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Biotechnology Alliances in the European Pharmaceutical Industry: Past, Present and Future

Jacqueline Senker
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Jacqueline Senker

SPRU Science and Technology Policy Research

University of Sussex

Brighton BN1 9QE, UK

Email: j.m.senker@sussex.ac.uk

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Abstract

This paper reviews how research collaborations between dedicated biotechnology firms and multinational pharmaceutical companies have changed over the past 25 years. A discussion of the impact that developments in the biotechnology have had on the process of pharmaceutical R&D will set the context for reviewing the various theoretical approaches used to analyse and understand these alliances, identifying changes in the nature of alliances over time and indicating the future in store for dedicated biotechnology firms.

Keywords

Biotechnology; dedicated biotechnology firms; pharmaceuticals sector; post-genome era; research alliances

Biotechnology Alliances in the European Pharmaceutical Industry:

Past, Present and Future

Research collaborations have been a distinctive feature of the pharmaceutical sector since the emergence of biotechnology. The development of biotechnology has been led by scientific research and the industrial exploitation of biotechnology has been characterised by the prominent role played by universities and other scientific institutions and the dedicated biotechnology firms (DBFs) created to exploit this scientific knowledge. DBFs emerged first in the US and, after a five year time lag, they also appeared in Europe.

The priority given to biotechnology by public research funding agencies has constantly expanded knowledge. The new knowledge and policies to encourage its commercial exploitation (for Europe see Reiss et al, 2003) has led to the appearance of successive generations of DBFs. They have played an important part both in pushing the technology forward and in helping diffuse these new technologies amongst the industrial community. The DBFs, who initially hoped to grow into large integrated pharmaceutical companies, were faced with long and costly product lead times. To sustain themselves, the DBFs raised money by entering into research contracts, mainly with large chemical and pharmaceutical companies. Some predicted that once the major pharmaceutical companies had built up their in-house competence in biotechnology, DBFs would disappear; some of them would be acquired by large companies and others would fail to survive (Sharp, 1985; Orsenigo, 1989). However, heavy investment in public sector biotechnology research around the world,

especially investment in the Human Genome Project (HGP), has led to an explosion of knowledge and rapid progress in the development of research techniques and instrumentation that have created a plethora of opportunities for successive generations of DBFs. Moreover, so-called "strategic alliances" have not vanished as biotechnology has matured and are more in evidence today than they were in the early days of the commercialisation of biotechnology. An analysis of the research alliances signed by 24 leading pharmaceutical companies shows rapid growth from the early years (1982-1986) when 27 research alliances were signed; in the period 1987-1992 there were 76 alliances rising to 112 between 1993-1997 (Tapon and Thong, 1997).

The prevalence of these biotechnology alliances has made them a major field for social science research. This paper will compare the usefulness of the various theoretical approaches used to analyse and understand these alliances, identify changes in the nature of alliances over time and indicate the future in store for dedicated biotechnology firms.

To provide general background to the topic, the paper will first explore the impact that developments in the biotechnology knowledge base have had on the process of pharmaceutical R&D and then review the large body of literature on these alliances.

Empirical evidence about the nature of biotechnology research alliances by European pharmaceutical multinational companies (MNCs) over the past 25-30 years, and the location of their partners provides the basis for drawing conclusions.

1 Biotechnology and pharmaceutical R&D

The pharmaceutical industry undertook little formal R&D until after World War II. Until that time most new drugs were either based on existing organic chemicals or derived from plants.

During the war, many companies participated in US government-organised R&D to develop commercial production techniques for penicillin. The experience gained from their participation and the recognition that R&D could be highly profitable led to a period when pharmaceutical companies invested in in-house R&D and developed their research capabilities. At this time biochemistry became a significant component of research. During the 1950s and 1960s several new classes of drug and many other chemical entities were identified by random screening of natural and chemical compounds; promising substances were tested on animals. High investment in public health related research increased knowledge about how some drugs worked and about the biochemical and molecular roots of many diseases. By the mid 1970s this knowledge enabled the development of sophisticated screens to identify substances that produced the required chemical reaction. By the early 1980s, utilising the explosion of knowledge in the biological sciences generated by generous government funding for public sector research in the United States, drug research in many large firms had shifted from random screening to science driven or rational drug discovery (Henderson et al, 1999, Cockburn et al, 1999). At that time, synthetic organic chemistry and pharmacology were the core R&D skills of the large pharmaceutical companies (Jungmittag et al, 2000).

