CREATING AND CAPTURING VALUE IN THE BIOPHARMACEUTICAL SECTOR

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Declaration

I, Bruce Rasmussen, declare that the PhD thesis entitled *Creating and Capturing Value in the Biopharmaceutical Sector* is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature

Date

Abstract

This study addresses the ongoing implications of the realignment of the pharmaceutical industry knowledge base – from small molecule methods to new biomedical technologies – for the competitive positions of traditional pharmaceutical companies and biopharmaceutical start-ups. The theoretical approach draws on the modern theory of the firm and related concepts, to define and develop the concept of the business model. This is employed to guide the empirical analysis, which utilises a combination of data analyses and case studies based on several sources, including detailed company reports and alliance databases. The thesis analyses how the pharmaceutical companies have successfully adjusted their business models to meet the challenge of biotechnology and so retain their powerful position in the industry. Central to this has been the breadth and depth of knowledge transfer through alliance formation. Not only has this been critical to the adjustment process for the large pharmaceutical companies but also for the development of the many biopharmaceutical start ups. Nonetheless the business models of these smaller companies have many weaknesses, which have led to the erosion of the value of their initial strategic assets. Despite the poor financial performance of the vast majority of these firms, the biopharmaceutical sector as a whole has created significant value. This has been captured disproportionately by a handful of large fully integrated biopharmaceutical firms and, to a lesser extent, by the largest dozen pharmaceutical firms.

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Chapter 1. Overview

The Issues

The discovery, testing and distribution of new medicines is one of the most knowledge intensive of all economic activities, and one that has delivered important benefits in terms of better human health over more than a century. When the knowledge foundations and the technological basis of such an industry undergo radical change – as is occurring with the rise of biomedicine – the ramifications of this change for the structure and operations of the industry are likely to be profound. In the case of the pharmaceutical industry the shift in the knowledge base is of recent origin and is still continuing, and hence the analysis in the literature of these ramifications remains incomplete.

This study is intended as a contribution to understanding the ongoing implications of the change in the knowledge base of the pharmaceutical industry from a focus on small molecule drugs to biomedicine and related technologies. It concentrates on four of the many questions that arise, namely:

i. *The New Knowledge Base*. What are the main characteristics of the shift in the knowledge base, and what are the implications of this shift for the discovery and development of new medicines?
ii. *The Impact on Large Pharmaceutical Firms*. How have the entrenched big pharmaceutical companies responded to this shift? Have they been able to preserve their dominant competitive position in the light of this shift, and if so how?
iii. *The Role and Competitive Position of Biotechnology Firms*. How have the many small firms established to commercialise biotechnology discoveries developed, and how have they tried to build competitive advantage? Have they in fact been able to compete successfully with the large established firms?
iv. *The Creation and Capture of Value*. Has the advent of biopharmaceuticals created value, and if so which types of firms have captured that value?

These questions are not, of course, new ones: in addressing them the new research reported here is situated within the findings of the existing literature on these issues.

This literature is fully acknowledged in the following substantiative chapters, but has been omitted from this Overview in the interests of easier reading.

The focus of this study is the role of firms in the development of new human therapeutics, and particularly in the role of biomedicine and biotechnology within that process. Two types of firms are distinguished, traditional pharmaceutical companies and biopharmaceutical companies. The dominant firms in the first category are very large, with the top dozen having market capitalisations in the $50-150 billion range. [1]The R&D expenditure of these firms in total exceeds $50 billion, about two and a half times the total global R&D expenditure by publicly listed biotechnology companies. Although established prior to the application of modern biotechnology, they have played an important role in the development of biopharmaceuticals.

The firms in the second category, those other firms engaged in the application of biotechnology to the creation of human therapeutics, are referred to as biopharmaceutical firms. There are an estimated 3500 biopharmaceutical companies globally, of which about 15% are public companies. The vast majority of these firms are small, with the majority even of the larger listed ones having a market capitalisation of less than $250 million. Drugs which are created by the use of modern biotechnology techniques are here called biopharmaceuticals, whether they are produced by biopharmaceutical or pharmaceutical firms.

The Approach

The phenomena being explored in this study are both complex and of recent origin, and the firms being studied are very diverse. Reflecting these and other factors, no single theory can be drawn on to explain the response of this diverse population of firms to the new knowledge base, nor is there a single unified data set covering all relevant aspects of their behaviour. Accordingly there is no single economic model which could be developed and empirically tested to isolate key explanatory variables. Rather a more pragmatic theoretical and empirical approach is required, one which assimilates available theoretical contributions to create an acceptable analytical framework and which utilises several different but partial data sets to test emerging

[1] Note that all $ used in this study are US$.

hypothesis. Such an approach is also inevitably iterative, with several iterations between empirical insight and selective theoretical explanation. A growing understanding of the empirical realities being studied (such as the importance of networks and alliances) leads to a search for a theoretical framework in which these realities can be interpreted, leading in turn to new empirical questions, and so on.

The theoretical approach draws on a range of supposedly competing bodies of literature on the theory of the firm and their relationships with other firms, in particular transaction cost economics, the resource based view and the open innovation paradigm– to define the framework for analysis. The key concept in that framework is that of the business model, which has a sufficiently open structure to accommodate a diverse range of theoretical contributions. While widely used in business analysis, the concept of the business model has played only a limited role in the academic literature to date. Here the business model concept is defined and enriched by drawing on those other strands, and is the main analytical concept employed to guide the empirical analysis.

The empirical strategy utilises a combination of data analysis and case studies, drawing on a number of data sets to examine particular hypotheses, as listed below.

- An alliance database sourced from Recombinant Capital (the Recap database), which contains summary information on over 20,000 biotechnology alliances classified by a range of variables, including the type of partners, the nature of the alliance technology and therapeutic focus.
- A database of summary financial information on over 200 US listed biotechnology companies, also available from the Recap website.
- The annual 10-K reports filed by US biopharmaceutical companies, and similar reports filed by foreign listed companies, contain business information presented in a standardised format that facilitates strategic analysis. Detailed analysis of reports for about 150 companies is undertaken for this study.
- A biopharmaceutical sales database, with sales and other data on 100 biopharmaceuticals sourced from IMS, the FDA and company filings.
- The US Patent Office patent database is also utilised, especially for the analysis conducted of bioinformatics patents.

These databases are supplemented by analysis of company information from web sites and published reports, such as prospectuses and investor presentations.

Thesis Outline

The thesis is divided into five parts. The first part, *Firms, Networks and Business Models*, is a theoretical development of the business model concept. The purpose of the section is to use the modern theories of the firm, the recently developed open innovation paradigm and other related theoretical contributions to enrich the concept of the business model, so that it can be used later in the study to better explain the roles of the various types of firms in the biopharmaceutical sector. The second part, *The Rise of Biotechnology: New Foundations for Biopharmaceuticals*, discusses the rise of biotechnology, which provides the foundation for the new biopharmaceutical knowledge base. This new knowledge base however does not change the fundamental economics of drug development, which remains costly and uncertain.

The third part, *Responding to the New Knowledge Base: Diverse Business Models*, uses the business model concept to present and analyse the pharmaceutical business model and its response to the impact of biotechnology. This discussion demonstrates not only how the pharmaceutical business model has changed as a result of the impact of biotechnology, but also endured and therefore why such firms remain powerful actors in the post biotechnology pharmaceutical world. Two different biopharmaceutical business models, one described as 'drug discovery and the other 'platform technology', based on their distinctive technological regimes are also defined. Each business model confronts in different ways the difficulty presented by the fragmented, as well as rapidly evolving, nature of the biopharmaceutical knowledge base. One response has been to create alliances to share and transfer this knowledge. Two chapters in this section discuss the overall trends in alliance formation and in particular examine the important differences in the pattern of alliance formation between the different business models.

The fourth part, *Four Case Studies*, then provides a series of case studies which are designed firstly, to test whether the business models developed earlier are supported by the evidence gathered from a cross section of biopharmaceutical firms, and secondly to use the business model framework to identify some of the critical

characteristics of successful and unsuccessful biopharmaceutical business models. These focus in particular on the shortcomings of the platform technology business model, the importance of the IP regime to capture shared value created in alliance networks, and the importance of internally owned strategic assets to provide the basis of sustainable competitive advantage.

The final part, *Value Capture and Creation: Conclusions*, is concerned with the question of sector-wide value. It attempts to answer the question of whether the application of biotechnology to the development of human therapeutics has been worthwhile, which types of firms have helped create value, those which have captured it and what are the implications for industry structure.

Some Methodological Contributions

The principal purpose of this study is to answer a series of questions about the development of biopharmaceutical firms and the response of pharmaceutical companies to the new knowledge of biotechnology. This analysis has been facilitated by better defining the concept of the business model and enhancing its explanatory power by the integrating it with existing theory. The outcomes of the thesis are therefore in part methodological, arising from this work on the business model, and in part substantiative, in terms of new results in relation to the questions about the pharmaceutical and biopharmaceutical firms noted above.

Complementarity of key theories of the firm

The four main theories considered here about the firm and its relationships with other firms – transaction cost economics, the resource based view, the open innovation paradigm and the relational view – are often presented as conflicting alternatives. But in the present context, and in relation to our questions, the key concepts and mechanisms of these theories prove complementary rather than conflicting. For example each of these concepts has a part to play in understanding the key role of alliances in the biopharmaceutical industry. Transaction cost economics focuses on the cost and risk reduction reasons for alliance formation, whereas the resource based view stresses the acquisition of complementary assets and dynamic capabilities and the relational view focuses on the joint asset that may be created by an alliance, and the relational rents to which it may give rise.

Enriching the concept of the business model

In the market place, the business model plays a major role in the commercialisation of technology. It acts as the value creation construct that mediates between the technical and economic domains, selecting and filtering technologies and packaging them into particular configurations to be offered to the market. For example, presenting a viable business model, expressed in a business plan, is critical for small companies seeking to raise money for technology development.. But in the literature, as an analytical concept, the business model is little more than a list of functions, which any business plan should potentially encompass. It has little analytical or explanatory power. This study shows how – by enriching it by drawing on the resources of the theories of the firm and related theoretical constructs – the concept of the business model can be better defined and can provide a stronger role in explaining the commercialisation process of technologies and in identifying the elements that provide the firm with sustainable comparative advantage. Of the numerous concepts that form part of this theoretical literature those of appropriability, relational rents, complementary and strategic assets and the technological regime have proved to be most useful.

Technological regimes and business models

In addition to that of the business model, the concept of the technological regime is widely used throughout this thesis. It is defined as a particular combination of the features of the knowledge base, of the processes for building cumulative knowledge and of the appropriability and opportunity conditions characteristic of a given technology. Quite different technological regimes are involved in the development of traditional small molecule drugs and of biopharmaceuticals, and it is shown that these differences help to explain the evolution of the pharmaceutical company business model, the development of the large biotechs and the enduring nature of the large company, vertically integrated business model. This thesis also shows that linking technology regimes and business models – that is, defining different biopharmaceutical business models based on two underlying technological regimes of platform and drug discovery technologies – is useful in explaining differences in behaviour of specialist biopharmaceutical firms.

Major Findings

(1) The new knowledge base

Many of the answers to the first question are documented in the existing literature, which is drawn on here. The nature and impact of the rise of modern biomedicine is best analysed in terms of the concept of the technological regime, for the development of traditional small molecule drugs and of biopharmaceutical drugs involve quite different technological regimes, both of which have been transformed by ongoing developments in biomedicine. In the small molecule regime, the creation of new drugs is based on large scale screening and rational drug design techniques for a small number of disease targets, rather than a detailed understanding of the disease being addressed. Much of this work has taken place in big company labs with, prior to the Bayh Dole Act, academic research being largely in the public domain. The biopharmaceutical regime exploits new knowledge from molecular biology and genomics about the nature of specific diseases, about disease pathways and about a much larger number of disease targets to create an array of newly engineered therapeutic proteins as drug candidates. The new foundational knowledge has been increasingly widely dispersed in universities and small companies, and the transition of 'star scientists' to biotech companies has been an important part of the commercialisation process in this regime. Clearly both of these technological regimes have evolved with further advances in molecular biology and genetics.

This thesis addresses the implications, for different types of companies, of the shifting balance between the small molecule and the biopharmaceutical regimes, and the continuing evolution of them both. It is also important to note that the average cost of developing a new drug and bringing it to market has continued to increase in real terms and that, contrary to earlier expectations, neither the average cost nor the average time taken to discover and prove a new drug are lower for biopharmaceuticals than for traditional drugs. Thus the shift in technological regime has in no way reduced the financial pressures within the industry.

(2) The impact on large pharmaceutical firms

The continued viability of the large pharmaceutical firm business model

It is demonstrated, within the business model framework, that the large vertically integrated pharmaceutical firm is a response to the fundamental economics of drug development in which there are economies of scale and scope, large sunk costs and advantages derived from an integrated value chain. In spite of the impact of biotechnology most of the factors leading to the large integrated model remain intact: Biotechnology has done nothing to reduce the value of scale and scope and of integration, at least in drug development, testing and marketing, if not in drug discovery. It is notable that the most successful biopharmaceutical firms (see below) are themselves adopting this large scale, integrated business model. The main qualification, at least for traditional pharmaceutical firms, about the continued viability of the business model lies in the declining productivity of its small molecule drug pipeline and the extent of patent expiries over the next decade or so, as drugs developed by traditional methods and patented in the 1990s are increasingly replaced by generics.

The changing pharmaceutical value chain: The role of alliances for platform technologies

The largest impact of the changing knowledge base has been on the structure of the value chain and value network. The value network has become significantly more complex as many specialist technologies have become integrated into the pharmaceutical value chain. For large pharmaceutical companies, alliance formation with the specialist firms to acquire platform technologies, and to build their absorptive capacity across a wide range of technologies, has been fundamental to this process.

Between 1990 and 2005, large pharmaceutical companies accounted for over 80% of payouts in alliances recorded on the Recap database. There has been much discussion of the use of alliances to obtain new products to build their drug pipelines, but the Recap data imply that alliances for platform technology acquisition have been significantly larger than for specific drug discovery technologies, both in terms of number of alliances and the value of payouts. This pattern is quite different from that of biopharmaceutical firms.

The position of individual companies

It is important to distinguish between the ongoing viability of the large fully integrated business model and the viability of individual traditional large pharmaceutical companies, of even of the pre-1980s large companies as a class. While these companies retain substantial financial and market power and strong knowledge capabilities, each is responding in different ways to the transformation of the knowledge and the commercial dynamics that go with it. This study does not provide any prognosis about the future of individual companies or groups of companies, although it does seem inevitable that large firms with an integrated business model will continue to play a dominant role in the industry.

(3) The role and competitive position of biotechnology firms

The dominant role of large biopharmaceutical firms

One of the key findings of this study is the central role of a small number of large biopharmaceutical companies, both within that sector and within the pharmaceutical industry more generally. Over 2002-2006 (inclusive) six large biopharmaceutical companies (led by Amgen and Genentech) accounted for 60.5% of global sales of biopharmaceutical drugs, by comparison with only 14.9% for all other biopharmaceutical companies and 25.0% for all pharmaceutical companies. This dominance in sales increased within the period, with the share held by these six firms being 63.0% by 2006, and is evident in other indicators also, such as R&D, alliance formation and profitability. While this study does not extend to a full examination of the reasons for this dominant role, it again highlights the continuing value of the large integrated firm business model in this industry.

The role of alliances for biopharmaceutical firms

In the development of biopharmaceutical firms, alliances play a dual role: they are sources of technology or products when the firms act as client, but also a source of revenue when firms act as developer. The analysis of the Recap alliance database illustrates two fundamental aspects of the biopharmaceutical knowledge base – its fragmented nature and the divide between the traditional and biopharmaceutical technological regimes. Large pharma is willing to pay large sums to acquire drug candidates and platform technologies from drug discovery and platform technology companies. In 2005 the payout value for big pharma alliances was $10.8 billion, with

drug discovery and platform technology companies gaining $4.2 billion each. To overcome the fragmentation problem a large number of alliances are formed between platform technology companies and between drug discovery companies. These are typically low value alliances but reflect the requirements of firms to combine complex systems of diverse technologies to assemble final products. For instance 64% of platform technology company alliances, in the period 1990 to 2005, have been for platform technologies.

Differences in biopharmaceutical business models: platform technology and drug discovery models

The evidence presented in this study suggests fundamental difficulties with the platform technology business model. In particular the process of integrating technological capabilities through alliances exposes companies to appropriation of relational rents. Only companies with strongly appropriable strategic assets appear capable of creating sustainable competitive advantage. More than half the platform technology companies have adopted a 'hybrid' drug discovery/platform technology model. Others have internalised their platform technology capabilities for use on their own drug discovery programs.

Drug discovery companies have truncated value chains without marketing and distribution capabilities. Some have used alliances to cover this deficiency. The success of drug discovery companies depends considerably on the serendipitous outcome of their drug discovery and development program. Given the uncertainties of this process most companies fail to establish a sustainable competitive advantage. However for those that do develop a valuable drug, the IP regime for drugs is generally superior to platform technologies and any value created can be captured. However the success of the large biopharmaceutical companies suggests that the fully integrated model is necessary to fully capture this value and establish sustainable competitive advantage.

Intellectual property, alliances and the business model

Biopharmaceutical firms inevitably face some difficult questions about shaping a business model and forming alliances in the context of the creation and protection of intellectual property (IP). How important is the enhancement and protection of IP

relative to other factors? Can a strong business model overcome a weak IP position? To what extent is IP put at risk in entering into alliances? The study does not purport to provide full answers to these and related questions, but the case study analyses do provide some support for three propositions. First, while some companies have ridden a strong early IP position to apparent success (e.g. Affymetrix), in many cases this has not proven sufficient to overcome deficiencies in the business model adopted. But, secondly, there is little evidence from any of the case studies that a strong business model can be effective in overcoming the limitations of a weak IP position. Thirdly, there are real risks of erosion of the value of intellectual property in alliances. For example, there is some evidence that in alliances between platform technology companies and large drug companies, the bulk of the relational rents created in the alliance have been appropriated by the large company.

(4) The creation and capture of value

The biopharmaceutical industry is creating value

An estimate has been prepared of the present value of actual and future global sales of 79 biopharmaceuticals for which there were sales in 2006, and also on the estimated net cost of development, production and marketing of those drugs. Analysis of these data indicated that the estimated net present value (NPV) of net sales of these drugs was more than three times their cost of development, implying that the biopharmaceutical industry is creating substantial economic value. This conclusion is robust across an alternative range of assumptions about the future growth of sales, discount rates, development costs, failure rates, and changes to the period of market exclusivity.

This value is largely captured by a few large biopharmaceutical firms

While the industry is creating substantial value overall, this analysis also shows that the bulk of that value is being captured by the six large biopharmaceutical firms. Expected sales net of costs by the six firms account for 61.9% of the NPV of net sales, and the ratio of the NPV of net sales to that of development costs for these six firms is 8.2. The twelve largest pharmaceutical companies account for 22% of the NPV of net sales, with a net sales/development cost ratio of 3.2. By contrast all other biopharmaceutical companies account for only 14.9% of the NPV of net sales, with a

net sales/development cost ratio of 2.3, while for all other pharmaceutical companies the net sales share is less than 3.8%, with a ratio of 1.2.

Implications for future industry dynamics

Several conclusions follow from the remarkable capture of value in biopharmaceuticals to date by a handful of large biopharmaceutical firms. For example, this dominance, together with the capture of value by big pharmaceutical firms, helps to explain why most specialist biopharmaceutical firms languish with low levels of profitability. The analysis of value also supports the view that the large fully integrated business model is the most successful of the models considered, especially when it is allied to the intellectual property base and the technological expertise of the large firms that were involved in the birth of biotechnology. It also highlights the ongoing difficulty for emerging successful drug discovery firms in establishing themselves as independent sustainable firms. There is a high probability that any firm with significant sales will be acquired by one of the major pharmaceutical or biopharmaceutical firms. The analysis also suggests that, while there remain major challenges ahead for large pharmaceutical firms in adjusting to the changing technological and business environment, it seems likely that many of them will have an enduring role in the biopharmaceutical sector, as a result of modifications being made to their business model.

Conclusion

The knowledge base of the biopharmaceutical sector continues to evolve, with each technological breakthrough creating a new set of specialist companies with ambitions of discovering new drugs or developing innovative and valuable technologies. Properly understanding this ongoing transformation remains challenging. Establishing the key variables in the process of commercialising new technologies, such as biotechnology is still clouded by the particular characteristics of complex knowledge, the difficult technical challenges to be overcome and the acceptance of the value proposition by a target market segment. In these circumstances generalisable propositions are difficult to confidently validate. Better data and further analysis is required that is beyond the scope of this study.

Nonetheless the findings presented in this study have advanced this understanding in important respects. It has established that the development of biopharmaceuticals has produced positive returns on their cost of development. It has indicated that these returns have been disproportionately captured by the large pharmaceutical and biopharmaceutical firms. This helps explain why so many biopharmaceutical firms have failed to generate the profits that would sustain their competitive advantage.

Weaknesses in the structure of biopharmaceutical business models have been identified that have contributed to their failure. There are fundamental difficulties with the platform technology company business model centred on the appropriation of relational rents. Nor does the drug discovery business model, given the highly uncertain drug discovery and development process, offer sustainable competitive advantage, unless success in drug development allows the firm to adopt the fully integrated model.

The essential role of alliances has been demonstrated in bridging the knowledge gaps, most importantly between traditional pharmaceutical firms and the sources of new biotechnology knowledge, and between the specialist biopharmaceutical firms themselves. Alliances have enabled the large pharmaceutical firms to 'remain in the game'. With their formidable resources and modified fully integrated business model, they appear likely, despite certain challenges, to continue to be important actors in the development of biopharmaceuticals.

However the best placed group of firms are the half dozen large biopharmaceutical firms, that have achieved a dominant position in the sector through their mastery of the new knowledge base and early success in drug development, which has allowed them to adopt the vertically integrated business model.

PART A.

FIRMS, NETWORKS AND BUSINESS MODELS

Chapter 2. Lessons from the Modern Theory of the Firm

Introduction

As suggested in the Overview, there is no single framework that provides a complete theory of the behaviour of firms in the biopharmaceutical sector but a number of approaches have been developed within the modern theory of the firm that are relevant. These are transaction cost economics and the resource based view of the firm. Adopting the single firm as the unit of analysis this chapter outlines the theoretical answers to the following questions. Why do firms exist? What causes vertical integration? What provides the firm with sustainable competitive advantage?

The first question considered in this chapter is the fundamental one asked by the modern theory of the firm. Why should firms exist at all, when each of the functions could be undertaken by contracting parties? Transaction cost economics has proved most useful in helping explain the existence of the firm, especially the vertically integrated one. On the other hand, the resource based view of the firm and related theoretical work helps explain what gives the specialist firm its sustainable competitive advantage.

Why Firms Exist and the Development of the Vertically Integrated Firm

Transaction cost economics

While at its simplistic level, transaction cost economics is about economising on market place transaction costs by conducting such transactions inside the firm, Williamson seeks to employ its key concepts in explaining the structure of the modern vertically integrated, multidivisional, multinational firm (Williamson 1971, 1981).

As observed by Coase (1937), ‘there is a cost to using the price mechanism’, most obviously in organising production. ‘The costs of negotiating and concluding a separate contract for each exchange transaction which takes place must be taken into account’ (Coase 1937). The need for such contracts, while not eliminated is much

reduced inside the firm. However the management of production inside the firm has its own costs and as Coase points out this provides a limit to the size of the firm. He suggests that:

> … a firm will tend to expand until the costs of organising an extra transaction within the firm become equal to the costs of carrying out the same transaction by means of the an exchange on the open market. (Coase 1937)

The firm as a governance structure

The concepts underlying the theory of transaction cost economics have been much developed since these early thoughts and its predictive powers usefully enhanced. These developments centre on shifting the view of the firm from a production function to a governance structure and 'that the evolving corporate structure has the purpose and effect of economising on transactions' (Williamson 1981, p. 1543). A transaction, the fundamental unit of analysis in transaction cost economics, 'is said to occur when a good or service is transferred across a technologically separable interface' (Williamson 1981, p. 1544). Williamson refers to a technologically separable interface as being between stages of processing or assembly (Williamson 1981).

As a governance structure, Williamson (1971) argues, a firm has certain advantages over the market. A firm is firstly able to provide incentives that 'attenuates the aggressive advocacy that epitomises arms length bargaining.' Secondly it has a 'wider variety and greater sensitivity of control instruments' and thirdly it possesses 'comparatively efficient conflict resolution machinery' (Williamson 1971, p. 113). These advantages in control, incentives and conflict resolution offer the potential for internal transactions to be undertaken with greater efficiency inside the firm than in the marketplace.

Defining assumptions of transaction cost economics

In transaction cost economics the behaviour of human agents is assumed to be fundamentally different to that assumed in the perfectly competitive economic model. Three concepts are used to distinguish the two approaches. These are bounded rationality, incomplete contracts and opportunism. Coined by Simon (Simon 1957; Klaes and Stent 2005), bounded rationality reflects the view that while economic

actors may be intendedly rational, they are limited in information processing and problem solving, such that they seek to optimise choices from a more limited set of alternatives, rather than those available in the total market. Incomplete contracts and opportunism are discussed in the section below.

Incomplete contracts and opportunism

Contracts are incomplete in two ways. The first is that the condition of bounded rationality precludes agents from having the capacity to contract with a complete set of all possible agents. 'All contracts in the feasible set are incomplete' (Williamson 1989, p. 139). The second (Williamson 1971) refers to the difficulty of drafting secure, all encompassing long term contracts for the supply of complex goods or services, that do not suffer from ambiguities or the need for modification through changed circumstances. Renegotiating contracts during their life however, exposes parties to opportunistic bargaining to alter the balance of costs and benefits from those originally agreed. In an effort to step around these difficulties, contracting parties sometimes opt for a series of shorter term contracts that allow for renegotiation. This however does little to alter the basis for opportunistic bargaining at the commencement of each new contract period. The party that has made a long-term investment, for instance in special purpose equipment to support the supply of a particular product, is most exposed.

Opportunism not only refers to this tendency to take advantage of contract renegotiation to improve one's position, but also to a failure of the parties to be altogether reliable and trustworthy in fulfilling contractual obligations. For instance a contractor may be tempted to reduce costs by compromising quality in a fixed price contract.

If a transaction in the market place is likely to be seriously compromised by bounded rationality and risks high cost opportunistic behaviour by the external party, then it may be preferable to undertake this activity inside the firm. In addition to these characteristics of the transaction, the nature of the assets at the heart of the transaction is also important in determining whether the transaction should be internalised. Two concepts, asset specificity and residual property rights are important in this regard

Asset specificity and residual property rights

Asset specificity 'is the degree to which an asset can be redeployed … without sacrifice of productive value' (Williamson 1989, p. 142). Asset specificity can take many forms, such as a special attribute attaching to human and physical resources that constrains redeployment to other uses without loss of value. Asset specificity acts to lock agents into bilateral relationships. Klien, Crawford and Alchian (1978) show how quasi rents can be generated in contracts involving specific assets because of opportunistic behaviour by the parties. Either the buyer or supplier may be at risk of paying rents depending on the circumstances of the contract. Joint ownership may be the only way of avoiding this risk.

The concept of 'residual property rights' (Grossman and Hart 1986; Hart and Moore 1990) provides further reasons for the internal deployment of assets. Ownership gives the firm control over the 'residual rights' of the assets – residual in the sense that the firm can use its assets in any way it chooses, other than that for which it is specifically contracted. In an incomplete contract, where it is too costly to specify a long list of particular rights over the asset, control of these residual rights may be of significant value through affording opportunistic behaviour.

Development of the vertically integrated firm

Vertical integration refers to the output of two sequential production processes being employed within the firm boundary. Vertical integration may be 'upstream' or 'downstream'. If 'upstream' then 'the *entire* output of the 'upstream' process is employed as *part or all* of the quantity of one intermediate input into the 'downstream' process' or if downstream then 'the *entire* quantity of one intermediate input into the downstream process is obtained from *part or all* of the output of the 'upstream' process' (Perry 1989, p. 185). The concept has particular application in analysing firm value chains. A vertically integrated firm is one which has complete ownership and control over each of the neighbouring activities in the value chain involving production and distribution (Perry 1989).

Williamson (1986) suggests that the choice between contracting and integration depends on the relationship between transaction frequency, asset specificity and uncertainty. For frequent transactions involving assets with low specificity the market

is preferred, because economies of scale can be achieved by many suppliers in the market. It is cheaper for the buyer to purchase from the market than produce in-house. However occasional transactions involving more specific assets are more likely to be dealt with by relational contracting, in which any necessary adjustments to the contract or adaptations are dealt with by bilateral negotiation. Where the asset is specific and the transactions are frequent, integration is favoured because economies of scale can be as fully realised within the firm, as through a supplier. With both uncertainty and asset specificity, contractual gaps will appear. If the transactions are frequent then integration dominates over the market and if they are infrequent then bilateral contracting is preferred. Integration then is likely when transactions involving specific assets and uncertainty are conducted regularly. Bilateral contracts, e.g. alliances are preferred, in these circumstances, if the transactions are infrequent.

In Williamson's view other factors favouring vertical integration include, in addition to considerations of bounded rationality and opportunism discussed above, avoiding moral hazard and economising on information exchange, in part, as a result of improving the quality of information exchanged. Overall integration harmonises interests and permits an efficient (adaptive, sequential) decision process (Williamson 1971).

While each of these transaction or asset characteristics argue for transactions to be undertaken inside the firm, ultimately the internalisation reaches a level of diseconomy, such as through attenuated incentives and bureaucratic distortions (Perry 1989) that limits the size of an efficient unitary firm. Williamson employs the key concepts of transaction cost economics to explain the development of vertically integrated, multidivisional and multinational firms which avoids some of the diseconomies of transactions conducted in large unitary firms (Williamson 1971, 1981).

The multidivisional form of organisation serves both 'to economise on bounded rationality and attenuate opportunism' (Williamson 1981, p. 1556) found in the unitary form of organisation. By promoting functional over firm-level goals, the behaviour of managers of functional divisions in the unitary form of organisation was seen as being opportunistic. By making each division a separate profit centre, central

management is able to align the goals of the division with that of the overall goal of the centre. In particular central management has the power to reallocate resources between divisions to maximise yield (Williamson 1981). Moreover the unitary firm was burdened by bounded rationality. Poorly directed information flows deprived central management of many of the options available for rational strategic management. Locating decision making regarding relevant operational matters within each business division, recognises the limits of rational decision making by the centre. On the other hand freed of operational matters pertaining to its divisions, the centre is able to focus on long range planning and resource allocation issues (Williamson 1975).

The development of the multidivisional form, with separate profit centres, overcomes some of the constraints of a unitary organisational structure, ultimately permitting such companies to become multinational. In Williamson's view the multinational enterprise was established as a natural outgrowth of the multidivisional firm, but offered in particular a way of achieving the international transfer of capital, technology and organisational skill (Williamson 1981). He suggests that these reasons are more important than achieving monopolistic gains.

Williamson (1981) draws on Chandler's formidable empirical work (Chandler 1977, 1990) to support his arguments about the formation of the multidivisional firm. Chandler (1977, 1990) linked vertical integration to economies of scale. Chandler (1990) ascribes the growth in large vertically integrated firms in the US and Germany between about 1860 and 1920 as being motivated by the capacity to achieve economies of scale and scope through investment in new industrial technologies. He argued that as these firms became more capital intensive to exploit economies of scale, there was an increased incentive to vertically integrate supply sources and distribution. This avoided the additional risks in large scale production of opportunism and hold up.

In addition to the economies suggested by transaction cost economics, the literature identifies various market imperfections and technological economies as being further reasons for vertical integration. Technological economies occur when production costs are reduced by using own sourced intermediate inputs, such as the energy

savings from using hot steel to produce sheet steel. Market imperfections result in various forms of price discrimination that encourage vertical integration (Perry 1989).

While using the transaction cost framework, Demsetz (1991) however took a different approach. He directly addressed the advantages of specialisation, one based on the economies of knowledge. While Williamson had argued that economising on the cost of exchanging information and improving on its quality was one of the reasons for the vertical integration of the firm, Demsetz (1991) placed emphasis on the corollary. He argued that the importance of economising on the cost of information was the prime determinant of the vertical boundary of the firm. '[T]he economics of the conservation of expenditures on knowledge' determines the boundaries of the firm (p. 173).

Demsetz argued that economic organisation must reflect the costs of producing and using knowledge. Firms use specialised knowledge to produce saleable products and services. Downstream users of a product or service can use that knowledge without themselves being knowledgeable in the production of that product or service. In his view the boundary of the firm is determined, or the extent of vertical integration reached, when the costs of acquiring and managing the specialised information required to produce a complex range of products is no longer economic. Rather than further vertical integration this suggests a strong reason for purchasing rather than developing in-house.

While Demsetz's views, like Williamson's also derive from an efficiency, cost minimising view of the firm, their implications are different in that they suggest that there are advantages to specialisation, rather than further vertical integration. The advantages accruing to specialisation is one of the themes taken up in the next section which discusses the resource based view.

Firm Performance and Sustainable Competitive Advantage

The above discussion of transaction cost economics focuses on explaining the existence of the firm and reasons for the vertically integrated firm. It does so, substantially in terms of the benefits provided by the firm in economising on the costs otherwise involved in establishing and maintaining contractual relationships in the market place. This proposition has gained considerable richness from the concepts of

asset specificity, opportunism and residual property rights in the context of incomplete contracts, which provides a guide as to whether production occurs inside or outside the firm.

While some of these concepts are useful in explaining how a firm creates value and generates sustainable competitive advantage, for answers to that question it is more fruitful to turn to other approaches to the theory of the firm, such as the resource-based view and other associated knowledge based approaches (Conner 1991; Barney 1991). The point of departure from transaction cost economics is to turn away from the contractual view of the firm towards one that focuses on the firm as a repository of distinctive (technological and organisational) knowledge, often accumulated over a long time period in a path dependant way (Foss 1996).

Sustaining competitive advantage implies that a firm can achieve, contrary to the competitive economic model, supranormal returns or rents over a significant period of time, without those rents being bid away by competitive forces. Resource based approaches to the theory of the firm have provided a persuasive set of explanations for this phenomenon.

Resource based view of the theory of the firm

Edith Penrose (1959) provided a sustained criticism of the static theory of the firm. In particular she focused on managerial diseconomies of scale as being the constraint on the growth of the firm. Her theory laid the foundation for much of the conceptual development of the resource based view of the firm. She argued that expanding the 'management team' was constrained by the knowledge and experience of the existing team. (p. 48). She described the limitations on transmitting experience, which she differentiated from 'objective' knowledge acquired by formal learning (p. 53). In considering the process of firm expansion she identified two groups of critical resources – those previously acquired or 'inherited' and those to be purchased from the market (p. 85). She also highlighted the role of scientific research in helping the expansionary processes of the firm (p. 115).

Development of the concept of strategic assets

The resource based view grew out of a need to explain differences in firm performance as a basis for advising on successful strategic options (Wernerfelt 1984; Barney 1986). The key to that explanation is the development of the concept of strategic assets which developed from a focus on the nature of the firm's resources. One of the early exponents of the resource based view, Wernerfelt (1984) argued in favour of analysing firms from the resource side rather than the product side. He suggested that possession of certain resources gave a competitive advantage to firms by conferring 'resource position barriers' to entry (p. 173). Such position barriers included customer loyalty, production experience and technological leadership. These resource position barriers were not easily tradeable except by way of mergers and acquisitions (p. 175).

Barney (1986) developed the idea further with the concept of strategic factor markets which were markets in which strategic factors, such as the capacity for low cost production, could be acquired. In perfectly competitive markets the cost of acquisition would be equal to the net present value of the factor and any rents competed away. However he argued that firms could only achieve above normal returns from acquisition strategies that correctly used superior non-publicly available information to identify synergies between their own capabilities and those of another firm. Ultimately the essential elements of the success of such strategies were business acumen and luck.

Deirickx and Cool (1989) took issue with Barney's assumption that strategic factors could be acquired. Indeed they argued that there was a set of firm specific non-tradeable assets that are accumulated internally which may generate a sustainable stream of rents. They set out a series of characteristics that make such factors less tradeable or substitutable. These include, time compression diseconomies (application of time to develop certain capabilities), causal ambiguity (e.g. unexpected outcome of R&D expenditure) and asset interconnectedness (value of one such asset being increased by the presence of another). From this analysis Deirickx and Cool conclude that 'asset stocks are *strategic* to the extent that they *are non-tradeable, non-imitable* and *non-substitutable* (italics in original) (1989, p. 1510).

Barney (1991) uses this analysis to suggest the reasons by which firms may achieve sustained competitive advantage, which he defines as 'a value creating strategy not simultaneously being implemented by any current or potential competitors [who] are unable to duplicate the benefits of this strategy' (p. 102). He argues that if firms' resources were homogeneous and perfectly mobile, no firm could achieve sustained competitive advantage. Since in fact some firm resources are neither homogenous not perfectly mobile, firms are able to achieve sustained competitive advantage. Employing a broad definition of resources, including 'all assets, capabilities organisational processes, firm attributes, information, knowledge etc controlled by the firm that enable the firm to conceive of and implement strategies that improve its efficiency and effectiveness' (p. 101) Barney, in a similar fashion to Deirickx and Cool (1989), outlines a series of attributes that may deliver sustained competitive advantage. These are that the resources are 'valuable, rare, imperfectly imitable and non substitutable' (p. 117). Unique historical conditions, causal ambiguity and social complexity are likely reasons for resources to be difficult to imitate.

Amit and Schoemaker, (1993) in further developing the resource based view, provided the key definition of strategic assets:

> … as the set of difficult to trade and imitate, scarce, appropriable and specialised *Resources* and *Capabilities* that bestow the firm's competitive advantage. (p. 36)

Resources are defined to include 'knowhow that can be traded (e.g. patents and licences), financial or physical assets … and human capital. Capabilities refer to a firm's capacity to deploy resources, usually in combination, using organisational processes to effect a desired end' (Amit and Schoemaker 1993, p. 35).

The concept of the firm possessing capabilities to use resources is an important aspect of value creation by the firm. As Conner (1991) points out, the resource based view and transaction cost economics share many assumptions about the firm such as asset specificity, imperfect information and bounded rationality but a key point of difference is that the resource based view emphasises the role of the firm as creating value from its unique ability to combine 'team-specific' assets (Conner 1991). It is not

possible for a collection of autonomous contractors to substitute for such firm specific assets.

Strategic assets and the technology based firm

For a technology-based firm, its competitive advantage arises from developing, enhancing and exploiting the technologies owned or developed by such companies as strategic assets. Such technology based strategic assets could arise from technological leadership acting as a barrier to entry and so generating economic rents (Wernerfelt 1984). This might arise from the individual human capital of scientists placing a firm in a unique position to create or exploit a scientific breakthrough which is difficult to imitate (Barney 1991). In turn this could lead to inter-firm differences in R&D capabilities such as those demonstrated by Henderson and Cockburn (1994) in pharmaceutical research. Since technological leadership can be easily eroded (Dierickx and Cool 1989) sustainable competitive advantage needs constant investment in R&D (Wernerfelt 1984).

Prahalad and Hamel (1990, p. 82) translated the concept of strategic assets of the firm into a corporate strategy that suggested that firms should focus on their 'core competencies':

> Core competencies are the collective learning in the organisation, especially how to coordinate diverse production skills and integrate multiple streams of technologies.

Linking these concepts to the development of corporate strategy, meant that as part of strategy formulation, firms should, despite the limitations of uncertainty and complexity (Amit and Shoemaker 1993), identify their rent generating resources and seek to use and develop their core competencies to secure sustainable competitive advantage (Grant 1991). It follows that for technology-based companies, a potentially viable corporate strategy is to utilise their particular technological capabilities as a rent generating resource and their core competencies in technology commercialisation to secure sustainable competitive advantage.

Amit and Schoemaker (1993) argue that the more durable, firm specific and scarce are the strategic assets the more valuable they are to the firm (p. 39). They do however point to an important dilemma faced by the management of technology firms who

must trade off between investing in specialised assets that will deliver economic rents and the robustness of these assets to provide flexibility in the face of uncertainty about future technological change and the strategies of competitors (Amit and Schoemaker 1993, p. 40).

The dynamics of the technological process means that an important part of corporate strategy is to constantly adjust and renew these capabilities in response to rapid technological change (Kogut and Zander 1992; Teece, Pisano and Shuen 1997). For those that have already achieved a degree of technological leadership it is important to maintain 'the technological capability for a continuing stream of innovations' (Grant 1991, p. 130). Similarly Teece, Pisano and Shuen (1997) place emphasis on the ability of firms to have 'dynamic capabilities' by which is meant that they have the ability to renew and adjust their capabilities in response to rapid technological change, future competition and markets (p. 515).

The result of the application of these strategies has been to focus on the internal capabilities and competencies of the firm and how they might be developed and maintained. Dierickx and Cool (1989) argued that strategy was choosing the optimal time path over which to accumulate the stocks of strategic assets (p. 1506).

It is evident that many of the authors who developed the resource based view had in mind large technology companies[2] with pre-existing technological capabilities, rather than addressing the issues faced by technology start-up firms, which had to firstly identify a technological opportunity before it could be commercialised and its competitive advantage developed and defended.

