology for materials and surface science	5	

(Because many publications have more than one classification number, the total are not a simple add up of all numbers, duplicates have been removed)

Appendix 3 Classification of immunoglobulins (C07K16)

& Classification of genetic engineering (C12N15)




C12N15/00
Mutation or genetic engineering, vectors, their isolation, preparation or purification, use of hosts therefor
C12N15/02
Preparation of hybrid cells by fusion of two or more cells
C12N15/04
Fungi
C12N15/09
Recombinant DNA technology
C12N15/10
Extracting or separating nucleic acids from biological samples; Isolating an individual clone by screening libraries; cDNA synthesis, subtracted cDNA library construction
C12N15/11
DNA or RNA fragments
C12N15/52
for enzymes or proenzymes
C12N15/62
for fusion proteins
C12N15/63
Introduction of foreign genetic material using vectors; vectors; use of hosts therefore; regulation of expression
C12N15/64
for preparing the vector, for introducing it into the cell or for selecting the vector containing host
C12N15/66
Inserting gene into a vector
C12N15/67
Enhancing the expression
C12N15/68
Stabilisation of the vector
C12N15/69
Increasing the copy number of the vector
C12N15/70
Vector or expression systems adapted for E.coli
C12N15/71
Regulatory sequences from the tryptophan
C12N15/72
Regulatory sequences from the lac operon
C12N15/73
Phage Regulatory sequences
C12N15/74
Vector or expression systems adapted for prokaryotic hosts other than E.coli
C12N15/75
For Bacillus
C12N15/76
For Actinomyces,for Streptomyces
C12N15/79
Vector or expression systems adapted for eukaryotic hosts
C12N15/80
For fungi
C12N15/81
For yeasts
C12N15/85
For animal cells
C12N15/86
Viral vectors
C12N15/87
Other methods, e.g co-transformation
C12N15/88
Using microencapsulation
C12N15/89
Using microinjection
C12N15/90
Stable introduction of foreign DNA into chromosome

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