During the early emergence of biotechnology it was not clear how biotechnology would affect pharmaceutical R&D. The early applications, pioneered by DBFs, were based either on monoclonal antibodies or on genetically engineering micro-organisms to produce human proteins with therapeutic uses (large molecule drugs). Some of these therapeutic proteins represented substitutes for similar products extracted from natural sources (e.g insulin, human growth hormone, blood factor VIII), but others were truly novel biopharmaceuticals (e.g. interferon). By the mid 1980s, however, it became clear that the major application of

biotechnology to the pharmaceutical industry would not lie in the development of therapeutic proteins. Pioneering pharmaceuticals companies found greater benefits in using biotechnology techniques such as polymerase chain reaction, protein engineering and antibody engineering as enabling technologies. (Henderson et al, 1999; Sharp and Senker, 1999). These enabling technologies played a central role in the drug discovery process by improving the ability of scientists to select therapeutic targets and modify lead compounds so they interacted more accurately with the disease causing protein (Nightingale, 2000). In other words, biotechnology techniques could be applied to the search for small molecule drugs that could be synthesized by using organic chemistry.

This process was accelerated by the human genome project (HGP)¹, which commenced in 1988 and led not only to new knowledge and instrumentation but also a new knowledge regime for life science research based on combining many complementary disciplines – biology, chemistry, software, computer science, materials etc. (Queré, 2004). Important techniques of the new knowledge regime include high-throughput screening, combinatorial chemistry, bio-informatics, functional and structural genomics, proteomics and pharmacogenomics. Nightingale's (2000) exploration and description of several of these new experimental technologies demonstrate that experimentation in both chemistry and biology have undergone major changes involving a shift towards more fundamental science, with experiments being complemented by computer simulations and to experiments and analysis being performed on populations of chemical entities and genes, rather than on single entities. The unprecedented amount of data produced by experiments on populations has required the development and use of database technologies.

¹ Queré (2004) notes that "HGP is a generic term encompassing all the research effort devoted to the sequencing of genomes, whether they are plants, animals or human beings. ...[It includes] a wide range of scientific activities including studies of human diseases, experimental organisms, development of new technologies for biological research, computational methods and ethical, legal and social issues".

In chemistry this involved using statistical analysis to explore similarities between compounds, and databases to cluster various ‘descriptors’ in the design of experiments. In biology it involved the generation of bio-informatics technologies.

Databases are also used to screen populations of chemical compounds for testing and using the results of genome sequencing programmes to search for genes and explore “their functions by relating them to ‘similar’ genes in other environments” (Nightingale, 2000). Identifying the functions of genes is a prerequisite for identifying potential drug targets (Jungmittag et al, 2000).

Pharmaceutical firms have invested in these new technologies in the hope of reducing the cost of identifying new drugs, including those previously too technically complex to develop, by exploiting economies of scale in the R&D process. They have shifted from conducting craft-based experiments on single compounds to employing an automated, mass-production process on populations of compounds and genes, and they complement this process with computer simulations (Nightingale, 2000).

2 Theoretical Approaches to Research Alliances in Biotechnology

Three main bodies of overlapping literature have been used to analyse alliances between firms: the economics, strategic management and economic geography literatures. Much of this literature concerns supply chain collaborations. This section concentrates on the theoretical approaches that are relevant to understanding research alliances

The economics literature focuses on the economics of networks and analysis usually begins with the Coase-Williamson theories of markets and hierarchies in which economic exchanges are arrayed on a continuum with market transactions at one end and the highly centralised firm at the other. Networks are a hybrid form of organisation lying halfway between the two traditional poles (Coase 1937; Williamson 1975, 1985). Chesnais (1988) argues that networks based on interfirm agreements have arisen because

the complexity of scientific and technological inputs, the uncertainty of economic conditions and the risks associated with uncertain technological trajectories have reduced the advantages of vertical and horizontal integration and made 'hierarchies' a less efficient way of responding to market imperfections. But the need to respond to and exploit market imperfections in technology has also increased ...