The characteristics of the technological opportunity, which might give rise to a start-up company, is explored by Shane (2001) who demonstrates, using a database of MIT inventions, that three characteristics are necessary. Firstly, the invention must be sufficiently important for the economic return to be great enough to induce an entrepreneur to overcome the opportunity cost of alternative activities. Secondly, it

[2] For instance the selection of some of the leading case studies and empirical work was of large IT (Prahalad and Hamel 1990) or pharmaceutical companies (Henderson and Cockburn 1994).

should be a radical invention, so that it is less likely to be developed by an existing firm and thirdly, the IP protection should be reasonably broad in scope.

The lessons to be drawn from this review of the resource based view are several. The first is that firms can achieve a sustainable competitive advantage by virtue of the development of a strategic asset, based on a core competency in the development of a new technology. Secondly, to maintain technological leadership it is important to retain a capability for producing a continuing stream of innovations and constantly adjust and renew these capabilities in response to rapid technological change. A start-up is unlikely to have a full range of strategic assets to complete the commercialisation process, so it will seek partners to provide those it is missing. This leads directly to the open innovation paradigm, to be discussed in the next chapter, where companies supplement their own strategic assets, with those of others through network activities.

While the resource based view is conceptually attractive, especially for analysing technology based firms, it has been subject to attack, particularly from the 'transaction cost economics school' because of an inability to operationalise its key concepts (see for instance, Priem and Butler 2001; Williamson 1999; Porter 1991). One of the criticisms is that its key concepts are fundamentally tautological. For instance that a core competence is one that is core (Williamson 1999) or that successful firms have unique resources that are valuable because the firm is successful (Porter 2001). Mosakowski and McKelvey (1997) tackle this problem, suggesting that focussing on the scarcity and value of intermediate outcomes produced by a firm's competencies will allow comparisons to made between firms to help identify those of particular importance.

Conclusion

This chapter has sought to explain from a theoretical perspective why firms exist, what factors led to the creation of fully integrated firms and what provides the start-up with sustainable competitive advantage. This review of transaction cost economics and the resource based view suggests that no theory has universal application. Each however provides insight into the reasons for the creation of economic value by the firm.

Transaction cost economics is most helpful in explaining the development of the vertically integrated firm. The reasons for the vertically integrated firm centre on the economies achieved by internalising transactions that would otherwise involve the payment of rents. These arise from opportunistic behaviour which is facilitated by transactions involving uncertainty and high asset specificity. Not only do these factors help explain the existence of large integrated unitary firms, but also the creation of the multinational multidivisional firm. The delegation by headquarters of all operating functions to its divisions helps explain how the expected diseconomies of such firms have been overcome.

The resource based view helps explain the emergence of the start-up, based on the value of strategic assets which are difficult to trade and imitate. Such assets will generate rents enabling the firm to achieve sustainable competitive advantage. The theory predicts that start-ups will have a strong focus on the appropriability of their assets and seek to protect them where possible, such as by using patents. The resource based view suggests that sustainable competitive advantage of the firm can be achieved, providing the value of the strategic assets is maintained.

While the two theories appear to be highly relevant to the creation of value by firms, they fail in two respects. The resource based view looses explanatory power in considering the transition from start-up to successful mature firm. It is noteworthy that the most successful biopharmaceutical firms have adopted the fully integrated model emphasising the relevance of transaction cost economics to this transition. On the other hand transaction cost economics undervalues the role of technological specialisation in the formation of firms. The function of strategic assets in creating the basis for sustainable competitive advantage would appear to be essential for start-up technology firms. In highlighting the central role of strategic assets, the theory also identifies the fundamental challenge for such firms, which is to maintain the value of such assets over time in a rapidly changing technological environment.

The next chapter turns to the question of whether firms which lack certain strategic assets are able to form alliances to acquire access to the strategic assets of other firms. Both transaction cost economics and the resource based view suggest reasons for

establishing alliances while other theories contribute to an understanding of how the value created in alliances may be shared by alliance partners.

Chapter 3. Open Innovation and the Networked Firm

Introduction

As discussed in the previous chapter, the resource based view suggests that firms can achieve sustainable competitive advantage through the accumulation of strategic assets that are hard to imitate, substitute or trade (Amit and Schoemaker 1993). It is also acknowledged however that start-ups often lack complementary assets (Teece 1986) and will seek them from alliance partners.

Equally there is scope within transactions cost economics to consider the appropriateness of contracting across the boundary of the firm for products and services. While alliances have a different governance structure to the firm, the same tests of appropriateness may be applied to an alliance to help explain its formation.

This chapter considers the theoretical reasons for technology firms to be networked in order to be successful innovators. These theories suggest that it is not sufficient to consider the requirements for sustainable competitive advantage for a single firm but also necessary to take into account the conditions for sustainable competitive advantage in cooperation with other firms. Cooperation may involve jointly created product and even strategic assets. This raises the problem of the distribution of the value created and how small firms in particular may defend themselves against loss.

In this chapter the unit of analysis moves from a focus on the individual firm to examining the behaviour of the firm in an alliance or network. In doing so, a set of related but independent theoretical concepts are employed. The open innovation paradigm provides something of a unifying framework by integrating these concepts within a networked view of innovation.

Open Innovation

'Open innovation' (Chesbrough 2003; Chesbrough et al. 2006) is a framework that suggests that technology companies adopt a networked approach to innovation, in which companies exchange ideas and technologies and bring products to market through licensing and other alliance arrangements. There are two key aspects of the

open innovation paradigm of particular relevance to this study. One is the networked nature of the innovation process and the other is the concept of the business model. As Chesbrough (2006) puts it:

> Open Innovation is a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as they look to advance their technology. The business model utilizes both internal and external ideas to create value, while defining internal mechanisms to claim some portion of that value. (p. 1)

Chesbrough (2006) claims eight points of difference for Open Innovation relative to prior theories of innovation. Perhaps the most important of these is the equal importance given to external knowledge, in comparison to internal knowledge as a source of innovation. Open Innovation is presented as the antithesis of the vertically integrated model of the firm in which new products are derived from internal R&D. In the Open Innovation paradigm, the firm is an active participant in the 'market in technology', proactively acquiring sought after technologies and dispensing with surplus technologies through spin offs and licensing arrangements. The second is the centrality of the business model in converting R&D into commercial value. The business model provides the framework within which the firm operates. It selects projects that 'fit' and rejects those that don't. This helps identify technologies that should be licensed in and those that should be spun off. Other differences identified largely follow from these two key differences. This includes, a change in attitude to the knowledge landscape, which is viewed as rich and prospective, and recognising the economic value to the firm of proactive management of IP and of exporting internally developed, but underutilised, technology.

Relationship to antecedent literature on alliances and networks

The emphasis placed by 'open innovation' on the importance of networks and shared knowledge in the innovation process is not new. Networks have a central role in the concept of innovation systems (Freeman 1987; Lundvall 1992; Nelson 1993) and their importance has been highlighted by Arora and Gamberdella (1990), Pisano (1991) and Powell et al. (1996). The central role of technology alliances in the innovation process has been noted by Hagedoorn (1993) and others, in business strategy by Gomes-Casseres (1996) and in the partnership between pharmaceutical companies

and dedicated biotechnology companies by Galambos and Sturchio (1996) and Orsengio et al. (2001) among others.

Powell has argued that inter firm collaboration can be viewed as a means of organizational learning (Powell 1998) through which core competencies can be enhanced. This raises entry barriers through restricting entry to networks, accelerates innovation and 'collaboration may itself become a dimension to the competition' (Powell 1998, p. 230). Powell (1998) argues that in innovation driven fields, firms are in engaged in learning races and that not only do firms learn from collaborations but they need to learn how to collaborate.

Empirical research suggests that participation in alliances has a positive effect on innovation output (Shan et al. 1994). Powell et al. (1996) demonstrates the value for innovative performance of firms in being deeply embedded in benefit rich networks, describing the network – not the individual firm as the locus of innovation. Furthermore Laursen and Salter (2006) illustrate the positive relationship between the external searches for new knowledge, until the point of decreasing returns is reached, and innovative performance.

The emphasis on alliances also reflects changes in the global business environment. For instance, Dunning, a prominent researcher of multinational enterprises since the 1950s, has described increased emphasis on cooperation between firms as 'alliance capitalism'. In his view this has been brought about by globalisation and a series of landmark technological advances (Dunning 1995).

Dunning (1995) outlines four reasons for the growth of alliances. These are to:

- enhance the significance of core technologies;
- increase the interdependence between distinctive technologies for joint supply of a particular product;
- truncate the product life cycle; and
- upgrade core competencies as a means of improving global competitive advantages.

Several of these are particularly relevant to the pharmaceutical industry, which has experienced significant globalisation and rapid technological change, particularly in its core technologies.

The OECD has conducted a series of studies of innovation using alliances, networks and innovation systems (see for instance, OECD 1999, 2000, 2001, 2002; Kang and Sakai 2000) which produced the following useful definition of an alliance:

> Strategic alliances take a variety of forms, ranging from arm's-length contract to joint venture. The core of a strategic alliance is an inter-firm co-operative relationship that enhances the effectiveness of the competitive strategies of the participating firms through the trading of mutually beneficial resources such as technologies, skills, etc. Strategic alliances encompass a wide range of inter-firm linkages, including joint ventures, minority equity investments, equity swaps, joint R&D, joint manufacturing, joint marketing, long-term sourcing agreements, shared distribution/services and standards setting. (Kang and Sakai 2000, p. 7)

Hagedoorn (1993) has produced a comprehensive list derived from the literature on the motives for strategic alliance formation grouped under three headings as shown in Table 1.1.

Table 1.1 An overview of motives for (strategic) interfirm technology cooperation

I	Motives relative to basic and applied research and some general characteristics of technological development:
	- Increased complexity and intersectoral nature of new technologies, cross-fertilization of scientific disciplines and fields of technology, monitoring of evolution of technologies, technological synergies, access to scientific knowledge or to complementary technology
	- Reduction, minimizing and sharing of uncertainty in R&D
	- Reduction and sharing of costs of R&D
II	Motives related to concrete innovation processes:
	- Capturing of partner's tacit knowledge of technology, technology transfer, technological leapfrogging
	- Shortening of product life cycle, reducing the period between invention and market introduction
III	Motives related to market access and search for opportunities:
	- Monitoring of environmental changes and opportunities
	- Internationalization, globalisation and entry to foreign markets
	- New products and markets, market entry, expansion of product range

Source: Hagedoorn (1993).

This list includes motives that might be ascribed to both the resource based view and transaction cost economics. The need for complementary technologies and capturing

tacit knowledge coincide with the approach of the former, while cost reductions, minimising risks and uncertainty speak more to the transaction cost economic approach. Motives such as internationalisation and globalisation are consistent with Dunning's views cited above about the changed business environment. These also relate to the resource based view however since global distribution capacities is one of the crucial complementary assets typically sought by start-up technology companies.

Theoretical Reasons for Alliances

Transaction cost economics and alliance governance structures

Alliances provide an alternative to either internal integration or market contract. For transactions involving highly specific assets, internalisation may be preferred because of the high costs involved in small number bargaining when switching costs are high (Kogut 1988). However alliances provide a form of organisation through which a co-operative venture can be administered. The two firms would share ownership of the residual and control rights. Although it would be expected that there would be difficulties in sharing ownership, transaction cost economics predicts that this would be worthwhile provided that the costs of internalisation or the risks of contracting out were higher than an alliance. Kogut (1988), referring to joint ventures, suggests that such collaborations resolve:

> … the high levels of uncertainty over the behaviour of the contracting parties when the assets of one or both parties are specialised to the transaction and the hazards of joint production are outweighed by the higher production or acquisition costs of 100% ownership. (p. 321)

From a transaction costs perspective, this suggests that the reasons for alliances are formed to reduce the risks of contracting out and to offer a cheaper alternative to either joint production or outright ownership.

Effectively therefore, transaction cost economics identifies a set of issues that need to be addressed in the governance structures of any alliance. These focus on the need to control residual property rights and reduce opportunism. This predicts that alliances will have incentive arrangements that reduce tendencies towards opportunism. In alliances in which there is an 'R&D party' which undertakes the research and a 'client party' which meets most of the expenses, it is common for alliance payments to be

paid on achievement of milestones and for the real value of the alliance to be in the shared revenue, such as drug sales, received well after the conclusion of the R&D phase. In such cases, both parties are equally 'hostage' to the successful outcome of the alliance (Hagedoorn et al. 2000).

Misuse of residual property rights can occur when knowledge obtained within one alliance is used to benefit another, formed perhaps with a competitor. This may be a real risk for any client party participating in an alliance to create a particularly valuable and inimitable strategic asset where the R&D party can insist on non-exclusivity. It may be one of the reasons for such alliances to involve an equity investment, which provides the client with greater influence over the total operations of the R&D firm.

Complementary assets

As indicated in the previous chapter, one of the key reasons for establishing an alliance, according to the resource based view is to acquire complementary assets (Teece 1986). In the resource based view, the firm's sustainable competitive advantage depends on its access to a portfolio of strategic assets. Not all these need be owned by the firm. Some can be accessed through alliances. For instance it is unlikely that a technology start-up will have, in addition to its core technology, a full set of manufacturing, marketing and distribution services necessary to make and distribute its product. It may also require complementary technologies which it needs to combine with its own core technologies. For instance companies developing bioinformatics, which combines information technology and biotechnology, may need other technology companies to provide aspects of one or the other of these two technologies.

Not all complementary assets have the same level of specialisation. Many accounting firms should be able to provide financial services, but only a single firm may have the capacity to supply the technology necessary to complement an innovator's core technology. Teece (1986) has classified complementary assets into three types. He has distinguished between generic, specialised and co specialised complementary assets:

> Generic assets are general purpose assets which do not need to be tailored to the innovation in question. Specialized assets are those where there is unilateral

> dependence between the innovation and the complementary asset. Cospecialized assets are those for which there is a bilateral dependence. (p. 289)

Acquiring access to these different types of assets through an alliance has implications for the relationship likely to be established by the alliance parties. In accessing specialised assets through an alliance there is a high level of dependence between the innovation and the asset. Loss of access such as the termination of an alliance may have major implications for the innovation. An alliance to acquire co specialised assets creates a mutual dependency between the alliance the parties. For instance, in a biopharmaceutical alliance between a drug discoverer and a pharmaceutical firm, the assets are likely to be cospecialised. The drug discoverer may need manufacturing and marketing support, while the pharmaceutical company needs the revenue from sales of the successfully developed drug, which it can distribute through its marketing channels. Termination is likely to have negative consequences for both parties. On the other hand, access to generic assets can be found in the market place without the need to establish an alliance.

Alliances and the dynamic capabilities approach

The concept of dynamic capabilities (Teece and Pisano 1994; Teece et al. 1997) was briefly mentioned in the previous chapter, in the context of a discussion about the need for a firm to adopt a corporate strategy which constantly adjusts and renews its capabilities in response to rapid technological change. Dynamic capabilities are defined by Teece et al. (1997) 'as the firm's ability to integrate, build, and reconfigure internal and external competences to address rapidly changing environments' (p. 572). A component of this process of constant adjustment is the incorporation of new technologies into the firm through alliances.

In a related approach, Prahad and Hamel (1990) suggested that missing competencies could be acquired through alliances at low cost. Quoting a case study involving NEC, which used over 100 strategic alliances aimed at building competencies rapidly at low cost, managers were specifically tasked with internalising partner skills. This aspect of learning from alliances was incorporated by Kogut and Zander (1992) into their definition of a firm's 'combinative capability' as being the capability to 'synthesize and apply current and acquired knowledge (p. 384). They contemplated knowledge

being sourced from both internal learning and external learning, such as acquisitions and joint ventures. The effectiveness of the process of knowledge transfer both inside and from outside the firm is considered central to the growth of firms by Kogut and Zander (1993) and depends on the degree to which the knowledge is difficult to understand and codify (p. 636). The effectiveness of this transfer and the ability of the firm to access and handle new knowledge can enhance the capacity for collaboration.

Absorptive capacity

Related to the question of the capability of firms to learn from their alliances and collaborations, Cohen and Levinthal (1990) have defined the concept of 'absorptive capacity' as the capacity of large firms to take advantage of new technologies. This typically involves the willingness of such firms to invest in basic science in order to better understand new technologies and identify opportunities presented by emerging specialist technology firms. Accordingly (Granstrand et al. 1997) found that large companies are becoming more diverse in their technological knowledge platforms in order to explore and experiment with new technologies in order to take advantage of such opportunities. Both Merck and Eli Lilly provide examples of pharmaceutical firms using early contracts with biotechnology pioneers to learn more about biotechnology, thereby increasing their 'absorptive capacity' in the new technology (Galambos and Sturchio 1996).

The recent development of the open innovation paradigm reflects the perception that the innovation process has evolved from one dominated by large multi divisional, vertically integrated firms, to one in which both large and small firms each plays a significant role in a networked environment (Langlois 2003; Rothwell 1994). In this model importance is placed on the coupling of the specialised knowledge of small firms to the greater product development and distribution capabilities of large firms through licensing agreements, joint ventures and other alliance structures. In the view of Arora et al. (2001a) this 'division of labour' has created a market in technology between upstream technology suppliers and downstream users.

Arora et al. (2001a) identify a series of changes in the markets for technology that have improved the ease with which technology can be transferred. In general, transferability is improved if the technology can be decomposed into independent

tasks and commoditised, that is, if the technology can be embodied in a product that requires little tacit knowledge to use it.

This overview of the literature provides a set of theoretical reasons for alliance formation focussed on transaction cost economics, the resource based view and the related dynamic capabilities approach. Transaction cost economics focuses on the cost and risk reduction reasons for alliance formation, while the resource based view and related approaches, focus on the acquisition of complementary assets, whether in the static framework of the resource based view, or the more time responsive, dynamic capabilities approach, involving alliances as a means of incorporating new technologies.

The reasons for alliances discussed in this review have been firm-centric. They have addressed the question of how the firm creates value from an alliance, such as how it supplements its own resources to create value or obtains assets at a lower cost or risk compared with either the open market or through integration.

Creating and Sharing Value in Alliances

The relational view

In contrast to this firm centric view, Dyer and Singh (1998) specifically address the question of the value created in an alliance through the creation of 'joint assets'. Their so called 'relational view' suggests that the alliance or network may develop a joint asset, which may form the basis of a shared competitive advantage. They define a 'relational rent':

> … as a supernormal profit jointly generated in an exchange relationship that cannot be generated by either firm in isolation and can only be created through the joint idiosyncratic contributions of the specific alliance partners. (p. 662)

Dyer and Singh (1998) argue that a number of factors will tend to increase the relational rents generated by an alliance. In general relational rents will be higher:

- the greater the value of the investment in alliance owned specific assets and the longer the alliance has been in existence;

- the greater the investment by the partners in knowledge sharing routines and the greater the partner specific absorptive capacities;
- the larger the proportion of synergy sensitive complementary resources devoted to the alliance, which are valuable rare and difficult to imitate; generating rents from combining complementary assets requires experience on the part of the alliance parties to identify each other and to choose partners that are compatible; and
- for alliances with more effective governance structures such as those that have informal self enforcing safeguards; Gulati (1998) emphasises the social origins of alliances and the embeddedness of firms within social networks that enhances trust between firms.

One risk for the partners is that others will simply imitate the partnering behaviour, eliminating any competitive advantage of the alliance (Dyer and Singh 1998). Dyer and Singh (1998) offer a number of suggestions for mechanisms that will preserve the joint rents. These include partner scarcity that may inhibit others forming competing alliances. There may not be other potential partners with such a level of complementary resources or relational capability. Other reasons may arise from the physical attributes of the shared asset, its indivisibility or its interconnectedness across corporate boundaries.

Relational rents have a potentially large role in any innovative activity in which alliance formation and in particular the creation of joint assets is an important aspect. Not only is it important to understand from a theoretical point of view, the circumstances in which the value of relational rents are increased or are protected from erosion by imitators, but it is also necessary to be able to predict how the value is shared between the partners within the alliance.

Importance of the IP regime

Teece (1986) addressed this question in his analysis of the impact of various appropriability regimes on the distribution of profits between innovator and imitators and/or the owners of the complementary assets that are specialised or co specialised to the innovation.

In a tight appropriability regime innovators who contract for access to complementary assets will gain most of the value, although some sharing of profits may be necessary if the innovator is disadvantageously placed with respect to those assets. A small company will therefore be more likely to form an alliance when it is confident about the appropriability of its own innovation i.e. where there is a strong IP regime, which will protect the innovation from expropriation by potential partners (Gans and Stern 2003). Alternatively the innovator may take the time necessary to integrate (or develop) those assets so as to guarantee a full profit share.

However if the appropriability regime is weak, Teece argues that the outcome will depend on the how the innovator or imitator is placed with respect to the owners of complementary assets. If such complementary assets are scarce then the innovator may be forced to concede a large share of the profits to the owners of the complementary assets. Should an imitator have better access to such assets then it is likely to gain greater benefits from the innovation than the innovator. As a corollary should the assets be specialised, but more generally available, then the innovator (or an imitator) will gain a better share of the profits.

Aghion and Tirole (1994) have used the framework of incomplete contracts to analyse the relationship between a 'research unit' and a 'customer' for the research in an alliance structure that places more emphasis on the value of the innovation. In such a framework, a 'research unit' is characterised as performing the creative task while the 'customer' who expects to benefit from the innovation, provides the financing. The framework is used to predict that research activities are more likely to be conducted in a research unit independent of the customer when the intellectual inputs are substantial relative to the capital inputs and the customer is in a weak position because of a scarcity of the research capability.

Lerner and Merges (1998) have used this framework to undertake an analysis of a small number of biotech alliances to determine the balance of control of the alliance between the biotech (research unit) and established pharmaceutical company (customer). Their main finding, in keeping with Aghion and Tirole, is that the biotechs ceded the least proportion of the control rights when their financial position is strongest. The study also examined which party was likely to control particular

aspects of the alliances. Importantly the model predicted that the biotech, as the owner and developer of the knowledge base, was more likely to retain control over the patents and related litigation, emphasising the importance of IP as a strategic asset for the biotech. The pharmaceutical company was most likely to control the marketing and manufacturing aspects, as well as the power to terminate the alliance.

Conclusions

This chapter has focussed on the theoretical reasons for alliances based in large part on the theories of the firm introduced in Chapter 2. As discussed, both transaction cost economics and the resource based view of the firm offer reasons for firms establishing alliances. Transaction cost economics focuses on the cost and risk reduction reasons for alliance formation, while the resource based view and related approaches, focus on the acquisition of complementary assets. The relational view offers a new perspective by demonstrating that an alliance can create joint assets and therefore the alliance, to some extent independent of the firm, can generate rents. For the individual firm it is essential to receive a share of these rents that is sustainable. Teece (1986) suggests that the appropriability of the innovation determines whether the innovator, the owner of complementary assets or an imitator receives the greatest share of these rents.

This chapter has explored the theoretical aspect of one of two essential features of the open innovation paradigm – the reasons for innovating firms to participate in networks and alliances. The other feature is the role of the business model which 'utilizes both internal and external ideas to create value, while defining internal mechanisms to claim some portion of that value' Chesbrough (2006). In the next chapter the concept of the business model is introduced and strengthened by the theoretical insights into value creation and distribution by the networked firm discussed in this and the previous chapter.

Chapter 4. The Business Model

Introduction

The concept of a business model facilitates analysis of the way in which a firm derives economic value from a newly developed technology. Indeed Chesbrough and Rosenbloom (2002) have argued that it is the business model adopted, more so than the technology itself, which is critical to the success of the commercialisation of new technology.

The function of the business model is to select and filter technologies for packaging into particular configurations to be offered to the market. The concept is concerned with how the firm defines its competitive strategy through the design of the product or service it offers to its market, how it charges for it and what it costs to produce. How it differentiates itself from other firms by the nature of its value proposition. It also describes how the firm integrates its own value chain with that of other firms in the industry's value networks.

One of the difficulties of employing the business model concept is that it is still in its infancy in academic usage. It owes its origins largely to pragmatic development and use in the business sector. Chesbrough and Rosenbloom (2002) quote a May 2000 search of the Web which found 107,000 references to the term 'business model' in general use while a search of the academic literature (EconLit[3]) found only three references to the term.

The purpose of this chapter is to outline some of the business origins of the concept, define the business model from the existing academic literature and finally, use the theories outlined in the previous two chapters, to enrich its explanatory powers about whether the model will create value. This model is used in chapters 7 and 8 to better understand the development of different business models in the biopharmaceutical sector and how they have sought to create and retain value.

[3] The American Economic Association's electronic bibliography, *EconLit*, indexes more than thirty years of economics literature from around the world (http://www.econlit.org/).

The Business Need for a Business Model

The concept of the business model is strongly associated with the emergence of e-commerce and other new economy businesses. It grew out of a need to encapsulate the essential features of a business in a short descriptive document in order that a judgement could be made, for example by potential investors, on whether the business was likely to achieve its financial and other objectives.

In this context the business model is designed to answer a series of questions essential to any business – who are the customers, what do they value, how that value can be delivered to the customer at an appropriate cost and how the business deploys its assets. It includes a description of the key assets, both physical and intangible such as intellectual property, governance structure and management. It consists of both a *narrative* of how the business works and the *numbers* – how it makes a profit. The concept came into vogue when the spreadsheet provided an easy way to test the financial implications of the narrative in a financial model which contained assumptions about costs, product demand, sales revenue and profit. The financial outcome of changes to the narrative, or assumptions about product demand etc can be tested in the spreadsheet model (Margretta 2002).

One reason for the popularity of the concept in the new economy, appears to have grown out of the need for the emerging dot com firms to have a comprehensive, but standard format, to explain to potential investors 'how they were going to make their money'. The value proposition of dot com firms typically involved an innovative service or process for attracting a customer base. The proposed business model was often radically different. Often there was no precedent, no business experience, for instance, on which to base likely demand levels.

Accordingly investors demanded that the entire business strategy, processes and outcomes be summarised and modelled in such a way that different scenarios could be tested. The narrative of the business model, once reduced to a spreadsheet based financial model that encapsulated and quantified all the salient features of the proposed business, enabled potential investors to 'stress test' the business assumptions ahead of the decision to invest. The quality of the documentation of the

business model was an essential part of the communication process between the entrepreneur and financier of the conceptualisation of the business model. Indeed the efficiency of this process was often critical to the business being successfully financed. An unsatisfactory documentation of a highly prospective business model, could result in the failure of the business to be financed (Eliasson 2000).

Academic Approaches to Defining the Business Model

One academic response has been to generalise this pragmatically adopted framework (Fisken and Rutherford 2002; Feng et al. 2001). Such a definition of a business model is provided by Fisken and Rutherford (2002) in the following terms:

> … the business model outlines how a company generates revenues with reference to the structure of its value chain and its interaction with the industry value system.

This definition focuses on how a company uses its value chain and interaction with the larger industry value system to generate revenues.

Another approach has been to seek to better define the concept of the business model, by combining the theoretical traditions of the strategic management literature with other relevant theories of innovation and the firm. For instance Amit and Zott (2001) in their seminal paper on value creation in e-businesses, have used the theoretical foundations of strategic management literature and other theoretical work, to formulate and empirically test a business model of value creation for e-businesses. They have turned to value chain analysis, Schumpeterian innovation, the resource based view of the firm, strategic network theory and transaction cost economics to provide the basis of an integrated model of value creation in the firm. They draw on aspects of the various theories of particular importance to e-commerce, such as from value chain analysis, the identification of the primary activities of the firm that deliver value, from Schumpeterian innovation, the generation of rents following technological change, from the resource based view of the firm, value creation from a unique bundle of resources and capabilities, from strategic networks, value created by co-specialisation of assets and finally from transaction cost economics, the need for transaction efficiency. Amit and Zott (2001) suggest that no framework ‘should be given priority over the others when examining the value creation potential of e-

businesses' and that there is a strong interdependence between the various sources of value (p. 509).

Hedman and Kalling (2002) adopt a similar approach in developing a business model for IT businesses. The theoretical antecedents of their business model are organisation theory including transaction cost economics, strategy theory, Porter's framework, the resource based view and the strategy process perspective. The components of their business model consist of a description of the:

- industry, customers and competitors
- product offering;
- activities and organisation;
- resources and competencies; and
- factor markets and suppliers.

Each of the components is substantially informed by the concepts provided by the theoretical antecedents to the business model concept. For instance the concept of bundling complementary assets is important in defining the product offering. The concept of the value chain is important in describing the organisation of business activities and the resource view of the firm is fundamental to defining resources and competencies of the firm.

Developing a generalisable business model is a challenge. To date most other academic formulations of the business model focus on taxonomic issues in defining the relevant components of the model but offering little by way of empirical support for their propositions or suggested causation between the components. Some business model formulations provide little more than a comprehensive check list of things that should be considered for incorporation in developing a business model (Afuah and Tucci 2001).

The Chesbrough Rosenbloom approach

The Chesbrough Rosenbloom exposition and definition of the business model is both comprehensive, and satisfactorily operationalisable for the analysis of technology firms including biopharmaceutical firms. It is also the concept that forms part of the open innovation paradigm and is the one adopted in this thesis.

Chesbrough and Rosenbloom (2002) suggest that the business model of a technology company is the construct that mediates the value creation process between the technical and economic domains, selecting and filtering technologies and packaging them into particular configurations to be offered to the market. In this value creation process between the technical and economic domains there are strong echoes of the concepts of 'economic competence' (Carlsson and Stankiewicz 1991; Carlsson and Eliasson 1994) and 'competence bloc' (Eliasson 2000) both of which emphasise the need for firms to take advantage of their business opportunities arising from innovation to effect economic change.

As Carlsson and Stankiewicz (1991) point out:

> Invention and innovation lead to economic change only to the extent that agents within the system are successful in taking advantage of the opportunities to which they give rise. This is where economic competence enters in. (p. 100)
>
> The economic competence of a firm may be defined, then, as the sum total of its abilities to generate and take advantage of business opportunities. (p. 101)

The business model then for a technology firm, needs to consider the many facets of the firm's operations required to utilise the technology opportunity profitably. Chesbrough and Rosenbloom (2002) suggest that:

> … the functions of a business model are to:
>
> - articulate the *value proposition*, that is, the value created for users by the offering based on the technology;
> - identify a *market segment*, that is, the users to whom the technology is useful and for what purpose; and specify the revenue generation mechanisms for the firm;
> - define the structure of the *value chain* within the firm required to create and distribute the offering, and determining the complementary assets needed to support the firms position in this value chain;
> - estimate the *cost structure* and *profit potential* of producing the offering, given the value proposition and value chain structure chosen;
> - describe the position of the firm within the *value network* linking suppliers and customers, including identification of potential complementors and competitors;

- formulate the *competitive strategy* by which the innovating firm will gain and hold advantage over rivals. (2002, p. 7)

These will be discussed in turn. The articulation of the *value proposition* and identification of the *market segment* are highly interdependent. The value proposition requires the articulation of the nature of the offering to the chosen market segment. This is seen as fundamental to the success of commercialisation of the technology. It means pitching the advantages of the technology, such as lower cost or new opportunities, to the appropriate market segment to generate value for the business. For many technologies there are a number of ways that a new technology can be offered to particular target market segments. Matching the two can be of critical importance. This involves developing the revenue model or how the firm is to appropriate value from the innovation (Amit and Zott 2001). Part of this process is specifying the revenue generation mechanisms best suited to the target market segment. Technologies may be packaged into products and sold, licensed to the end user or embodied into a service which is hired out. Each has quite implications for pricing.

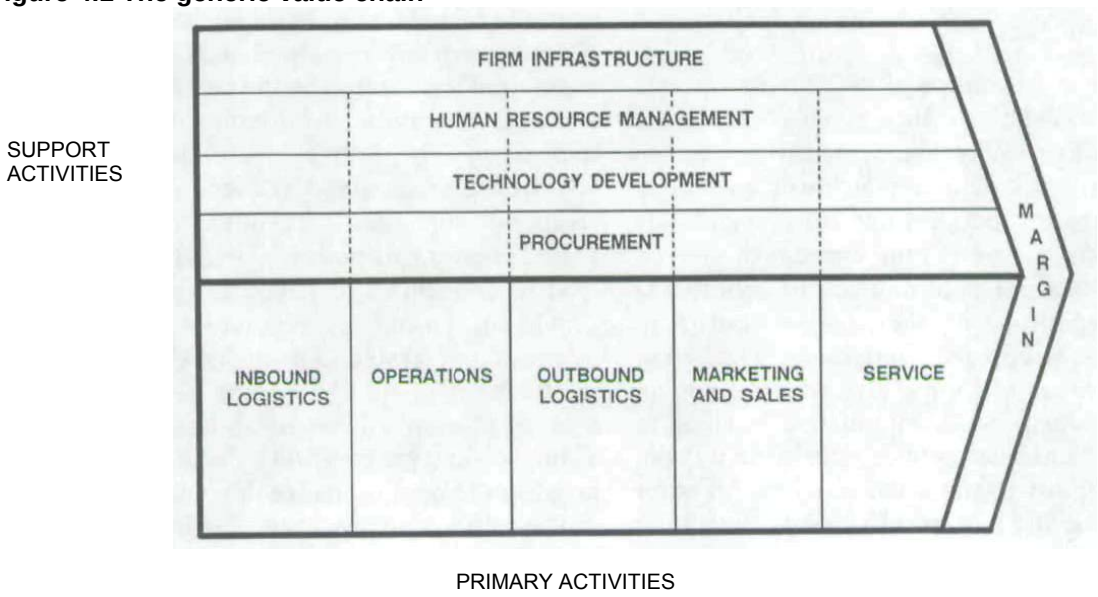
A further task in the Chesbrough and Rosenbloom concept of the business model is to define the structure of the *value chain*, and determine the complementary assets needed to support the firm's position in this value chain. This follows Porter (1985), who has argued that analysing the value chain of a firm provides the source of its competitive advantage. This may either be as a result of a cost advantage or through product differentiation.

The value chain displays how total value is created by the firm and consists of *value activities* and a *margin*. *Value activities* are physically and technologically distinct activities performed by the firm (Porter 1985, p. 38), not unlike *transactions* defined by Williamson (1981), by which the firm creates a product of value to its buyers. Every value activity employs purchased inputs, human resources, some form of technology and makes use of information. Porter divides value activities between *primary* activities and *support* activities. *Primary* activities focus on the creation and sale of the product to buyers, whereas *support* activities include technology development, procurement and human resources. These may be tailored to particular

segments of the value chain or support the entire value chain. The value created by the chain is measured by the total product revenue. The *margin* is this value less costs (Porter 1985, p. 38).

The activities can be schematically shown in the value chain which provides a way of examining the interaction of the activities of the firm (see Figure 4.1)

Figure 4.1 The generic value chain



Source: Porter (1985, p. 37).

Porter argues that the performance of each activity is a potential source of competitive advantage, either by its performance at a lower cost or by delivering superior buyer value and hence *differentiation* (Porter 1985, p. 39). Moreover the manner in which activities are linked may also be a source of competitive advantage. Firms belonging to the same industry may adopt value chain analysis as a diagnostic tool to regularly compare their performance with their peers and identify activities in need of improvement as part of creating and sustaining competitive advantage.

In Porter's framework, technology development is one of the support activities. It may enter at any stage of the value chain such as to lower the costs of outbound logistics through improved information management or to feature in the operations phase. However this conception of the role of technology has greater application to mature manufacturing companies where technology development is more likely to be

exogenous to the primary activities. For a firm whose main activity is innovation, consigning technology development to the category of support activity is inappropriate. For such firms R&D forms a core part of their operations and accordingly its performance needs to be viewed as a primary activity.

The Chesbrough and Rosenbloom business model contemplates the firm's use of complementary assets (Teece 1986) to supplement those owned by the firm. This causes the firm's value chain to intersect with the value chains of the owners of complementary assets and raises the issue of distribution of value between the participants discussed in the previous chapter. Chesbrough and Rosenbloom use the term 'value network' (Christensen and Rosenbloom 1995) to describe the relationship between the firm and its suppliers and customers. The role of the business model is to position the firm in the value network in such a way that the firm can capture value from its innovation.

The concept of the value network developed by Christensen and Rosenbloom (1995) describes 'a nested commercial system' (p. 240) of firms which contribute to the production of a particular computer component or set of components. These are then sold downstream to the assemblers of these components for integration into the next stage of the product pipeline.

Porter argues that a source of competitive advantage is optimising or better coordinating the linkages between the firm's value chain and the value chains of other firms. Integration of firm value chains with supplier or buyer value chains, for instance can provide the opportunity for a realignment of activities that jointly optimises activities across the firm boundaries. This is described by Porter (1985) as a value system but is in some ways analogous to Christensen and Rosenbloom's value network. However the concept of the value system has the greater application to a traditional manufacturing process whereas Christensen and Rosenbloom's concept of the value network has a greater focus on the integration of the joint contribution by firms to innovative production processes.

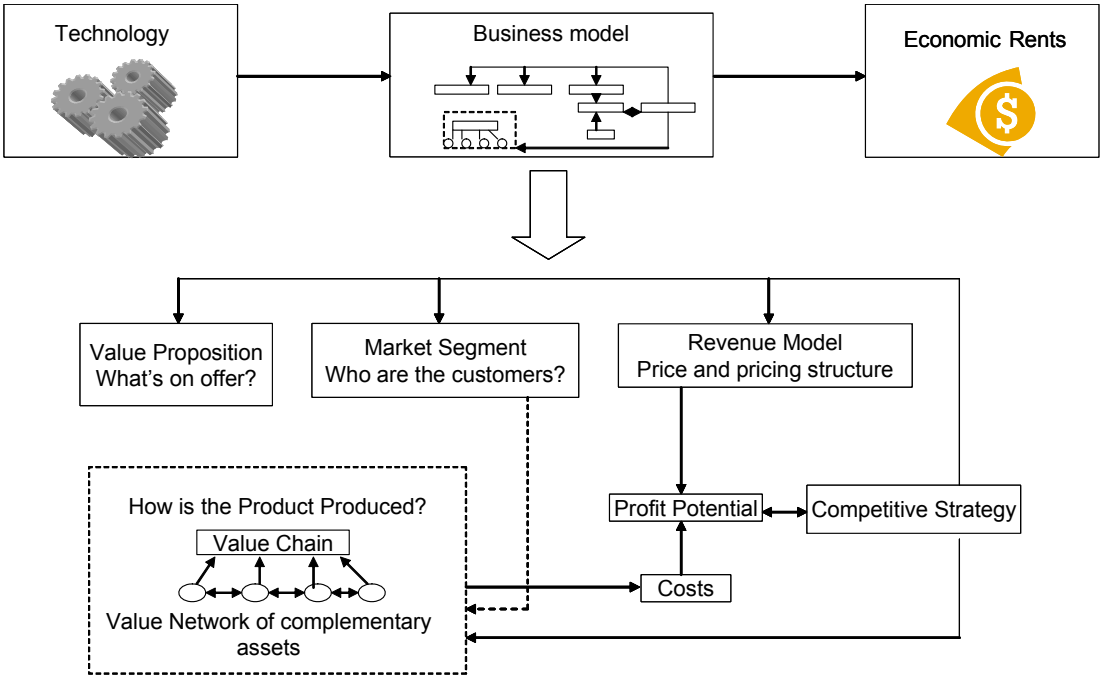
The value proposition and the target market help determine the likely pricing of the chosen form of the product offering and its cost structure. Chesbrough and

Rosenbloom (2002) suggest that having determined what the market will pay for the new product or service, places a discipline on the costs of development and production. The development of the business model is not static but a dynamic process subject to change through learning and adaptation. For instance the process of deriving value from a technology based offering requires a learning process of developing and adapting the technology to meet market requirements. Accordingly it may be necessary to adopt an iterative process between adjustments to product and the market segment to align the product with the cost of production.

Finally the concept of the business model includes consideration of the competitive strategy by which the innovating firm gains and holds an advantage over its rivals. There are a range of theoretical approaches to this problem suggested in previous chapters. The resource based view suggests that the development of strategic assets is the key to gaining and holding competitive advantage while the relational view would be more concerned with gaining a share of the value of joint assets. If the firm was to follow the resource based view this component of the business model would be concerned with the formulation of a strategy to develop and preserve the value of strategic assets. Transaction cost economics suggests an approach which would carefully consider integration of activities into the firm's value chain. Economising on external transactions is likely to favour more integrated company structures. The Porter approach would be more concerned with a strategy for cost management or developing a differentiated product.

The relationship between the business model, including its functions or components, and the technology and economic domains are illustrated in Figure 4.2. This attempts to capture some of the complexity of the feedback loops involved in developing competitive strategy for the firm through the business model. Each of the components bears on the formulation of the competitive strategy and the competitive strategy helps determine each of the components. In addition it shows how the prospects for value creation of each technological project can be hypothetically tested and modified in the business model structure before being accepted or rejected by the firm.