Powell (1990) points out that networks can be so complex that they cannot be reduced to either the explicit criteria of the market nor the well organised routines of the hierarchy. He assumes that partners in network relationships are mutually dependent upon resources controlled by each other, but they benefit from pooling resources. There are also costs associated with the bureaucracy of setting up and co-ordinating the collaboration, and the risk of opportunism in the Williamson sense, namely of one partner being exploited by the other. Networks and collaborations are not therefore always the answer to the market imperfections associated with innovation. Rather they represent a response to quite specific circumstances. Thus analyses of strategic alliances now focus more on theoretical approaches in the strategic management literature than on an economic perspective based on transaction costs (Oliver, 2001).

The strategic management literature has several theoretical approaches to technology alliances. In the resource-dependent approach a firm's competitive strategy is influenced by its accumulated tangible and intangible resources. Research collaboration is beneficial when two firms possess what Teece (1986) has called 'complementary assets' (i.e. a mutual matching of resources, be they technological, manufacturing or marketing) and where these assets are bound up with tacit, firm specific and often proprietary knowledge. Research collaboration allows access to these complementary assets but avoids the high costs of a merger or an acquisition. The exchange of assets with a significant tacit component requires learning through close contacts and personalised relationships. Ciborra (1991) argues that the exchange of tacit knowledge via technological alliances can be viewed as "learning experiments".

A second approach stresses the importance of the capabilities and knowledge possessed by a firm as a competitive asset. The 'dynamic capabilities' approach (Teece and Pisano, 1994) reflects on a firm's ability to adapt to a rapidly changing environment where the time-to-market and timing is critical, the pace of innovation is accelerating and the nature of competition and markets is difficult to predict. It emphasises the need for strategic management to adapt, integrate and restructure in-house and external skills, resources and functional competencies towards the changing environment. Cohen and Levinthal (1990) note, however, that the ability to introduce external knowledge depends on a firm's absorptive capacities, or the scientific and technological competences in the R&D department. The "knowledge-based" view of the firm emphasises how alliances can allow a firm to access specific knowledge-based capabilities in its partner (Mowery et al, 1996). Both these approaches are part of the organisational learning perspective, in which strategic

alliances are a recognised method to acquire external technology and knowledge (Hamel and Prahalad, 1989). The strategic network model (Di Maggio and Powell, 1983) reminds us that issues of power can dominate alliances. Partners anticipate that reciprocity will prevail, implying the existence of an element of trust and some guarantee that opportunism will be punished. This is especially important in relations between large and small firms when power relationships might be expected to prevail. In these circumstances DBFs need to be very wary and seek to protect any proprietary knowledge involved in the deal through patent or other IPR mechanisms. Finally, in relation to the strategic options approach, which considers how management can decide on the optimal set of resources and capabilities it needs to acquire, research alliances offer flexibility and the possibility of preserving reversibility of decisions. In other words, inter-firm agreements are easier to dissolve than internal or merger commitments (OECD, 1992).

The economic geography approach to research alliances focuses on the importance of the knowledge within a region (or nation) to economic growth. In particular, it is argued that R&D and other knowledge generating activities (e.g. public sector research) within a specific geographic area generate externalities, which lead to economic benefits near the area where the knowledge was generated (Krugman, 1991). There are several explanations why this arises. The proximity of actors involved in research activities creates opportunities for interaction and learning through informal networks, as well as the diffusion of knowledge when employees change jobs (e.g. Saxenian, 1994). A second factor thought to link regional knowledge production to economic growth is the idea of localised knowledge spillovers, based on Romer's characterisation of the outputs of basic research as codifiable with "non-

rival” and “non-excludable” properties (Romer, 1992).² However, this view has now been discredited for a number of reasons including the fact that such knowledge is not easy to transmit because it has a significant tacit dimension and the output of leading edge research is highly excludable as it can be understood only by a small number of experts (see Brink, 2004 for a full review).

The economic geography literature also considers the determinants of multi-national companies' overseas R&D activities. The early literature stressed the role of home markets in determining firms' technological advantages. Successful export activities led on to the establishment of overseas production facilities and any associated R&D activity was mainly concerned with adapting products to meet local tastes (Vernon, 1966). Vernon (1979) later amended these views to suggest that in some high technology sectors firms engaged in programmes of almost simultaneous innovation in several major markets. The process of globalisation of large multinational firms' technological activities has now accelerated and firms' decisions to locate R&D outside the home country have changed, particularly in pharmaceuticals (Reger, 2000). Firms now assess the location of R&D in terms of the strength of the science and technology base and the availability of qualified scientists and engineers. It is further suggested that advances in information and communications technology (ICT) will solve the problems of co-ordinating R&D activities in several locations (for a review see Patel, 1995). However, it is unclear whether the home or overseas laboratories of pharmaceutical companies are the main participants in research alliances with overseas firms.

² “Non-rival” means that the possession of such knowledge by a firm or individual will not reduce its possession by others. “Non-excludable” means that others cannot be excluded from possessing such knowledge.

3 Research Alliances

This section first describes the early commercialisation of biotechnology through the emergence of dedicated biotechnology firms (DBFs). This description provides the context for discussing the empirical results of a selection of studies of research alliances between pharmaceutical multinational companies (MNCs) and dedicated biotechnology firms. These studies suggest that the reasons for pharmaceutical MNCs' alliances have changed over time, and three different phases are identified. The section concludes with a review of studies that explore the importance of co-location for partners in research alliances.

3.1 Background

Dedicated biotechnology firms (DBFs) first emerged on the East and West coasts of the US in the late 1970s and 1980s. They were the creation of a new generation of academic entrepreneurs, supported by venture capitalists. The DBFs possessed what were very scarce skills at that time: genetic engineering and protein expression. They often retained close links with academia either through retaining a part-time academic appointment, or through close links with former colleagues, many of whom sat on the companies' Scientific Advisory Boards. These companies had the long-term aim of applying biotechnology to the development of therapeutic proteins. To finance the long and costly process of getting products to market, they entered into research contracts, selling their unique capabilities and knowledge.

In the early 1980s many European governments became concerned that DBFs, who seemed to be key actors in the commercial exploitation of biotechnology, were not emerging in Europe. They introduced policies to rectify this omission: redirecting public research funds into academic biotechnology research, encouraging links between the science base and industry and promoting the creation of academic spin-off companies.

3.2 Phase 1: Early Alliances

Large US chemical and pharmaceutical companies who lacked biotechnology skills took the lead in entering collaborations with US DBFs or with university centers so as to build up in-house capability in the new technology. Most European chemical and pharmaceutical firms were slow to take up the challenge posed by biotechnology. Their main method for acquiring the new knowledge was through research alliances with European universities and research institutes. Some companies, like Bayer, ICI and Ciba-Geigy set up small biotechnology research teams in their corporate research laboratories to keep abreast developments in science, and monitor the activities of their competitors. Hoechst was an exception, but its method of learning about biotechnology was through a collaboration with US academic science. In 1981 it entered a 10-year, \$67 million contract with Massachusetts General Hospital, with arrangements for some of its researchers to be trained there. UK MNCs primarily built up their expertise through links with university researchers (Senker, 1996). This first phase of research collaboration can be seen mainly as a contract research or exploration phase when large, progressive pharmaceutical companies were trying to understand the significance of biotechnology developments and build up their absorptive capacities. During this early period recombinant DNA and monoclonal antibodies were the main technology covered by alliances (Tapon and Thong, 1997; 1999).

3.3 Phase 2: Ursurge of Alliances

The mid 1980s witnessed an explosion of DBFs in the US; by 1991 there were approximately 1,000 in the US. European DBFs also began to appear but even by 1996 there were less than half the number in the US, and their total turnover, R&D expenditure and number of employees represented only 10-15% of that of their US counterparts (Sharp and Senker, 1999).

During this second phase, established US pharmaceutical MNCs began a slow process of exploiting genetic engineering techniques as a production tool. The process involved collaborations with DBFs which could be followed by acquisition of the small firm or by strengthening in-house capabilities. Large pharmaceutical companies with in-house biotechnology capabilities also recognised the value of biotechnology as a research tool and began to apply these new techniques to drug discovery (Henderson et al, 1999).