Figure 4.2 Schematic outline of a business model



Contribution of Theories of the Firm to the Concept of the Business Model

The advantage of the Chesbrough and Rosenbloom approach to the business model concept is that its functions or components provide a comprehensive structure by which to analyse different sources of value in firms. Compared for instance with Amit and Zott's (2001) approach its functions or components are generic, rather than specific sources of value for a particular type of business. However the Chesbrough and Rosenbloom business model is still more of a framework than a theory (Teece 2006). By itself is does not enable predictions to be made of the behaviour of firms, although it has attempted to identify the key factors that may make such predictions possible. At the same time there are theoretical underpinnings that could be incorporated into many of the components of the business model to increase its capacity to be used as a predictive model. As with Amit and Zott's (2001) development of the business model, this analysis suggests that there is no single applicable theoretical framework, but that an integration of the various theoretical frameworks is useful in examining the value creation potential of the firm's business model.

The approach adopted here is to enrich the concept of the business model with the various theoretical concepts which were outlined in chapters 2 and 3. The principal theories are transaction cost economics, the resource based view and the relational view of the firm. In addition the concepts of dynamic capabilities, absorptive capacity, complementary and strategic assets and value chain analysis as well as Teece's (1986) analysis of the appropriability regime are all helpful.

Table 4.1 below summarises the relevant theories and their implications for the innovative firm with respect to each of the functions of the business model defined by Chesbrough and Rosenbloom. There is no single one for one mapping of the theories to the business model functions. Rather there is a good deal of overlap between the key theories and the functions. For some functions several of the major theoretical constructs are relevant. However different aspects of the theories are of particular relevance to certain of the functions. These are discussed in turn.

The resource based view (RBV) would suggest that the value proposition would be based on the most valuable offering that the firm can make in accordance with its strategic assets. By definition, strategic assets are those that are valuable and inimitable. However this may be complicated by the firm's participation in joint products.

The relational view suggests that the offering may not be the product of a single firm but be a joint product developed by the alliance or value network. Any relational rents generated will need to be shared between the participants of the alliance or network. The manner of sharing their value is suggested by Teece's appropriability regime. Firms which have contributed assets with strong appropriability are likely to gain an economic share. However those not so well protected will tend to lose out. Such firms may be able to address this problem through their business models. For instance they may be able to recast their value proposition to offer a product capable of being protected by a suitable appropriability regime.

Table 4.1 Theoretical contributions to the business model

Business model functions	Relevant theories	Implications
Value proposition	RBV	Offering based on value derived from strategic assets/core competencies
	Relational view/ appropriability regime	Value proposition designed to avoid appropriability problems
Market segment and revenue model	RBV	Market segment chosen follows the value proposition to gain maximum value from strategic assets
	Relational view	Revenue model designed to gain economic share of relational rents
Value chain	Transaction cost economics	Optimise level of vertical integration
	RBV	Identify need for complementary assets
	Value chain analysis	Comparative efficiency of individual activities
Cost structure and profit potential	Relational view	Profit depends on share of value
	Value chain analysis	Comparative efficiency of individual activities
Value network	Transaction cost economics	Cost and risk reasons for alliance formation
	RBV	Access complementary assets
	Dynamic capabilities	Adjust (build/acquire) internal and external competences to dynamic environments
	Absorptive capacity	Increases capacity of the firm to gain from alliances
Competitive strategy	RBV	Development of strategic assets
	Appropriability regime	Decision to access or acquire complementary assets
	Relational view	Preserve adequate share of relational rents
	Transaction cost economics	Considerations of transaction integration vs contract or alliance

The market segment is substantially decided by the value proposition which targets the firm's offering to a particular group of consumers. As for the value proposition, the RBV and the relational view are relevant to the choice of market segment. In doing so, the pricing structure, costs and profitability are likely to be substantially determined, because the choice of market segment is likely to establish, given the value of the offering to the customer, how much the customer will be prepared to pay

(Chesbrough and Rosenbloom 2002). The revenue model is likely to depend on appropriability factors. The revenue model is primarily concerned with how the firm charges for its product in such a way as to appropriate value (Amit and Zott 2002). This effects the options available for the pricing structure, such as whether to license the technology, sell outright, or incorporate in a product so as to maximise the firm's share of relational rents.

Analysis of the firm's value chain is instructive from a number of theoretical aspects. One is to assess the efficiency of its existing activities using value chain analysis. This may be helpful in identifying which strategic assets it possesses and which it needs to access by alliances. The RBV would predict that it would form alliances to gain missing complementary assets. Whether these were specialised, co specialised or generic would be expected to have a bearing on the form of alliance and the likely distribution of relational rents. The RBV would predict that access to generic assets would be acquired through market transactions. On the other hand, transaction cost economics would be concerned with opportunism and asset specificity in predicting whether such assets would be accessed through alliances or integrated.

Value chain analysis would suggest that the efficiency of activities in the value chain would deliver competitive advantage through a lower cost structure and therefore higher profit potential. The relational view is concerned with the need to ensure an adequate share of relational rents for the firm to achieve sustainable profitability.

The importance of the firm's value network and the theoretical reasons for its existence have been the subject of most of Chapter 3 which examined the theoretical reasons for firms to form alliances and those arguments will not be repeated here. Each of transaction cost economics, the resource based view, dynamic capabilities and the concept of absorptive capacity contributed to various aspects of that analysis. In summary, the reasons for firms to participate in alliances or a network are to acquire access to complementary assets and/or form a governance structure that reduces the costs or risks of innovative activity. Dynamic capabilities emphasises that this alliance formation is dynamic, in that firms need to be constantly adjusting their competencies in the light of a rapidly changing environment. Firms with a greater complementary

knowledge base are likely to have a greater absorptive capacity and therefore to have a greater capability to benefit from this participation.

Gaining an appropriate share of the relational rents becomes a central issue for competitive strategy of an innovative start-up firm. Positioning the firm's offering in relation to its network partners is as important as positioning the product in relation to its competitors. The RBV however suggests that it is the value of the firm's strategic assets which are vital to the capacity to gain and hold competitive advantage. These views are not necessarily in conflict, but there is a tension between the need for the firm to develop strategic assets which are inimitable and the need to contribute these assets to an alliance or value network, which increases the risk of them being copied unless the appropriability regime is tight. This may have a bearing, as discussed by Teece (1986) as to whether the firm should acquire the complementary assets rather than risking diminution of the value in its strategic assets. Transaction cost economics would also suggest that if there was risk of opportunism or the assets were highly specific then they should be integrated rather than accessed through alliances or contracts.

Conclusions

From its origins as a tool of business, some progress has been made in defining the business model in an academic sense. Its purpose has been described by Chesbrough and Rosenbloom (2002) as providing the construct that mediates the value creation process between the technical and economic domains, selecting and filtering technologies and packaging them into particular configurations to be offered to the market. While a number of approaches have been adopted in the literature, the Chesbrough and Rosenbloom (2002) which sets out six generic functions of the business model is the one that has been adopted here.

Its functions offer a framework that can be enriched by integrating the theories of the firm. From this framework a set of hypotheses about value creation and its capture by the networked firm can be developed and tested. This is undertaken firstly in the analysis of the biopharmaceutical and pharmaceutical business models in chapters 7 and 8 and secondly in the case studies discussed in Part D of the thesis. These use the framework developed in this chapter to address the origins of sustainable competitive

advantage of each business model, their likely weaknesses and how they might evolve.

Before addressing these issues, it is necessary to understand the knowledge base of the biopharmaceutical sector and how this has changed over time (Chapter 5), with implications, not only for the long duration and cost of the drug discovery and development process (Chapter 6) but also for the different business models adopted by firms in the sector (chapters 7 and 8).

PART B.

THE RISE OF BIOTECHNOLOGY:

NEW FOUNDATIONS FOR BIOPHARMACEUTICALS

Chapter 5. Drug Discovery and Development Technologies

Introduction

The purpose of this chapter is firstly to describe the evolution of the traditional pharmaceutical technology and secondly to trace the development of modern biotechnology. It is suggested that the two technologies represent different technological regimes with significant implications for their commercialisation. Malerba and Orsengio (1990, 1993) argue that the pattern of innovative activities such as the concentration of innovators, ease of innovative entry and stability of the hierarchy of innovators is a function of the specific features of the technological regime.

The biopharmaceutical regime exploits new knowledge from molecular biology and genomics about the nature of specific diseases, about disease pathways and about a much larger number of disease targets to create an array of newly engineered therapeutic proteins as drug candidates. The development of the new foundational knowledge has been increasingly fragmented and widely dispersed in universities and small companies.

A key date in the adoption of modern biotechnologies is 1975 when Genentech was founded, the first firm established to apply the recently developed techniques of genetic engineering to the development of human therapeutics (McKelvey 1996). An alternative date is 1973 when Stanley Cohen and Herbert Boyer discovered the basic technique for recombinant DNA (Cohen et al. 1973). Since then a range of different bio and other technologies have been developed in the search for new therapeutics and to improve the efficiency of the drug discovery and development process.

While biotechnology represented a major breakthrough in the development of new medicines, the pharmaceutical industry was already technologically advanced. As the two have developed, traditional pharmaceutical technology and biotechnology have followed different technological trajectories (Nelson and Winter 1982). Nonetheless each has borrowed from the other. Biotechnology has been built on the platform of

traditional pharmaceutical technology but embodies much new knowledge. As it has developed in parallel, traditional pharmaceutical technology has incorporated some of the drug search techniques of biotechnology.

Traditional Pharmaceutical Technologies

Small molecule drugs

The drug discovery process can be described as the identification and validation of a disease target and the discovery and development of a chemical compound as a drug candidate to interact with that target. This interaction can be to block, promote or otherwise modify the activity of the target (Sweeny 2002). The history of drug development over the past century has been about the accumulation of a progressively more detailed knowledge of this interaction, largely through a much improved understanding of disease and its causes. This learning process has been complex and many new techniques have been developed as part of the discovery process.

Two fundamentally different technological approaches to the identification of drug candidates have been developed. One is that of rational drug design, a structured approach in which a chemical compound is specifically designed to disable a disease target by binding to it, fitting in the manner of ‘a key to a lock’. The other is random screening in which many thousands of compounds are randomly tested to determine their effectiveness against a disease target.

While initially the task of finding the molecular ‘key’ in rational drug design was somewhat serendipitous, the technique has been refined with greater understanding of the molecular structures of both the ‘key’ and the ‘lock’. Paul Erlich early in the twentieth century formulated a theory of how a small organic molecule with a particular structure could bind to, and disable, a disease protein ‘as in a key to a lock’. The first successful drug with these properties was Salvarsan used effectively against the syphilis, previously treated with mercury (Scherer 2000; Walsh 2003). This discovery in 1909-10, and continuing work on red dyes, led to the discovery of sulpha drugs to combat lethal streptococcal infections (Scherer 2000). Initially it was thought that it was the action of the dye that provided the antibacterial action, but later, sulphanilamide was identified as the active ingredient (Gambardella 1995).

The second approach, random screening owes its development to Waksam's search for antibiotics in the early 1950s. Penicillin, a naturally occurring mould, first observed by Fleming, but recognised by Florey and Chain for its therapeutic properties, played a life saving role during the Second World War (Weatherall 1990). Waksam thought that other naturally occurring spores could have antibiotic effects and he began to screen and test soil samples seeking new antibiotics. Not only was he successful in discovering streptomycin but he established a new methodology, random screening, for discovering drugs (Scherer 2000).

Rational drug design and screening methodologies

Pharmaceutical companies thereafter followed these two methodologies, either the Erlich model, in which it sought small molecules of particular structures, as keys to fit the 'lock', or the Waksam methodology in which vast numbers of naturally occurring substances, where screened and tested for their therapeutic properties. (Scherer 2000). The two models were not entirely distinct. Indeed Erlich's team screened 606 compounds before discovering Salvarsan.

The large screening programs adopted by the pharmaceutical companies in the 1950s and 1960s reflected the limited knowledge of the link between potential drugs and physiological and pathological conditions. Trial and error was more economically advantageous for large firms with sizeable R&D budgets. Until relatively recently there were only about 500 known disease targets, so one method of drug discovery was to randomly test the efficacy of many potential drug candidates, against a subset of the drug targets, until one was found to work (Walsh 2003). Using this methodology, drug discovery was a matter of serendipity.

However, as the knowledge of the action of drugs on diseases increased, the 'discovery by design' model gained momentum (Gambardella 1995). In the 1940s and 1950s there were advances in virology and shortly after breakthroughs in microbial biochemistry and enzymology (Galambos and Sturchio 1998). Tagamet, an anti ulcer drug developed by Sir James Black to block the secretion of gastric acid in the stomach, was produced by design to deal with a particular physiological condition, known to be one of the causes of the disease (Gambardella 1995). The greater

understanding of cell receptors, which are proteins on the surface of cells that either activate or block the functions of cells, led to further advances in drugs, which were specifically designed to bind to the receptors. Diseases that resulted either from the failure of these proteins to be active when they should be, or vice versa, could be alleviated by drug molecules that had the appropriate geometric shape and/or electric charge to bind to the receptors. This technique continues to be applied to the drug search process for many disease types (Gambardella 1995).

The efficiency of rational drug design and screening methodologies was considerably enhanced by x-ray crystallography and computer based search methodologies respectively. X ray crystallography and NMR (nuclear magnetic resonance) provided scientists with a way of inspecting molecular structures. X ray crystallography is based on passing X-rays through protein crystals and linking the x-ray diffraction pattern to the spatial distribution of the electrons. Resolution of the diffraction pattern has been much enhanced by using high energy sources of radiation such as synchrotrons. NMR uses radio waves in magnetic fields to determine the position of atoms to deduce the structure of the molecule. Both techniques enable scientists to understand the structure of the disease protein molecule, although there are difficulties and shortcomings with crystallising the normally dynamic structure of protein (Walsh 2003).

Together with advances in computer-based screening technologies, these techniques enable drug candidates to be rapidly screened against possible disease targets, so called *in vitro*, without the need to test each one on an animal model. An early screening system developed by Nova Pharmaceuticals in the 1980s enabled 1200 compounds to be screened in a week, in contrast to a month required to screen a similar number using animal models (Gambardella 1995). Computers enable three-dimensional visualisation of prospective proteins by scientists as they search for a match for target receptors. Only then are they tested in animal models. Libraries of potential compounds have been developed to speed up this process.

These techniques developed primarily within the traditional drug discovery paradigm have become even more powerful with advances in genetic engineering.

Vaccines and antitoxins

The development of vaccines and anti-toxins has followed a somewhat different technological trajectory. Vaccination seeks to exploit the natural defence mechanisms conferred by the body's immune system. A vaccine is prepared from the antigenic components of a pathogen which when administered activates the immune system, often giving long lasting protection against that particular disease. Vaccines are biologics, but at least prior to the 1980s, their production was in no way dependant on modern biotechnological methods (Walsh 2003).

The origins of modern vaccination go back to Edward Jenner, who immunized patients against small pox, by inoculating them with the less virulent cow pox. Louis Pasteur however provided the breakthrough in understanding the cause of infectious diseases through his discovery of staphylococcus, streptococcus and pneumococcus. His first success with a vaccine was when he developed an attenuated form of the chicken cholera vaccine. He later developed vaccines for anthrax and most famously for rabies, which he used to successfully treat a young boy badly mauled by a rabid dog.[4] Emil von Behring and his colleagues developed toxin mixtures neutralised by the anti toxins. They found that immunity to diphtheria could be produced by the injection into animals of the diphtheria toxin neutralised by the diphtheria antitoxin. Behring later used such toxin-antitoxin mixtures to immunize humans against diphtheria.[5]

Exploiting new knowledge about the bacteriological origins of disease, the US firm, H K Mulford Company was the first to bring an antitoxin for diphtheria to market. Subsequently the company brought out antitoxins and vaccines for a wide range of common diseases (Galambos and Sturchio 1996). Although this cycle of innovation in vaccines faded as greater emphasis for the treatment of infectious diseases came to be placed on the development of anti-infectives, the development of vaccines based on research in virology, for measles, mumps and rubella emerged in the 1960s from the laboratories of Merck Sharpe & Dohme, which had previously acquired the Mulford business (Galambos and Sturchio 1996).

[4] http://www.louisville.edu/library/ekstrom/special/pasteur/cohn.html
[5] http://nobelprize.org/nobel_prizes/medicine/laureates/1901/behring-bio.html

These vaccines and antitoxins were derived by extracting the relevant antibodies from large animals (e.g. horses) or human donors previously immunised with the particular antigen. As will be discussed, for many vaccines this technology was replaced by recombinant technology. This permitted large-scale production of clinically safe vaccines. Their defined composition, which all but precluded the possibility of undetected pathogens, made them less likely to cause unexpected side effects (Walsh 2003).

Biotechnology

Biotechnology can be defined as:

> … the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services. (OECD 2005a)

The term biotechnology refers to long established processes such as brewing and cheese making, as well as the modern processes relating to drug development (Walsh 2002). Modern biotechnological techniques used in drug development include, but post date, recombinant DNA technology and hybridoma technology used in monoclonal antibody products (Walsh 2002). This includes recombinant techniques used also to synthesise old drugs previously extracted from biological materials.

Biotechnology is not a single technology but a cluster of technologies. Moreover other technologies drawn more broadly from science, engineering and informatics have been incorporated to solve particular problems and developed as branches of biotechnology such as, for example, bioinformatics. Modern biotechnology has also incorporated and modified the traditional pharmaceutical technologies of screening and rational drug design discussed in the section above.

Modern biotechnology has led to a dramatic increase in the understanding of the molecular basis of disease, of how the body functions in health and the deviations that cause disease. This has enabled strategies to be developed to cure or control particular diseases. The simpler are those that are promoted by the deficiency or absence of just a single regulatory molecule, such as insulin to treat diabetes, or human growth

hormone to treat dwarfism. Others are multifaceted, such as cancer and inflammation, and hence it is more complex to develop remedies for them (Walsh 2003).

Recombinant DNA

The first attempts to apply recombinant technology to drug development were in the mid 1970s, to synthesise insulin and human growth hormone (hGH), until then extracted from animal and human sources respectively. The initial approach taken for the generation of recombinant insulin was to follow a three stage process. Firstly the human insulin DNA sequence was isolated. Then it was recombined with a DNA sequence in an E. Coli cell. Finally the DNA in the E. Coli then 'expressed' the desired insulin protein (McKelvey 1996). These cells were cultured in large commercial sized batches. Following purification, the recombinant insulin was chemically and functionally identical to 'native' human insulin (Walsh 2003).

Similar techniques were used to manufacture hGH. The supply of hGH had previously been constrained by the availability of human cadavers, from which it was extracted. By using recombinant chemistry, supply could be expanded to meet demand. In addition a link was discovered between the treatment, using the cadavers derived hGH, and the fatal Creutzfelt-Jakob disease. Following the death of one recipient, the commercial production of recombinant hGH was brought forward and approval fast tracked (Walsh 2003; McKelvey 1996).

The recombinant DNA technique was developed by Stanley Cohen of Stanford University and Herbert Boyer of University of California, San Francisco (UCSF) in 1973. In 1975 Boyer established Genentech, with the venture capitalist, Robert Swanson, while continuing to work under contract to Genentech at UCSF. Through the 1970s a number of senior scientists at UCSF, in particular Baxter, Goodman and Rutter, and the City of Hope public research hospital, and a number of their post doc fellows, worked on various aspects of the recombinant DNA technology, including insulin and hGH.

The scientific research at the publicly funded university and research hospital, and that conducted by Genentech, became inextricably entwined. The two largest suppliers of human growth hormone and insulin, the Swedish firm, Kabi and the US

pharmaceutical firm, Eli Lilly respectively contracted Genentech to produce recombinant versions of their leading products. Lilly also supported research work being conducted by Baxter and Goodman at UCSF. The working arrangements between the various scientists were characterised by both cooperation and competition. Announcements of breakthrough discoveries were, on occasions, released within hours of each other, by rival groups.

A number of the researchers from UCSF joined Genentech, taking with them knowledge acquired in projects with Baxter and Goodman. More controversially one of them, Peter Seeburg took some hGH clones with him to Genentech (McKelvey 1996, p. 153). Genentech's initial contract with UCSF entitled it to negotiate a future licence agreement, but all inventions and research samples remained the property of the University. Under a licensing agreement signed in 1980, Genentech was required to pay substantial royalties to UCSF on sales of hGH and human insulin (McKelvey 1996, p. 104). In 1982, reflecting the difficulties in resolving the potential conflicts of interest involved in research conducted on behalf of start-up companies, established pharmaceutical firms and publicly funded research grants, the Presidents of the leading research universities Harvard, MIT, Stanford CalTech and UC, meet at Pajaro Dunes with eleven corporations, in an attempt to set up better procedures to deal with contracts, patents, licences and conflicts of interest (McKelvey 1996, pp. 166, 168).

In parallel with developments at UCSF, Prof Walter Gilbert of Harvard University was also working on an expression system for insulin but could not make it work (McKelvey 1996, p. 264). Gilbert, along with Frederick Sanger and Paul Berg won the Nobel Prize in 1980 for their pioneering work on cutting and pasting DNA fragments (McKelvey 1996, p. 86), precursors to Cohen and Boyer's breakthrough in creating recombinant DNA. Gilbert, along with other Harvard, MIT and Swiss scientists, established Biogen in 1978, with finance from the same venture capital company as funded Genentech (McKelvey 1996, p. 161). In 1980, Biogen had some success in cloning interferon with the hope of producing a cure for cancer, but the therapeutics had a more limited range (Orsengio 1989), with applications to leukaemia (1986) and multiple sclerosis (1996). Other leading scientists, Baxter and Rutter also went on to establish pioneering biotech companies, California

Biotechnology (renamed Scios in 1992)[6] and Chiron respectively (McKelvey 1996, pp. 102-103). Thus a number of the biotechnology pioneers established biotechnology companies that have had an enduring role in the sector.

Hybridoma technology and monoclonal antibodies

Following these pioneering efforts, biotechnology continued to advance with new techniques being developed to develop drugs to target particular diseases. Each of these new techniques produced a cluster of new biotechnology companies dedicated to employing the particular technique to address the most likely disease target. Most prominent amongst these was the development of monoclonal antibodies, initially to attack cancer. There are several hundred potential monoclonal antibody cancer drugs undergoing preclinical and clinical trial, the largest single category of biopharmaceuticals currently undergoing investigation (Walsh 2003, p. 414).

Monoclonal antibodies offer something of a 'magic bullet' solution to killing specific cancer cells. The body produces *polyclonal* antibodies in response to an antigen entering the body which bind to it and identify it as a cell to be destroyed. The construction of *monoclonal* antibodies using genetic engineering offered the possibility of creating a highly specific antibody that would bind to particular cancer cells which the body would then destroy. Monoclonal antibodies were first created in 1975 by César Milstein and Georges Köhler, in England using a so called 'hybridoma' process using murine (mouse) models. A number of difficulties have been experienced with the therapeutic use of monoclonal antibodies. One has been the immune response to the murine derived monoclonal antibodies. This has lead to the development of humanised antibodies formed by grafting the murine monoclonal to a human antibody.

A number of techniques were developed to increase the potency of monoclonal antibody treatment, such as attaching a radioactive or drug toxin load to the antibody. While cancer has been the focus, monoclonal antibody treatment has been extended to cardiovascular and infectious diseases.

[6] Scios was purchased by Johnson & Johnson for about $2.4 billion in 2003 (New York Times, February 11, 2003).

Other extensions of recombinant DNA technology

The early recombinant techniques such as those developed for human growth factors, insulin and monoclonal antibodies have been extended to many other classes of regulatory molecules such as proteins, hormones and enzymes. Each area has produced new drugs for particular diseases. Interferons have been developed to combat chronic hepatitis and multiple sclerosis, colony-stimulating factors (CSFs) for use in treating neutropenia and erythropoietin (EPOs) for treatment of anaemia. Genetically engineered EPOs such as Epogen have become blockbuster drugs (Walsh 2003, p. 270).

One of the outcomes of the advances in biotechnology has been to shift the focus of drug discovery from drug candidate to target. The earlier 'small molecule' approach was to search for drugs from amongst a large number of candidates, matched against a small number of disease targets. Biotechnology, and in particular the mapping of the human genome, has led to a greater understanding of the source of disease and the disease pathways. The number of known disease targets has jumped, from about 500 to over 4000, and is expected to increase, with greater emphasis on understanding and characterising the genetic source of disease (Walsh 2003, p. 482).

Gene therapy and antisense technology

This increased genetic knowledge has led to a focus on nucleic acid preparations such as gene therapy and antisense technology. Gene therapy appears to offer the ultimate solution to many genetic diseases that have so far been characterised. These genetically based deficiencies could simply be corrected by inserting a 'healthy' copy of the appropriate gene into the relevant cells of the patient. However the procedures for inserting the gene have been anything but straightforward. In addition while some diseases, such as cystic fibrosis, result from relatively simple genetic deficiencies, others are quite complex, with a number of organs affected, making genetic treatment difficult in practice (Walsh 2003).

Antisense technology has been developed to block the inappropriate production or overproduction of gene products associated with certain diseases. Research using the technology has to date focused on cancer therapy. The most common form of antisense agents used in research are oligonucleotides which bind to the mRNA

molecule and prevent the translation of that particular DNA (Walsh 2003, p. 491). The advantage of this approach is its high level of selectivity, in blocking expression of only the gene known to be the cause of the disease. However many challenges remain in achieving operationality of the technology. One difficulty is the design of successful delivery mechanisms for getting the oligonucleotide drug to the desired site in the body. However one drug, Vitravene produced by ISIS, became, in 1998, the first using the antisense technology to receive FDA approval.

Platform technologies

Assisting in the development of each new area of biopharmaceutical therapeutics, is a set of platform technologies that has led to greater efficiencies in the drug discovery and development process. In part these platform technologies were borrowed from those developed by the traditional pharmaceutical industry. These included rational drug design and advanced screening techniques, which have been given a new twist in the context of genetically engineered drugs.

Other technologies were invented prior to rDNA technology but gained impetus with the need to create and screen arrays of DNA. This included automated systems for peptide and nucleic acid analysis based on Bruce Merrifield's simplified techniques developed in 1964. In 1985, Richard Houghten established the new discipline of *combinatorial chemistry*, by synthesising millions of peptides, which he tested for biological activity. The technique was also widely adopted by the mainstream pharmaceutical industry (Beeley and Berger 2000).

In 1967 the first gene transfer was accomplished and the microbe that was the ultimate source of heat stable taq polymerase, the enabling enzyme for modern *polymerase chain reaction (PCR),* was discovered in a hot spring in Yellowstone National Park. PCR was the technique, invented in 1983 by Kary Mullis, for replicating DNA without using a living organism, such as E. Coli. Techniques associated with genomics were at first not widely known and the sequencing and study of a single gene was a significant task. This process has now been made more widely accessible and much faster by *'high throughput' sequencing processes*, which can sequence over 1000 bases per hour (Walsh 2003, p. 45).

Other technologies related to the drug manufacturing process. Various techniques, such as *High Pressure Liquid Chromatography (HPLC)* developed to resolve chemical mixtures into their component compounds and *gel electrophoresis* to separate and purify high molecular weight compounds and various machines to synthesise DNA and proteins were developed in the 1960s. In the 1970s *computer systems* were integrated into some of these machines. Hewlett-Packard offered the first microprocessor controlled HPLC in 1979 and the PC became a laboratory standard in the late 1970s (ACS 2000). The incorporation of computing and information management technologies into large scale, frequently robotic, industrialised processes became a characteristic of modern biotechnology.

Integrating these various technologies enabled the *sequencing of the human genome*, which was completed in 2003. The human genome consists of about 3.2 billion base pairs. However of these only about one third are transcribed into RNA and only 5% of that RNA thought to encode proteins. Thus the number of encoding genes is of the order of 30,000 or less than 2% of the total genome, much smaller than expected (Walsh 2003, p. 46; US Department of Energy Office of Science 2008). For drug discovery, the significance of the sequencing of the human genome is to increase the number of potential drug targets from about 500 targeted by the present range of drugs, to perhaps between 3,000 and 10,000 new protein based drug targets.

However the function of a vast proportion of the genome remains unknown. The process of understanding the functions of the genome has stimulated the development of a set of new techniques and technologies that are largely based on *sequence structure/data interrogation/comparison methodologies* that requires powerful computer programs to achieve high throughput screening and the development of various libraries including those of DNA or expressed genes. The libraries use combinatorial chemistry to produce compounds based on the controlled and sequential modification of generally immobilised or otherwise tagged chemicals. (Walsh 2003; ACS 2000).

This process has been much assisted by the development of *DNA microarray technology*. A microarray is a small membrane or glass slide, containing samples of many genes arranged in a regular pattern, which are used to determine the expression

levels of hundreds or thousands of genes in a single cell. The microarrays have become standardised products such as those known as 'gene chips' that are marketed by Affymetrix. Fluorescence is used to detect biological activity between drug candidate and the target. The experiments are conducted by robots, producing huge volumes of data, with the results being analysed by powerful computers using *bioinformatics* software. Thus, information technologies have been joined to biotechnology to manage and analyse the enormous volumes of data produced by this requirement for high throughput screening technologies.

Microarrays and other technologies have been used in the search for the genetic cause of disease. SNPs, a small genetic change in a person's DNA sequence may point to predisposition to a disease or influence a person's drug response. SNPs can be used as diagnostic tool, which using miroarray technology, can screen a patient's SNPs to test for the likelihood of an adverse reaction to a particular drug. Such testing, which could allow a drug to be matched to an individual, brings with it the promise of 'personalised medicine' (NCBI 2004).

Rational drug design has been given a new impetus, with the capacity to more accurately model target proteins and to better understand their role in disease. An advance over the earlier 'lock and key' structures suggested by Erlich, has been achieved by using molecular modelling software to model proteins and design drugs that will act as blockers for the normal activity of disease targets. *Molecular modelling* of target proteins has been vastly improved by high resolution x ray crystallography using high powered synchrotron generated light beams, Nuclear Molecular Resonance (NMR) machines, electron microscopy and various imaging techniques. As focus shifted from genomics to proteomics, NMR in particular has enabled the structure of proteins and peptides to be viewed in aqueous environment, as they exist in biological systems (ACS 2000).

Virtually all drug targets are protein-based but the protein expression levels measured by DNA array technology is not necessarily accurate. Therefore protein-based drug leads/targets are often more successfully identified by direct examination of the expressed protein complement of the cell, i.e. its proteome (Walsh 2003). The comprehensive and systematic study of proteins expressed in the cell and their

functions, known as '*proteomics*', has become a special line of business in the search for new drugs. The proteome, unlike the genome, is constantly changing and therefore best studied in living cells (in vivo). Various techniques such as 'green fluorescent protein' have been developed to study cell biological processes, molecular networks and interactions over time and space (European Commission 2005, p. 14). HPLC and high resolution mass spectrometry are also part of the sequencing toolkit (Walsh 2003, p. 50).

Biopharmaceutical and Pharmaceutical Technological Regimes

In the introduction of this chapter, the biopharmaceutical and pharmaceutical technologies were referred to as two technological trajectories (Nelson and Winter 1982) which have followed two associated but different paths. The pharmaceutical technology based on small molecule drug candidates has continued to evolve and to successfully produce new drugs, over the same period that biotechnology has increased the knowledge of new disease pathways leading to the development of new biopharmaceutical drugs. The traditional pharmaceutical technologies were based on a more limited understanding of the cause of disease, had only a small number of disease targets and used large scale screening processes to match drug candidates to these targets. While traditional pharmaceutical technologies have provided a platform for the development of biotechnology, the biopharmaceutical discovery techniques exploit new knowledge about disease pathways that have increased the number of disease targets and allowed a narrowing of the search process for drug candidates.

Although closely related, the two represent different technological regimes. A technological regime is a particular combination of the characteristics of the knowledge base, degrees of cumulativeness of technological knowledge together with the particular appropriability and opportunity conditions (Orsengio 1989; Malerba and Orsengio 1990, 1993). In most respects these factors are quite different for the two technologies.

Biotechnology has provided a new knowledge base, new understanding of disease and many new associated drug discovery and development techniques. With that, new

opportunities for specialist firms have emerged. Malerba and Orsengio (1993) have shown that the specific patterns of innovative activities of a sector in terms of concentration of innovators, ease of innovative entry and stability of the hierarchy of innovators is a function of the specific features of its technological regime. Thus the characteristics of the biotechnological regime help explain the emergence of the plethora of specialist start-up companies. The knowledge base is diverse and it as been difficult for a small number of large firms to control it (Malerba 2005).

The traditional pharmaceutical technology also has been subject to continuing innovation. Not only has it imported a diverse range of platform technologies from biopharmaceutical firms, but it has continued to apply the increasing knowledge of disease to a growing array of disease problems. This has resulted in continuing innovation in small molecule drugs such as antidepressants and antipsychotic drugs, 'statins' to lower cholesterol, nonsteroidal anti-inflammatory drugs and antivirals to control HIV/AIDS (Scriabine 1999).

The commercialisation process for biopharmaceuticals has been quite different from traditional pharmaceuticals. Zucker et al. (1998) have shown that biotechnology knowledge was transferred from the universities and research labs by 'star scientists' to collaborating specialist firms. While the tacit knowledge of the scientists working in collaboration with associated firms was important in the process of knowledge transfer, this was reinforced by formal intellectual property ownership. It is noteworthy that Zucker et al. (1998, p. 5) found that 'university stars' affiliated with firms were very different in their patenting activity compared to unaffiliated university stars: half had patented discoveries versus only 15.6% of the unaffiliated university stars. This and the other evidence presented earlier in this Chapter about the prominent role of the leading scientists in establishing the early biopharmaceutical companies, suggests that the nature of the biotechnology knowledge being transferred between university and specialist start-up companies was naturally excludable knowledge held by a small group of 'pioneer scientists'.

This was quite a different appropriability regime from the one under which the traditional pharmaceutical technologies had developed. Previously scientists had generally felt obliged to place the results of their research in the public domain for

common benefit and many felt uncomfortable about benefiting personally from their discoveries even when they held the relevant patents.[7] The Bayh Dole Act of 1980, not only granted IP ownership to the university employed scientists, but also gave them 'permission' to derive personal benefit from their discoveries (Sampat 2006). Secondly the value of the discoveries in biotechnology was the catalyst for a review of relations, dealing with intellectual property, between the universities and industry. In 1982, the Presidents of the leading research universities Harvard, MIT, Stanford CalTech and UC, meet at Pajaro Dunes with eleven corporations, in an attempt to set up better procedures to deal with contracts, patents, licences and conflicts of interest between university employed researchers and their role as owners, employees and associates of the start-up companies (McKelvey 1996, pp. 166, 168).

The traditional pharmaceutical technologies had developed when scientific knowledge generated by universities was relatively 'open source'. The pharmaceutical companies had free access to basic science research conducted at universities and were able to commission work of particular interest. This university derived research, supplemented work conducted in the company laboratories. In order to gain access to the new technologies the pharmaceutical companies had to change their strategies. University research was less likely to be available in the public domain, making it more necessary for the companies to enter into formal contracts. The close connection between the university staff and the new start-up companies made a transition to alliances with such companies a natural development.

Conclusions

In tracing the development of traditional pharmaceuticals and the contribution of biotechnology to its application to human therapeutics, this chapter has demonstrated that the two have followed different technological trajectories and may be viewed as two different technological regimes. The traditional pharmaceutical technological regime was based on a relatively low understanding of disease, but developed large scale screening and rational drug design techniques that were effective in developing many important drugs.

[7] For example, Frederick Gardner Cottrell established the Research Corporation, an independent legal structure, to administer his patents on an electrostatic precipitator, a pollution control device, rather than benefit from the sales royalties himself (Sampat 2006).

Biopharmaceuticals on the other hand are based on a different technological regime, which has used new knowledge, principally about genomics, to revolutionise the provision of pharmaceuticals by overcoming problems of source availability, product safety and generated an array of newly engineered therapeutic proteins that has led to the development of a significant number of new drugs to treat disease (Walsh 2006). Biotechnology however is not a single technology, but a cluster of related technologies each reflecting new insights into genomics and other aspects of molecular biology. In tandem with these developments in drug discovery, a range of platform technologies have been developed to make the process of drug discovery and development more efficacious.

The transfer of knowledge from the universities has also followed a different path. Star scientists have transferred knowledge from universities, in an excludable form, to specialist start-up companies. This has led to the innovation process for biopharmaceuticals taking place in a large number of small specialist companies, owing their establishment to the latest technological breakthrough and focusing on exploiting the competitive advantage of their particular competence and expertise in that technology. The knowledge base for biopharmaceuticals is therefore fragmented as well as rapidly evolving.

However the pharmaceutical companies have remained innovative. They have continued to extend the traditional pharmaceutical technological trajectory in small molecule drugs while borrowing from the developments in biotechnology.

Later chapters deal with the implications of these technological differences for the business models of the new and incumbent firms and the relationships that have developed between them.

Chapter 6. Economics of Drug Development: Process, Uncertainties and Cost

Introduction

The economics of the drug discovery and development process has a considerable bearing on the business models of pharmaceutical and biopharmaceutical companies. Compared with the commercialisation of most innovations, drug discovery and development is expensive and has a high risk of failure. Drugs for human consumption are also required to undergo stringent tests and meet high regulatory standards. In particular it requires the investment of a significant amount of capital to achieve the approval of a single drug, while at the same time sustaining the loss of capital invested in unsuccessful drug development programs.

This chapter examines three aspects of the drug development process:

- the long development path of a drug from discovery to regulatory approval;
- the low probability that a drug candidate will satisfy the rigorous clinical testing process; and
- the high cost of drug development, partly as a consequence of the above two factors.

The regulatory process is much the same for biopharmaceuticals as for small molecule drugs. Despite earlier hopes that the costs and risks of developing biopharmaceuticals would be lower than for small molecule drugs, the available information presented in this chapter suggests that this is not the case.

Development Path

Drugs are required to meet stringent tests for safety and efficacy. Before being tested on humans, drug candidates are tested in preclinical trials on animals and in the laboratory for any adverse effects. They are then tested in clinical trials on humans in three distinct phases. At each phase, the drug is tested on a selected population of increasing size. It is then submitted to the regulatory authorities for marketing approval. This phased testing process is known as a ‘pipeline’. The successful passage of a drug through this pipeline is to a large extent under the control of the regulatory

authorities. While the United States, Europe and other individual countries each have drug approval agencies, the US FDA and the European Medicines Agency (EMEA) are the leading drug regulatory agencies. The US represents about 50% of the world pharmaceutical market and most firms follow the process administered by the US FDA.

How long a drug takes to pass through this pipeline depends on many factors, varying considerably with the nature and novelty of the drug. Some biopharmaceuticals that are a recombinant version of an existing drug have had shorter approval periods compared with those based on more novel technologies (Gosse and Manocchia 1996). Time spent at each phase of the pipeline under the control of the regulatory authorities is well documented. Establishing the time of discovery may be more difficult particularly for biopharmaceuticals where it may be necessary to trace the origins of drugs through alliance partners. Accordingly early studies of the development period of biopharmaceuticals have been concerned only with the better documented regulatory period (see for instance Gosse and Manocchia 1996; Reichert 2001).

Discovery and pre-clinical

Following the discovery phase, the drug enters the preclinical phase to establish the necessary evidence to obtain approval to be tested on humans. During this period, the drug candidate is given a thorough testing in the lab and in animal models to give an indication of its likely toxicity and efficacy in humans.

DiMasi et al. (2006)[8] has used an estimate of 52 months for the total discovery and preclinical trial period for a biopharmaceutical, the same as for small molecule drugs (DiMasi et al. 2003). A figure from composite sources published by PAREXEL (2005) put the early research and preclinical period at 3.8 years (about 46 months) for drugs approved in the period 2000-04.

Development phase

The data collected in the preclinical phase is used to support an application to the FDA for approval as an Investigational New Drug (IND), which must be obtained

[8] Pre-publication version.

before a drug can be tested in humans. Once the IND is obtained, clinical trials can begin, which have three phases as summarised below:

Phase I

- Testing of a new compound in 20-80 healthy human volunteers to determine tolerance, pharmacological effects, and absorption, distribution, metabolism and excretion (ADME) patterns.

Phase II

- Trials in 100-300 patients with the targeted condition to determine effectiveness in treating disease or medical condition and short term risks.

Phase III

- Trials on 1000-5000 patients to determine clinical benefit and incidence of adverse reactions (Sweeny 2002).

To gain a New Drug Approval (NDA), the trials are generally conducted with a significant involvement of the FDA, so that issues of concern to the FDA are thoroughly researched before regulatory approval to market the drug can be obtained. The FDA also has to be convinced that there is a satisfactory manufacturing process, which has the capacity to produce in large volumes, with the assurance of stability, uniformity and overall quality. A Bioavailability Study must be conducted to show that the formulation used in the trials is equivalent to product to be marketed. Following marketing there are continuing trials (Phase IV) to identify any previously undetected adverse effects and a long term morbidity and mortality profile (Sweeny 2002).

Most studies seeking to estimate the length of the development period have focussed on small molecule drugs for large pharma. These studies provide estimates of about 6 years on average for the clinical phase and another one and a half years for the approval period. Altogether the period from discovery phase to FDA approval totals about 11.5 years on average.