The late development of DBFs in Europe left biotechnology innovation to the established pharmaceutical MNCs. Recognition that biotechnology tools and techniques had an important role to play in future product innovation led to a variety of strategies for assimilating biotechnology. Some built up in-house capabilities through links with academic research, others acquired new biotechnology firms or set up joint ventures with them, and most emulated their US counterpart by entering research alliances with US and European DBFs (Sharp and Senker, 1999, Henderson et al, 1999). By the mid 1980s several companies had expanded or set up new R&D laboratories in the US (Sharp and Senker, 1999). They increased their US R&D mainly to reinforce their position in the US market, but there was another benefit. The new US laboratories were set up at about the time that biotechnology began to be applied to pharmaceutical research, and biotechnology often diffused through the new US laboratories more quickly than in Europe. Sometimes the US laboratories demonstrated the power of the technology to such good effect that biotechnology became more fully integrated into European research efforts (Senker et al, 1998).

It was difficult, however, for the people with the new capabilities to influence corporate strategy, as company culture was based on the exploitation of synthetic organic chemistry and senior management was schooled in this mode of thought (Galimberti 1993). As a result,

when, by the end of the 1980s, biotechnology began to provide significant new drugs and new techniques to speed up drug discovery, many of the European companies found that despite having built up in-house competence they were short on new product ideas and/or expertise. Some companies then used DBFs as a source of exploitable product ideas; others to license the scarce new tools and techniques, proprietary to DBFs, which promised to reduce drug discovery time.

A study of biotechnology research alliances in the early 1990s found that the DBFs were extremely selective in their choice of partners. They not only sought collaborators ready to provide them with money, but also companies with the requisite knowledge or skills in the areas they wished to exploit, and they were prepared to spend time and resources searching for the right partner. The study also found that access each other's complementary assets was the main benefit for all, but questioned the traditional view that large firms are merely supplying finance in return for small firms' technology. Although the finance involved was crucial to the DBFs, they also benefited from substantial organisational learning as well as credibility both to enter further collaborations and to get access to investment capital. Above all they gained knowledge and competence in a wide variety of areas including about how to set up collaborations, how to conduct clinical trials, developing an appropriate work culture and enhancing their research knowledge and competence through learning-by-doing, and by many informal interactions with their partners' research teams. Organisational learning went far beyond Ciborra's "learning experiments".

The main flow of knowledge, however, was from the DBFs to the large companies. Research alliances were not used by large firms as a substitute for building up internal competence. In most cases, the large European multinationals already had some capabilities and collaboration

enhanced those capabilities Collaboration also fostered learning at management level, with growing understanding about how new biotechnology-derived products could fill a gap in the product portfolio (Senker and Sharp, 1997). For instance Audretsch and Feldman (2003) give several examples of therapeutic proteins with large sales developed by DBFs but marketed by MNCs. Similarly, Tapon and Thong (1999) show that of 527 collaboration agreements signed by the world's top pharmaceutical companies 1988-1997, almost two-thirds were signed at the discovery stage.

This second phase can be viewed as a time when research alliances were used as the basis for large firms to acquire new skills to augment their absorptive capability and cut the time required for companies to enter new areas of technology. In other words firms adjusted their dynamic capabilities to cope with the changing technological and competitive market. There was also a growing belief that developing products discovered by DBFs and applying the new technologies had the potential to reduce the rising expense and time taken by the discovery phase of new pharmaceutical products. Chemistry-based technologies (high-throughput screening, combinatorial chemistry, peptides and oligonucleotides) rise in importance as the focus of research alliances during this second phase, with rational drug design first appearing in 1987 (Tapon and Thong, 1997).

There are two longitudinal studies of DBFs' alliances over time. The first shows that alliances do not increase as DBFs grow which suggests that the process of learning through alliances is not linear. It is surmised that the growth of alliances in the early years of a DBF's life are connected to exploration and learning. There is a subsequent reduction in alliances that now seem to be connected to exploitation. However these two phases are followed by a new cycle of alliances for exploration and learning, indicating that the growth of DBFs is

connected to greater use of networks for learning (Oliver, 2001). The second study shows that DBFs' exploration alliances "predict products in development, which in turn predict exploitation alliances" which lead on to products in the market (Rothaermel and Deeds, 2004). However the speculation by Rothaermel and Deeds that exploitation may drive out exploration is not substantiated by Oliver's study. The need for renewed exploration may be explained by the the emergence of a new knowledge regime for life sciences, discussed in the next section.

3.4 Phase 3 – the Post Genome Era (PGE)

A recent analysis of the industrial research alliances of the world's top twenty pharmaceutical companies from 1978 to 1997 suggests that, since the mid 1990s, large pharmaceutical companies have become more cautious about which new technologies to bring in-house. Over the period there has been a constant growth in the number of research alliances, with similar growth patterns for different types of alliances (R&D cooperations including joint ventures, R&D contracts and purchases of technology or licenses). Since 1995 technology purchases and mergers have begun to decline but R&D cooperations and R&D contracts have continued to increase (Hullman, 2000).

This caution could be a reaction to what has been described by Queré (2004) as the Post Genome Era (PGE). The Human Genome Project (HGP), the international research effort that determined the DNA sequence of the entire human genome³ started in 1990/1991 and was completed in April 2003. It has been estimated that over this period public sector investment in the HGP was around \$3 billion in the US and of the order of \$500 million in the UK.⁴ Queré (2004) notes that the new knowledge and technologies produced by the HGP have

³ The US Department of Energy and National Institutes of Health have a wider definition of HGP as "a wide range of scientific activities including studies of human diseases, experimental organisms, development of new technologies for biological research, computational methods and ethical, legal and social issues" Queré (2004)

created a massive shock to the life science industry because they demand changes to companies' learning regimes and methods of knowledge accumulation. In addition firms are confronted with a massive number of technological opportunities in an industrial context in which knowledge accumulation and evolution takes place in “inter-organisational exchanges, R&D alliances and networks of learning” for exploring the post-genome era. Firms not only have to learn about new research avenues and new instrumentation techniques, they also have to learn how to manage the unprecedented amounts of information created by the HGP and new research disciplines and areas arising from the hybridisation of technologies. Thus the PGE has created a new wave of research collaborations which not only allow MNCs to explore the potential of uncertain and complex new technologies, they also enable MNCs to share the costs and risks involved.

An important place in the exploratory infrastructure is provided by “technological platforms” – combinations of firms and scientific institutions that bring together complementary competence to develop knowledge and offer services in the targeted area under investigation. Technological platforms are related to new experimental technologies such as combinatorial chemistry, bio-informatics, instrumentation techniques, genomics and proteomics. In parallel, the PGE also provides numerous, divergent opportunities for DBFs to market specialised applications based on PGE knowledge (Queré, 2004).

The formation of these networks of R&D alliances and their development has been characterised as an adaptive response by the pharmaceutical industry to cope with the explosion of molecular biology knowledge, a radical new technology for the sector. Rapid growth of knowledge, as well as the diversity of research areas and approaches makes it

⁴ Personal communication from Peter Senker

difficult for any firm to meet all its knowledge needs alone (Orsenigo et al, 2001; Santos, 2003). This is demonstrated by a study of the genomics alliances of two British MNCs (AstraZeneca and GlaxoSmithKline and the predecessor companies from which they were formed) in the past decade. The high number of alliance partners of these two MNCs (demonstrate that it is impossible to acquire genomics from a single source, and the required capabilities have to be brought together from multiple sources. It has even been necessary to these firms to source sub-components of some genomics technology (e.g. bioinformatics) from many firms (Hopkins, 2005). The DBF partners include instrumentation makers, software houses, database sellers, and platform technology providers as well as service providers. The pharmaceutical companies have also engaged in pre-competitive research collaborations with each other, as in the SNP consortium (Hopkins, 2005).

What is the effect of this fragmentation of PGE knowledge on the DBFs? A recent analysis of collaborative agreements in the pharmaceutical sector shows that established, research-intensive pharmaceutical MNCs can absorb new specialised knowledge more easily than specialised biotechnology firms can absorb the general knowledge required to become integrated pharmaceutical companies; in other words, specialist firms, especially those marketing PGE knowledge, tend to remain specialists (Orsenigo et al, 2001).

Nonetheless, large pharmaceutical companies are facing a continuing challenge to identify, absorb and integrate relevant new knowledge with their existing knowledge as well as discovering how to benefit from organisational learning in an innovation network. Research alliances to acquire new technologies are not a substitute for in-house research. Indeed the increase in interfirm collaboration has been paralleled by rising expenditure on industrial research (Santos, 2003). The number of drugs approved by the FDA each year have not

shown a commensurate increase. Indeed it has been difficult to find evidence that the biotechnological revolution is yet having a major impact on drug discovery because, in common with other major technological changes, it will require complementary technical and organisational innovation and many years before its benefits are realised (Nightingale and Martin, 2004).