However there have been several studies of biopharmaceuticals (see Gosse and Manocchia 1996; Reichert 2000, 2001) including the recent study by DiMasi and Grabowski (2006), which has provided a comparison between traditional drugs and biopharmaceuticals. The DiMasi and Grabowski study, based on the experience of

522 biopharmaceuticals and 534 traditional drugs, indicates that the clinical trial period for biopharmaceutical drugs is 81.7 months, 9.6 months longer than traditional drugs. Most of this additional time was in the early clinical period, Phase I (additional 7.2 months extra) and Phase II (additional 3.3 months), offset to some extent by a shorter Regulatory Review period. The total for phases I-IV was found to be 97.7 months on average for biopharmaceuticals compared with 90.3 months for small molecule drugs. Together with a period of 52 months for preclinical trials, the total from discovery to FDA approval for biopharmaceuticals was found to be 150 months (or 12.5 years).

Other studies have indicated that the clinical phase for biopharmaceuticals has been increasing rapidly since the first biopharmaceutical approved in 1982. A Tufts CSDD report (Tufts CSDD 2003) indicated that for four cohorts of approved drugs the clinical period increased from 2.6 years for drugs approved in the period 1982-1989 to 6.2 years for those approved in the period 2000-2002. One difficulty with this analysis is that the clinical trial period can vary substantially and with the relatively small numbers involved (14 and 23 respectively) the averages can be distorted. Nonetheless the trend has been maintained, with a more recent study indicating an increase from 5.7 years for biopharmaceuticals approved in the period 1996-2000, to 6.9 years for those approved in the period 2001-2005. The increase between these two most recent periods was found to be particularly large for oncology therapeutics, which increased by 79.2% to 9.2 years for the clinical period (Reichert 2006). The period of regulatory review has also increased as estimated by Reichert from 15.9 months to 18.5 months between the two periods. On this basis the total for phases I-IV for the Reichert study is 101.5 months compared with the DiMasi and Grabowski (2006) study of 97.7.

On the basis of this evidence, the early optimism that biopharmaceuticals may require a shorter time in clinical trial because of a fewer number of clinical studies and a smaller number of subjects being required, compared with small molecule drugs, (see Reichert 2001) has not been translated into a shorter trial period. It has been suggested that this is due to a shortage of eligible patients with the necessary specific requirements to participate in the clinical trials (Kittredge 2005).

Uncertainties of Drug Discovery

Successful drug development is highly uncertain. This arises not only from the limited knowledge of the disease mechanisms, but also the diverse reaction of patients to drugs in the clinical trial process. Knowledge of the disease pathways is improving with advances in molecular biology. However many successful drugs have been discovered by accident with only a limited understanding of their action on disease. Moreover individual reactions vary, meaning that drugs, which appear safe and efficacious in early clinical trial, fail in the later stages when tested on larger populations. Accordingly even drugs commencing Phase III trial have only a two-thirds chance of reaching market.

Again most of the work estimating probabilities of success at each development stage is for small molecule drugs. A commonly cited ratio is that for every drug that is finally approved by the regulatory authorities for sale, 5 enter Phase I testing, and 250 enter preclinical testing after 5,000-10,000 have been tested in the discovery stage (PhRMA 2006). CMR International has made more precise estimates of attrition rates at each stage, based on reports from pharmaceutical companies, as shown in the Table 6.1 below. These are compared with those produced by DiMasi and Grabowski (2006), for both traditional pharma drugs and biopharmaceuticals. This suggests that biopharmaceuticals may be somewhat more successful in the early phases of the clinical trial period, but less so in Phase III.

Table 6.1 Attrition rates for compounds, 1998 and 2006

Start of stage	Probability of reaching market (%)		
	CMR 1998	DiMasi and Grabowski (2006)	
		Pharma	Biotech
Preclinical development	10.3	n.a.	n.a.
Phase I	18.4	21.5	30.2
Phase II	28.1	30.3	36.1
Phase III	65.8	68.5	64.2
FDA review and approval	90.6	n.a.	n.a.

Source: CMR International survey of 29 pharmaceutical companies in 1998 as reported in PAREXEL (2001, p. 195) and DiMasi and Grabowski (2006, p. 25).

Whichever estimate is used, it confirms that a high proportion of drug candidates are culled from the development process during clinical trial. The toughest part of the process is in phase II when the number of patients in the clinical trial increase and the

trials focus on the effectiveness of the drug candidate. One of the factors that adds to the cost of drug development is that the failure rates throughout the process, including phase III, are high, meaning that failure can still occur after a significant investment of time and money.

Cost of Drug Development

The arithmetic sum of the out of pocket costs of successfully taking a drug from discovery to marketing approval is estimated to be several hundred million dollars, a very substantial investment. However the economic cost of the development of pharmaceuticals is not simply the sum of the out of pocket expenses incurred from discovery to final approval. The total economic cost also needs to factor in the long development period and the high rate of failure. Changes to either of these factors, such as through increased regulatory requirements or changes in technology to speed up the discovery process, have an impact on the total economic cost. The better estimates of the cost of drug development therefore include the cost of failures, based on the average historical probabilities of success discussed in the section above. They also include an estimate of the cost of capital which is used to time-adjust the out of pocket costs incurred over the development period.

The most authoritative estimates of the cost of developing drugs have been provided by DiMasi, Grabowski and colleagues,[9] first published in 1991 (DiMasi et al. 1991) and since then in 2003 (DiMasi et al. 2003), and in 2006 (DiMasi and Grabowski 2006). The 2006 study provides estimates for biopharmaceuticals. Earlier estimates are for traditional small molecule drugs. These estimates include, not only of out of pocket costs, but also an estimate of the cost of capital and an allowance for development failures. The cost of capital is based on the Capital Asset Pricing Model (see for instance Brealey and Myers 2003).

The allowance for failure is achieved by adjusting the average out of pocket costs for a successful drug, at each stage of its clinical trial, by the probability of success at each stage. The probabilities of success at each stage, used in the 2006 estimates, are those quoted in the table above for biopharmaceuticals and are used to adjust the

[9] Earlier estimates include Hansen (1979) and Wiggins (1987).

expected cost per pharmaceutical that has received an IND approval. This gives a total expected out of pocket cost, for both clinical and preclinical periods, of $169 million, for each drug with an IND approval (see Table 6.2).

Table 6.2 Out-of-pocket preclinical and clinical period cost per investigational biopharmaceutical compounds (millions of 2005 dollars)[a]

Testing phase	Mean cost	Probability of entering phase	Expected cost
Preclinical	$59.88	100%	$59.88
Phase I	$32.28	100%	$32.28
Phase II	$37.69	83.70%	$31.55
Phase III	$96.09	47.10%	$45.26
Total			$168.97

Note: [a]All costs were deflated using the GDP implicit price deflator.

For every successful drug however there are over 3.3 drugs with an IND. The average cost per successful drug is therefore $361 million. However many more drugs enter clinical trial than achieve an IND. To allow for the cost of development work on these failures, DiMasi and Grabowski estimate that the additional cost at the preclinical stage is $198 million per successful drug. The total out of pocket cost per approved drug is therefore $559 million.

To estimate the appropriate discount rate, to adjust for the lengthy development period, DiMasi and Grabowski (2006) use the Capital Asset Pricing Model developed by Sharpe (1964) and others. They employ a methodology specifically developed for estimating the cost of capital for pharmaceutical companies by Myers and Shyam-Sunder (1995 quoted in DiMasi and Grabowski 2006) and others and apply it to the cost of capital for biotechs. The result is a cost of capital of 11.5%. This is applied as a discount rate, to the average expected out of pocket costs for each successful drug at each development stage, using the average development time for each phase estimated in DiMasi and Grabowski (2006). Including this allowance for the time cost of funds, increases the total cost to $1,241 million. Thus the time cost of the funds invested in the development is more than half of the total cost [10].

[10] There is evidence that the cost of capital used by DiMasi and Grabowski (2006) is too low. Golec and Vernon (2007) estimate that the nominal cost of capital for biotech firms is 16.25% (or 13.25% real) while Ibbotson's Cost of Capital Yearbook 2008 reports that the median real cost of capital for companies with the SIC biotechnology code is 17.49%. Given that the time cost of funds is a large component of the estimated cost of developing a successful drug, adoption of these higher rates would tend to increase the cost of development.

This estimate of the total cost of developing biopharmaceuticals is higher than DiMasi's earlier (2003) estimate for traditional pharmaceuticals. However after taking into account likely cost increases between the two periods and differences in the cost of capital, DiMasi and Grabowski (2006) conclude that preclinical trial cost is 41% higher for biopharmaceuticals, but the clinical period is 29% lower. After netting out the various effects, they conclude that the total cost on average of developing biopharmaceuticals is 6% lower than for the total time-adjusted cost of developing traditional drugs.

Conclusions

This chapter has served to establish that developing drugs including biopharmaceuticals is costly and uncertain. The time from discovery for a biopharmaceutical drug to be approved is about 12.5 years compared with 11.5 years for a traditional pharmaceutical. Early optimism that the development period for biopharmaceutical drugs would be less than traditional pharmaceuticals has proved to be unfounded. The time for clinical trails of biopharmaceuticals has increased from an average of 2.6 years to 6.9 years over a period of about 20 years.

Calculating the cost of the discovery and development of drugs is complex. In addition to the 'out of pocket costs', it needs to take into account the time value of money and risk of failure. The out of pocket cost of developing a single drug is estimated to about $169 million from entering clinical trial to approval (that is excluding the discovery phase). However the probability of a drug candidate entering preclinical phase being approved is about 10%. After allowing for the risk of failure the costs rise to about $559 million. Because of the length of time in development the time value of money increases this amount to an estimate of over $1.2 billion.

These factors have had a significant impact on the industry structure and business models of all firms that participate in the industry. The entry of many small firms into the biopharmaceutical and related sectors has made the industry much more complex. However the business models and strategies of all these firms have been greatly influenced by the fundamental economics of the industry. It has meant that in general, only large firms with significant resources can afford the cost of developing a drug and successfully distributing it to a global market. This has established a hierarchy of

firms, with large traditional pharmaceutical and some biopharmaceutical companies at the top of the hierarchy with the capacity to support the full drug development program and smaller companies, dependant for R&D support and access to global markets, on these large companies. The hierarchy is however far from simple with many specialist technology companies providing critical knowledge and technologies to both small and large companies in complex innovative networks. These themes are taken up in the following two chapters.

PART C.

RESPONDING TO THE NEW KNOWLEDGE BASE: DIVERSE BUSINESS MODELS

Chapter 7. Response of Pharmaceutical Companies to Biotechnology: Structure and Business Models

Introduction

Using the framework of the business model developed in Chapter 4, this chapter presents an outline of the traditional pharmaceutical company business model, and how it has responded to the new biotechnology.

Chapter 5 argued that the biopharmaceutical regime exploited a new knowledge base - one that was fragmented and favoured the innovation process being substantially conducted by small specialist firms. Pharmaceutical companies have remained innovative, not only with respect to the traditional small molecule based technology regime, but also in their adjustment process to the new technology. However this fragmentation of the biopharmaceutical knowledge base and its 'ownership' by small specialist firms has provided a significant challenge for large pharmaceutical firms in achieving access to the new technological regime.

Chapter 6 outlined the lengthy, uncertain and costly process of drug development. It indicated that to date neither the cost, nor the development period, of biopharmaceuticals was much different from than that for traditional pharmaceuticals. Accordingly the economics of biopharmaceutical development remains much the same as for traditional pharmaceuticals. To the extent that the economics of traditional pharmaceutical production have encouraged large fully integrated firms, then the economics of biopharmaceutical production may similarly favour large firms.

The Traditional Pharmaceutical Company Business Model

In Chapter 4 the purpose of the business model was described by Chesbrough and Rosenbloom (2002) as providing the construct that mediates the value creation process between the technical and economic domains, selecting and filtering technologies and packaging them into particular configurations to be offered to the market. One of the major tasks for pharmaceutical firms is selecting drug discovery and other technology projects for continued investment while rejecting or dispensing

with others. In an open innovation model, firms would be expected to seek knowledge externally and licence out knowledge that did not fit their business model.

In the traditional business model, pharmaceutical companies adopted the closed innovation model (Chesbrough 2006). They conducted the majority of their research internally which provided the basis for the development of their own drugs (Chandler 2005). Firms conducted basic research confident of their downstream commercialisation capabilities (Rosenberg 1990). Serendipitous discoveries that did not fit the therapeutic interests of the particular pharmaceutical firm were more likely to be cancelled, rather than licensed out.

The next sections discuss the components of the business model in turn using the theoretical framework in Chapter 4.

Value proposition

Chesbrough and Rosenbloom (2002) define the value proposition as the value created for users by the offering based on the technology. For the user, the value proposition of the pharmaceutical companies has been quite powerful. Modern scientifically based medicines have had a major impact on saving and improving the quality of life. In the post war period, pre biotechnology, this was based on the success of a range of new drugs including antibiotics, contraceptives, vaccines and anaesthetics. The value proposition has been supported by the increasingly scientific based knowledge accumulated by pharmaceutical firms and the predictability of the outcomes of the drugs. This has been assisted in the public mind by clinical testing processes and by the certification provided by the FDA and/or equivalent agencies in other countries.

A difficulty of the definition of the value proposition as applied to pharmaceutical companies is that the patient (the 'user') does not typically decide which drug is to be purchased. There are many actors that bear on the decision to purchase a particular drug and the value proposition developed by the pharmaceutical company must be multifaceted to appeal to each of these 'non user' decision makers.

Firstly the major innovative drugs can not be purchased without a prescription provided by a doctor. The pharmaceutical companies' main selling task has been

directed therefore, not at the user, but at physicians. The value proposition to physicians needed to address the scientific basis of the drugs safety and efficacy compared with other similar drugs.

Other actors such as insurers and government agencies controlling the listing of drugs for sale need to be persuaded of the drugs' cost effectiveness. Pharmaceutical companies have considerable pricing power. Each approved drug has, for a period, patent protection and typically only limited competition from other drugs treating a particular disease. This monopoly position, when combined with a powerful value proposition has provided the pharmaceutical company with the ability to price well above marginal cost. Insurers and governments agencies have acted as a countervailing power in pricing pharmaceuticals.

For such actors the value proposition needs to extend beyond questions of patient health to the drug's relative performance. If a new drug was to be more expensive, then it needs to demonstrate that its superior performance is worth it, before it is listed on an insurer's formulary. In the US insurance is provided by Pharmacy Benefit Managers (PBMs). For countries such as Australia, in which the government determines whether a drug is to be listed for subsidised use, arguments about its impact on the overall health budget, such as by reducing the length and increasing the effectiveness of a hospital stay, may be important. Findings such as that provided by Lichtenberg (1996), who reported that for the period 1980 to 1992, a $1 increase in the purchase of pharmaceuticals was associated on average with a $3.65 reduction in hospitalisation expenditures have become for the pharmaceutical companies, an important part of their value proposition.

Market segment and revenue model

Market segment

Rather than the consumer of the medicine, the key market segment for the pharmaceutical company has been the physician. A team of sales representatives, so called 'detailers', have been employed by the pharmaceutical firms to meet with physicians to explain the advantages of a particular drug. In this model each major new drug has been launched with a comprehensive and expensive global marketing

campaign that involved the full range of marketing tools including media advertising, comprehensive information packs, special events for doctors, conference presentations, and a dedicated sales force.

A further market segment that needed to be persuaded of the value of any new drug has been organisations discussed above, such as insurers, which bring countervailing power to the price negotiations. Not only have these organisations affected sales and prices of new drugs but their insistence on generic substitution once patent protection expired also had a major impact on sales revenue.

Revenue model

The revenue model developed by the pharmaceutical companies since the 1970s increasingly depended on the sales of a relatively small number of drugs (Achilladelis 1999). This revenue model became known as the as the 'blockbuster' model (see for instance Mercer Management Consulting 2001). It involves the search for, and distribution of a small number of drugs that achieve substantial global sales (say in excess of $1000 million per annum). The success of this model depends on achieving large returns from a small number of drugs in order to pay for the high cost of the drug discovery and development process for a large number of candidates. Total revenues are highly dependant on sales from a small number of drugs as shown in Table 7.1.

Table 7.1 Top 10 Bestseller prescription drugs in the United States, 1998

Drug	Use	Manufacturer	Sales ($m)
Prilosec	Anti-ulcerant	Astra Merck	2,993
Prozac	Antidepressant	Eli Lilly	2,181
Claritin	Antihistamine	Schering-Plough	1,848
Lipitor	Cholesterol reducer	Warner-Lambert/Pfizer	1,544
Zocor	Cholesterol reducer	Merck	1,481
Epogen	Anti-anaemia	Amgen	1,455
Zoloft	Antidepressant	Pfizer	1,392
Prevacid	Anti-ulcerant	TAP	1,245
Paxil	Antidepressant	SmithKline Beecham	1,190
Norvasc	Calcium blocker	Pfizer	1,086
Total			16,415

Source: IMS America quoted in Landau (1999, p. xx).

Table 7.1 shows the top 10 drugs by sales in the US in 1998 totalling $16.4 billion representing 15% of total sales. Analysis based on more recent data for 2005, shows

that the global sales of just 68 drugs by the top 10 companies by global sales represents 58.5% of their sales, confirming the continuing dependency of the largest firms on the sales of a small number of drugs

Value chain and value network

Prior to the advent of biotechnology, the structure of the value chain of the individual pharmaceutical company was relatively self-contained. Each pharmaceutical company was fully integrated, conducting its own research, development, manufacturing and distribution of its own drugs.

The innovation processes of the large firms were largely closed (Chesbrough 2006). As discussed in Chapter 6, the pharmaceutical industry product pipeline is highly structured, being governed to a large degree by the drug approval process, in which successful drugs are 'moved' down the drug pipeline through a succession of stages - from discovery, to preclinical, clinical, regulatory approval to manufacturing marketing and sales. The value chains of the large firms closely reflected this pipeline with only limited interaction with other firms. Most complementary assets were available in house.

The reasons for this fully integrated structure are suggested by transaction cost economics and were discussed in Chapter 2. These centred on achieving transaction cost economies by integrating transactions that would otherwise have been conducted in the marketplace or by bilateral contract. Whether the transaction was integrated depended on the nature of the assets involved in the transaction (asset specificity), uncertainty and the regularity of the transactions. In general those transactions conducted less frequently, involving more specific assets and having more uncertain outcomes were more likely to be integrated. The nature of the drug discovery and development process outlined in Chapters 5 and 6 provides ample evidence of transactions of this nature. The process of discovering and developing drugs is highly uncertain and involves the investment in assets of great specificity, as evidenced by the high proportion of failures, as well as the highly specific successes. In addition, transactions such as drug candidates passing from one clinical stage to another are clearly irregular.

Moreover the transfer of information about drug development is complex and more efficiently conducted internally (Williamson 1971). Mowrey's study of US manufacturing firms found that the costs of organising innovation inside the firm was lower than attempting to contract for the supply of idiosyncratic knowledge through the market (Mowery 1983). In addition, by generating knowledge internally, the pharmaceutical company retains all residual property rights (Grossman and Hart 1986; Hart and Moore 1990). The value of any spillover of knowledge between projects that was conducted internally is retained by the pharmaceutical company.

Williamson (1975) saw value in the ability of the headquarters of a multi divisional firm to allocate cash flows away from their sources to divisions offering higher yields. This 'internal capital market' (Stein 1997) which characterises the project decision making processes of large integrated firms, has been shown by Guedj and Scharfstein (2004) and Guedj (2005) to outperform equivalent processes employed by start up firms.

The essential argument developed by Guedj and Scharfstein (2004) is that mangers of cash rich start-up biopharmaceutical firms tend to over invest in projects because they have only one or two projects to support, compared with large integrated firms, where management is choosing between multiple projects and therefore have a greater tendency to terminate lower performing projects. For start-up firms with a single project, the decision not to proceed with a project may spell the end of the firm.

Following an examination of a large sample of drug development projects managed by both start-up and large mature firms, Guedj and Scharfstein (2004) demonstrate that there is a greater tendency for projects managed by start-ups to proceed from Phase 1 to Phase 2 than in large mature firms. However the proportion of projects which are ultimately successful i.e. are approved by the FDA, are higher for mature firms than start ups. This difference in ulimate success is most significant for cash rich start up firms where the tendency for projects to proceed from Phase 1 to Phase 2 is most marked.

These factors help explain the internal development of the R&D function, but they leave open the reasons for the internalisation of the sales and distribution function. As

their operations evolved, all the large pharmaceutical companies acquired their own distribution function. Companies that previously had little distribution capacity developed their own or in other cases acquired it. For instance, Merck in 1953 acquired Sharpe and Dohme, a company that had a sizeable network (Galambos and Sewell 1995; Galambos and Sturchio 1998).

With only a small number of drugs being approved each year for the whole industry, control over manufacturing and distribution components of the value chain is of critical strategic importance to individual companies. Chandler (1990) has suggested that with the faster throughput and increased productivity arising from economies of scale, vertical integration reflects the increased risk of hold up or opportunism by contracted suppliers and distributors. While the manufacturing context of Chandler's views reduces their direct relevance, the scope for opportunism by distributors through inadequate or under-resourced marketing campaigns is nonetheless high. Moreover marketing drugs is knowledge intensive and specialised.

Pharmaceutical companies have also instituted organisational efficiencies to improve the progress of drugs through the value chain and reduce costs. These initiatives may have been difficult or impossible to implement were it not for the vertically integrated structure. For instance Ely Lilly made a significant effort through the 1990s to improve the focus and efficiency of its drug development pipeline (Malknight 1999a, 1999b; Verlinder 2000). These targeted improving speed to market, narrowing the therapeutic focus of its R&D and creating product based teams to break down the functional silos – development, marketing, sales etc into multi functional teams that were designed to take a single drug through the testing process, launch and subsequent marketing (Burgleman et al. 2001).

Cost structure and profit potential

One of the tasks of the business model is to estimate the cost structure and profit potential of producing the technology offering, given the value proposition and value chain structure chosen (Chesbrough and Rosenbloom 2002). For analysing pharmaceutical companies this involves understanding the economics of drug discovery, development, manufacturing and distribution. In particular the economics of pharmaceutical companies are governed by high failure rates of drug discovery and

development, the high cost of producing an approved drug and as a result the very substantial sunk costs. Once approved, the economic returns from drugs are highly skewed. This follows from the blockbuster revenue model discussed above in which a high proportion of pharmaceutical sales arise from a small number of drugs. Economies of scale and scope have also been found to be important in the drug discovery process and economies of scope in development.

Economies of scale and scope

As outlined in Chapter 5, pre biotechnology drug discovery relied on large scale, relatively automated processes. For instance, in the absence of a detailed understanding of the underlying reasons for most diseases, large scale screening processes were undertaken to match a large number of drug candidates against a relatively small number of known disease targets.

Henderson and Cockburn (1996), employing firm level data for the period 1960-1988, have shown that there were economies of both scale and scope in drug discovery, indicating that there were gains to be made from spreading various fixed costs, such as investment in common search technologies over multiple projects, as well as gaining scope advantages from applying knowledge gained in one project to another. With respect to drug discovery, Henderson and Cockburn (1996) concluded:

> … larger firms benefit more from the economies of scope arising from the public goods aspect of knowledge capital accumulated within the firm, and from the ability to internalize information externalities within the firm. (p. 56)

Cockburn and Henderson (2001) also examined the possibility of economies of scale and scope in the drug development phase. Employing firm level data for 708 development projects for a similar period to that for discovery, 1960-1990, they found that there were economies of scope for development projects, but not economies of scale. Thus firms conducting diverse programs were more productive, suggesting that larger firms are able to efficiently transfer general knowledge about clinical trials across different projects within the firm (Cockburn and Henderson 2001, p. 1038). These economies of scale and scope have favoured large company structures.

Scale in sales and marketing delivers clear advantage. One indicator of this is that each major new drug is launched with a comprehensive and expensive global marketing campaign that benefits from the infrastructure already established. There is some evidence of increased sales productivity with company size. For instance sales per detailer typically rise with company size (Walton 2001, p. 90). Distribution capability is an important component of firm success. A survey of US pharmaceutical companies suggests that marketing and sales capability accounts for 42% of the variation in financial performance (George and Perrone 2001; Blumberg and Perrone 2001).

Sunk costs

As outlined in Chapter 7, drug discovery and development involves very sizeable sunk costs (Baumol and Willig 1981; Sutton 1991, 1998), arising from both its high cost and high rate of failure. For every ten drugs entering preclinical trial only one is approved and many more candidates are 'discovered' without entering preclinical trial. Thus on average for each approved drug, a pharmaceutical company expects to invest in nine drug trials that will fail. The cost of a single approved drug, including failures, is about $1.2 billion and the average time to gain regulatory approval from time of discovery is 12.5 years. More than half of this cost ($682 million) relates to the cost of financing the drug development over the extended discovery and clinical trial period. Of the remainder, $559 million, an average of $390 million or 70% of the expenditure per successful drug is spent on failed projects and is of little ongoing value to the pharmaceutical company. Thus approximately 70% of the cost of developing each successful drug is a sunk cost.

Skewed returns

The returns from drugs once approved are highly skewed. Grabowski and Vernon (1994a, 2001) have calculated the sales profiles for all new chemical entities (NCEs) for two periods 1980-84 and most recently 1988-92. This showed that half of the value of sales was in the top 10% of drugs. Comparing the sales profiles for the two periods, Grabowski and Vernon demonstrate that the peak sales achieved by the top decile drugs ($US3.2 billion in the later period) had more than doubled. They also calculated the NPV of drug sales for the earlier period. The NPV of a drug in the top decile of sales in the period 1980-84 was of the order of $US1000 million. They

compared the NPV of each decile with the estimated average cost of R&D for a drug, which they put at just over $200m for that period, showing that only the top 20% of drugs exceeded this amount.

These formidable economics, particularly those of sunk costs and skewed returns, help explain why pharmaceutical firms need to be of such size to finance and bear the risks inherent in drug development. Together with the economies of scale and scope these factors have all tended to encourage pharmaceutical firms to be of large size.

Profitability

Despite these challenges, simple measures have placed pharmaceutical companies at or near the top of industry profitability rankings (Scherer 1996). However estimating the profitability of pharmaceutical companies is complex, given the long lead times on the return on investment in R&D. Nonetheless estimates of return on capital which have attempted to measure true economic profitability still tend to suggest above average returns for the industry (Scherer 2000).

This above average profitability arises from a combination of demand and supply considerations. Each drug has a near monopoly position for the life of its patent period or at least until similar drugs enter the market. Given the combination of a powerful value proposition and the availability of reimbursement arrangements through insurers, the price of pharmaceuticals tends to be fairly inelastic (Scherer 2000). Berndt et al. (1995) provides an estimate of -0.69 for anti ulcer drugs over the period 1977 to 1994. The marginal cost of production is relatively low and pharmaceutical firms have strong incentives to spend heavily on promotion to shift out the demand curve for their product. Promoting drugs through detailers has been shown to be the most effective of a range of promotion activities undertaken (Berndt et al. 1995).

In summary, the cost structure of the pharmaceutical firm is characterised by economies of scale and scope, high sunk costs and relatively low marginal costs of production. High sunk costs arise from the combination of high R&D costs and high failure rates. Economies of scale and scope favour larger firms with diversified development projects. Returns from approved drugs are highly skewed but sufficient

given favourable demand conditions (e.g. relatively inelastic prices) to provide pharmaceutical companies with at least above average profitability.

Competitive strategy

The principal sustainable competitive advantage of pharmaceutical firms has been their core competency (Prahalad and Hamel 1990) in the discovery, development and distribution of innovative pharmaceuticals. The resource-based view, with its emphasis on strategic assets as the basis for sustainable competitive advantage, is as relevant to the competitive strategy of the pharmaceutical company as the start-up biopharmaceutical firm. The strategic assets may not have been of the same nature, but nonetheless the knowledge assets of the pharmaceutical companies comprising the combination of knowledge and experience in the details of the whole drug discovery, development and distribution have been quite formidable. The details of this strategy, such as which particular therapeutic classes were chosen over others, are beyond the scope of this thesis. However two points illustrate the centrality of the firms' core competence in pharmaceuticals and the importance of maintaining the value strategic assets.

Firstly the pharmaceutical companies have regularly tested the natural boundaries of the firm, through flirtation with diversification outside the core innovative pharmaceutical business. Pharmaceutical companies have regularly extended their activities into related markets and then drawn back (Chandler 2005). For instance in 1968, Merck purchased Calgon, a large water treatment enterprise and in 1993 purchased Medco for $6.6 million,[11] a large US pharmaceutical benefits management company. Other companies such as Pfizer, expanded into low tech toiletry and other products. In each case the companies shed these diversified activities, retreating to their core competencies in pharmaceutical discovery and development. Merck sold its water treatment business in 1993 and Medco in 2003 (Merck 2003). Pfizer refocussed on pharmaceuticals by divesting itself of its other activities in the 1990s (Chandler 2005).

Thus the resource based view has helped to define the corporate boundaries of the major pharmaceutical companies. Investment in other activities has proved to be a less

[11] New York Times, 20 August 2003.

effective use of capital and a distraction to management. It also failed to properly utilise the firms' considerable internal knowledge of the development and sale of pharmaceuticals.

Secondly, while diversifying into related areas has proved to be a strategic error, so too is the mistake of failing to maintain the value of the key strategic asset (Amit and Shoemaker 1993) represented by the number and quality of drug discovery and development projects. Pharmaceutical companies are knowledge intensive companies and the top 10 companies invested in 2005 an average 18.1% of their pharmaceutical sales revenue in R&D.[12] Their knowledge of the impact of drugs on disease and the capacity to take drugs through clinical trials is an essential core competency and, providing the necessary investment is maintained, a source of sustainable competitive advantage. In Chapter 6, the high cost of developing a successful drug was discussed and there have been periods when companies have failed to maintain the level of investment in R&D necessary to keep sufficient drug development projects in the product pipeline. Gambardella (1995) outlines the case of SmithKline which failed to reinvest the proceeds of its success with an anti ulcer drug, Tagamet, in upstream research and it was forced to merge with Beecham in 1989. More often than not mergers occur to cover weaknesses in the R&D pipeline.

Summary: Traditional pharmaceutical company business model

Using the framework of the business model, the key characteristics of the traditional pharmaceutical business model have been outlined and explained. Pharmaceutical companies have a powerful value proposition which combined with patent protection provides considerable pricing power. Marketing is complex because the consumer is not the key decision maker for the purchase of drugs and the revenue model is dependent on selling a disproportionately small number of drugs in huge volumes. The discovery and development of pharmaceuticals suffers from very high sunk costs but benefits from economies of scale and scope. The value chain is highly integrated with little interaction with a wider value network. Accordingly the favoured business model is one which is large and fully integrated.

[12] Author analysis sourced from Pharmaceutical Executive May 2006, Company 10-K SEC filings and annual reports.

The Impact of Biotechnology on the Pharmaceutical Company Business Model

The next sections analyse the way in which the pharmaceutical company business model has changed in response to the development of biotechnology. It follows the theoretical framework of the business model used in the section above.

The most serious impact of biotechnology has been on the pharmaceutical company value chain and integration into the value network. In other aspects of the business model, the key features are unchanged or in some instances the entry of biopharmaceutical drugs onto the marked is too limited to assess the likely impact.

Value proposition

There is little difference between the value propositions for biopharmaceuticals and traditional drugs. For the patient they offer the promise of still better treatment. For the other actors in the purchasing system, such as the physician and other 'gatekeepers', the same issues of efficacy and cost effectiveness apply. The main difference with biopharmaceuticals is that they are generally much more expensive than traditional small molecule drugs and are typically delivered by injection in a clinical setting. Approval for their use is likely to have a higher level of institutional intervention which may limit access.

Market segment and revenue model

Market segment

As indicated in the section on the traditional model, the marketing strategies developed by pharmaceutical companies have been developed to deal with the complexities of the approval process and pricing negotiations with government agencies and private insurers. The skills learned and marketing infrastructure available are likely to be immediately transferable to the marketing of biopharmaceuticals and accordingly many biopharmaceutical companies have entered into distribution arrangements with large pharmaceutical companies.

Many of the biopharmaceuticals developed to date are for use in hospitals, which will require the pharmaceutical companies to adjust the emphasis to niche rather than mass

marketing requirements. The existing distribution system is stressed in a number of ways and marketing increasing numbers of biopharmaceuticals may harbinger other changes. For instance pharmaceutical companies have been seeking alternatives to detailers as the major sales channel. The number of detailers has increased to the extent that, even if so inclined, physicians would only be able to allocate less than a few minutes per year to each one (AstraZeneca 2001). Other avenues are being explored such as the greater use of the Internet and more controversially direct-to-consumer advertising.

Revenue model

To date biopharmaceuticals have had only a modest impact on the pharmaceutical company blockbuster revenue model. Table 7.2 lists the 10 largest global pharmaceutical companies by sales of pharmaceuticals for 2005, together with total sales of those drugs with global sales exceeding $US1 billion ('blockbuster'). For comparison the table also lists sales of biopharmaceutical drugs and the number of blockbuster biopharmaceutical drugs.

To date the impact of sales of biotechnology derived drugs on total pharmaceutical sales is quite modest. Of total sales of $249 billion for the top 10 pharmaceutical companies only $5.4 billion[13] are biopharmaceuticals, of which three are blockbusters accounting for a large share of the total. Two are recombinant insulins and the other is an interferon. For these companies, sales of traditional pharmaceutical blockbusters remain the main feature of their revenue model, with 58.5% of their pharmaceutical sales represented by only 68 blockbusters. Merck had the highest dependency on blockbusters with a ratio of 73.2%. The highest selling blockbuster was the Pfizer drug Lipitor, with global sales of over $12.1 billion, 23.7% of Pfizer's total pharmaceutical sales.

[13] This sales figure is derived from an analysis of 104 biopharmaceutical drugs approved by the FDA since 1982. Sales are allocated according to the sponsor/applicant. The definition of biopharmaceuticals is derived from Walsh (2002). This analysis forms a significant part of Chapter 15 where the data sources are more comprehensively discussed. The inclusion of Roche and Abbott, ranked 11 and 12 by total sales respectively increases the total 'large pharma' sales of biopharmaceuticals to $7.7 billion.

Table 7.2 Blockbuster sales by major pharmaceutical companies, 2005

Company	Total pharma sales	Total blockbuster sales	Blockbuster ratio	Total no. of blockbuster drugs	Biopharma sales	No. of biopharma blockbusters
	$ billions	$ billions			$ billions	
Pfizer	44.28	28.28	63.9	8	0.05	
Glaxo	33.96	21.31	62.7	13	0.01	
Sanofi-Aventis	32.24	17.71	54.9	10	2.69	2
Novartis	24.96	9.28	37.2	5	0.05	
Astrazeneca	23.95	17.53	73.2	10	0.00	
J&J	22.32	15.34	68.7	7	0.05	
Merck	22.01	13.59	61.7	4	0.00	
Wyeth	15.32	7.74	50.5	4	0.05	
BMS	15.25	6.08	39.9	2	0.00	
Lilly	14.65	8.78	59.9	5	2.52	1
Total Top 10	248.94	145.61	58.5	68	5.38	3

Source: IMS, Pharmaceutical Executive May 2006, Company 10-K SEC filings and annual reports.

This illustrates that from a revenue point of view the paradigms of the traditional business model remain of great consequence to the current profitability of the largest pharmaceutical companies. However this revenue model is under threat from the expiration of patent protection of many of the largest selling blockbusters over the next 5 years. Thus pharmaceutical companies are expected to source an increasing proportion of their pipeline from biopharmaceutical drugs.

The main impact on the pharmaceutical business model has been for drug candidates to be sourced from outside the firm either by way of alliance or by acquisition. For the revenue model it means negotiations about royalties and milestone payments that have been of less concern in a more closed innovation system. The implications of these changes for the pharmaceutical business model forms an important part of the analysis presented in later in this thesis.

Value chain and value network

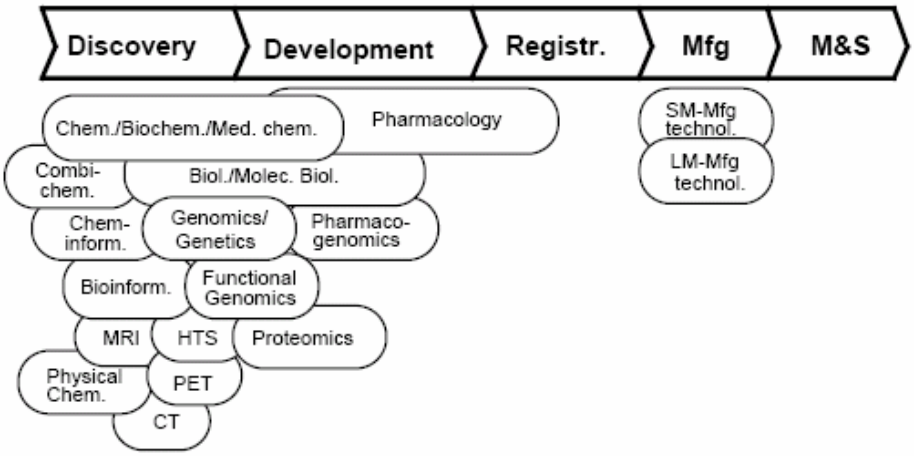
The impact of biotechnology on the pharmaceutical business model has been perhaps the greatest through its effect on the value chain and value network. The theoretical outline of the business model developed in Chapter 4 predicted that gaining access to the range of complementary assets would be central to the new business model of the pharmaceutical companies. Pharmaceutical companies have required access to new biotechnologies and the array of associated platform technologies outlined in Chapter

5. In doing so the companies have become practitioners of 'open innovation'. As will be documented in Chapter 10 they have been active participants in a large number of alliances that have involved a considerable range of both drug discovery and platform technologies.

The individual pharmaceutical company value chains have formed the basis of industry based value networks. As the specialist companies, representing the new technologies, have been integrated into the existing value chain through alliances, a value network between the pharmaceutical companies and the specialist companies has been formed (Cockburn 2004).

An illustration of how this new value chain developed is shown in Figures 7.1 and 7.2, sourced from Granberg and Stankiewicz (2002).

Figure 7.1 Pharmaceutical value chain: Major specialisations



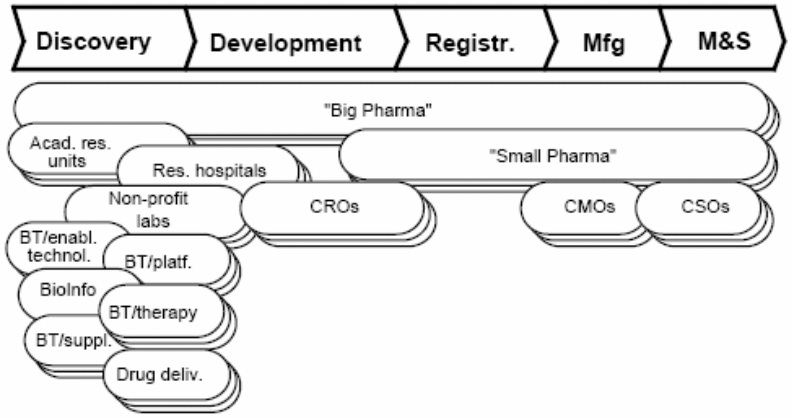
Source: Granberg and Stankiewicz (2002).

Figure 7.1 illustrates some of the main specialist biotechnologies in the drug discovery and production process such as molecular biology, combinatorial chemistry, genomics and proteomics at the drug discovery and development phase which were discussed in Chapter 5. It also shows at the discovery phase some of the main platform technologies, such as high through put screening (HTS) and bioinformatics.

Rather than originating within the large pharmaceutical companies, most of these innovations spawned a new set of specialist start-up companies (Figure 7.2). As Galambos and Sturchio (1998) comment that:

> It was, for instance, the first twentieth-century transition in this industry in which the initial stages of applied research and commercial development were centred in small, start-up companies rather than the large, well financed organisations that have for many decades been the primary innovators in pharmaceuticals. (p. 252)

Figure 7.2 Pharmaceutical industry value chain and the set of specialist firms



Source: Granberg and Stankiewicz (2002).

Figure 7.2 shows, in an industry value chain format, how these specialist technologies have generated an array of new specialist companies. These companies range from those focusing on drug discovery and development to those providing platform technologies. In addition, specialist companies in clinical trials (CROs), contract manufacturing (CMOs) and sales organisations (CSOs) have emerged. These companies comprise a complex value network providing services to one another, through alliances and market transactions as well as supplementing the knowledge base of the pharmaceutical companies.

While these two charts show the way in which the pharmaceutical industry structure has been transformed by the specialist firms, it also illustrates the way in which the integrated pharmaceutical company has remained active across the whole value chain. While the fully integrated model has become more complex, through the formation of many alliances, pharmaceutical companies have retained their capabilities across the

each of the major value chain activities of drug discovery, development, manufacturing and distribution.

A detailed study by Danzon, Nicholson and Pereira (2005) of some 1900 compounds, being developed by 900 pharmaceutical and biopharmaceutical firms over the period 1988-2000, suggests that drug development projects conducted in alliance structures by large firms have a higher success rate than internally managed projects. The study finds that while there was no advantage in Phase 1 for small and medium sized firms to engage in alliances, projects developed in alliance structures in Phase 2 and 3 were significantly more successful than those conducted internally. This suggests that there are positive returns to experience for large pharma in conducting later stage trials[14].

A subsequent study by Arora et al (2007) of 3000 drug R&D projects, further disentangles the advantages of alliances for large firms. In particular the study finds that the success of large pharma in developing drugs in alliances is in part due to the higher expected return thresholds for in licensing compounds set by established incumbents.

Arora, Fosfuri and Gambardella (2001a, p. 67) suggest that the industry is consolidating 'toward a structure in which an upstream industry of specialised technology suppliers has become a stable source of new products and technologies … to the downstream producers'. Orsengio et al. (2001) have also argued that the specialists have found it difficult to modify their structural position in this hierarchy and that the 'early entrants have enjoyed significant first mover advantages, precisely because they have been able to embody knowledge at a high level of generality' (p. 501).

Another dynamic is the constantly changing technological regime. Biotechnology and its potential application to produce new biopharmaceuticals are constantly evolving and the concept of 'dynamic capabilities' (Teece et al. 1997) has clear application to the predicament of pharmaceutical companies. They must be constantly evaluating

[14] Higgins and Rodriguez (2006) demonstrate the value of superior knowledge in the choice of acquisitions made by large pharma of biopharmaceutical firms. In particular knowledge about the firm gained in the course of an alliance reduces the asymmetrical information effect and leads to significantly better returns from the acquisition.

new technologies so as to adjust their internal and external competences to a rapidly evolving environment.

The impact of biotechnology on the value chain and network of pharmaceutical companies has been substantial. As predicted by the resource based view, the strategic assets of biopharmaceutical firms has been accessed through alliances, which has extended the scope of the pharmaceutical value chain and incorporated it into a complex value network. This is also consistent with transaction cost economics for irregular transactions involving specific assets with high levels of uncertainty. This applies to many drug development projects and platform technologies as well. In some cases however the pharmaceutical company may decide on integration. One prominent case is the purchase of Rosetta, a leading bioinformatics company, by Merck. Perhaps contributing to this decision was the need for frequent interaction to make maximum use of the new technology, which made acquisition more cost effective.

While the pharmaceutical company has adapted its value chain to the opportunities afforded by biotechnology, it has retained its integrated structure. This emerging relationship between the specialist firms and pharmaceutical companies has led some observers to suggest that the core competitive advantage possessed by global pharmaceutical companies is their organisational and resource management capabilities to develop and distribute new pharmaceutical products (Kay 2001).

Guedj (2005) further demonstrated the advantages of these organisational capabilities when he extended the analysis by Guedj and Scharfstein (2004), referred to earlier, to different governance structures, which demonstrated the superior performance of projects conducted internally with those conducted through alliances. Given their contractual nature, alliance projects had a greater tendency to proceed to Phase 2 than internally managed projects, but a lower level of ultimate success[15]. Mathews and Robinson (2008) have developed a theoretical model to demonstrate the superiority of alliance structures over integration in certain circumstances. Although on the face of it

[15] Arora et al (2009) in the previously referenced study, find that while for incumbent firms there is little difference in success for internally and in-licensed compounds, new entrants perform significantly worse with licensed compounds.

this may appear contrary to the findings of Danzon et al (2005) the two studies focus on different things. The Danzon et al study is focussed on the comparison between drugs developed internally by small firms with those developed in an alliance structure with large firms. The Guedj study in concerned with comparing drugs developed internally in large firms with those conducted in alliance structures in large firms. The Guedj findings highlight the advantages of the higher thresholds and disciplined decision making process of the large firm. The Danzon et al study demonstrates the complementarity of the alliance structure for both large pharma and smaller biopharmaceuticals.

Cost and profit potential

The costs of developing biopharmaceuticals, as indicated in Chapter 6, are about the same as for traditional pharmaceuticals. After various adjustments, DiMasi and Grabowski (2006) estimate that the cost is just 6% lower. Hoped for savings from more targeted clinical trials have not to date eventuated. This means that the economics of producing biopharmaceuticals, such as high sunk costs still holds. There is no evidence either that the extent of skewness in the returns is likely to be any different. Sales of a small number of blockbusters continue to dominate sales of biopharmaceuticals. These factors suggest that the advantages accruing to firms of large size will continue. Indeed overall most indicators suggest that pharmaceutical companies remain financially successful despite the challenges of modern biotechnology.

Economies of scope however may be less relevant in the post biotechnology period. Cockburn and Henderson's findings quoted earlier (Cockburn and Henderson 2001) related to the period 1960-90. These results have been challenged by the more recent and detailed study by Danzon, Nicholson and Pereira (2005) quoted earlier for the period 1988-2000. The Danzon et al study did not find evidence of returns to scope in the development period. However the samples of the two studies are quite different, with the Danzon et al study dominated by many small and medium sized companies, reflecting current industry structure, rather than the earlier period of large pharma dominance, characterising the Cockburn and Henderson study. However one of the findings of the Danzon et al study was that large pharma's experience of drug

development significantly enhanced success, providing another reason for the continuing importance of large pharma.

Aspects of the impact of biotechnology that are still to develop however, centre on the distribution of relational rents from alliances formed between pharmaceutical and biopharmaceutical companies, which may erode the returns from sales by the pharmaceutical companies. In addition the manufacture of biopharmaceuticals is typically more difficult and more expensive than small molecule drugs. This may also act to lower profitability from biopharmaceutical sales.

Competitive strategy

In the post biotechnology period, the main strategic issue facing pharmaceutical firms is how best to acquire access to the new technology. Galambos and Sturchio (1998) have identified two strategies adopted by large pharmaceutical companies to build absorptive capacity to gain access to the new genetics based rDNA technologies. One was to develop an expertise in a highly specific field with a view to generalising it across a range of therapeutic areas. The second was to build or acquire general capabilities through licensing and equity relationships with emerging biotechs.

Those at the forefront of the first strategy gained a competitive advantage. Eli Lilly as the first to contract both with the biotech, Genentech and university researchers at Berkeley to acquire access to the new recombinant technology for insulin. Insulin was the first recombinant drug approved by the FDA and secured Eli Lilly's continuing prominencee in that market. Similarly Merck contracted William Rutter at the University of California, San Francisco to produce the first recombinant vaccine, Recombivax for hepatitis B, approved by the FDA in 1986 (Galambos and Sturchio 1998; Chandler 2005). Being in this leading position gave Merck and Eli Lilly considerable advantages (Chandler 2005).

Roche adopted the second strategy, purchasing 60% of Genentech's equity for $2.1 billion in 1990, the first biotech to be established and one of the most successful. For late entrants however, access to the new technologies has been expensive. For instance, American Home Products (now Wyeth) paid $9.7 billion in cash for American Cyanamid in 1994 to provide it with a learning base for the innovative

technologies of the 1970s and 1980s (Chandler 2005, p. 227). Rather than outright purchase, a less expensive option was forming alliances with biopharmaceutical companies with the targeted technology. This is explored in some detail in chapters 9 and 10. Pharmaceutical companies have sought through alliances, both platform technologies and involvement in drug discovery projects.

However, the extent to which the large pharmaceutical companies applied their resources to acquiring access to the new technologies has presented most with a considerable dilemma. The relatively new, but pre biotechnology areas of microbial biochemistry and enzymology, have provided a steady stream of valuable new drugs. Companies were reluctant to abandon these projects in favour of those based on the much less well understood (and higher risk) recombinant rDNA technologies (Galambos and Sturchio 1998). Merck resolved this dilemma by focussing 'its use of biotechnology on supporting its core competencies in developing small organic molecules as drugs' (Galambos and Sturchio 1998, p. 268).

Conclusion

The purpose of this chapter has been to analyse the traditional pharmaceutical business model and examine how it has changed with the impact of biotechnology. It has demonstrated that the adoption of the large fully integrated business model is largely the outcome of the economics of traditional pharmaceutical drug discovery, development and distribution methodologies. This has included economies of scale and scope, sunk costs and the advantages of the integrated value chain. Pharmaceutical companies have a powerful value proposition, which combined with patent protection, provides considerable pricing power. Despite the difficulties and complexities of distributing drugs and the skewed returns achieved by the revenue model, pharmaceutical companies using this business model have achieved above average profitability

In considering the impact of biotechnology most of the reasons for the large integrated model remain. Moreover the impact has been muted by the relatively low proportion of biopharmaceutical sales as a proportion of total sales by the largest pharmaceutical companies. The largest impact appears to be on the structure of the value chain and value network. The value network has become significantly more complex as many

specialist technologies have become integrated into the pharmaceutical value chain. At the same time the pharmaceutical companies have remained substantially in control of the value chain, while gaining access to a wide range of complementary assets. It is not clear how the relational rents are being shared between the pharmaceutical companies and the specialists. Chapters 9 and 10 will examine in some detail the extent to which alliances have been formed between pharmaceutical and biopharmaceutical firms and later chapters consider how the relational rents for particular technologies may have been shared.

Although the proportion of new biopharmaceuticals drugs is increasing, the total numbers remain relatively small, so their sales remain a relatively small proportion of total sales. This means that the impact on key aspects of the business model including the value proposition, market segments, pricing and revenue model are still difficult to assess. Typically biopharmaceuticals are expensive to manufacture, about as expensive to develop and more likely to be targeted at smaller market segments. The effect on pricing and reimbursement of large numbers of biopharmaceuticals remains uncertain for the future of the business model.

Despite these challenges and uncertainties, the fully integrated pharmaceutical business model has endured, albeit in somewhat modified form. The powerful value proposition of the pharmaceutical companies can incorporate biopharmaceuticals and the advantages of scale, resources, in house manufacturing and global distribution reach do not appear to have been diminished by the new technologies.

Chapter 8. Biopharmaceutical Company Business Models

Introduction

This chapter examines the impact of biotechnology on the creation and development of biopharmaceutical firms. In Chapter 7 it was argued that one of the major changes to the pharmaceutical business model was the creation of a new value network comprising pharmaceutical companies and the multitude of firms, specialist in the many aspects of the new biotechnologies. As suggested in Chapter 5 these specialist firms were fostered by the highly fragmented biotechnology knowledge base.

In this chapter the concept of the technological regime, introduced in Chapter 5, is used to further categorise biopharmaceutical firms into two broad classes, drug discovery and platform technology firms. It argues that the different technological basis of these two types of firms helps explain their adoption of two quite different business models. Employing the framework developed in Chapter 4, an outline of the characteristics of the two contrasting business models is proposed and implications drawn for the different outcomes of the two business models.

Brief Outline of Industry Structure: Biopharmaceutical Firms

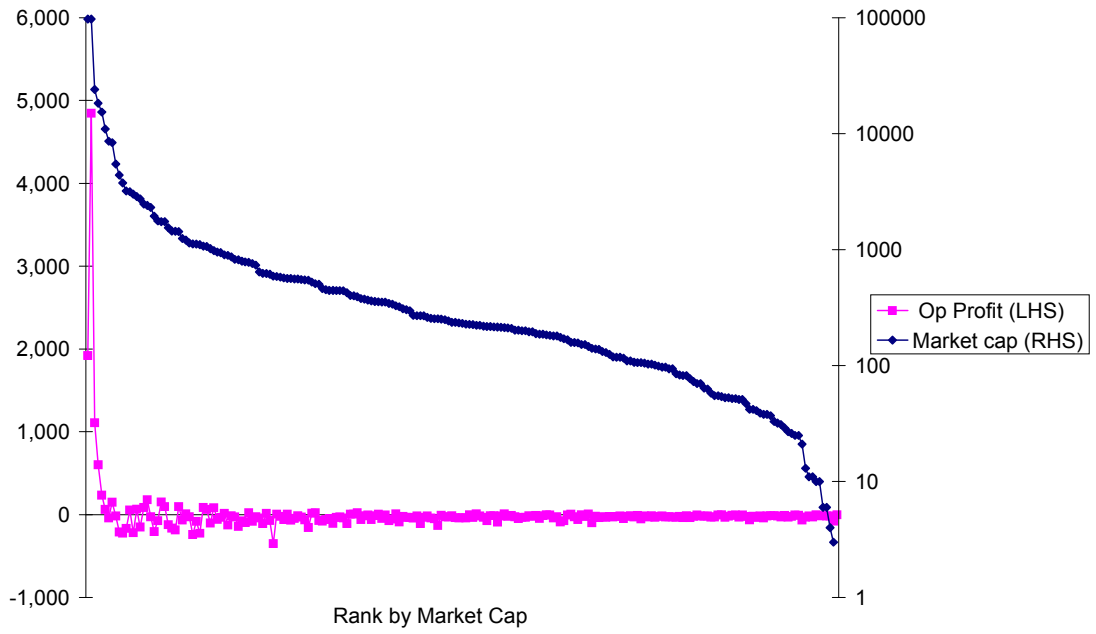
In 2004 there were an estimated 4416 biotechnology companies globally of which 641 were public companies. The public companies had revenues of $54.6 billion and R&D expenditure of $20.9 billion. The US companies dominate, accounting for 78.2% of revenues and 75.2% of R&D expenditure (Ernst and Young 2005). Of course not all of these companies are focussed on human therapeutics, some specialise in agriculture, veterinary and industrial applications. Nonetheless human therapeutics represents about 80% of the industry (Lähteenmäki and Lawrence 2006).

The performance is quite diverse and therefore averages tend to conceal this diversity. Few companies are profitable. For the vast majority, R&D expenditure exceeds revenue generated either through contract research, product sales or fees. Only a handful have substantial revenues from drug sales, make significant profits and have market caps approaching the larger pharmaceutical companies.

Figure 8.1 shows the market capitalisation and operating profit of 215 selected public biopharmaceutical companies listed in the United States in December 2005. These companies account for more than 90% of R&D expenditure by US public biotechnology companies. The stock market performance of these companies is tracked by the biotechnology database company Recombinant Capital (in its *Signal* magazine) (Degami and Van Brunt 2006).

It shows the enormous diversity of size, at least as measured by market capitalisation, of the 215 selected firms which ranges from almost $10 billion to zero. The majority of companies (59.5%) have a market cap of between $1000 million and $100 million. Sixteen per cent have a market capitalisation of over $1000 million. Only a handful of the largest companies generate a significant profit, just three exceed $1 billion. Most of the remainder make a loss, although on average it is relatively small, $35 million, of which the largest component is expenditure on R&D, $42 million on average.

Figure 8.1 Selected US biopharmaceutical companies ranked by market cap, December 2005 ($ million)



Source: Degami and Van Brunt (2006); author analysis.

The Technological Basis of Two Distinct Business Models

In Chapter 5, a technological regime was defined as a particular combination of the characteristics of the knowledge base, degrees of cumulativeness of technological knowledge together with the particular appropriability and opportunity conditions. (Orsengio 1989; Malerba and Orsengio 1990, 1993). Orsengio et al. (2001) suggest that two technologically based search regimes are distinguishable in biopharmaceutical research:

> The first regime is essentially based on biological hypotheses and molecules that tend to be specific to given fields of application (co-specialised technologies), while the second regime is characterised by the emergence of new generic tools (transversal technologies). (Orsengio et al. 2001, p. 488)

Examples of co-specialised technologies are those drug discovery technologies discussed in Chapter 5, such as recombinant DNA, interferons and monoclonal antibodies. Each of these technologies has been derived from a new set of scientific hypotheses that have produced a particular class of drugs. On the other hand, transversal technologies are generic tools, providing a common platform for a range of drug discovery and development projects. In Chapter 5 they are referred to as platform technologies, such as high throughput screening, combinatorial chemistry, gene expression and sequencing.

As will be considered in some detail, the two regimes, platform technology and drug discovery, have dissimilar appropriability and opportunity conditions that leads their paths to commercialisation to be quite different. Platform technologies can be brought to market quickly (Casper and Kettler 2001) compared with the drawn out drug discovery and development process. Partly as a consequence they also have lower short term risks, R&D costs and capital requirements (Gambardella et al. 2000).

In Chapter 7 it was argued that each breakthrough technology, such as each new co-specialised and transversal technology, led to the establishment of a ‘cohort’ of small specialist companies based on their expertise in a particular technology (Galambos and Sturchio 1998). Therefore it is possible to classify these specialist firms according to one of these two identifiable technological regimes:

- a set of ‘platform technology companies’, developing generic or transversal technologies to improve the efficacy of the drug discovery and development process for a range of pharmaceutical and biopharmaceutical client companies; and
- ‘drug discovery companies’ using a set of co-specialised breakthrough techniques in drug discovery to engage in drug discovery and development.

These fundamental differences in technologies have had a major influence on the business model adopted.

Support for this view comes from Fisken and Rutherford (2002) whose work on European biotech business models distinguished between a product business model, generally followed by the drug discovery and development companies and a platform or tool business model generally adopted by companies commercialising a platform technology.

By co-specialised technologies Orsengio et al. (2001) mean ‘research hypotheses and techniques that tend to be specific to particular domains’ (p. 486). This is clearly a different use of co-specialisation from that of Teece (1986) who refers to co-specialised complementary assets developed between alliance partners where the nature of the asset establishes a co dependency between the partners. Nevertheless the two concepts are related.

An alliance involving a co specialised technology is likely to develop a co-specialised asset whereas this would appear to be less likely with a transversal or generic technology. Alliances formed by platform technology companies with weaker co dependency may be less successful because of the less exclusive relationships established. This is an issue to be discussed further in the context of the relative success of the platform technology business model.

Based on the theoretical work in Chapter 4, the following section provides an outline of expected differences between the two biopharmaceutical business models, one based on drug discovery and the other on platform technologies. The discussion follows the form of the Chesbrough and Rosenbloom (2002) business model.

A Comparison of Drug Discovery and Platform Technology Business Models

Value proposition

The value proposition is based on the value created for users of the technology product or service offering. This value is derived from the firm's strategic assets, ones that are by definition hard to imitate, substitute or trade, from which it derives competitive advantage (Amit and Shoemaker 1993). For a technology company, this can mean a unique technology, developed by the firm, and supported by appropriability regime. For start-up biopharmaceutical companies this competitive advantage is derived from the commercialisation of a breakthrough biotechnology innovation, based on an initial stock of knowledge, frequently linked to university research (Kenney 1986; Orsengio 1989; Zucker et al. 1998).

Deeds et al. (1999) develop a model of new product development for biotechnology firms at the time of public offering, which indicates that the quality of prior research, conducted by the firm's scientific team, is a significant variable. A variant of the model, but with market capitalisation at IPO as the dependant variable, also indicates that research quality, as measured by publication citations of the scientific team, is a significant variable (DeCarolis and Deeds 1999). A wide variation in the initial stock of knowledge is therefore one variable explaining the difference in the financial performance between biopharmaceutical firms.

The nature of the value proposition however, is likely to be quite different as between drug discovery and platform technology companies. The drug discovery company offers to the market, expertise in a class of drugs, or perhaps its discovery of a single drug candidate. Following development of the drug candidate its value proposition is analogous to that of a pharmaceutical company discussed in the previous chapter. The value of the drug will depend on its efficacy relative to other drugs in its class and the size of the potential market segment.

The value proposition of a platform technology company is likely to be somewhat different. Its product is an intermediate good or service which depends for its value on its impact on the efficiency of the drug discovery and development process. The

manner in which the technology is offered may also have a bearing on its value. For instance whether the technology is embodied in a product or a service or whether it is marketed exclusively or non-exclusively have different implications for the target market segment and revenue model as discussed below.

For each type of business model appropriability is a key issue, either to gain full value from the commercialisation of the technology, or an economic share, should commercialisation proceed through an alliance (Teece 1986; Gans and Stern 2003). The drug discovery company is likely to hold a patent over its discovery, and appropriability will depend on the security of the patent. The platform company may rely on a range of IP protection regimes including patents, but its generic nature may make appropriability less secure. The more successful business model will be one that adjusts its offering to maximise the likelihood of appropriability. For instance, the IP for a product may be more easily protected than a service offering.

Market segment and revenue model

Following from the value proposition, the resource based view suggests that the market segment targeted should be the one to maximise the value of the firm's strategic assets. For the drug discovery company, it may have no final product but rather a number of drug candidates in various stages of development. The choice between these depends on their ultimate comparative value to the target patient group. Alternatively the market segment may be pharmaceutical or larger biopharmaceutical companies. The choice of partner will be the one which both provides most support for further development and the greatest share of the potential relational rent. For the platform technology company, the target market is likely to be other biopharmaceutical companies or pharmaceutical companies.

The specialist company must be able to deliver value in an economic sense and be able to appropriate adequate returns on its investment to support its ongoing R&D program. While this is the central function of the business model, (Chesborough and Rosenbloom 2002) the complementary task of the revenue model is to devise the means by which these returns are to be appropriated to the firm (Amit and Zott 2001). The design of the revenue model is of paramount importance in determining the success of the firm. In part this hinges on the appropriability of the underlying IP

(Teece 1986; Gans and Stern 2003). The firm needs to be able to adequately protect its IP from competitors and collaborators.

The appropriability conditions for platform technology products and drugs are likely to be quite different. IP protection of generic technologies is likely to prove more difficult than for drugs, which are more readily patentable. This means that designing the revenue model for platform technologies, including such considerations as product exclusivity and licensing or sale, needs to take account of these appropriability conditions. However this may prove to be difficult. The revenue model for platform technology companies may ultimately simply reflect the nature of the technology and the weak appropriability of products and services offered. The revenue model is more likely to include 'fee for service' type payments as part of technology access licensing fees. Such services, with high sunk costs and low marginal costs, are easily undercut by competitors if the IP protection is weak. Accordingly, gaining an economic share of the value created has higher risks for a platform technology company, unless its appropriability is strong, than for a drug discovery companies.

A further consideration for the revenue models of specialist companies participating in value networks is gaining an adequate share of relational rents generated in alliances. In Chapter 3 it was suggested that this depended on both the 'tightness' of the appropriability regime and the relative scarcity of the complementary assets (Teece 1986; Gans and Stern 2003). Again these conditions are likely to favour drug discovery companies over platform technology companies for the reasons outlined above. The challenge for platform technology companies is to structure their business and revenue models to overcome these weaknesses.

Value chain

For biopharmaceutical firms a full value chain is one that takes a technology from discovery, through development to manufacturing and distribution. The value chains of the two models are likely to be quite different. The drug discovery company model is likely to have a truncated value chain, with research and perhaps early stage clinical trials as its main activities. Drug discovery companies typically lack the resources to establish their own manufacturing and distribution activities. These can be expected to be contracted out or the subject of alliances. The value chain is likely to incorporate a

number of complementary assets. These are likely to range from a collection of platform technologies to the aforementioned manufacturing, distribution and possibly contract clinical trial capabilities.

The value chains of platform technology companies can be expected to be relatively integrated, with manufacturing and distribution being an integral part of the development process. The expectation that the value chain will encompass the full range of activities arises from a number of factors. The first is that platform technologies are generally developed more quickly than drugs and at a much lower cost. Nor do they require the same degree of regulatory approval. Iterative feedback from marketing personnel is a very important input to product enhancement. The distribution task is less daunting and the number of individual customers fewer than for drug distribution. Moreover, as for the fully integrated pharmaceutical firm, the advantages of internalising the marketing function apply. The product or service is technically sophisticated and specialised, so internal information transfers about the products' attributes are more efficient than contracting out. The product or service appropriability regime is likely to be lower than for medicines and therefore, as predicted by Teece (1986), integration of complementary assets such as marketing is a lower risk strategy.

Value network

In the open innovation paradigm (Chesbrough 2006), the value network connecting various suppliers to one another and ultimately to their customers is of central importance to the innovation process. In Chapter 7 the value network from the pharmaceutical company perspective was outlined. This illustrated the explosion in the number of technology specialists, which now form part of and contribute to the value network for the pharmaceutical companies. However specialist technology companies contributing a particular advanced product or service to the industry value network, also requires a range of complementary assets. These will include, both other specialised transversal and co-specialised assets (Orsenigo et al. 2001), as well as a range of complementary generic assets such as finance, manufacturing and perhaps marketing services (Teece 1986).

Platform technology companies are likely to be participants in a complex value network of technology specialists and downstream technology users (Gambardella et al. 2000). The specialised nature of platform technologies is likely to require support from other specialists, as well collaboration with potential customers. Following from the co-specialised nature of the technology, the drug discovery company is likely to have a smaller network of which its drug development alliance partners such as large pharmaceutical companies are likely to be the most significant.

The large network of platform technology companies can be expected to make the task of obtaining an economic share of relational rents more complex and therefore potentially more difficult. As discussed in Chapter 3, participation in such networks is essential to obtain access to complementary assets, but this puts gaining an economic return on the firm's strategic assets at risk. The appropriability of its products and services is crucial to the sustainability of the firm's competitive position.

Both types of companies can be expected to adopt a flexible approach to adjusting their competencies to the changing technological environment in which they operate, as predicted by the dynamic capabilities approach (Teece, Pisano and Shuen 1997). To this end, it can be expected that they will use alliances with companies offering new technologies as a way of gaining access to these new technologies. Those with the greatest absorptive capacity can be expected to do this most effectively

Cost and profit potential

As previously discussed, the evidence to date suggests that developing biopharmaceuticals are no less costly and just as uncertain as developing traditional pharmaceuticals. While for the drug discovery company, these risks can be shared through alliances, this places the company in a dependent position with respect to its alliance partner in gaining an appropriate share of the revenue. This has an impact on its profitability. Nonetheless the rewards from drug discovery can be high, and if the drug discovered for instance is a blockbuster, then the royalty stream may be sufficient to sustain the company into the future.

As Dierickx and Cool (1989) highlight with particular reference to the pharmaceutical industry, this process is not continuous, but highly stochastic and discontinuous,

which they describe as the 'jackpot model'. As pointed out in Chapter 5, the drug development process is both uncertain and product development is drawn out. Technological breakthroughs are infrequent.

Platform technologies typically require less capital to be developed and are expected to have a lower risk of failure (Gambardella et al. 2000). Nonetheless maintaining the competitive value of the technology is relatively high, as a result of the need to sustain ongoing levels of R&D investment. This may reduce the profit potential of platform technology companies.

As illustrated earlier in the chapter, most biopharmaceutical companies are unprofitable. Few have sales of significance and reflecting the research intensive nature of their operations all have high R&D costs.

Table 8.1 below provides a set of financial indicators for the selected public biopharmaceutical companies considered earlier in the chapter. They have been classified according to their specialisation, either by therapeutic area (disease focus) or platform technology. Excluded from the table is the handful of the large profitable biotechs which would otherwise overwhelm the other companies.

A number of observations may be made about these company groups. The first is the similarity on average of the two groups representing the two specialist company business models. On average each broad group has a somewhat similar market cap (about $610 million for platform technology companies and $525 million for drug discovery companies) and in 2005, invested a similar amount in R&D ($48 million for platform technology companies and $39 million for drug discovery companies). However on average, platform companies generate more than twice the revenue, $102.1 million, compared with $46.1 million for the drug discovery companies and consequently make a loss on average of about 60% of the amount, $23.9 million compared with $40.2 million for drug discovery companies. Few companies in either group make a profit, approximately 9% of the therapeutic group and 23% of the platform companies.

Table 8.1 Financial indicators of selected biopharmaceutical companies, 2005, expressed as an average per company

Recap group	No. of companies	Market cap ($m)	R&D ($m)	Revenue ($m)	Operating profit ($m)
Platform technology					
1st generation genomics	5	1079.4	147.8	138.2	-137.8
Chemistry	10	538.5	44.2	70.8	-25.9
Delivery	22	856.8	50.0	164.9	-13.9
Diagnostic/image	21	509.2	17.7	105.8	12.7
Genomic supply	10	492.1	20.5	76.1	-18.3
Genomic targets	12	397.6	70.6	41.3	-59.1
Screening	7	435.4	64.1	53.4	-55.7
Total platform technology	**87**	**609.9**	**47.7**	**102.1**	**-23.9**
Therapeutic area					
Autoimmune	9	873.0	60.1	65.5	-50.8
Cancer	44	568.5	36.8	43.1	-40.7
Cardiovascular	9	582.9	46.9	23.4	-67.7
CNS	15	637.1	53.9	96.1	-44.4
Infection	17	323.5	33.9	34.6	-22.6
Gene/Cell therapy	12	144.5	21.9	9.6	-25.8
Metabolic	11	703.2	44.3	26.0	-55.6
Wound	4	222.5	4.8	111.5	-13.5
Total drug discovery	**121**	**525.0**	**39.1**	**46.1**	**-40.2**

Source: Degami and Van Brunt (2006).

The similarities in the averages between the two groups, drug discovery and platform technology, conceal widely divergent results within each group. For the averages presented in the table the standard deviation ranges from 1.5 for platform technology companies to 2.3 for drug discovery companies, lending some support to the view that platform companies have a lower risk. They are at least less divergent in their performance.

Competitive strategy

Sustainable competitive advantage is only achieved by maintaining the innovativeness of the firm and producing a steady stream of innovations. Dierickx and Cool (1989) conceive of the knowledge of firms as both a stock and a flow. The stock is accumulated through the flow of new knowledge into the firm generated by R&D activity. Knowledge is lost to the firm through obsolescence or irrelevance, such as from shifts in consumer requirements. An important part of corporate strategy is to choose the time paths over which this stock is accumulated. These knowledge stocks deliver competitive advantage because they are not easily imitable or tradeable, in contrast to commonly available resources available on the factor markets (Dierickx and Cool 1989). The accumulation of such strategic assets by the firm requires a core

competency (Prahalad and Hamel 1990) in developing a steady stream of innovations and adjusting its capabilities in response to rapid technological change, future competition and markets (Teece, Pisano and Shuen 1997).

The nature of the assets of the two types of firms, although both grounded in technology is different. This has implications for the manner in which the value of the strategic assets is protected and enhanced. Typically the drug discovery company can be expected to have a core competency in the application of a particular drug discovery technology. The value of its strategic assets however varies with the progress of its drug candidates through the drug pipeline. Progress lifts value, while failure may result in a swift decline in value. Drug discovery companies can be expected to progress multiple projects through the pipeline to protect against a single failure. While drug discovery companies are always under threat from companies which may produce better drugs, the relatively open patenting and approval process means that the competitive universe is reasonably well known and generally only drug candidates with significant advantages are pursued.

Platform technology companies typically face a different environment, particularly where appropriability is weak. Platform technology products and services generally have a relatively short product cycle, which means that platform technology companies can be expected to be under constant pressure from competitors to improve their service and product offerings. Speed to market will be an important factor in success (Casper and Kettler 2001). This implies the need for continuous R&D investment which can be draining on the company's resources. Sales revenue therefore needs to be ramped up relatively rapidly after product launch.

As previously discussed a key component of the competitive strategy is to obtain an economic share of the relational rents. For drug discovery companies the focus of its strategy is on the terms of alliances with larger partners such as large pharmaceutical companies. For platform technology companies its competitive strategy is to protect the value of its strategic assets in a complex networked environment.

A question raised in the literature is whether a competitive strategy can be adopted that overcomes deficiencies in the quality of the initial strategic assets. Cockburn,

Henderson and Stern (2000) developed a simple econometric model to disentangle the source of competitive advantage in 'science driven' drug discovery between the competing theories of Porter's structuralist analysis and the resource based view. The model attempts to distinguish between the view that competitive advantage is largely determined by firm specific 'historical' factors or the firm's strategic response to a changed environment or profit opportunity. It does so by examining intermediate outputs of scientific discovery – patents, number of scientific papers published by staff, number of authors, and links between publications and patents. The results suggest that while the initial conditions of the firm are a very significant factor in the adoption of science based drug discovery methodologies, there is also evidence of 'catching up' by lagging firms, suggesting that strategic intent also has a role.

One of the distinctive features of biopharmaceutical companies is the frequency of business model failure, when it becomes clear to the firm that the current business model is likely to fail and the internal and external competencies need to be reconfigured (Teece Pisano and Shuen 1997). It is an extreme form of competitive strategy, when a firm completely transforms its business model by closing its existing operations and acquiring a new capacity to create new strategic assets, such as through the recruitment of a new scientific team or the IP of another company. This typically occurs when the commercialisation of a particular technology completely fails. In drug discovery companies this may be when the particular discovery technology fails to produce predicted outcomes in clinical trials and in platform technologies when revenues generated clearly no longer support continued R&D.

Table 8.2 below outlines the key differences between the two business models.

Table 8.2 Business model functions: Drug discovery and platform technology companies

Function	Drug discovery	Platform
Value proposition	Development of drug to reduce disease using particular expertise/ technology	Development of technology to increase efficacy of drug discovery and/or development process
Market segment	Drug sold to a particular patient group or licensed to a pharmaceutical coy for further development. Revenue model based on product sales or royalties	Technology likely to be licensed to a number of pharma/ biopharma coys. Revenue model based on fee for service or technology may be embodied in a product and sold to pharma/biopharma coys
Value chain and complementary assets	Focus on drug discovery phase. Complementary assets likely to include certain platform technologies and pharma development and distribution capabilities	Encompass full value chain from technology discovery and development to marketing and distribution. Requirements for complementary assets may be large to supplement own technology specialisation
Cost structure and profit potential	High cost structure, high risk, very high profit potential if successful	Moderately high ongoing cost structure, lower risk and more modest profit potential than drug discovery
Value network	May be a modest sized value network of platform tech and partner pharma coys. May include CRO and/or CMOs	Likely to be a large and complex network of other technology companies and client pharma/biopharma coys.
Competitive strategy	Maintain value of strategic assets in drug disc and dev. expertise	Maintain value of strategic assets in platform tech through constant product or service improvement

Implications of the Two Business Models

This comparison of the two business models suggests two quite different outcomes for firms adopting the two models. The platform technology company needs to invest less to launch its product, has a potentially broad market and faces lower risk. Its challenges however are that its products may have weak appropriability, a possibly poor revenue model and relatively high cost structure due to ongoing R&D expenditure. This means that the design of its business model is likely to be critical to its success. It needs to take care to develop products for which the IP can be protected and to participate in the value network in such a way so as to maximise its share of relational rents. Platform companies are likely to face a highly competitive environment. Their strategy is likely to need to be devoted to maintaining the competitive advantage of their strategic assets, through on going investment in their products.

On the other hand, the drug discovery business model faces challenges associated with the high cost and uncertainty of drug development but this is offset by the potentially high profitability of a single success. It has the advantage of a stronger appropriability regime, with the patenting of drugs likely to be more effective than that for many platform technologies. If the drug is a failure then the firm may also fail, unless it can achieve support for another drug project. However if its drug is a success, then the firm may achieve the size and sustainability evident in the handful of biopharmaceuticals with significant profits shown in Figure 8.1.

The Successful Drug Discovery Business Model

What happens when a drug discovery company is successful at creating a blockbuster? Does it remain as a drug discovery company generating drug candidates in alliance with pharmaceutical companies or does it seek to become a fully integrated firm? The theoretical and empirical evidence to date suggests that it should seek to become a fully integrated firm. The advantages of the fully integrated pharmaceutical company business model apply equally to successful drug discovery companies. Each is likely to have substantial sunk costs, to benefit from economies of scale and scope and the transaction cost efficiencies of vertical integration. The issue for successful companies is to achieve the size threshold for these factors to be influential. This requires drug discovery companies to have been successful in developing one or more 'blockbuster' drugs that generate sufficient surplus to have the capacity to invest the proceeds in developing a sustainable product pipeline and distribution and other infrastructure. This suggests that there is a further business model for 'large biotechs', which is based on a biopharmaceutical technological regime but is fully integrated with its own drug discovery, development, production and distribution capabilities.

This proposition is further tested later in the thesis. Later chapters illustrate how the drug discovery company business model is transformed into a large fully integrated one and because of the central importance of the large biotech as a generator of significant value in the sector, the large fully integrated business model as adopted by biopharmaceutical companies is defined as a separate business model for the purposes of later analysis.

Conclusion

Arising from its disaggregated nature, as discussed in Chapter 5, it would be expected that the commercialisation of the biopharmaceutical knowledge base would be carried by a large number of predominately small firms. There are thought to be over 4000 biotechnology firms globally of which perhaps 3500 specialise in human therapeutics. Even the largest of these are predominately relatively small companies. An analysis of 215 biopharmaceutical firms from the Recap database, representing over 90% of biopharmaceutical R&D, indicates that the market capitalisation of 60% of the firms is between $100 million and $1000 million and 24% less than $100 million.

This chapter argues that there are two different biopharmaceutical business models based on two distinct technological regimes. One is a platform technology business model based on generic or transversal technologies, while the other is a drug discovery business model based on co-specialised drug discovery technologies. Analysis of the two models within the Chesbrough Rosenbloom framework identifies the likely sources of significant differences in the sustainability of the two models.

In particular this analysis has indicted potential areas of weakness for platform technology companies relating to weak product appropriability, and an associated poor revenue model and relatively high cost structure. The drug discovery business model faces challenges associated with the high cost and uncertainty of drug development, but this is offset by the potentially high profitability of a single success. In general drugs are more readily patentable and the rents received more easily defended.

This raises the question of whether the successful drug discovery firm transitions to the large fully integrated business model adopted by the large pharmaceutical companies. The evidence developed later in the thesis supports this and accordingly the large fully integrated biopharmaceutical business model is treated as a distinct business model for the purposes of subsequent analysis.

Chapter 9. An Overview of Trends in Biomedical Alliances

Introduction

This chapter provides an overview of biopharmaceutical alliance formation from 1990 to 2005. In Chapter 3, it was argued that alliances and networks were essential to the innovation process (Chesbrough 2003; Chesbrough et al. 2006) and a number of reasons were offered for alliance formation. These included cost and risk minimisation and access to complementary assets that are specialised or co-specialised.

Chapter 5 described the evolution of the traditional pharmaceutical technology and traced the development of modern biotechnology. It suggested that the two technologies represent different technological regimes which represent a significant knowledge divide between the newly emerging biotechnology and the small molecule technology of the traditional pharmaceutical firms. In addition one of the characteristics of the biopharmaceutical knowledge base is that it is highly disaggregated and dispersed through many firms. This means that no single firm is able to encompass the entire knowledge base. Networks and alliances are required not only to bridge the knowledge divide between pharmaceutical and biopharmaceutical firms, but also to connect the disaggregated biopharmaceutical knowledge base

In chapters 7 and 8, both pharmaceutical and biopharmaceutical business models predicted a high demand for complementary assets. It was expected that pharmaceutical companies would have an increasing propensity to establish alliances to meet their requirements for new technologies. The role of biopharmaceutical companies in alliance formation was expected to rest on two technological regimes, specialised platform (or transversal) technologies and co-specialised drug discovery technologies.

This chapter seeks firstly to provide empirical evidence for the increasing role of alliances in the biopharmaceutical innovation process and secondly to examine in

some detail the nature of the technologies being transferred through alliance formation. In particular it seeks to determine whether the distinction between platform and drug discovery technologies can be supported by examining the nature of the alliances formed.

Empirical Evidence for the Increasing Role of Alliances in the Innovation Process

Recap database

A great deal of the empirical work presented here is based on an analysis of a database of biopharmaceutical alliances drawn from the Recap biotechnology alliance database,[16] which contains details on about 25,000 alliances. It seeks to be a comprehensive global source of information about biotechnology alliances, but does not include informal alliances (Hagedoorn et al. 2000). Alliances listed on the Recap database are classified by various criteria. This includes the types of alliance partners, the technology and disease involved, the stage in the drug pipeline at signing of the alliance and the nature of the alliance (research, licensing etc) together with as many of its financial details as are publicly available, such as its size, milestone payments and royalty rates. Although some of the alliances listed on Recap date back to the 1970's, this analysis is based on the period since 1990, which by cross checking, is judged to be the most comprehensive.

As suggested by the definition of strategic alliances offered by Kang and Sakai at the OECD, quoted in Chapter 3 and reproduced in part below, alliances encompass a wide range of inter firm linkages including ,

> … joint ventures, minority equity investments, equity swaps, joint R&D, joint manufacturing, joint marketing, long-term sourcing agreements, shared distribution/services and standards setting. (Kang and Sakai 2000, p. 7)

A feature of the Recap database is the broad treatment of alliances. Those included range from research collaborations to equity investments and various asset purchases. It also includes alliances that cover the entire value chain from early stage discovery to later stage marketing and distribution agreements. One difficulty with such a broad

[16] Recombinant Capital, see www.recap.com

treatment is that the boundary between alliance and merger or acquisition is blurred. For instance in acquiring access to a technology, companies may enter into a licensing arrangement, or they may choose to acquire the company or business unit outright. Each such transaction would be recorded as an alliance on Recap. However, in terms of the OECD definition, the second transaction would not be considered an alliance. Accordingly for this analysis those classified as 'mergers and acquisitions' have been excluded.

Recap is a biotechnology database and although its overwhelming focus is on medical applications, it includes alliances involving various agricultural applications of biotechnology. Since the focus of this thesis is on the use of biotechnology for medical purposes, alliances classified as involving agriculture or livestock have been excluded from the analysis.

Recap has other shortcomings. As would be expected in such a large database, it contains occasional errors, such as in the misclassification of particular alliance attributes, but these are not sufficiently numerous to distort the overall results. Also Recap is limited to publicly disclosed alliances and there can be long lags in the addition of new alliances to the database. This means that alliance activity that is undisclosed is not included and some newly formed alliances may take over 12 months to be added to the database. However, by cross checking with other sources, it does appear to be remarkably comprehensive.

Recap classifies alliances according to the parties involved. These are divided between pharmaceutical companies, biotechs, and universities. Pharmaceutical (or 'drug') companies include both those identified as large pharmaceutical companies in earlier chapters and smaller regional or more specialist firms. 'Biotechs' include large biotechs, drug discovery and platform technology companies. 'Universities' also include research institutes and government research organisations. For purposes of gaining an overview of the longer term trends these categories are adopted.