3.5 Globalisation and Location of Partners

This section first considers some scanty information on the location of European pharmaceutical MNCs' partners in biotechnology research alliances. Identifying the location of the partners of pharmaceutical MNCs in biotechnology research alliances is complicated by the sector's international expansion of R&D (Zeller, 2004). It is therefore also necessary to consider the role of the MNCs' home or overseas R&D facilities in these partnerships and the recipients of knowledge flows.

There is scanty research on the location of the industrial research partners of European pharmaceutical MNCs. Those studies that have been carried out find few examples of research alliances with national DBFs. In this context it is relevant to mention that there seems to be a division a labour in the development of entrepreneurial biotechnology firms within Europe. The British innovation system supports DBFs involved in therapeutic technologies, whereas firms involved in platform technologies are better suited to the institutional environment in Germany and Sweden. This division of labour is connected to differing national institutional frameworks, especially those concerning skill formation and the organisation of labour markets (Casper and Whitley, 2004).

An examination of the formal knowledge collaborations of Swedish R&D performing companies involved in the bioscience and pharmaceuticals sector found that regional or

national co-location of partners is less common than anticipated. One exception is collaborations with universities where firms are more likely to collaborate with those in close proximity, not international ones. However, large Swedish pharmaceutical MNCs had no formal knowledge collaborations with smaller national firms in the biotech-pharma sector while these smaller firms collaborated with both international and national companies. It is suggested that patterns of collaboration are related to a global division of labour, with Swedish “cliques around specific and specialized knowledge areas ...” (McKelvey, Alm and Riccaboni, 2003). A further example of this specialisation is shown by an analysis of research alliances in auto-immune diseases by Hinze and Reiss (2000). It shows a growing intensity of research alliances between large European pharmaceutical firms and small biotech firms since the early 1990s. However, many of these alliances are international because the majority of small biotech firms involved in auto-immune diseases are located in the US.

A study of the genomics partners of AstraZeneca and GlaxoSmithKline during the period 1993-2004 also shows few examples of alliances with DBFs in close proximity. Of the 76 DBF partners identified, 51 were in the US and 25 in Europe (12 UK, 5 German, 2 Danish and 1 Swiss) (Hopkins, 2005).

Two studies indicate that there has been a change over time in the location of MNCs’ laboratories forming links with new biotechnology knowledge. The first study, conducted in the early 1990s found that the ten European MNCs involved first explored the potential applications of biotechnology in their European laboratories, but by the early 1980s biotechnology was also important to their US research efforts. All companies subsequently increased their US research efforts. Two firms did this specifically to tap into strong US biotechnology research, but most increased US R&D to reinforce their position in the US

market. At that time the European laboratories employed roughly twice as many biotechnology researchers as in their US subsidiaries. However, several companies were moving some areas of research to the US because of gaps in European expertise, especially in bio-informatics and combinatorial chemistry. Other companies were considering increasing biotechnology research in the US at the expense of Europe, because it was easier to attract high calibre people in the US, both in terms of the numbers and expertise available.

Links with DBFs ranged from acquisitions to investments, strategic alliances and licensing. The European laboratories of many of MNCs had 20-30 important strategic alliances with US DBFs. Funds for these alliances were provided by the European Head Offices and the US laboratories acted as licensing agents and/or talent spotters. Strategic alliances between European companies and EU DBFs were rare. The US laboratories appeared to be less involved in strategic alliances than their European HQ (Senker, Joly and Reinhard, 1996).

The second study examined the activities of Novartis and the three companies⁵ from which it was formed before they merged in 1996 (Zeller, 2001). It indicates an intensification of the trends identified in the first study although it is based on fewer firms. The intensification is linked with the boom of DBFs that occurred in the late 1980s that were spatially concentrated into a few areas of the US – mainly San Francisco, Boston and San Diego. The predecessor firms of Novartis all had alliances with DBFs in the San Francisco and Boston regions. During the 1990s their alliances increased and they also acquired or took equity holdings in leading DBFs. They also had many formal collaborations with universities in San Francisco and Boston. Among these was a long-term collaboration between Sandoz and the Scripps Institute in the San Diego area, connected to significant rights to technology developed there.