In most alliances there is a 'client', which directs and pays for the work done and another party, called here the 'developer', which undertakes the R&D work and receives payment. Some alliances have high degrees of cooperation, where these

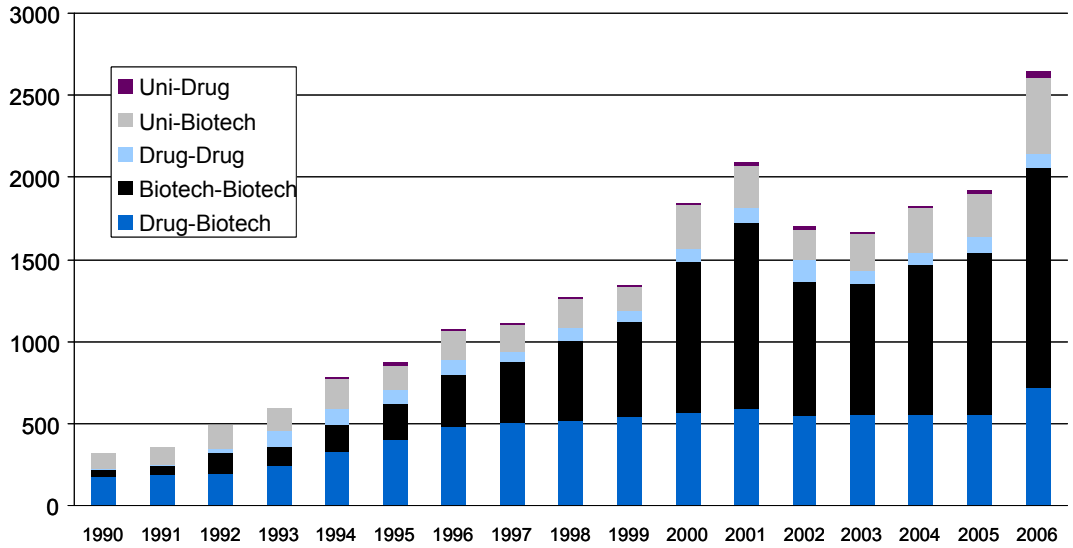
distinctions are less clear or where payment may be in kind. In many alliances payment is contingent on success and made over an extended time. Some alliances bring together more than one company in the role of client or developer.

Nonetheless for most alliances the distinction between the 'client' party and the 'developer' party is clear and Recap classifies the alliance parties based on this distinction. For instance in most alliances between pharmaceutical companies and biotechs, the pharmaceutical company is the client and the biotech the developer.

Number of alliances

The total number of biopharmaceutical alliances classified by the parties involved and by date of commencement is shown in Figure 9.1. This shows the significant increase in the number of global alliances that have been formed in the period since 1990. The number appeared to have peaked in 2001, however recent analysis of the database indicated that the number had recovered in 2006. Because the number for 2006 may be incomplete the analysis in this chapter is based on 2005 data.

Figure 9.1 Number of global biopharmaceutical alliances, 1990 to 2006



Note: Data for 2006 may not be complete.
Source: Recap, February 2008.

There are a number of notable aspects to Figure 9.1. The first is the growth in the number of alliances, which totalled 310 in 1990 and reached 1912 by 2001. This growth has three aspects. The first is the rapid growth, between 1990 and 1996, in

alliances between pharmaceutical (drug) companies and biotech companies from 176 to 456, after which the number broadly stabilised. The second is the rapid growth in the number of alliances between biotechs throughout the period to 2001, from 37 in 1990, to 993 in 2001. Since 2001, there has been a decline and then recovery in total numbers. Most of the variation in this later period has occurred in bio-biotech alliances.

Table 9.1 showing the growth rates at 5 year intervals provides greater detail on these changes. Drug biotech alliances grew rapidly at 17.0% per annum between 1990 and 1995, but in the period to 2000, the growth rate fell to 7.1% per annum. Biotech – biotech alliances grew very rapidly, at 37.5% to 1995 and 33.2% between 1995 and 2000 but growth halted in the period 2000 to 2005. Uni-biotech alliances also grew significantly in the period to 2000 at 11-12% per annum, declining somewhat in the period 2000 to 2005. Overall alliances grew at an average of 18.2% for the decade to 2000 before the decline and substantial recovery in the period 2000 to 2005.

The growth in alliances between biotechs and pharmaceutical companies in the first period is a product of complementary pressures. Pharmaceutical companies need to maximise the productivity of their pipelines and biotech companies require funding. This phase coincides with the identification of an 'innovation deficit' within the pharmaceutical industry (see for instance Drews and Ryser 1996) and with attempts by the pharmaceutical companies to seek new product through alliances.

Table 9.1 Number and annual growth in biomedical alliances, 1990 to 2005

		1990	1995	2000	2005
Drug-Biotech	Number	176	386	543	497
	CAGR		17.0%	7.1%	-1.8%
Biotech-Biotech	Number	37	182	762	777
	CAGR		37.5%	33.2%	0.4%
Uni-Biotech	Number	90	150	270	255
	CAGR		10.8%	12.5%	-1.1%
Other	Number	7	90	77	99
	CAGR		66.7%	-3.1%	5.2%
Total	Number	310	809	1653	1628
	CAGR		21.1%	15.4%	-0.3%

Note: CAGR = compound annual growth rate.
Source: Recap, February 2007.

By 2005, more than half of all alliances formed were *between* biotechs. This was in accordance with the predicted response to the highly specialised and fragmented nature of the biopharmaceutical knowledge base and the need to rapidly commercialise newly emerging technologies by harnessing complementary knowledge from a network of firms.

The growth in alliances with universities or research institutes was relatively modest. Perhaps this reflects a tendency for academics engaging in the commercialisation process to first establish a company (Zucker et al. 1998), which is often the alliance vehicle, rather than the university itself. Most of the university alliances are with biotechs. The number of direct links with pharmaceutical companies is included in 'other' and is very small, an average of about 11 per annum over the period. The number of alliances between pharmaceutical firms has also been relatively modest. While the number grew rapidly between 1990 and 1995, it has remained fairly static since then. This emphasises that pharmaceutical companies formed alliances to access the new technologies being offered by the biotechs.

Alliance 'intensity' or greater sector fragmentation and specialisation?

The growing propensity of firms to participate in alliance formation could arise from increased alliance activity by each firm i.e. 'alliance intensity', or, with increasing specialisation of the firms in the sector, it could result from an increased number of firms participating in alliances. In fact both trends are evident from the data, although the largest impact appears to be from an increased number of firms.

Overall the total number of companies participating in alliances has been growing almost as quickly as the total number of alliances, suggesting that much of the growth in alliances arises from a increase in the number of firms, rather than 'alliance intensity'. This is shown in Table 9.2 below.

For instance, in the period from 1990 to 1995, the growth in the number of alliance forming firms is 19.8% p.a. compared with a 21.1% p.a. for the growth in alliance numbers. Again for the period 1995 to 2000, the growth in the number of alliance forming firms, 12.8% p.a. accounted for most of the growth in alliances of 15.4%.

The higher growth rate in alliances however, indicates that there was some moderate growth in intensity, i.e. an increase in the number of alliances per firm.

Table 9.2 Number and annual growth in biopharmaceutical alliances and alliance parties, 1990-2005

	1990	1995	2000	2005
Number of alliances	310	809	1653	1628
CAGR		21.1%	15.4%	-0.3%
Number of alliance parties	404	997	1821	1981
CAGR		19.8%	12.8%	1.7%

Note: CAGR = compound annual growth rate.
Source: Recap, February 2007; author analysis.

This increase in intensity is almost entirely from alliances formed between pharmaceutical companies and biotechs (drug bio). This is the only type of alliance showing a clear trend towards increased alliance intensity. The average number of alliances per pharmaceutical firm grew from about 1.5 in 1990 to 3.1 in 2005. This is likely to be due to the increasing requirements of pharmaceutical companies for drug discovery and platform technologies. However there is no matching trend amongst biotech firms of an increase in the average number of alliances per pharmaceutical firm. The average number of alliances for biotechs forming alliances with pharmaceutical companies remained at about 1.4 for the period. This suggests that pharmaceutical companies were widening the net, rather than increasing the number of alliances with individual biotechs. Again this is understandable given the fragmented knowledge base and therefore the highly specialised nature of the products or technologies being offered by individual biotechs.

Overall this analysis suggests that the rapid increase in alliance formation has been largely a function of the enormous increase in the number of specialised biotech firms in need of alliance partners, rather than more intense networking by existing biotech firms. The pattern of alliance formation by pharmaceutical firms appears to be different in that, on average, each firm formed an increasing number of alliances with biotechs, over the course of the 1990s.

The value of alliances

Not all alliances are equally valuable. Mirroring the uncertainties of drug development, some alliances emerge as winners and others ultimately have little

value. Another perspective on the growth trends in alliances is to examine an indicator of its value. Recap collects and classifies certain financial details, as are available, about the alliance. In some cases such details are confidential, but typically for major alliances a 'headline' amount is announced and recorded on the database as the 'size' of the alliance. This is generally the estimated total lump sum payable through the term of the alliance. It incorporates actual upfront as well as contingent payments dependent on milestone achievements. So it is a measure of firm intention to pay, rather than the actual amount paid. The actual payment depends on the satisfaction of various outcomes typically specified in the alliance agreement. Given the uncertainties of most drug development programs the correspondence between the announced contingent payments and actual payments may be low. Nonetheless at the time of the announcement it is a measure of the value of the alliance and an indicator of its financial importance to the alliance parties. The term 'alliance payouts' rather than 'size' is the term adopted for the discussion below.

Alliance payouts tend to be disclosed when the outcomes of alliances are less uncertain. So the larger amounts tend to be for alliances formed in the later stages of clinical trials, when the likely revenue to be earned from drugs under development can be estimated with some certainty. The alliance payouts therefore reflect the risk adjusted expected cash flow from the drug under development.

The position with 'technology only' alliances is somewhat different. Access to technologies is generally obtained through exclusive or nonexclusive licensing arrangements. Where exclusive access was being obtained, the alliance would be structured more like a drug development alliance with upfront and milestone payments, but may also include an equity contribution. In extreme cases the most efficient access is obtained by outright purchase of the company or relevant business unit. In Recap such acquisitions are recorded and the purchase price classified as the alliance 'size'. Typically these transactions are outside the definition of an alliance and their size can be large and their inclusion would distort the analysis. Accordingly they have been excluded from this analysis.

Table 9.3 below shows alliance payouts recorded at five year intervals between 1990 and 2005. It shows the proportional shift that has occurred between alliances, in which

the pharmaceutical company has been the resource rich client, to this role being increasingly adopted by biotechs. While the highest proportion of alliance payouts continues to be for alliances between pharmaceutical companies and biotechs (drug_bio), over the period this share has declined from 86.8% in 1990 to 63.0% in 2005. On the other hand the share of payouts for alliances between biotechs (bio_bio) increased from 9.5% in 1990 to 29.0% in 2005. This reflects the increasing resources available to the larger and more successful biotechs to support the activities of other biotechs.

Table 9.3 Alliance payouts classified by alliance parties ($ million)

	1990		1995		2000		2005	
	$m	Share	$m	Share	$m	Share	$m	Share
Bio_Bio	107	9.5%	639	10.0%	3,090	24.7%	6,392	29.0%
Drug_Bio	981	86.8%	5,460	85.3%	5,310	42.4%	13,890	63.0%
Drug_Drug	17	1.5%	166	2.6%	3,605	28.8%	737	3.3%
Uni_Bio	25	2.2%	119	1.9%	491	3.9%	1,013	4.6%
Uni_Drug	0	0.0%	16	0.2%	30	0.2%	33	0.1%
Total	1,130	100.0%	6,402	100.0%	12,526	100.0%	22,064	100.0%

Source: Recap, February 2007.

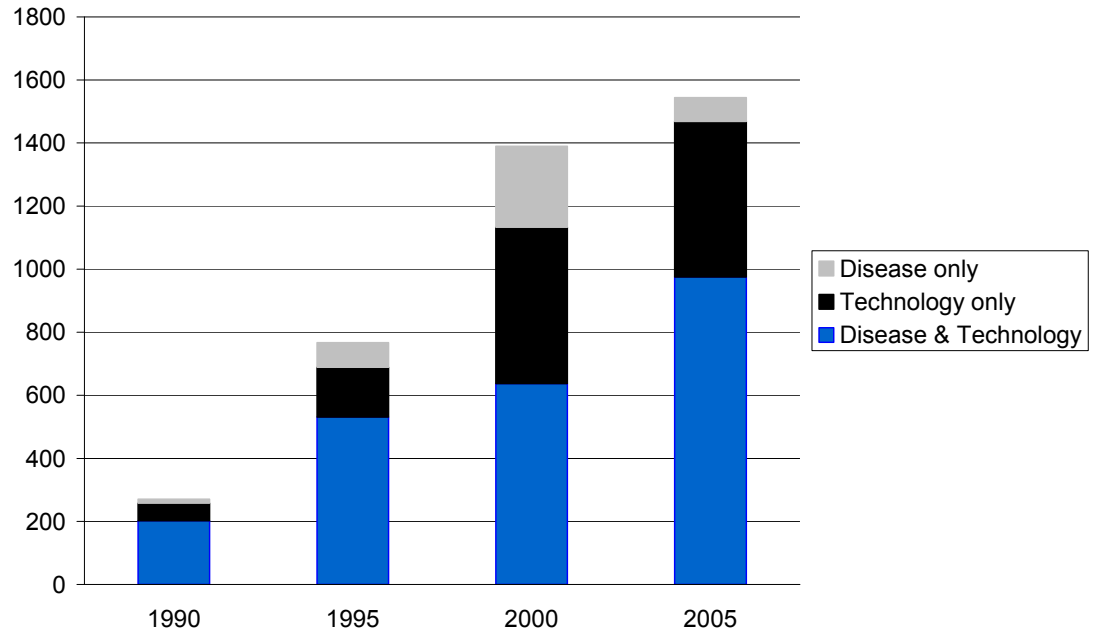
The total payout for both types of alliances has increased substantially over the period, 19.3% p.a. for drug_bio alliances and 31.3% p.a. for bio_bio alliances. The increase in payouts has continued through the period 2000 to 2005 when there was no growth in the number of alliances. It is beyond the scope of this thesis to examine this trend in more detail but other analysis indicates that this arises from an increased focus by large pharma on accessing drugs through later stage alliances (see Rasmussen 2004).

Purpose of alliances

As discussed in Chapter 3, it was argued that alliances are critical to the innovation process as mechanisms for the transfer of technologies and other knowledge and that one of the reasons for alliance formation is to access complementary assets. It was suggested that accessing specialised and co-specialised assets, rather than generic assets, is more likely to be through an alliance. In Chapter 8 an important distinction was drawn between co specialised drug discovery technologies and specialised transversal or platform technologies (Orsengio et al. 2001). This formed the basis of the two business models presented in Chapter 8, platform technology and drug discovery.

Using further analysis of the Recap data, this section demonstrates that the dominant driver of the growth in alliances is indeed the need to transfer new drug discovery and platform technologies. The large majority (over 90%) of alliances recorded on Recap are classified according to the technology being transferred and/or the disease being targeted by the alliance parties. Only a small proportion of alliances are focussed on the more generic assets, such as marketing (1.2% of the total) and manufacturing (1.9%). Indeed more than half of the alliances listed involve both a technology transfer and disease target. These broad trends are shown for alliances classified according to a technology or disease in Figure 9.2 below.

Figure 9.2 Number of alliances classified by technology and disease



Source: Recap, February 2007; author analysis.

Averaged over the four years shown covering the period 1990 to 2005, alliances involving disease and technology represented 59% of these alliances, technology only a further 30% and disease only 11%. This means that 89% of these alliances have involved some form of technology transfer, most of it targeted at a particular disease.

The growth rates for these alliance categories by type of alliance party are shown in Table 9.4 for the full period, 1990 to 2005. Technology only alliances have the highest growth rate for the period of 15.6% p.a., driven in part by the growth of

'technology only' alliances between biotechs (22.8% p.a.) but also notably by the growth in alliances between pharmaceutical (drug) companies and biotechs of 17.6% p.a., emphasising the importance of the access to new technologies for pharmaceutical companies.

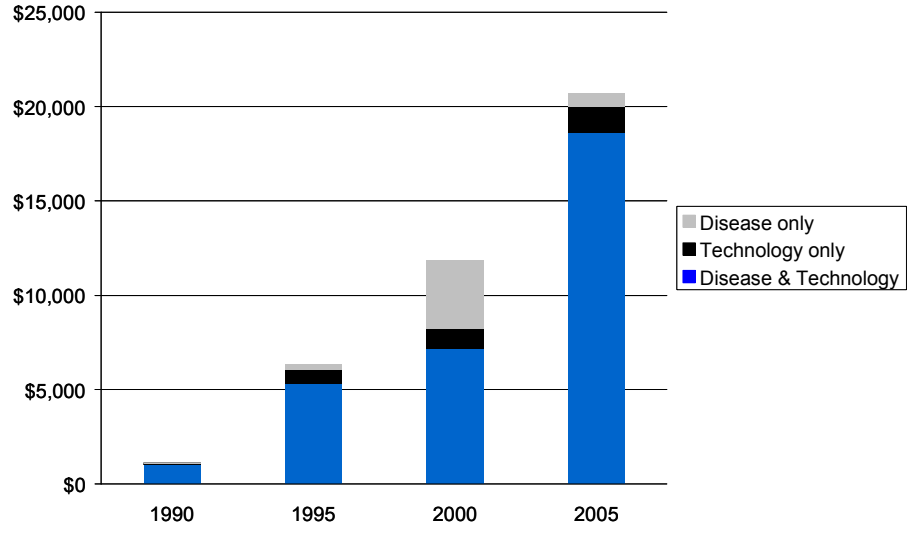
Table 9.4 Growth rates for number of alliances classified by technology and disease, 1990 to 2005, CAGR

	Bio Bio	Drug Bio	Uni Bio	Other*	Total
Disease & technology	21.7%	5.9%	8.0%	26.7%	11.1%
Technology only	22.8%	17.6%	2.9%	12.0%	15.6%
Disease only	21.5%	6.3%	8.7%	16.6%	12.5%

Note: * Very low base in 1990 has distorted the growth rates. CAGR = compound annual growth rate.
Source: Recap, February 2007.

Figure 9.3 shows the total payouts for alliances classified according to a disease and/or technology, for years 1990, 1995, 2000 and 2005. Over the four years shown payouts for disease and technology alliances totalled 80% of alliance payouts, compared with only 8% for technology only and 12% for disease only. This compares with the proportions based on the *number* of alliances of 59%, 30% and 11% respectively. This indicates that on average alliances incorporating technology targeted on a disease area were likely to receive substantially more via alliance payments than a technology only alliance. This indicates that while technology only alliances form a useful part of the biopharmaceutical network, the substantial financial commitments are made in support of alliances formed around disease targeted technology transfers.

Figure 9.3 Alliance payouts classified by technology and disease ($ million)



Source: Recap February 2007.

Alliance Technologies

The Recap database classifies alliances according to over 50 technologies. These cover the major platform technologies such as screening, combinatorial chemistry, genomics, bioinformatics, drug delivery, etc. as well as the focus of many drug discovery technologies, such as monoclonal antibodies, oligonucleotides, peptides and stem cell therapies. Sometimes an alliance may involve more than one technology, e.g. both screening and combinatorial chemistry. For the purposes of this analysis, which focuses on technology transfer, the alliance details are cross referenced against each technology, so as to capture all the technology categories. This means that there is a possibility of duplication of some of the alliances for which there is more than one technology. Care is therefore required in comparing the number of alliances discussed above with the number of 'alliance technologies' discussed in this section.

The Recap alliance categories have been divided between the main platform and drug discovery technologies[17]. These technologies have been discussed in Chapter 4. The principal platform technologies include screening, microarrays, combinatorial chemistry, rational drug design, bioinformatics, gene sequencing and expression. These are all technologies which assist the drug discovery and development process, but are not of themselves a therapeutic. In contrast monoclonal antibodies, oligonucleotides, peptides and stem cells require a particular technology for their creation but also form a definable class of therapeutics. These are termed drug discovery technologies. The principal drug discovery and platform technologies have been selected from the technology categories used by Recap[18]. They are listed in Table 9.5 below.

[17] The classification of technologies is that adopted by Recap while the division of technologies between 'platform' and 'drug discovery' is by the author.
[18] In selecting these particular technology categories, attention was paid to the key technologies constituting biotechnology as discussed in Chapter 5. This resulted in the exclusion of a number of smaller alliance technology categories, such as transcription factors and phototherapy and some categories less central to the knowledge base, such as devices and synthetics.

Table 9.5 Selected biopharmaceutical technologies

Platform	Drug discovery
Bioinformatics	Cell therapy
Combinatorial	Monoclonals
DNA probes	Oligonucleotides
Drug delivery	Peptides
Gene expression	Vaccines
Gene sequencing	
Microarrays	
Pharmacogenomics	
Proteomics	
Rational drug design	
Recombinant DNA	
Screening	
Transgenics	

The number and payout values for the main platform and drug discovery alliance technologies listed on the Recap database are shown in Table 9.6 below. It shows a contrasting pattern in the number and rates of growth of platform and drug discovery alliance technologies. In the period from 1990 to 2000, platform alliance technologies grew considerably more rapidly than drug discovery alliance technologies. This difference was particularly pronounced in the period 1995 to 2000 when platform alliance technologies grew at 21.5% p.a. to 891, compared with 7.1% p.a. to 231, for drug discovery alliance technologies. In 1995 the payout values for platform alliance technologies was $3136 million, more than double that for drug discovery alliance technologies of $1365 million.

Table 9.6 Payout values and number of alliances classified by selected technologies, 1990 to 2005

	Selected platform technologies				Selected drug discovery technologies			
	#	CAGR	$m	CAGR	#	CAGR	$m	CAGR
1990	112		499		78		292	
1995	336	24.6%	3136	44.4%	164	16.0%	1365	36.2%
2000	891	21.5%	3491	2.2%	231	7.1%	1890	6.7%
2005	966	1.6%	2002	-10.5%	432	13.3%	4889	20.9%

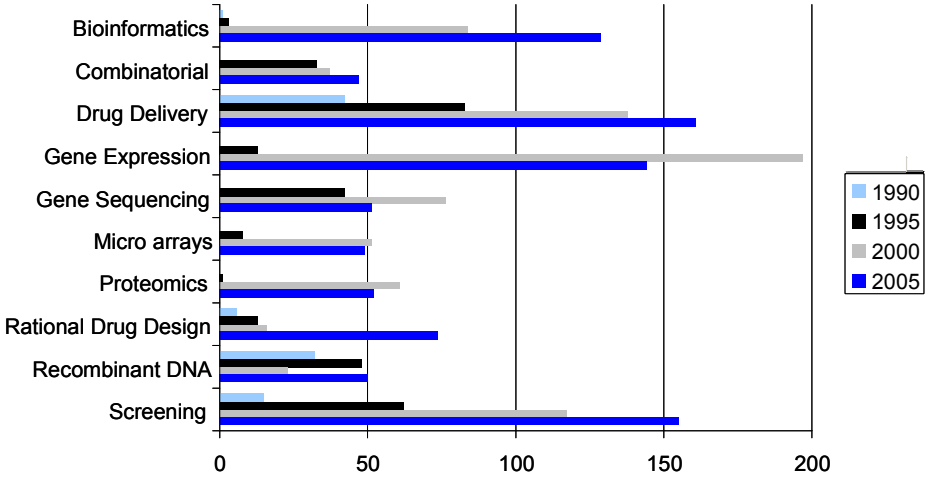
Note: CAGR = compound annual growth rate.
Source: Recap, February 2007.

By 2005 the position had been entirely reversed. In the period 2000 to 2005 platform alliance technologies grew at only 1.6% p.a. while drug discovery alliance technologies grew at 13.3% p.a. In 2005, the payout value of alliances involving selected drug discovery technologies was more than twice that of platform alliance technologies, $4889 million compared with $2002 million.

These shifting patterns reflect the changing priorities of the biopharmaceutical sector. The formation of alliances focussing on particular technologies is a good indicator of the rise and fall of commercial interest in new technologies (Orsengio et al. 2001). Early in the 1990s there was a strong focus on increasing the efficiency of the pharmaceutical industry through the adoption of new platform technologies. In the later part of the decade the focus shifted again, to the opportunities afforded by genomics – gene sequencing, gene expression and recombinant DNA technologies. In the period 2000 to 2005 the sector turned to drug discovery as the large pharmaceutical companies found their drug pipelines relatively empty, as patent expirations loomed for many of the larger selling drugs.

Some of these trends are evident in Figure 9.4 which provides details of the trends in individual alliance technologies. Screening and drug delivery, both critical to the efficiency of the drug development process, were important over the whole period. The largest number of alliances formed however involved genomics. Gene expression alliances were largest in 2000, while the number of alliances involving gene sequencing, recombinant DNA and bioinformatics increased substantially. In the period since 2000, some of the enthusiasm for genomics has waned in the light of a more cautious assessment of its commercial prospects, following the release of the results of the human genome project. Nonetheless the number of bioinformatics alliances has continued to increase.

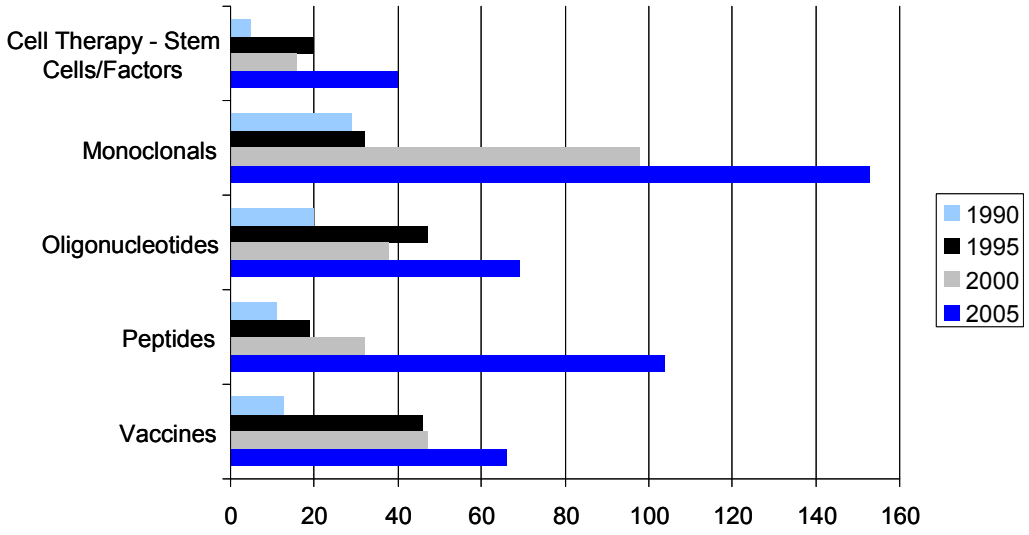
Figure 9.4 Number of alliances involving selected platform technologies



Source: Recap, February 2007.

Figure 9.5 below shows the number of alliances involving the main drug discovery technologies listed on Recap. The pattern is quite the reverse of the platform technology alliances, with slow growth or decline in the majority of such technologies between 1995 and 2000, followed by a period of recovery in all drug discovery technologies in the period 2000 to 2005.

Figure 9.5 Number of alliances involving selected drug discovery technologies



Source: Recap, February 2007.

The growth in alliances involving monoclonals, from 29 in 1990 to 153 in 2005, however, has followed its own distinct growth path. As discussed in Chapter 4, humanised monoclonal antibodies have been pursued as a likely treatment for cancer and a large number of alliances have been formed for that purpose. Oligonucleotides also have a cancer focus. Both types of alliances have large payout values. For instance in 2005 payout values were $2.2 billion for monoclonals and $1.7 billion for oligonucleotides. Alliances involving peptides, which have application to a wide range of diseases, have increased from 11 in 1990 to 104 in 2005. Alliances involving the development of vaccines have grown steadily focussing on cancer and infectious diseases, including HIV/AIDS. The recent focus on stem cells and cell therapy is reflected in a doubling of the number of alliances formed between 2000 and 2005.

Use of alliances to apply technologies to disease groups

The reasons for alliances considered in Chapter 3 accord a central role to alliances as a mechanism for the transfer of technology. The section above has illustrated the changing relative importance of alliances involving a range of biopharmaceutical technologies over four five year intervals from 1990 to 2005. This section illustrates the role of alliances in the application of these technologies to the search for medicines to combat certain major diseases.

Most alliances listed in the Recap database are classified according to one or more diseases. For those involving more than one disease, the most important is generally listed first. The table above shows the number of alliance technologies cross tabulated with the first named disease. It also includes the number of platform and drug discovery alliance technologies with no disease recorded in the database. This is an important measure for platform technologies. Firms could be expected to enter an alliance for the purpose of securing or developing a platform technology without the objective of developing a particular drug[19].

Table 9.7 Number of selected alliance technologies applied to the main disease groups, 1990 to 2005

	Total selected platform		Total selected drug discovery		Total all selected technologies	
Anti-inflammatory	54	2.4%	42	4.6%	96	3.0%
Autoimmune	74	3.3%	43	4.8%	117	3.7%
Cancer	252	11.1%	222	24.5%	474	14.9%
Cardiovascular	76	3.3%	20	2.2%	96	3.0%
Central nervous system	98	4.3%	37	4.1%	135	4.2%
Infection	139	6.1%	156	17.2%	295	9.3%
Metabolic disorders	58	2.6%	9	1.0%	67	2.1%
Pain	25	1.1%	3	0.3%	28	0.9%
Other	269	11.8%	110	12.2%	379	11.9%
No disease	1229	54.0%	263	29.1%	1492	46.9%
Total	2274	100.0%	905	100.0%	3179	100.0%

Source: Recap, February 2007.

As Table 9.7 shows, only 29.1% of drug discovery alliance technologies are not allocated to a disease whereas over half, 54% of the selected platform alliance technologies have no disease. Of those with a disease classification, the table shows

[19] It may also indicate a lapse in the coding by Recap. However such a lapse, if it was to occur, would be random, affecting all categories equally. In fact a significantly higher proportion of alliances coded as platform alliances have no disease as would be expected.

that the alliance technologies tend to focus on the development of drugs in particular disease areas with, cancer being the most prominent with 14.9% of the total and infection, largely HIV/AIDS, the next highest with 9.3%. As would be expected, the drug discovery alliance technologies are however even more heavily concentrated, with over 40%, or 60% of those with a disease, focused on two disease areas, cancer with 24.5%, and infection with 17.2% of the total. The selected platform technologies are more dispersed. Only 11.1% and 6.1% of platform technology alliances focus on cancer and infection respectively. The proportion allocated to the diverse range of diseases included in 'other' is also higher, 12.4% compared with 10.7% for drug discovery alliance technologies indicating the wide application of platform technologies. The significance of these results is confirmed by a chi square test on the two distributions. The chi square is 42.4, which is significant at the 0.0003% level. Even excluding the influence of the high proportion of alliance technologies categorised with 'no disease' from the distribution has little effect on the chi square, which remains high at 40.8, still significant at the 0.0003% level.

Conclusions

This chapter has demonstrated the rapid growth in the use of alliances in the biopharmaceutical industry since 1990. This growth has occurred both in alliances between pharmaceutical and biopharmaceutical firms and between biopharmaceutical firms. Alliances involving pharmaceutical and biopharmaceutical firms grew rapidly between 1990 and 1995 and then tapered off. On the other hand alliances between biopharmaceutical firms have increased rapidly between 1990 and 2000, comprising almost half the alliances being formed, before also plateauing in the period to 2005.

The analysis of alliance technologies has demonstrated that access to new technologies is the most important reason for the alliances formed between 1990 and 2005 and recorded on the Recap database. About 90% of biopharmaceutical alliances involve a technology transfer and more than half of these alliances were centred on a disease. Only a very small proportion has been focussed on the more generic assets of marketing and manufacturing. This supports the proposition that alliances are formed to access specialised and co-specialised assets.

Alliances involving platform technologies have a quite different pattern to those involving drug discovery technologies. Platform technology alliances are either broadly spread across disease areas or, as for more than half, have no disease listed at all. This is consistent with these technologies being applied, either to assist with the discovery and/or development of drugs dealing with a wide of range of diseases, or to the discovery and development of drugs in general. The most prominent alliances involving platform technologies are the key technologies discussed in Chapter 5, namely screening, bioinformatics, rational drug design, microarrays and gene expression and sequencing, indicating that alliances have been important in their development and transfer between biopharmaceutical firms and with pharmaceutical firms. On the other hand drug discovery technology alliances, as would be expected, have mostly involved particular diseases. Only 29% have no disease listed, compared with 54% for platform technologies.

This broad application of platform technologies across many disease classes and the relatively more focussed application of drug discovery technologies, as evidenced by the classification of alliances, supports the value of distinguishing between transversal technologies and co specialised technologies suggested by Orsengio et al. (2001). In so far as the nature and purpose of the alliance reflects the role of the firm, then it also supports the distinction between the two biopharmaceutical business models proposed in Chapter 8, one based on drug discovery and the other on platform technologies.

Alliances also provide documentary evidence of the shifts in focus from one technology to another, as different commercial opportunities and pressures have emerged. This is illustrated by the surge of interest in genomics based alliances in the later part of the 1990s and then the switch in focus to new drug development alliances in the 2000s. Between 2000 and 2005 drug discovery alliances grew rapidly, as it became increasingly clear that pharmaceutical company pipelines were about to be adversely impacted by the threat of generics and a failure of new drugs in the later stages of development.

Producing therapeutics to treat cancer appears to be the single most important purpose of the biopharmaceutical alliance network. The most important drug discovery technology is monoclonal antibodies with a strong focus on cancer. Cancer ranks

highest amongst the alliances involving disease. The key alliance technologies, both drug discovery and platform alliance technologies, are disproportionately directed towards its solution.

To relate these results more closely to firm behaviour and differences in business models it is necessary to examine the alliances of the four groups of firms, large pharmaceutical companies, drug discovery, platform technology companies and large biotechs. The results of this analysis are presented in the next chapter.

Chapter 10. Trends in Biopharmaceutical Alliances for Key Business Models

Introduction

The previous chapter has served to emphasise the much increased importance of alliances in the period since 1990, illustrating the growth in their number and the payout values attached to them. The major role of alliances as a transfer mechanism for technology is also established. The discernable difference between platform technology and drug discovery technology alliances supports the distinction, made in Chapter 8, between the two biopharmaceutical business models based on two different technological regimes. The major role of pharmaceutical firms in forming alliances to obtain new technologies is also confirmed. For most of the period they grew rapidly, although the number of new alliances declined in the period 2000 to 2005. However their payout values continued to increase.

This chapter examines in greater detail the nature of alliances formed between firms, broadly conforming to the business models defined in chapters 7 and 8. Chapter 7 outlined a number a ways in which pharmaceutical firms were adjusting their business models in response to developments in biotechnology. It was suggested that the fragmentation of expertise in the industry presented challenges to pharmaceutical firms. One response was to expand their own value chains by forming alliances with biopharmaceutical firms to access these new technologies. This chapter examines the types of platform and drug discovery technologies accessed by large pharmaceutical companies through alliances.

Chapter 8 defined two distinct biopharmaceutical business models, based on two different technological regimes, transversal or platform technology and co-specialised or drug discovery technology. This chapter examines alliances formed by the two groups of companies, one specialising in platform technologies and the other in drug discovery. A further set of biopharmaceutical companies is distinguished, the ‘large biotechs’ which are biopharmaceutical companies that have more diversified

operations than the specialist companies and have adopted fully integrated business models analogous to the large pharmaceutical companies.

The different alliance formation patterns of these four sets of firms is used to demonstrate the different roles played by these firms in the biopharmaceutical value network. For instance there are differences in the alliance formation patterns between platform and drug discovery companies that go to the heart of the different business models of such firms. The significant contribution of large pharmaceutical companies, both to the development of platform technologies and new drugs, is also evident from their alliance formation activity.

The Companies Included in each Business Model

The four groups of firms to be analysed are the top 10 pharmaceutical companies by sales listed in Table 10.2, two groups of specialist biopharmaceutical firms listed in the US, which are tracked and classified according to their principal technologies by Recap.[20] The Recap classification enables this group of companies to be divided into two specialist groups, drug discovery and platform technology companies. The fourth group consists of the largest six biopharmaceutical companies which in this thesis will be called 'large biotechs'. These are Amgen, Biogen IDEC, Chiron, Genentech, Genzyme and Gilead Sciences, which are all also tracked by Recap.[21]

Table 10.1 below list the categories of companies for the two specialist groups together with the number in each. There are a total of 87 platform technology companies, 121 drug discovery companies, all of which are publicly listed in the US. Together these two groups of companies represent only about 8% of the biopharmaceutical companies with alliances listed on Recap for the years 1990, 1995, 2000 and 2005, but are involved in over 30% of the bio biotech alliances and almost 25% of the drug biotech alliances for those years.

[20] www.signalsmag.com

[21] Medimmune has been recently included in this group of companies by Recap but has yet to become profitable. Previously it was classified in the 'infection' category and has been so classified in this analysis. Chiron has recently been acquired by Novartis but was independent for the period of this analysis.

They are by no means a representative sample, but rather a group of leading biopharmaceutical companies. As discussed in Chapter 8, most are unprofitable and significantly smaller in size to the 'large biotechs'. Sixty per cent of the companies had a market capitalisation of between $100 million and $1 billion in December 2005. On average there is little difference in the average market capitalisation of the platform and drug discovery companies although average revenue of the platform technology companies is more than twice the average for drug discovery companies.

Table 10.1 Number of platform and drug discovery companies classified by Recap company group

Recap biopharmaceutical company groups			
Platform technology	No. of companies	Therapeutic group	No. of companies
1st generation Genomics	5	Autoimmune	9
Chemistry	10	Cancer	44
Delivery	22	Cardiovascular	9
Diagnostic/image	21	Gene/Cell therapy	12
Genomic Supply	10	CNS	15
Genomic Targets	12	Infection	17
Screening	7	Metabolic	11
		Wound	4
Total platform technology	**87**	**Total therapeutic**	**121**

Source: www.signalsmag.com

The pharmaceutical companies selected for analyses of their alliances are the top 10 by sales in 2005 (see Table 10.2).

Table 10.2 Top 10 pharmaceutical companies by sales, 2005

Company	Pharma sales ($ billions)
Pfizer	44.28
Glaxo	33.96
Sanofi-Aventis	32.24
Novartis	24.96
Astrazeneca	23.95
J&J	22.32
Merck	22.01
Wyeth	15.32
BMS	15.25
Lilly	14.65

Source: Pharmaceutical Executive May 2006, SEC 10-K reports and annual reports.

Alliance Formation Trends for the Selected Biopharmaceutical and Pharmaceutical Firms

The two tables below (tables 10.3 and 10.4) provide an overview of the alliance formation trends of these companies, both in terms of alliance numbers and payout values.

Table 10.3 Number of alliances formed at five-year intervals by company type, 1990 to 2005

Type	Role	1990	1995	2000	2005
Drug discovery	Client	4	19	67	57
	Developer	50	68	131	107
Platform	Client	2	8	80	49
	Developer	40	76	242	133
Large biotech	Client	7	22	25	28
	Developer	15	7	17	10
Large pharma	Client	50	151	214	184
	Developer		19	11	14

Table 10.3 shows the number of alliances formed by the selected companies in their role as both client and developer. The overwhelming majority of alliances formed by large pharma is in the role of client, in which it contracts with other companies to obtain technologies or other complementary assets. Over the period, the number of alliances formed has increased substantially from 50 in 1990 to 184 in 2005. On the other hand, in 1990, the large biotechs were forming more alliances in the role of developer than client. By 1995 this had switched to the majority being as client, as the larger biotechs began to adopt a role more analogous to large pharma. However even allowing for their smaller number, six versus ten, the number of alliances per firm is significantly smaller than the top pharma companies.

Both the drug discovery and platform technology companies have formed a far greater number of alliances as developer than as client. While this gap has closed for the drug discovery companies, the primary role of the platform companies is as a developer. The drug discovery companies included here are the larger more successful ones, and presumably their role has evolved over the period, to one in which they have the senior, or client role, in a larger number of their alliances.

The payout values for these alliances shown in Table 10.4 serve to emphasise the patterns illustrated by the number of alliances formed shown in Table 10.3 above. Of

greatest significance is the size of the payouts by large pharma in their role as client, which increased from $459.6 million in 1990 to $10,825 million in 2005. By contrast, the payout amount by large biotechs in 2005 was only $1,274 million, indicative of a much smaller role in resource transfers to developer companies through alliances. The Recap listed drug discovery and platform technology companies were major recipients of alliance payout commitments as developers, with developer payouts of $4.2 billion each in 2005. About 46% of the amount committed to these drug discovery companies and 52% of the amount for platform companies was committed by the large pharmaceutical companies.

Table 10.4 Payout values for alliances formed at five year intervals by company type, 1990 to 2005 ($ million)

Type	Role	1990	1995	2000	2005
Drug discovery	Client	2.8	25.4	309.7	1141.3
	Developer	242.2	856.8	1738.4	4184.8
Platform	Client	0.3	2.5	293.3	167.5
	Developer	174.4	1237.7	2430.9	4221.6
Large biotech	Client	116.8	428.3	576.7	1274.1
	Developer	22.6	276.0	83.0	640.0
Large pharma	Client	459.6	2952.1	4861.6	10825.0
	Developer		142.8	2890.1	32.0

In the previous chapter, as part of the explanation for the increasing alliance formation, the annual average number of alliances formed per company was analysed and found to be relatively constant, except for those alliances involving pharmaceutical companies, for which it was increasing. This result is confirmed by the analysis presented in Table 10.5.

Table 10.5 Average number of alliances formed by type of company, 1990 to 2005

	1990	1995	2000	2005
Drug discovery	2.3	1.6	2.1	2.0
Platform	1.9	1.6	2.8	1.9
Large biotech	2.8	4.8	3.8	3.8
Large pharma	6.3	8.5	16.1	13.2

The top 10 pharmaceutical companies increased their rate of alliance formation from an average per company of 6.3 in 1990 to 13.2 in 2005. This is consistent with expectations of behaviour of the pharmaceutical business model. One of the anticipated responses of the large pharmaceutical firms to biotechnology is a growing

trend in alliance formation per firm, as increasing access is sought to the new technologies.

Large biotechs also increased their average number of alliances from 2.8 to 3.8. Neither drug discovery nor platform companies demonstrated much of a trend in their rate of alliance formation although the average for platform technology companies rose from 1.6 to 2.8 between 1995 and 2000 reflecting the significant increase in genomics based alliances. However overall these results are consistent with those of the previous chapter, which suggested that the increasing trend in alliance formation was largely explained by an increasing number of biopharmaceutical firms forming alliances.

Interdependencies between Business Models

As noted above, the classification of many of the alliances by type of business model provides an opportunity to examine the interdependencies between the four business models. Table 10.6 shows the number of alliances cross tabulated by role (client or developer) and type of company. The client role is listed down the column and that of developer by row. For instance it shows that large pharmaceutical companies, in their client role, formed 59 alliances with drug discovery companies, 79 alliances with platform companies 8 with large biotechs, 10 with other large pharmas and 443 with companies not classified, that is neither included in the Recap list of biotechs or as one of the top 10 large pharma companies. In their role as developer, platform companies have formed 10 alliances with drug discovery companies 27 with platform companies, 9 with large biotechs, 79 with large pharma and 366 not classified.

Table 10.6 Total number of alliances by role and type of company for years 1990, 1995, 2000, 2005

	Developer					
	Drug disc.	Platform	Large biotech	Large pharma	Not classified	Total developer
Client						
Drug discovery	14	10	3		120	147
Platform	13	27	3		96	139
Large biotech	15	9	3		55	82
Large pharma	59	79	8	10	443	599
Not classified	255	366	32	34		687
Total client	356	491	49	44	714	1654

There are a number of results to be drawn from Table 10.6. The first is the large number of developer alliances formed by platform companies (491). A high proportion of these are with companies not classified, but of those that are, 79 are with large pharma. By comparison, large pharma have formed only 59 alliances with drug discovery companies, indicating the high relative demand from large pharma companies for platform technologies. The second is the relatively large number of alliances formed between platform companies (27) which are indicative of the specialised nature of the platform technology companies and the need for collaboration between such firms to produce marketable products. About half of these alliances involve three technologies, screening, gene expression and sequencing.

The third is that compared with large pharma, the large biotechs, as client, have relatively more alliances with drug discovery, than with platform companies. As will be illustrated below this reflects a greater focus on cancer and consequently a greater interest in alliances involving monoclonals than large pharma.

These results however must be tempered by the high number of alliances that have not been classified. Although there is no expectation that their inclusion would skew the results away from those identified, if they were different then their number would swamp the alliances that have been classified. This also applies to the results to be drawn from table 10.7.

These three features are given sharp relief by Table 10.7, which shows the payout values for alliances by role and type of company for the total period. In particular, the large payout values for alliances between large pharma and platform companies emphasises the value of such alliances to large pharma. The relatively small amount committed in alliances by the non pharmaceutical companies, including large biotechs, is also very evident. While there were a relatively large number of alliances formed between the platform companies the total value of alliance commitments is low.

Table 10.7 Total payout values for alliances by role and type of company for years 1990, 1995, 2000, 2005 ($million)

	Developer					
	Drug disc.	Platform	Large biotech	Large pharma	Not classified	Total developer
Client						
Drug discovery	331.7	544.5			603.0	1479.1
Platform	39.3	166.8			257.5	463.6
Large biotech	522.2	180.7			1692.9	2395.8
Large pharma	3235.8	4165.4	298.5	1771.0	9627.6	19098.2
Not classified	2893.3	3007.2	723.1	1293.9		7917.5
Total client	7022.2	8064.6	1021.6	3064.9	12180.9	31354.2

These results serve to illustrate the importance of alliances to the large pharmaceutical firms relative to the other types of firms. Platform technology alliances, which are larger both in number and value of payout than drug discovery alliances, are particularly important. This suggests that platform technologies that assist large pharmaceutical firms with their own drug discovery and development programs are at least as significant as accessing the new drug discovery technologies. The analysis below of the individual technologies provides further evidence of this.

Technology and Disease Focus of the Different Business Models

Table 10.8 shows the breakdown of alliances by technology group for each of the business models. The alliance technologies of large pharma and large biotechs are shown only in their role as client, given their relatively minor role as developer.

Large pharma companies have a much greater focus on platform technologies than large biotechs. Of the alliances classified, the ratio of platform to drug discovery alliances is 3.4 to 1. Over 53% of large pharma alliance technologies involve platform technologies compared with only 38.4% for large biotechs. Interest in bioinformatics, screening and a range of genomics based technologies is higher than for large biotechs. Large biotechs have 38.4% of their alliances in drug discovery, of which 18.2% are in monoclonals. In contrast, large pharma have only 15.5% of their alliances in drug discovery of which only 4.5% are in monoclonals. The drug discovery companies as clients appear to have a very strong need for drug delivery technologies (16.7%) and monoclonals (28.9%). In contrast, in their role as client, platform technology companies have their greatest interest in gene expression and

gene sequencing. Both these differences, firstly between large pharma and large biotechs and secondly between drug discovery and platform technology companies are statistically highly significant. The chi square for the former is 140.2 and the latter 125.0.

With respect to platform technology and drug discovery alliances, the previous chapter illustrated the distinction in the pattern of alliances of the two types. It showed that about half of platform technology alliances had no particular disease focus and the remainder were relatively broadly spread across a large number of disease areas. By comparison a high proportion of drug discovery alliances were focussed on a particular disease area. In this more disaggregated analysis of company behaviour by business model, Table 10.8 confirms these earlier conclusions.

In the role of developer, platform technology companies have 64.5% of their alliance technologies involved in platform technologies and only 13.5% involving drug discovery. The platform technologies are broadly distributed, but with genomics based technologies a high proportion of the total. Drug discovery companies, again as developer, have 37.3% of their alliance technologies in drug discovery technologies, almost 20% involve no technology and only 21.5% involve a platform technology of which recombinant DNA and screening appear to be the most important. These differences, between the distribution pattern of alliances of drug discovery and platform technology companies, are highly significant, with a chi square of 207.2.

Table 10.8 Alliance technologies by role and business model type (%)

	Role as client				Role as developer	
Technology group	Large pharma	Large biotech	Drug discovery	Platform	Drug discovery	Platform
Platform						
Bioinformatics	6.1	2.0	2.0	5.4	0.3	2.4
Combinatorial	3.8	4.0	3.4	2.0	0.6	3.7
DNA probes	0.3	2.0	0.0	2.9	0.3	3.2
Drug delivery	9.2	3.0	10.7	5.4	4.2	9.0
Gene expression	7.9	4.0	4.7	16.7	1.8	16.0
Gene sequencing	3.1	0.0	0.7	8.3	0.3	7.3
Microarrays	1.7	0.0	0.0	6.4	0.0	7.3
Pharmacogenomics	2.1	1.0	0.0	2.5	0.6	2.4
Proteomics	2.4	0.0	1.3	2.5	0.3	2.0
Rational drug design	2.1	0.0	0.7	1.0	0.9	1.6
Recombinant DNA	3.2	13.1	2.7	2.5	7.5	1.0
Screening	11.3	9.1	6.7	7.8	4.8	8.5
Total selected platform	53.1	38.4	32.9	63.2	21.5	64.5
Drug discovery						
Cell therapy	0.8	6.1	0.7	1.0	3.0	0.9
Monoclonals	4.5	18.2	28.9	6.9	19.7	3.6
Oligonucleotides	4.0	6.1	1.3	4.4	2.1	5.6
Peptides	2.1	3.0	2.0	1.5	6.3	1.3
Vaccines	4.0	5.1	4.0	1.0	6.3	2.1
Total selected drug disc.	15.5	38.4	36.9	14.7	37.3	13.5
Other	19.5	17.2	12.1	11.8	21.8	12.8
No technology	11.9	6.1	18.1	10.3	19.4	9.3
Grand total	100.0	100.0	100.0	100.0	100.0	100.0
Total no. of alliances	717	99	149	204	335	698

In Table 10.6 it was noted that a good proportion of platform technology alliances were between platform technology companies. The alliance patterns between the platform companies as client and developer indicates a relative concentration of such alliances in the major platform technologies, such as gene expression and sequencing, drug delivery and screening. This suggests that networks of platform technologies provide mutual support in specialist technologies. Platform technology companies specialising in a particular technology will form a dense support network with other platform technology companies specialising in the same technology. These patterns are consistent with those of the open innovation paradigm discussed in Chapter 3.

Disease focus of alliance technologies by business model type

Table 10.9 shows the alliances classified by first named disease. It helps confirm the widely differentiated roles of the four business models. Platform technology

companies are not disease specialised, whereas 81.7% of alliance technologies of drug discovery companies, as developer, are focussed on a particular disease, most importantly cancer[22]. The pattern of alliances formed by large pharma also tends not to be particularly disease focussed, with 42.3% of alliance technologies not disease related. In contrast large biotechs are much more disease focussed with only 30.4% of alliance technologies not disease related and correspondingly high proportion of alliance technologies focussed on cancer.

Table 10.9 Alliances by disease and company role and business model type (%)

	Role as client				Role as developer	
Disease group	Large pharma	Large biotech	Drug discovery	Platform	Drug discovery	Platform
Anti-inflammatory	3.9	2.7	1.1	2.1	2.7	2.0
Autoimmune	3.7	4.5	2.2	2.1	5.8	3.5
Cancer	10.3	18.8	28.6	9.8	27.2	11.1
Cardiovascular	5.4	2.7	1.1	1.3	4.1	4.7
CNS	6.0	6.3	4.4	3.0	8.4	4.3
Infection	9.2	10.7	17.6	6.0	14.9	8.4
Metabolic disorders	2.9	1.8	0.0	0.9	2.7	1.6
Pain	1.3	0.0	0.0	0.0	1.0	0.5
Other	15.1	22.3	12.6	9.4	14.9	15.9
No disease	42.3	30.4	32.4	65.4	18.3	48.0
Grand total	100.0	100.0	100.0	100.0	100.0	100.0

Conclusions

This chapter has confirmed a number of features of biopharmaceutical alliances noted in the previous chapter. For instance platform companies have quite different technology and disease focus profiles from drug discovery companies. As would be expected a higher proportion of their alliances have no specific disease involvement and those in which disease is involved are more evenly spread.

The strong interdependencies between the types of firms are also evident in the formation of the alliances. The large pharmaceutical companies have formed a considerable number of alliances with platform companies and committed to a somewhat higher value of alliance payouts than to the group of drug discovery

[22] As with Table 9.7 this may also indicate a lapse in the coding by Recap. However such a lapse if it was to occur would be random, affecting all categories equally.

companies. This indicates an even higher level of interest in acquiring platform technologies than drug discovery technologies.

The analysis has also demonstrated the high level of interdependency between platform companies. This confirms the importance of technology exchange between specialist platform companies to develop marketable products. The alliances indicate that screening, gene expression and sequencing are the major technologies of joint interest to the platform technology companies.

The comparison between large pharma and large biotechs indicates significant continuing differences. In particular, large biotechs show a relatively low level of interest in platform technologies. Even if some aspects of the two business models are drawing closer, the pattern of alliance formation by large biotechs is different from large pharmaceutical companies in several respects.

As noted, large pharma has a much broader disease interest and a more intense interest in a wide range of platform technologies. This may reflect more complex pharmaceutical development pipelines but it also illustrates the extent of their knowledge deficiency. Large pharma companies lack knowledge about the newer genomics based technologies. The large biotechs on the other hand are more likely to have internal access to these technologies.

The significant role of the large pharmaceutical companies in funding a great diversity of alliances, with both platform and drug discovery companies, is again consistent with the role expected of them as they adjust their business models to biotechnology. It is noteworthy that more than half of large pharmaceutical company alliances involve platform technologies and only 15% involve the major selected drug technologies. This compares with an almost equal distribution between platform and drug discovery alliances by ‘large’ biopharmaceutical counterparts. Moreover the value of alliance payouts to platform technology companies exceeds that committed to drug discovery companies.

This illustrates the significant knowledge divide between the traditional pharmaceutical companies and the new biotechnologies discussed in chapter 5.

Pharmaceutical companies have a broad interest in a wide range of such technologies. They lack knowledge of the new genomics based technologies and seek to acquire these through alliances. They also seek a broad range of drug technologies. This not only reflects a knowledge deficiency in the newer knowledge, but also a more complex existing pipeline. In contrast the large biotechs are much more focussed. They already understand the new genomics based technologies and so have a lower propensity to form alliances with platform technology companies. On the other hand they need access to the newer drug discovery technologies, especially in those targeting cancer. So while the large biotechs may have adopted the fully integrated model as will be discussed in later chapters, they have not had to modify the model to develop such extensive value networks.

The large number of alliances between smaller companies, especially platform technology companies, demonstrates the development of a complex value network in platform and drug discovery technologies. It is indicative of the importance of the interdependencies between small specialist companies in the innovation process, as highlighted by Langlois (2003) and Rothwell (1994) in the search for complementary technology assets.

Most importantly the differences in the alliance patterns between the firms classified as drug discovery and platform technology confirms the earlier hypothesis about the technological basis of the different business models. Platform technology companies have large and comparatively diverse value networks in order to draw in specialist complementary technologies. Their technologies are generic or transversal and have application across a broad range of disease areas. By comparison, drug technology companies are more focussed on particular disease areas and have a lesser need for a range of platform technologies. Instead their technologies are co specialised resulting in alliances with particular pharmaceutical or large biotech partners.

While this chapter has explored the nature of the alliances established between different business models in some depth, it has provided little insight into a number of important theoretical issues raised in Chapter 3, such as about the alliance governance structures, IP regimes and appropriability of strategic assets. These issues will be

developed further in subsequent chapters which largely focus on the behaviour of individual firms.

PART D.

FOUR CASE STUDIES

Chapter 11. Case Studies in Biopharmaceutical Business Models

Introduction

This chapter employs the business model concept, presented firstly in Chapter 4 and further developed in chapters 7 and 8, to analyse a cross section of types of biopharmaceutical firms. One aim of the chapter is to demonstrate the usefulness of the business model framework to identify some of the key differences in the business models being adopted by biopharmaceutical companies.

Secondly and more importantly, the chapter seeks to test the hypothesis developed in Chapter 8 that there are three definable biopharmaceutical business models, drug discovery, platform technology and 'large biotech'. In Chapter 8 it was argued that specialist biopharmaceutical companies could be expected to adopt one of two different business models depending on their technological regime. It was predicted that those companies developing transversal technologies would adopt a platform technology business model while those developing co specialised drug discovery technologies would adopt a drug discovery business model. Possible problems were identified with both models, arising from the costs and uncertainties of drug discovery for the drug discovery model, and issues relating to the potentially weak appropriability regime of platform technologies for the platform technology model. A third business model, the so called 'large biotechs', was also outlined. It was suggested that successful drug discovery companies would adopt a fully integrated business model analogous to the large pharmaceutical business model discussed in Chapter 7.

This chapter presents the results of an empirical analysis of the business models of a cross section of twelve biopharmaceutical companies, to test whether the business models adopted by the different types of biopharmaceutical companies can be defined in these terms. The results also suggest strengths and weaknesses of the models

adopted and, to the extent that these are recognised by the companies themselves, how they are adjusting their business models to cover identified weaknesses

Methodology

This chapter examines the business models of a cross section of 12 biopharmaceutical companies. The companies were chosen on the expectation that at least 2 or 3 would fall into each of the three types of biopharmaceutical business models. While in no way a random sample, the companies were chosen to represent a range of sizes, whether measured by market capitalisation or number of employees and to include a number of non-US origin. Table 11.1 sets out the companies and some of their characteristics.

The case study companies cover a vast range of sizes, from Amgen with a market cap of over $70 billion to Xenova with $45 million. Most companies were established in the 1990s; the exception being the two large biotechs, Amgen and Biogen, established in 1980 and 1978 respectively. Given the lead-times of the drug development process, more than a decade is required to establish the business model of the large research based biotech. For the newer drug discovery companies, their start date is an important factor in structuring their current business model and may be an important guide to their state of development.

Table 11.1 Case study companies

Name	H/Q	Market cap $m(1)	Staff no.(1)	Establishment date	Technology
Affymetrix	US	1541	905	1993	Genomics/ bioinformatics
Alexion Pharmaceuticals	US	200	140	1992	Autoimmune
Amgen	US	70325	7700	1980	
Biogen	US	5298	1992	1978	
Cambridge Antibody	UK	289	293	1990	Monoclonal antibodies
Human Genome Sciences	US	874	1010	1992	Genomics
ICOS	US	1238	469	1990	Autoimmune
ImClone Systems	US	982	399	1984	Cancer
LION Bioscience	Germ	66	590	1997	Bioinformatics
Millennium Pharmaceuticals	US	2055	1900	1993	Genomics
Qiagen	Neth	849	n.a.	1996 (IPO)	Diagnostics
Xenova Group Plc	UK	45	134	1987	Cancer

Note: (1) February 2003.
Source: SEC filings, Recap, annual reports and other company information.

Based on the technologies in which the companies specialise, as indicated in Table 11.1, it would be expected that Affymetrix, Human Genome Sciences, LION Bioscience, Millennium Pharmaceuticals and Qiagen would adopt a platform technology business model while Alexion Pharmaceuticals, Cambridge Antibody, ICOS, ImClone Systems and Xenova would adopt the drug discovery business model

The most important source of information on which the case studies are based is the 10-K reports provided by US listed biotechs to the US Securities Exchange Commission (SEC).[23] Failing that, in the case of non-US listed companies and in any case as back up, annual reports and company web sites were also consulted. The 10-K reports are a particularly valuable source being specifically structured to elicit company information in a business model format. At the time of the analysis, about half the companies had filed their 2002 reports. For the remainder, their 2001 reports where used. In addition, as part of obtaining a better understanding of the value network for each company, an analysis was undertaken of alliances listed on the ReCap database.

The decision to rely almost exclusively on company generated material, and 10-K reports in particular, as the source for much of the business model analysis, rather than secondary sources, reflects a view that the business model of each case study company is best developed from primary source material. The focus of this study is a comparison of how the different business models are structured by the firm and to some extent how this changes over time. The best source material for this is the firms own statements on these issues. As indicated above the 10-K reports require each firm, within a consistent format, to provide full disclosure of the same set of strategic issues. This allows the business model attributes to be analysed based on a consistent set of material across the case study firms.

The information available from these sources was used to document each company's business model within the functional structure suggested by Chesbrough and Rosenbloom (2002) referred to above.

[23] Available at http://www.sec.gov/edgar/searchedgar/companysearch.html

Business Model Attributes

This analysis of company business models follows the Chesbrough Rosenbloom (2002) framework used and developed in previous chapters.

Value proposition, market segments and competitive strategy

The largely qualitative data for the first three of the business model attributes, value proposition, market segments and competitive strategy is summarised in Table 11.2. More detail on the individual companies is presented in Appendix 11.1. This material consists, almost entirely of direct quotes taken from the companies' 10-K filings and annual reports.

Table 11.2 summarises the case study results for these three attributes. The value proposition describes the particular value of the companies' services or products, which is being offered to its users. The market segment identifies those which are the likely users of the products and services and how the revenue is generated. The competitive strategy is how the value generated by the firm is to be enhanced or otherwise protected from competitors. In reviewing and summarising the company information about these business model attributes, the biopharmaceutical companies appear to cluster into four groups.

Table 11.2 Qualitative business model attributes of biotech companies

Grp	Company	Value proposition	Market segment	Competitive strategy
1	Alexion Pharmaceuticals ICOS ImClone Systems Xenova Group Plc	Specialist expertise in discovery and development of therapeutic products.	Targeted on selected therapeutic area but no sales at this stage. Dependant on alliance revenues from large pharma or biotech partners.	Drugs offering superior efficacy. Superior competences/ capabilities.
2	Cambridge Antibody Human Genome Sciences Millennium Pharmaceuticals	Combine expertise in specialist technology with discovery and development of therapeutics.	Marketing technology platform or expertise to largely pharma companies. Also targeting therapeutics to particular areas. Dependant on alliance revenues from large pharma or biotech partners.	Unique technological basis for development of therapeutics.
3	Affymetrix LION Bioscience	Leadership in one or more specialist	Sale or licensing of technology products to a	Maintain technology leadership over

	Qiagen	technologies to improve efficiency of drug discovery and/or development process.	wide range of pharmaceutical and biotech companies.	competitors in specialist technologies offering significant cost savings in the drug disc. and development process.
4	Amgen Biogen	Expertise in integrated discovery, development and marketing of biotech products.	Have one or more blockbuster drugs which are sold globally.	Managerial and technological superiority and establishing proprietary positions through R&D.

Source: SEC 10-K reports and company annual reports.

Value proposition

There are four different value propositions identifiable from the company information. Group 1 companies seek to use their specialist expertise to develop human therapeutics. Group 2 companies have a leading position in a particular drug discovery technology, such as monoclonals in the case of Cambridge Antibody and offer this expertise to other companies as well as developing their own drugs. Group 3 companies have an expertise in a transversal platform technology which they are offering to other pharmaceutical and biotechnology companies to increase the efficiency and/or lower the cost of the drug discovery and development process. Group 4 offer an integrated capability in discovering, developing and marketing their own drugs. Each of Groups 1, 2 and 4 are focussed on drug development. While Group 4 companies are advanced in this process, Group 1 and 2 are at the earlier drug discovery and development phase.

The difference between Groups 1 and 2 is the willingness of the Group 2 companies to share their technology platform with other pharmaceutical and biopharmaceutical companies. In the case of Cambridge Antibody, the technology has been monoclonal antibodies, a drug technology. The Millennium Pharmaceuticals platform has been a comprehensive and integrated genomics based drug discovery platform and initially was dedicated to drug development for external parties. Human Genome Sciences has had a leading position in genomics based technologies to which it allowed access, through alliances, as well as using it for internal drug development.

Market segment

The market segment followed closely from the value proposition of the four groups of companies. The market segment for Group 1 companies was ultimately the

therapeutic user group. However there was typically an intermediate requirement to target one or more alliance partners to obtain funding. Group 2 companies also sought alliance revenues but typically in a different way. Alliance revenues came from granting access to the technology. This included both up front fees and royalties for successful use of the technology. These funds were then used to help finance internal drug development. Group 3 companies have licensed their technology or sold their technology based products to a broad range of pharmaceutical and biopharmaceutical companies and academic research centres. Group 4 companies were engaged in marketing their drugs to one of more major therapeutic user groups on a global basis.

Competitive strategy

The main distinction between the competitive strategies of the four Groups was the primacy afforded to either, expertise in a particular technology, or to the development of therapeutics. Both Group 2 and 3 companies stressed the need to maintain a technological superiority, while Group 1 companies stressed the need to develop therapeutics of superior efficacy. Group 4 companies were seeking advantage from their superior technological, organisational and proprietary position. According to the SEC 10-K reports and other documents, protection of intellectual property was an important aspect of competitive strategy for all companies. Patents were the key mechanism used, but the platform technology companies in particular, also used trademarks and copyright to provide IP protection. It is difficult to judge from the documents, the level of protection afforded by these strategies and therefore the relative appropriability of the products developed by these companies. This is a subject for the case studies presented in chapters 13 and 14.

Preliminary conclusions from analysis of value proposition, market segment and competitor strategy

On the basis of this analysis of these three qualitative components of the business models a number of preliminary conclusions can be drawn. Group 1 and Group 3 companies conform to the drug discovery and platform technology business models respectively defined in Chapter 8. Both these business models can be defined in terms of their different technologies, one drug discovery and the other platform technology. Accordingly their market segments are distinct, with the former focussed on the ultimate value of drugs marketed to a therapeutic area, while the intermediate

products and services of the latter are being marketed to pharmaceutical and biopharmaceutical companies. Some of the platform technology companies are distinguished from the drug discovery companies by having sales revenues and therefore already having identifiable market segments. The drug discovery companies, on the other hand, still have this aspect of their business model largely in prospect. They are operating on the basis that they will be able to establish a market for their product, either by themselves or in partnership, once or providing, it passes the necessary approval process. While the competitive strategies of both seek to enhance the value of their respective expertise and technology, one is in therapeutics and the other in platform technologies.

Group 2 companies appear to have adopted a hybrid business model. Their value proposition derives from the value created by having developed a technology expertise that can be used more broadly than developing drugs in house. The degree to which these companies stress the platform technology side, compared with their drug discovery capabilities, varies between companies. Their revenue model is a blend of the two. They seek earlier revenues from licensing access to their drug discovery platform, ahead of obtaining drug sales revenue. As with the pure form models, maintaining the value of their expertise in both technology and drug discovery is fundamental to their competitive strategy.

Thus as predicted by the resource based view, maintaining and enhancing their strategic assets in the form of technological expertise is fundamental to the competitive strategy for each of these three groups of companies.

The Group 4 companies have adopted value propositions and competitive strategies dependent on an integrated business model. They stress their integrated expertise in discovery, development and marketing of biotech products. They have successful drug selling programs and therefore established market segments. In this way they are analogous to the fully integrated business models of the large pharmaceutical companies.

Value chain structure

The pharmaceutical industry value chain is well defined as previously discussed in Chapter 6, with drug products passing down a pipeline from discovery to development, through to production and marketing. The changes in the industry value chain, arising from the impact of biotechnology, were discussed in Chapter 7. It was suggested that the pharmaceutical company value chain had become less integrated as it incorporated strategic assets provided by biopharmaceutical specialists. Some of these specialists were suppliers of platform technologies, while others where alliance partners providing drug discovery technologies. These specialists have their own value chains which reflect their role in this new industry value chain.

Table 11.3 sets out the two value chains, one for drug discovery and development and the other for the development of a specialist technology. A ☒ indicates engagement in a particular value chain activity. Although platform technologies tend to be intermediate products, which are inputs to the drug development value chains of other companies, their value chains are integrated, encompassing their own discovery, development, production and distribution activities. Each activity phase is likely to be much shorter than for drug development (Casper and Kettler 2001). Accordingly in Table 11.3, the discovery and development phases and the production and distribution of the technology have each been compressed into one phase.

Table 11.3 Value chain structure

Group	Company	Drug discovery & development				Platform technology	
		Disc.	Dev.	Prod.(1)	Dist.	Disc./ Dev.	Prod./ Dist.
3	Affymetrix					☒	☒
1	Alexion Pharmaceuticals	☒	☒				
4	Amgen	☒	☒	☒	☒		
4	Biogen	☒	☒	☒	☒		
2	Cambridge Antibody	☒	☒			☒	☒
2	Human Genome Sciences	☒	☒			☒	☒
1	ICOS	☒	☒				
1	ImClone Systems	☒	☒				
3	LION Bioscience					☒	☒
2	Millennium Pharmaceuticals	☒	☒			☒	☒
3	Qiagen					☒	☒
1	Xenova	☒	☒				

Note: (1) Excludes pilot or manufacturing for clinical trials.
☒ = comparatively low status of activity.

With the exception of the Group 3 companies discussed above, each of the companies is involved in drug discovery and development. The Group 1 drug discovery companies have a truncated version of the industry value chain lacking both production and distribution capabilities. Group 4 companies, on the other hand, have a fully integrated value chain involving discovery, development, production and distribution.

Group 3 companies also have the capacity to produce and distribute their technology based products. The complication arises with the value chains of those companies that have adopted hybrid models (Group 2). In addition to their drug discovery value chains, they have the capacity to both develop and distribute access to their technology platforms. However in contrast to Group 3 companies, they have no product to market other than access to these platforms. This distribution activity may not be as fully developed as for Group 3 companies and accordingly is marked with a grey ☒ to symbolise the comparatively low status of this activity.

Value network

It is acknowledged that value networks can involve many actors including venture capitalists, universities, government agencies as well as firms. However this analysis will focus on the network created by alliances between firms. In particular it provides details of the alliances, as listed on the Recap database, between the case study companies and other biopharmaceutical and pharmaceutical companies.

The analysis will firstly contrast trends in alliances over time, in which the case study company is the 'client' and those in which it is the 'developer'. The second is to examine the types of technology transfers being undertaken and the third is to study the value of alliance payments, particularly to observe whether they are revenue or expenditure and how this changes over time. It is not possible within the constraints of this thesis to examine in such detail every case study company. Instead this analysis of alliances is provided for a selection of the case study companies. One is chosen from each company group. The purpose of the analysis is to contrast the value networks formed by each case study company.

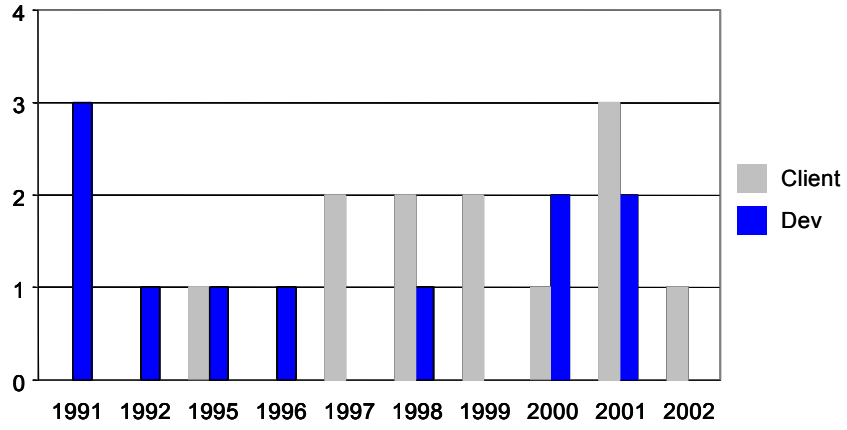
In Chapter 8, it was suggested that the value networks of platform technology companies were more extensive than those of drug discovery companies, because of their need for a wide range of upstream complementary assets, as well as a broad base of customer support. Drug discovery companies, on the other hand it was suggested, require a small number of important alliances, especially with pharmaceutical companies, to assist in the development of its drug or drug technology. This is one of the propositions tested in the following analysis.

ICOS

ICOS has successfully produced, in collaboration with Ely Lilly, its first approved drug – for erectile dysfunction, which was approved for sale in Europe in November 2002.

Since its establishment in 1990, ICOS has entered into a small but equal number of alliances as developer and client partner (see Figure 11.1). The technologies involved in the alliances are not extensive but concern screening and combinatorial chemistry. However a number as developer, such as those with Lilly and Biogen, have been extremely significant, and the reported revenues received far exceed alliance payouts as shown in Table 11.4 below[24].

Figure 11.1 ICOS: Number of client and R&D alliances



Source: ReCap, March 2003

[24] In this section alliance revenues and payouts have been manually extracted from data that Recap provides for selected companies in its database and is generally available only for the period since 1997. These are the alliance payments actually made or received rather than the payout values analysed in chapters 9 and 10.

Table 11.4 ICOS: Alliance revenues and payouts 1997 to 2001 ($ million)

	1997	1998	1999	2000	2001
Revenue	31.6	110.8	79.6	90.7	93.4
Payout				1.1	1.4

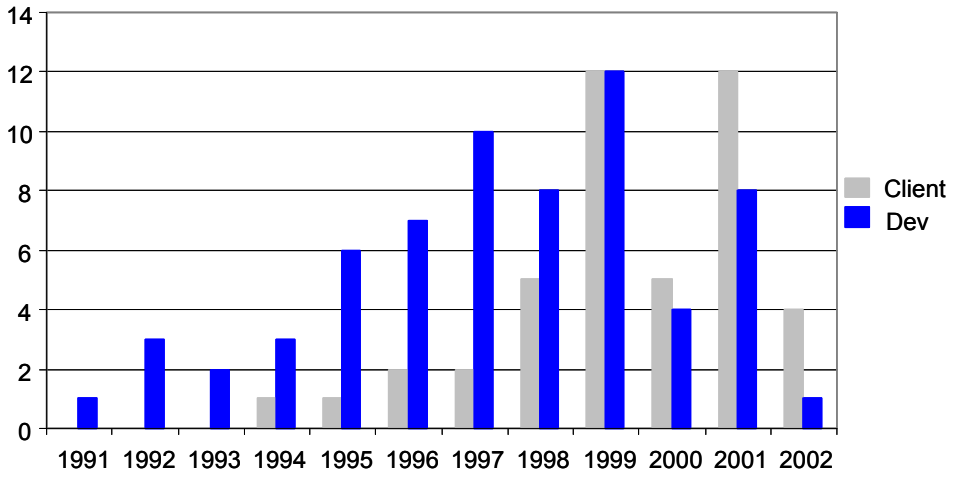
Source: ReCap, March 2003.

Millennium Pharmaceuticals

Millennium has previously been described as having adopted a hybrid model in which it used its science and technology platform not only to attract alliance partners but also to support an internal drug development program. The alliances show how the relative importance of these two activities has changed over time (see Figure 11.2).

In the first phase of its development until about 1998, Millennium formed a large number of significant alliances with large pharmaceutical companies, Hoffman La Roche, Lilly, Wyeth and Astra AB. With acquisitions, Millennium inherited additional important alliances such as with Schering-Plough. Through these alliances it effectively rented its considerable science and technology platform, particularly in genomics, to large pharmaceutical companies. The terms of the alliances typically involved substantial up front payments, milestone payments and royalties or other revenue sharing should the research produce marketable drugs.

Figure 11.2 Millennium Pharmaceuticals: Number of client and R&D alliances



Source: ReCap, March 2003

While the strategy of forming alliances with large pharmaceutical companies continued, those with Bayer (payout value $465 million), Aventis ($450 million) and Abbott ($250 million), being particularly significant, the number of alliances in which Millennium acted in the role of client increased dramatically rising from 2 in 1997, to 12 in 1999. This reflected the need to buy in new technology, particularly access to various types of databases as its own internal drug development program became relatively more important. For the first time ReCap records significant alliance payouts, $12 million in 2000, by Millennium.

In 2002, Millennium received for the first time significant product revenues ($160 million or 46% of total revenues). Revenue from strategic alliances fell for the first time in at least five years, from $246 million in 2001 to $193 million in 2002 as shown in Table 11.5.

Table 11.5 Millennium: Alliance revenues and payouts, 1997 to 2001 ($ million)

	1997	1998	1999	2000	2001	2002
Revenue	90.0	133.7	183.7	196.3	246.2	193.1
Payout	0	0	1.3	12.0	4.3	n.a.

Source: ReCap, March 2003. Millennium 10-K Report for year ended 31 December 2002.

Table 11.6 provides more details of the technologies involved, both as client and R&D provider.

Table 11.6 Millennium: Alliance technologies, 1981 to 2002

Technology	Client	R&D
Bioinfomatics	3	2
Combinatorial	3	12
Devices	1	
Gene Expression	8	13
Gene Sequencing	3	13
Microarrays	3	
Monoclonals - Transgenic Mice	5	
Pharmacogenomics	1	1
Rational Drug Design		5
Screening	6	5
Separations	1	
Service Laboratory		1
Transcription Factors	1	
Transgenics	1	
Total	36	52

Source: ReCap, March 2003.

As a contract researcher, Millennium's expertise is in genomics and combinatorial chemistry. As a client, while some of the technologies accessed are also in these areas, they also include a broad range of technologies such as microarrays and monoclonals (most notably in a $100 million alliance with Abgenix for XenoMouse technology).

This transition in Millennium's business model from pure platform technology to a hybrid and ultimately perhaps a 'large biotech' is reflected in its 2002 and 2003 10-K filings. In the Overview of the 2002 filing Millennium said:

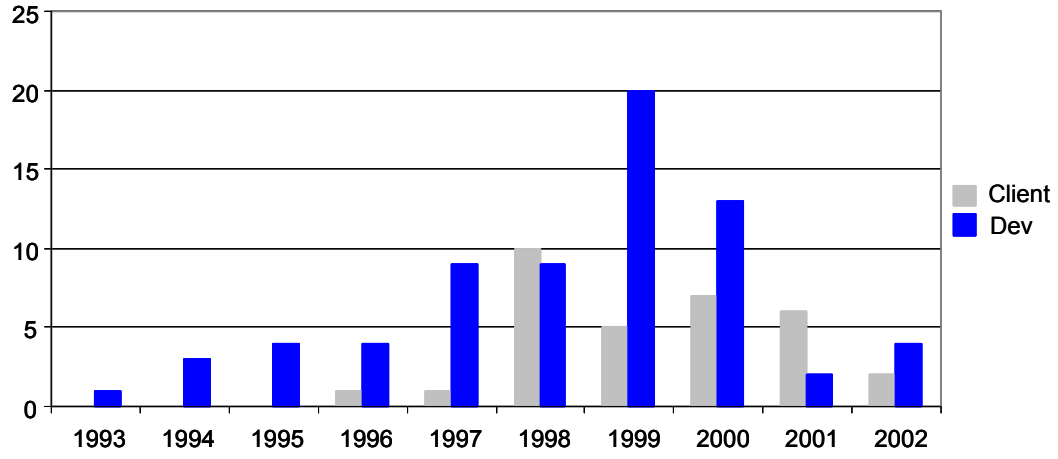
> We are a leading biopharmaceutical company focussed on *applying our comprehensive and integrated science and technology platform* to discover and accelerate the development of breakthrough drugs and predictive medicine product (author emphasis). (Millennium Pharmaceuticals, Inc. 2002)

Whereas in its 2003 10-K filing it made no mention of its 'comprehensive and integrated science and technology platform' simply stating 'we are a leading biopharmaceutical company focused on developing and commercializing products in several disease areas' (Millenium Pharmaceuticals, Inc. 2003).

Affymetrix

Affymetrix is a bioinformatics company specialising in the production of gene chips. In its early years 1993 to 1997 the vast majority of its alliances were in the role of providing R&D to a number of client companies. In the 5 years since then, alliances in which it was in the client role, commissioning research from other companies, had become more numerous (see Figure 11.3).

Figure 11.3 Affymetrix: Number of client and R&D alliances



Source: ReCap, March 2003

The nature of the technologies involved both as a client and as a developer is shown for the whole period in Table 11.7 below.

This shows the technologies of the alliances in which Affymetrix has been involved.[25] Not surprisingly for a specialist in gene chips a large number of 'developer' alliances are in gene expression (58) with an almost equal number in microarrays (47). Interestingly however, a similar pattern emerges for alliances in which it is in the role of the client. This emphasises the role of the platform technology company as an assembler of technology from other companies, as well as a provider of technology. Key alliances have been with bioMerieux, HP (Agilent Technologies), Human Genome Sciences, Glaxo and Roche.

Table 11.7 Affymetrix: Alliance technologies, 1993 to 2002

Technology	Client	Developer
Bioinfomatics	2	2
Devices		5
DNA probes	7	15
Gene expression	22	58
Gene sequencing	2	1
Microarrays	20	47
Pharmacogenomics	2	
Screening		2
Transgenics		1
Total	55	131

Source: ReCap, March 2003.

[25] As discussed in Chapter 10, although the majority of alliances involve only one technology some involve more than one. On average there are about 1.2 technologies per alliance.

This two way nature of its alliances is in contrast to its reported alliance revenues and payouts which as shown in Table 11.8 below appear to be quite one sided in favour of those in which it was the developer rather than client.

Table 11.8 Affymetrix alliance revenues and payouts, 1997 to 2001 ($ million)

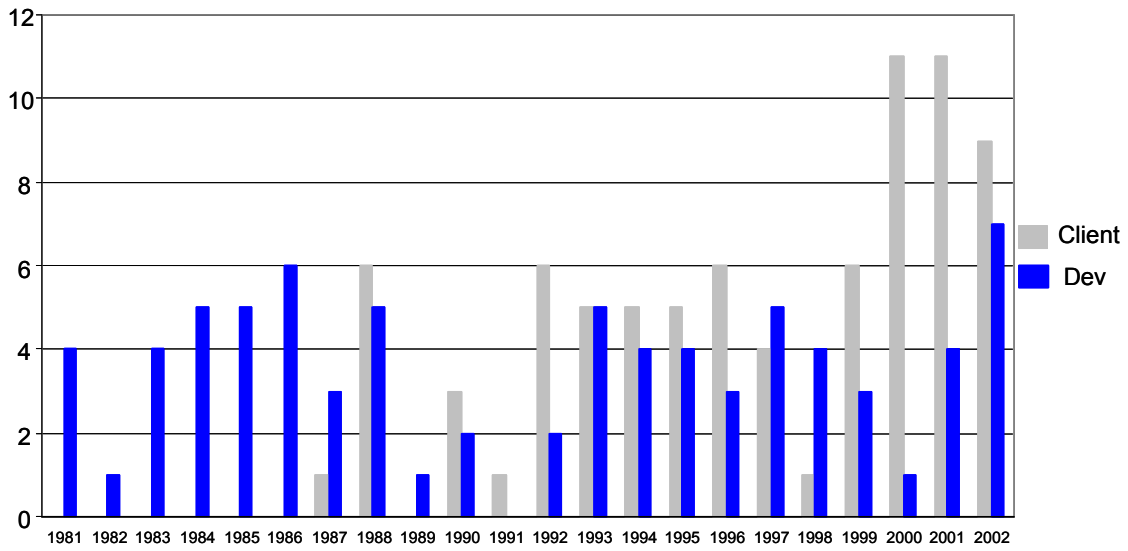
	1997	1998	1999	2000	2001
Revenue	19.8	52.0	105.3	200.8	224.9
Payout					0.8

Source: ReCap, March 2003.