⁵ Hoffman-La Roche, Ciba-Geigy and Sandoz

In 1997 Novartis invested significantly in functional genomics in its Swiss laboratory as well as its main research facility in New Jersey. The next year it announced the establishment of a Genomics Institute in San Diego, adjacent to the Scripps Institute, which opened in 2002. The three in-house genomics centres are nodes of an internal genomics network of Novartis European and US research centres that also has many alliances with external partners. The Genomics Institute of Novartis has several dozen independent research collaborations with DBFs as well as with universities in California and other parts of the US, and research institutes in Sweden and other parts of the world. Zeller (2001) notes Novartis is not alone in embedding its activities in the knowledge-rich regions of San Diego, San Francisco and Boston. Collaborations, acquisitions and new research facilities in these regions by other leading pharmaceutical MNCs have led to spatial concentration of research in a few inter-linked regions; outside the US regions, the Oxford/Cambridge region in the UK is the most important European innovation hub. The number of these regions is limited because companies are very selective about the knowledge and technology they wish to acquire. Spatial concentration results from a combination of public investment in research in leading universities and other research centres, spin-off firms, and private investments by oligopolistic rival MNCs fighting over privileged access to spatially concentrated centres of specialised technology expertise (Zeller, 2001). Decisions by MNCs to invest in corporate research facilities in these regions further accelerates spatial concentration.

This section suggests that the location of MNCs' partners is determined, especially in the PGE, by the availability of leading-edge knowledge in a few spatially concentrated regions.

4 Conclusions

This paper has described the dynamism of the biotechnology knowledge base and its impact on the research activities of European pharmaceutical MNCs and their research alliances during the past two to three decades. This material permits the conclusions to discuss:

- a) a comparison of the usefulness of the various theoretical approaches used to analyse and understand these alliances;
- b) the identification of any changes over time in the nature of alliances; and
- c) an indication of the future in store for dedicated biotechnology firms.

Many theoretical approaches have been used to explain biotechnology research alliances in pharmaceuticals. The organisational learning and dynamic capabilities approaches from the business management area are the most robust in their explanatory power and ability to cope with changes in biotechnology alliances. Economic geography approaches capture some of the factors underlying the growth of some regions as biotechnology innovation centres.

However, these theories fail to acknowledge that the potential for significant knowledge-based growth is limited to a very few regions, and is mainly linked to regions with pioneering DBFs exploiting radical new technology. The limited relevance of some of the other theoretical approaches presented is connected to a rather static analysis of an extremely dynamic and volatile situation for many variables including the knowledge base, the type of firms, their alliances and firm structure.

The nature of inter-firm research alliances, their focus and the motivation for pharmaceutical MNCs to enter these alliances has undergone significant change since the early emergence of biotechnology. The earliest alliances were usually between two partners, with MNCs linking

with DBFs to explore the significance of biotechnology and build up in-house capabilities. Alliances mainly focused on recombinant DNA and monoclonal antibodies. During the second phase MNCs used alliances both to acquire new tools and techniques for speeding up drug discovery and as a source of exploitable product ideas based on therapeutic proteins. During the most recent phase, the interest of the MNCs in alliances seems to have shifted away from therapeutic proteins (large molecule drugs) to alliances with a network of DBFs, each with specialist expertise in a different sub-field of PGE technologies, with the aim of absorbing and integrating knowledge to facilitate the drug discovery process. In other words they are trying to taking a more scientific approach to drug discovery, with the intention of using synthetic chemistry to produce the resulting (small molecule) drugs.

Knowledge dynamism has led to continuing opportunities for the formation of DBFs. What prospects are there for their growth? Few of the early DBFs saw themselves as long term research contractors. For most, their long term target was to become a fully integrated pharmaceutical company, to be achieved by carrying one or two 'blockbuster' biotechnology drugs through to the market and earning multi-million dollar profits. In 2005, only two US companies, Amgen and MedImmune, had achieved these ambitions (Nightingale and Martin, 2004). Many DBFs failed and others were taken over by pharmaceutical MNCs. It appears that the recent generation of DBFs based on specific PGE technologies will face insuperable difficulties in absorbing the general knowledge required to become integrated pharmaceutical companies (Orsenigo et al, 2001). This suggests that even successful DBFs will fail to grow significantly or to enter the pharmaceutical sector.

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