Amgen

Amgen is a well established 'large biotech'. The nature of its alliance partnerships show that with maturity the number of alliances, in which it has played the role of developer, has declined and those in which it is the client have increased substantially in recent years.

Figure 11.4. Amgen: Number of client and R&D alliances



Source: ReCap, March 2003

As shown in Figure 11.4, Amgen was active in alliance formation in which it was the developer, but not as client, during the first 8 or 9 years of its existence. Following that period, there was a second phase in which the number of alliances in which it was in client and R&D roles were similar. In 2000, a third phase appears to have

commenced in which Amgen's role, as client is the dominant one. This is confirmed by the data on financial flows since 1997.

Table 11.9 Amgen: Alliance revenues and payouts, 1997 to 2001 ($ million)

	1997	1998	1999	2000	2001
Revenue					
Payout	19.1	10.2	70.9	72.7	12.0

Source: ReCap, March 2003.

This third phase completes Amgen's transformation from a drug discovery company to a major fully integrated biopharmaceutical company with a business model that is analogous to those of the large pharmaceutical companies.

Not surprisingly its call on new platform technologies is wide ranging, although relatively low in total number, as shown in Table 11.10 below of alliance technologies. As client they feature combinatorial chemistry, drug delivery, gene expression and sequencing.

This section has illustrated differences in the value network of four of the case study companies. It has shown that ICOS, a drug discovery company has a relatively small number of highly valuable alliances. Affymetrix, a platform technology company, in contrast has a large number of alliances both as client and developer. The alliance patterns for Millennium and Amgen have also been quite distinctive.

Table 11.10 Amgen: Alliance technologies, 1981 to 2002

Technology	Client	R&D
Bioinfomatics	2	
Combinatorial	13	
Devices	3	1
DNA Probes		1
Drug Delivery	9	2
Gene Expression	6	
Gene Sequencing	3	1
Immunoassay	2	
Implantable Devices	1	1
Microarrays	3	
Monoclonals - Transgenic Mice	2	
Rational Drug Design	2	2
Screening	12	2
Transgenics	1	
Total	59	10

Source: ReCap, March 2003.

Both ICOS and Affymetrix have received significant revenues from alliances and paid out very little as might be expected of early stage technology companies. Despite this imbalance, both companies have a large number of alliances in which they are client as well as developer, confirming the networked nature of their innovation processes. However the intensity of Affymetrix's alliance network is striking. Over the decade depicted, Affymetrix has entered into almost 100 alliances, compared with only 23 for ICOS. Both companies are of roughly similar size (market caps for Affymetrix of $1.5 billion and ICOS of $1.2 billion). However, as the leading producer of 'gene chips', Affymetrix has used a vast number of alliances to both access complementary assets and support the development of its products. ICOS on the other hand, has had a relatively small number of alliances, some of which have been highly significant, such as its alliance with Lilly producing a successful large selling drug.

As discussed, Amgen alliances are characteristic of a biopharmaceutical company undergoing a successful transition from drug discovery company to large biotech. The early years are marked by mostly R&D alliances and revenues. With success, the number and value of alliances as client came to dominate. Millenium shows signs of being on this path. Its early strategy was to use its powerful discovery platform, grounded in a knowledge of genomics, to attract very large alliance payments, not only to undertake work for its clients, but also to help fund its own successful drug development program. Its own statements indicate that it is no longer wishing to be viewed as a platform company, but more as a drug development company, perhaps suggesting that at least in this case, the 'hybrid' model is in fact a transition between a platform technology and drug discovery, or if successful, a 'large biotech' business model.

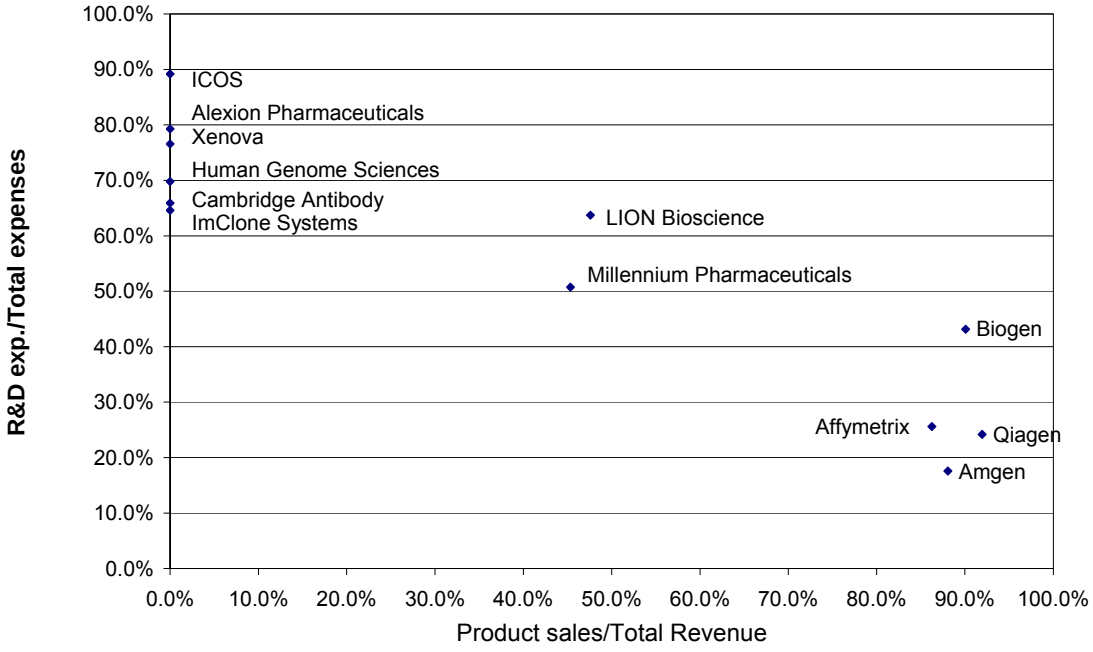
Cost structure and profit potential

The ultimate test of any business model is in its financial outcomes. Will it eventually produce an adequate profit? Will the investment in R&D, which for technology companies is always high, but in the initial stages overwhelmingly so, be adequately repaid? In other words is the business model financially sustainable? In particular will the firm through its revenue model be able to appropriate a sufficient share of the economic value created to be sustainable. It is beyond the scope of this thesis to

attempt a rigorous financial analysis of the case study companies. However there are some relatively simple financial parameters that help distinguish the business models and suggest something of their sustainability.

Two of the distinguishing features of the three business models are firstly, the proportion of total expenses devoted to R&D, and secondly, the proportion of total revenue derived from product sales. As a technology company successfully develops it would be expected that R&D as a proportion of total expenses would fall as other expenses such selling and administration would rise. Likewise product sales should rise as a proportion of total revenues as the importance of sales relative to other forms of revenue such as alliances rises. Figure 11.5 shows the two measures plotted against each other for each of the case study companies. For instance for Qiagen, product sales are 92% of total revenues and R&D is 24% of total revenues.

Figure 11.5. Expenditure on R&D vs. product sales: Case study companies 2002(1)



Notes (1) except for Qiagen, Affymetrix, Imclone Systems and Xenova which are 2001
Source: Company 10K and annual reports

The case study companies are clustered in three zones. The first contains largely, Group 1 companies, those found to be following the drug discovery business model. These devote almost all of their financial resources to R&D, ranging from 89% for ICOS to 70% for Human Genome Sciences, but receive no revenue from product

sales. Also included in this cluster is a Group 2 company, Cambridge Antibody following a hybrid business model. The second clearly discernible cluster is formed by those companies deriving most of their revenue from product sales. This cluster contains both of the larger biotechs, Amgen and Biogen, as well as two platform technology companies Affymetrix and Qiagen. With high product sales as a proportion of total revenues and low R&D as a proportion of total expenses these companies appear to have reached a position of greater sustainability. Product sales are sufficient to fund R&D expenditure and generate a profit. Only Affymetrix of this group is still unprofitable, although at only about 13% of revenues, breakeven is not far away[26]. In the middle are two companies, LION Bioscience and Millennium.

The sustainability of the first cluster depends on the successful discovery and development of a drug. Of those in the middle, Millennium appears to be seeking a path to join the 'large biotechs', its future being dependent on sales revenue from drugs it has discovered on its own or as part of its research collaborations.

Table 11.11 is a summary of financial data and provides some confirmation of the above analysis. The table shows current profit (or loss) as a percentage of total expenses and a measure of cash flow sustainability (total cash and marketable securities as a ratio of current net cash from operations). The latter provides a measure of the number of years the company can continue to spend at its current rate.

The four companies in the second cluster identified in Figure 11.5 above, Qiagen, Amgen, Biogen and Affymetrix are the most profitable or least unprofitable. They are either cash positive or have very comfortable cash reserves. Four of the five drug discovery companies in the first cluster are the least profitable of the sample, although they each appear to have comfortable cash reserves. Similarly the 'hybrid' companies have relatively high losses. LION Biosciences has both high loses and with very low cash reserves appears to be at risk.

[26] Amgen also reported a loss for 2002 after writing off $3 billion arising from its Immunex acquisition. Excluding this write-off its profit was $2.3 billion.

Table 11.11 Summary financial data: Case study companies, 2002

		Profit/Loss	Sustainable cashflow
		% expenses	Recent cash burn rate (years)
Qiagen	(1)	51%	Cash positive
Amgen		36%(2)	Cash positive
Biogen		32%	Cash positive
Affymetrix	(1)	-13%	13.7
Camb. Antibody	(3)	-67%	4.8
Human Genome Sci		-56%	3.2
Millennium		-59%	5.0
LION	(3)	-64%	0.8
Camb. Antibody	(3)	-67%	4.8
Alexion		-75%	6.7
ImClone Systems	(1)	-76%	4.8(4)
Xenova	(1)	-86%	6.3
ICOS		-99%	4.9

Notes: (1) 2001.
(2) Excludes $2,991.8m write off of in-process R&D resulting from the Immunex acquisition. Net income in 2001 $1,686.3 million.
(3) Converted from STG @ $US1.5563 and Euro @ 0.8766.
(4) Includes deferred revenue from BMS of $197.4 million.
Source Company 10-K and annual reports

Conclusion

The purpose of this chapter has been to analyse the business models of a cross section of twelve biopharmaceutical firms to test whether they could be defined in terms of three business models, drug discovery, platform technology and so called 'large biotechs'. In doing so, it sought to illustrate the usefulness of the business model concept. As set out in Table 11.12, the majority of firms have fallen into the business models predicted by their technological regime. There are four companies predicted by their technology and confirmed by the analysis of their business model as drug discovery companies. Their value proposition, market segment and competitive strategy were each focused on the firms' specialist expertise in drug discovery and development and producing drugs of superior efficacy. None had developed distribution or production capabilities and the value network of the one reviewed, ICOS, had a small number of important alliances. None of the companies had product sales and as a group had the highest proportion of losses to expenses.

The three companies expected to be platform technology companies based on their technologies were also confirmed as such by the business model analysis. Their value proposition, market segment and competitive strategy were each focused on specialist expertise and leadership in a particular platform technology. Each had adopted a full

value chain for the development and marketing of their products and services. The value network of the single company reviewed, Affymetrix, had a large number of alliances with diverse technologies. One company was profitable Qiagen and Affymetrix was close to breakeven.

The business model analysis of the two large biotechs also confirmed their status as having fully integrated business models. They were seeking to exploit their management expertise in integrated discovery, development and marketing of biopharmaceutical products with a view to developing at least one global blockbuster. These firms also appeared to be the most financially successful. The one whose alliances were analysed, Amgen, demonstrated a trend towards greater in-licensing of a range of platform and drug discovery technologies in a similar pattern to large pharmaceutical companies.

Table 11.12 Comparison of predicted and actual business models

Company	Technology	Predicted BM	Actual BM
Affymetrix	Genomics/ bioinformatics	Platform Tech	Platform Tech
Alexion Pharmaceuticals	Autoimmune	Drug Discovery	Drug Discovery
Amgen		Large biotech	Large biotech
Biogen		Large biotech	Large biotech
Cambridge Antibody	Monoclonal antibodies	Drug Discovery	Hybrid
Human Genome Sciences	Genomics	Platform Tech	Hybrid
ICOS	Autoimmune	Drug Discovery	Drug Discovery
ImClone Systems	Cancer	Drug Discovery	Drug Discovery
LION Bioscience	Bioinformatics	Platform Tech	Platform Tech
Millennium Pharmaceuticals	Genomics	Platform Tech	Hybrid
Qiagen	Diagnostics	Platform Tech	Platform Tech
Xenova Group Plc	Cancer	Drug Discovery	Drug Discovery

However three companies, two predicted to be platform technology companies, Human Genome Sciences and Millennium Pharmaceuticals, and one predicted to be a drug discovery company Cambridge Antibody were better classified as having a ‘hybrid’ business model since they combined aspects of the two pure model forms

Does the hybrid model offer advantages over the two other start-up business models? One advantage is the diversification of funding sources. The technology access fees can be used to assist the funding of internal development. It may also help establish contacts that lead to new alliances. However, it risks exposing the firm’s key strategic

assets to firms that may be better placed to exploit them. The firm would need to be confident that the commercial fees for access were adequate relational rent.

The other issue raised in Chapter 8 is the potentially weak appropriability regime for platform technology companies. It has not been possible in these case studies to deal satisfactorily with the appropriability issue. Adequate protection for IP is raised as a key strategic issue in many of company reports reviewed but it has not been possible to make a comparative evaluation between the companies. Nonetheless in general, patented drugs are better protected than platform technologies. This may help to explain the adoption of the 'hybrid model'. One of the motivations for the hybridisation of the business model by companies, such as Millennium and Cambridge Antibody is that internal drug discovery programs offer the potential to gain a greater share of the upside from drug development.

Platform technology companies, such as Qiagen and Affymetrix sell a product and have dedicated sales forces. Qiagen sells kits for the separation, purification and handling of nucleic acids (DNA/RNA). Affymetrix, as discussed, sells 'gene chips'. This revenue model appears to be more successful than one based on a 'fee for service' adopted by platform companies, such as LION Bioscience. The fees charged for access to technology platforms tend to provide an inadequate return on funds invested.

More work is required to analyse the sustainability of the drug discovery business model. It would appear from this analysis, that none of the drug discovery companies currently receive sufficient alliance revenues to sustain a 'contract research' revenue model, in which a combination of milestone payments and royalties provides sufficient revenue to meet R&D expenses and ongoing profitability. Each of these case study companies will need to make a discovery breakthrough to be sustainable. The large biotechs, Amgen and Biogen, which have developed fully integrated business models, seem to have a sustainable business model.

The tentative conclusions to be drawn from this analysis are that, of the case study companies, seven of the ten specialist biopharmaceutical companies could be defined by their technological regimes. Two large biotechs could also be identified as

successful fully integrated drug discovery companies. However three companies, one drug discovery and two platform technology companies had adopted ‘hybrid models’. This issue will be explored in greater detail in the next chapter.

In terms of the sustainability of the various business models, only the large biotechs and the platform companies with a product for sale, such as Qiagen, appeared sustainable. The business model of the drug discovery companies and the ‘fee based’ platform companies appeared, for different reasons, to be uncertain.

Appendix 11.1 Detailed Business Model Attributes

Direct quotes from company annual reports, SEC 10-K filings and company web sites.

Company	Value Proposition	Competitive Strategy
Group 1		
Alexion Pharmaceuticals	We believe that our GeneChip® system can facilitate the drug discovery and development process and improve the effectiveness and efficiency of health care. Our business strategy is to capitalize on our leadership position in the DNA probe array field by applying our GeneChip® technologies to three primary areas: gene expression monitoring, DNA analysis and health management (Alexion Pharmaceuticlas 2001, p. 4).	Company believes its drugs have superior performance to those being researched by or under trial or sale by competitors (Alexion Pharmaceuticlas 2001, p. 24).
ICOS Corp	ICOS is a product-driven company that has expertise in both protein-based and small molecule therapeutics. We combine our capabilities in molecular, cellular and structural biology, high throughput drug screening, medicinal chemistry and gene expression profiling to develop highly innovative products expected to have significant commercial potential (ICOS Corporation 2002, p. 1).	We believe our strategy of targeting multiple therapeutic areas with drugs that act through distinct molecular mechanisms increases our chances of successfully developing commercial products (ICOS Corporation 2002, p. 1).
ImClone Systems	ImClone Systems' goal is to become a fully-integrated biopharmaceutical company that has the capability and resources to take its novel pipeline compounds and develop them from the research and development stage through to commercial manufacture, marketing and sales (www.imclone.com).	The Company has dedicated significant resources to hiring a talented group of scientists and establishing new laboratory facilities for its chemistry department. This department has been charged with identifying and developing novel therapeutics that interrupt the internal cancer cell-signaling pathways that enable tumors to grow, spread and survive cell damage. Our manufacturing capabilities remain a cornerstone in building a strong commercialization infrastructure to support this effort (ImClone Systems 2001).
Xenova Group Plc	Xenova is an integrated drug discovery and development company with both small molecule and biologics capabilities (Xenova Group PLC 2003).	Technology represents a unique approach to the biological assessment of new chemical entities (NCEs). The key advantage … is the provision of high-quality data at earlier time points, thus accelerating the discovery of NCEs, while providing real savings in the time and cost of drug development (Xenova Group PLC 2003).

Group 2		
Cambridge Antibody Technology Group Plc	CAT's strategy is to exploit the power of its platform technology to build a balance of long-term revenues from the development of novel antibody-based therapeutic products, and short-term revenues from research collaborations and licences of its technology (Cambridge Antibody Technology Group PLC 2003).	The foundation of CAT's business is its unique antibody technologies, which it continues to develop and exploit. Based on this, CAT has established a position as a world leader, in the development of human monoclonal antibodies as new treatments for disease (Cambridge Antibody Technology Group PLC 2003).
Human Genome Sciences	We are a leading genomics and biopharmaceutical company focused on therapeutic product development and functional analysis of genes using our proprietary technology platform (Human Genome Sciences 2001, Overview).	We have extensive capabilities in gene discovery, intellectual property protection and preclinical and clinical development (Human Genome Sciences 2001, p. 36). Human Genome Sciences holds patents on 205 human genes, pending patents on another 7500 genes (in 2002). We initially set out to find as many genes as possible and are now using that information to develop medical and pharmacological products. We use automated high-speed technology to: - rapidly identify the function of and obtain proprietary rights to a substantial number of genes; - select genes with the greatest potential for the treatment and diagnosis of human disease. (Human Genome Sciences 2001, p. 21).
Millennium Pharmaceuticals	'…focused on applying our comprehensive and integrated science and technology platform to discover and accelerate the development of breakthrough drugs and predictive medicine product' (Millenium Pharmaceuticals 2001, p. 1).	'…quality and breadth of our technology platform the skill of our employees and our ability to recruit and retain skilled employees, our aggressive program of seeking patent protection for gene discoveries, our capabilities for early stage research and drug discovery and our capital resources are comp strengths (Millenium Pharmaceuticals 2001, p. 28).
Group 3		
Affymetrix	We believe that our GeneChip® system can facilitate the drug discovery and development process and improve the effectiveness and efficiency of health care. Our business strategy is to capitalize on our leadership position in the DNA probe array field by applying our GeneChip® technologies to three primary areas: gene expression monitoring, DNA analysis and health management (Affymetrix 2001, p. 4).	Our business strategy is to capitalize on our leadership position in the DNA probe array field by applying our GeneChip® technologies (Affymetrix 2001, p. 5).
LION Bioscience	LION Bioscience is dedicated to enabling life science companies to bring products to market faster through comprehensive process integration and	LION's SRS platform is the industry standard for data integration. More than 60 leading life science companies and over 130 academic institutions use

	decision support solutions across the entire research and development value chain. LION's team of scientific and IT experts combine their domain expertise to develop performance software solutions best suited to life science research (Lion Bioscience AG 2002a).	SRS. The core strength of the SRS system is to provide rapid access and query functionality to more than 500 mainly flat-file or text-based databases, representing the vast majority of public biological databases. Their content is required predominantly for the early steps of the R&D process (Lion Bioscience AG 2002b).
Qiagen	'…is the world's leading provider of innovative enabling technologies and products for the separation and purification of nucleic acids' (Qiagen 2001, p. 11). 'Its technologies represent substantial advances in the speed, reliability and ease of use of nucleic acid separation and purification processes and the purity and yield of the resulting nucleic acids' (Qiagen 2001, p. 13).	The Company believes that its competitors do not have the same comprehensive approach to nucleic acid separation and purification and therefore cannot provide the broad range and depth of products and services offered by QIAGEN in that area. QIAGEN believes that its proprietary technologies and products offer significant advantages over competitors' products, with regard to purity, speed, reliability, and throughput (Qiagen 2001, p. 31).
Group 4		
Amgen	Discovers, develops, manufactures, and markets human therapeutics based on advances in cellular & molecular biology (Amgen 2001a, p. 2). The Company focuses its research and development efforts on human therapeutics delivered in the form of proteins, monoclonal antibodies, and small molecules in the therapeutic areas of nephrology, cancer, inflammation, and neurology and metabolism (Amgen 2001a, p. 2).	Summary of points from *Annual Report 2001* and 10-k filings. - Licensing and other collaborative arrangements important source of product candidates that complement internal R&D (Amgen 2001b, p. 23). - Combination supplies 'robust pipeline of potential therapeutics' supported by clinical development capabilities around the world.(high value drug development pipeline). - Able to leverage recently built-up sales and marketing infrastructure. - Speed with which the Company can develop products, complete the testing and approval process, and supply commercial quantities of the product to the market is expected to be important to Amgen's competitive position (Amgen 2001a, pp. 10-13).
Biogen	Global biopharmaceutical company that develops, manufactures and markets novel human therapeutic products. Our primary focus is developing pharmaceutical products that meet unmet medical needs, particularly in our core therapeutic areas of neurology, dermatology and rheumatology (Biogen 2002, p. 2).	We believe that competition and leadership in the industry will be based on managerial and technological superiority and establishing proprietary positions through research and development. Leadership in the industry may also be influenced significantly by patents and other forms of protection of proprietary information (Biogen 2002, p. 9).

Chapter 12. Biopharmaceutical Value Chains

Introduction

In the previous chapter a series of company case studies was used, firstly to test whether the concept of the business model, based on the technological regime of the companies, provided a useful framework of analysis, and secondly whether the nature of the business model could provide a guide to the likely sustainability of the firm. Two issues arose from that analysis, which are to be further tested in this chapter.

The first is that, as noted, a number of case study companies appeared to be following a hybrid model in which aspects of the two models, drug discovery and platform technology are merged. That is, not all the specialist biopharmaceutical companies fell neatly into the two business models based on one of the two technological regimes. Is this hybrid a more sustainable business model than either separately?

The second issue is the sustainability of the pure form drug discovery business model. It was noted that companies that had adopted this model had no revenue from product sales and were thus dependent on cash flow largely from alliances and equity raisings. On the other hand, the model of the most successful biopharmaceutical companies appeared to be the fully integrated one, analogous to the large pharmaceutical companies. Is this the model to which each of the drug discovery companies aspire or is there another model, as suggested by Arora, Fosfuri and Gamberdella (2001a, p. 67), of the contract research company, providing drug candidates for large pharmaceutical companies, but not seeking to develop their own drugs ?

The purpose of this chapter is to use value chain analysis of a large number of biopharmaceutical companies to further examine these two issues. The first is to examine the value chain activities of companies specialising in the commercialisation of platform and drug discovery technologies to determine the extent to which this indicates that the hybrid model has been adopted. The second is to examine the extent to which drug discovery companies have adopted the contract research model.

Methodology

In this exercise, the 2002 SEC 10-K report[27] for each of 145 US-listed specialist biopharmaceutical companies was reviewed to identify the activities being undertaken by each company as part of a simplified value chain. The companies are a subset of 233 companies classified by Recombinant Capital (Recap) (Degami and Van Brunt 2003) according to their principal technology or therapeutic area. The selected subset excludes those companies which were not classifiable as specialist biopharmaceutical companies, such as the 'large biotechs', agricultural biotechs and clinical research and development organisations or for which information was not available.

As previously explained the 10-K SEC filings provide a reasonably comprehensive report of the activities of each company in a standardised format, with some of the headings matching those of the business model. In reviewing the 10-K reports, evidence was sought for the following value chain activities being conducted by each company:

- Drug discovery
- Drug development – in-house
- Drug development – contract
- Commercial platform technology development
- Manufacturing – in-house
- Distribution – own marketing team

Hybridisation

The first issue is to examine the extent of hybridisation, that is the extent to which firms engage in both technology development and drug discovery. Technology development in this context is that undertaken for external sale. It includes new drug discovery and platform technologies sold or licensed to other companies. It does not include new technologies developed for the exclusive use of the developer, as part of its own drug discovery and development program.

[27] Available at http://www.sec.gov/edgar/searchedgar/companysearch.html

Table 12.1 presents the results for the value chain analysis for technology development and drug discovery by technology or therapeutic area. These are categories adopted by Recap and allow the companies to be divided between the major platform technologies and therapeutic areas. The therapeutic areas do not match exactly to drug discovery technologies but some correspondence may be inferred. The technology categories are reasonably high level, but useful as an approximate guide to the major platform technologies.

Table 12.1 Value chain analysis by technology/therapeutic area

Type of technology/ therapeutic area	No. with tech dev.	No. with drug disc.	No. hybrid	Total
1st generation genomics	5	5	5	5
Autoimmune	2	8	2	8
Cancer	7	29	7	32
Cardiovascular	0	4		4
Chemistry	4	5	2	7
CNS	0	6		6
Delivery	14	4	4	15
Diagnostics/imaging	13	3	3	13
Genomic targets	9	7	7	9
Genomic supply	4	1	1	4
Gene therapy	8	7	6	9
Infection	1	12	1	14
Metabolic (1)	0	5		6
Other	6	2	2	6
Screening	7	7	7	7
Grand total	80	105	47	145

Note: (1) One of the metabolic companies undertakes no drug discovery activities having decided to specialise in drug development of in-licensed drugs.
Source: Recap, SEC 10-K reports for 2002.

Of the total 145 firms, 80 are involved in technology development and 105 in drug discovery and 47 are involved in both. The largest groupings of hybrids are in genomic targets, screening and cancer.

Table 12.2 shows the data from Table 12.1 in the form of proportions of the total number of firms in each technology or therapeutic group ranked by the extent of hybridisation.

Firstly Table 12.2 shows the strong correspondence between the companies classified by Recap as being involved in platform technologies and the proportion of companies engaged in technology development. For most of the platform technologies, 100% of

the firms so classified are engaged in technology development. Only those firms classified by Recap as 'chemistry', a mixed collection of seven companies, have a relatively low proportion at 57% engaged in technology development. This reflects the varied functions of the firms included in that classification. Some are engaged in platform technologies, such as bioinformatics while others are drug discovery companies engaged in structural biology.

Table 12.2 Value chain analysis by technology/therapeutic area (% of total)

Technology/ Therapeutic area	Platform/ drug disc.	% tech. dev.	% drug disc.	% hybrid
1st generation genomics	PT	100	100	100
Screening	PT	100	100	100
Genomic targets	PT	100	78	78
Gene therapy	PT	89	78	67
Other	PT	100	33	33
Chemistry	PT/DD	57	71	29
Delivery	PT	93	27	27
Genomic supply	PT	100	25	25
Autoimmune	DD	25	100	25
Diagnostics/imaging	PT	100	23	23
Cancer	DD	22	91	22
Infection	DD	7	86	7
Cardiovascular	DD	0	100	0
CNS	DD	0	100	0
Metabolic	DD	0	83	0

Source: Recap, SEC 10-K reports for 2002, author analysis

Secondly, there is a high correlation between those adopting a hybrid strategy and a specialisation in a platform technology. All of the companies specialising in first generation genomics and screening and a high proportion of those focussing on genomic targets and gene therapy are following the hybrid strategy. In general the proportion of drug discovery specialists in each therapeutic area that have adopted a hybrid strategy is low, the highest being autoimmune with 25%.

Does the hybrid model perform better than the 'pure form' models? One indicator of financial performance adopted in Chapter 8 was market capitalisation. This has the advantage of reflecting a market assessment of the future value of the company's sales from existing products and those under development. The use of the market to value a company's intangible assets follows Griliches (1981), Cockburn and Griliches (1988) and Hall (1993).

Table 12.3 provides average market capitalisations, for end December 2002, sourced from Recombinant Capital as previously described, for platform technology and drug discovery companies, together with their pure form and hybrid variants. The average valuation for the two platform technology models is $300.9 million for the 'pure form model and $339.5 million for the hybrid. Although the t statistic indicates that the difference is not significant at the 5% level, the higher market cap for the hybrid model may suggest that there is some advantage in adopting the hybrid model for platform technology companies. Indeed much of the difference is explained by the successful adoption of the hybrid model by Human Genome Sciences and Millennium Pharmaceuticals both with market capitalisations over $1000 million. On the other hand the small number of drug discovery companies adopting the hybrid model has on average a significantly lower average value at $155.3 million compared with $470.6 million for the pure form, suggesting that there is little value in the in the hybrid model for drug discovery firms.

Table 12.3 Average market capitalisation by business model type, 2002 ($ million)

	Pure form	Hybrid	Total	t Stat
Platform technology	300.9	339.5	321.8	0.371
No. of companies	33	39	72	
Drug discovery	483.1	155.3	438.2	2.332
No. of companies	63	10	73	

Source: Recap, SEC 10-K reports for 2002, author analysis

These results are not inconsistent with the hypotheses that there is an advantage for platform technology companies with poor business models, or weak appropriability in particular, to diversify into drug discovery and development. For instance, the key to the relative success of the genomic supply companies such as Affymetrix may be that their offering is more typically a consumable product and more easily appropriable, than the supply of a service. In contrast the screening and genomics target companies, such as Celera Genomics have specialised in developing and providing licensed access to compound libraries. The cost of maintaining these libraries is high, compared with the fees charged. It is not therefore surprising that such companies have adopted a hybrid strategy, using their technology platforms for their own drug discovery programs.

Contract Research Model

Arora, Fosfuri and Gamberdella (2001a, p. 67) suggest that the biotech industry is consolidating 'toward a structure in which an upstream industry of specialised technology suppliers has become a stable source of new products and technologies … to the downstream producers'. Undoubtedly this relationship between upstream technology suppliers and downstream producers has been facilitated by the much increased use of various types of alliances, as discussed in chapters 9 and 10. This tendency has also been assisted, as argued by Arora, Fosfuri and Gambardella (2001a), by changes in the markets for technology, including biotechnology, that have improved the ease with which technology can be transferred because of the increased extent to which the relevant technology can be decomposed into independent tasks and commoditised. This has been particularly the case for information technology, but also holds true in biotechnology, both for platform technologies, e.g. 'gene chips' and for patentable drugs and drug candidates.

The upstream developers in this model are the drug discovery companies, which specialise in producing new drugs for the pharmaceutical company product pipelines and platform technology companies, focussing on new technologies that address pipeline productivity improvements. If such a model was to be stable, then it could be expected that the objectives and business strategies of the upstream companies would be directed primarily towards generating business as upstream specialists.

To test this proposition, value chain analysis was conducted for the companies analysed in the previous section. The company 10-K reports were reviewed to identify drug development activities and whether they were conducted in house or under contract. As discussed in Chapter 6, drug development is the next stage along the pipeline from discovery, when preclinical trials commence. An attempt was made to identify those companies conducting contract research, but the results were considered unreliable.

Table 12.4 presents the number of companies engaged in drug discovery and in-house drug development classified by their technology or therapeutic area. It shows that of the total 145 companies, 105 were engaged in drug discovery and an even higher

number, 111 were involved in in-house drug development. The higher number for in-house drug development reflects the decision of a number of firms to in-licence drug candidates for development rather than engage in the discovery process themselves.

Of the 70 companies specialising in one of the therapeutic areas, 69 or 99% of companies are engaged in drug development in house. Only one company Xoma Ltd, which develops and manufactures antibodies and other protein-derived products is engaged in collaborative only development of its products.

Table 12.4 Value chain analysis by technology/therapeutic area: Drug discovery and in-house drug development

Technology/ therapeutic area	Drug discovery		Drug dev. in house		Total
	No.	% total	No.	% total	No.
Drug discovery					
Autoimmune	8	100	8	100	8
Cancer	29	91	32	100	32
Cardiovascular	4	100	4	100	4
CNS	6	100	6	100	6
Infection	12	86	13	93	14
Metabolic	5	83	6	100	6
Total drug discovery	64	91	69	99	70
Platform technology					
1st generation genomics	5	100	5	100	5
Chemistry	5	71	2	29	7
Delivery	4	27	7	47	15
Diagnostics/imaging.	3	23	3	23	13
Genomic targets	7	78	8	89	9
Genomic supply	1	25	1	25	4
Gene therapy	7	78	7	78	9
Screening	7	100	7	100	7
Other	2	33	2	33	6
Total platform	41	55	42	56	75
Grand total	105	72	111	77	145

Source: Recap, SEC 10-K reports.

As expected the proportion of companies classified as specialising in one of the platform technologies is lower than those specialising one of the therapeutic areas. Nonetheless a majority of platform technology companies are engaged in drug discovery and in house development, 55% and 56% respectively. This high average reflects the almost universal adoption of the hybrid strategy for companies specialising in screening technologies, first generation genomics and genomic targets.

Overall the proportion of companies pursuing their own in-house drug development programs is very high. There were only a few companies, such as the one referred to above, that had a stated strategy of contract only research. If a stable hierarchy is to be established between upstream contract research firms and downstream large pharmaceutical firms as Arora, Fosfuri and Gamberdella (2001a) suggest, then it will be in spite of the stated strategy of the vast majority of biopharmaceutical firms.

This strategy of in house drug development is not surprising. Companies cannot afford to forgo the possibility of hitting the 'jackpot' as a result of a successful in-house drug development (Dierickx and Cool 1989). Although the results presented here are necessarily partial, they confirm other results in this thesis that suggest that the ultimate aim of the vast majority of drug discovery companies, and a fair proportion of platform technology companies, is to achieve success in drug development and migrate to a fully integrated business model.

For platform technology companies this means devoting an increasing proportion of their resources to drug discovery and for the drug discovery companies it means conducting in-house drug discovery activities, perhaps in parallel with collaborative research. This suggests that for such firms to be fixed in the value chain as upstream suppliers of drug candidates for large pharmaceutical firms would be inconsistent with their aspirations. The current alliance structure between the drug discovery or platform technology company and pharmaceutical companies may be transitory. It may be a temporary funding mechanism for companies with a strategic development objective of becoming fully integrated biopharmaceutical companies.

Summary

This analysis, summarised by type of company in Table 12.5, demonstrates that while almost all of the companies classified as drug discovery and platform technology companies are as expected, specialists in drug discovery and technology development respectively, more than half of platform technology companies are involved in drug discovery and development. On the other hand, only a small proportion, 16% of drug discovery firms are involved in technology development for external commercial use.

Table 12.5 Proportion of companies engaged in each value chain activity (%)

Category	Drug discovery	In-house drug development	Technology development
Platform technology	55	56	97
Drug discovery	91	99	16

Source: Recap, SEC 10-K reports for 2002

Although the majority of platform companies appear to be adopting a hybrid strategy, some 45% are 'platform technology only' specialists. It is beyond the scope of this thesis to provide a detailed analysis of this group of companies, but as might be expected they include the platform technology companies, such as Qiagen and Affymetrix with well defined platform technology products.

This analysis is based on the activities undertaken by a cross section of biopharmaceutical companies at a point of time. Clearly the conclusions could be more confidently drawn if this value chain analysis was to be conducted at intervals over a period of a decade or more. The process of reviewing each of the 10K reports for each company is time consuming and further analysis is beyond the scope of this thesis. Nonetheless the case study analysis to be presented in the next chapter, which includes a study of bioinformatics companies over time provides further support for these conclusions.

Conclusions

This chapter set out to test two propositions using value chain analysis of 145 specialist biopharmaceutical companies. The first was to examine the extent of hybridisation and whether the hybrid business model was likely to be more sustainable than the pure form models. The second was to test for evidence of the contract research model suggested by Arora, Fosfuri and Gamberdella (2001a).

The analysis indicated that the extent of hybridisation was high amongst platform technology companies, with 55% involved in drug discovery, as well as technology development. The technologies in which such companies had specialised, such as screening and genomics offer the opportunity of internal drug discovery and this can be expected to have attracted such companies to the hybrid model. It was low amongst drug discovery companies, with only 16% of such companies also involved in technology development for external commercial use.

Although the results are partial, there was some evidence to support the proposition that the hybrid model is more sustainable for platform technology companies. The 'hybrids' had a somewhat higher market capitalisation than the specialist platform technology companies. However for the drug discovery companies, the reverse was true with the hybrids having a significantly lower market capitalisation than the specialist drug discovery companies.

In adopting the hybrid model, these companies have taken on the higher risk profile of the drug discovery companies. However one of the advantages of the hybrid model for platform technology companies is the higher level of appropriability attaching to drugs. For platform technology companies developing products or services with weak appropriability, the tighter appropriability regime for drugs has considerable appeal (Teece 1986). This may offset some of the additional risks of the drug discovery business model. While beyond scope, it would have been interesting to test for any relationship between appropriability and hybridisation in this data set. However the issue will receive more attention in the case study on bioinformatics in Chapter 14.

There was also little support for the proposition that biopharmaceutical firms would choose to form a stable supply platform of novel products for downstream pharmaceutical firms. On the contrary, almost all (99%) of firms engaged in drug development had internal drug development programs, indicating that few wanted to be contract research specialists. Indeed the results of the value chain analysis suggests that the majority of biopharmaceutical firms, almost all drug discovery and a majority of platform technology companies, have the aspiration to follow the lead of the 'large biotechs' and become fully integrated biopharmaceutical firms.

This is not surprising in the sense that the evidence presented to date suggests that the fully integrated biopharmaceutical business model is clearly sustainable. As will be demonstrated in Chapter 15 the 'large biotechs' have successfully captured a high proportion of the value generated within the sector and accordingly other companies will seek to emulate this success. Whether the best outcome that can be achieved by many drug discovery companies is to become reluctant participants in a hierarchy which serves large pharmaceutical and biopharmaceutical firms cannot be discounted.

However the evidence presented here suggests that it would not be their preferred option.

Chapter 13. Bioinformatics: A Case Study in the Development of a Platform Technology

Introduction

This case study moves the focus of analysis from a large group of selected biopharmaceutical companies studied in Chapter 12 to a group of companies representing a single platform technology. This is to provide an example of the commercialisation of a particular platform technology by a group of largely start-up bioinformatics companies. It deals in particular with the value of strategic assets and their IP regime.

Chapter 9 showed that bioinformatics alliances were amongst the leading group of platform technology alliances formed over the period 1990 to 2005. Bioinformatics, which arises from the convergence of IT and biotechnology, has been a key enabling platform technology of the genomics revolution. The frame of reference for this group of bioinformatics companies is determined by their position as the initial assignees of the most valuable bioinformatics IP. The Chapter examines the networks formed by this group of companies and finally looks in some detail at how the business models adopted by them developed over time.

The chapter focuses on three issues. Firstly whether being a pioneer, with a leading position in bioinformatics IP, gave sufficient advantage to these companies to enable each of them to develop a strategic asset, which provided a basis for sustainable competitive advantage. Secondly, what was the nature of the alliance network established by these pioneers and how were the relational rents shared? Thirdly does the choice of the business model adopted help determine whether the company is able to create and capture the value created? In the previous chapter more than half of the platform technology companies reviewed had adopted a hybrid business model, possibly as a defence against the failure of a ‘pure form’ platform technology business model. Was this strategy adopted by these bioinformatics companies and how successful has it been?

Definitions of Bioinformatics[28]

Bioinformatics is a radical innovation (Henderson and Clark 1990; Dewer and Dutton 1986; Ettlie et al. 1984; Dosi 1982) relying on significant new biotechnology and IT knowledge and the development of 'super' computing capabilities. This has spawned new companies and facilitated the introduction of a new drug discovery paradigm.

There is no single universally agreed definition of bioinformatics. At its broadest, bioinformatics is the application of information technologies and sciences to the organization, management, mining and use of life-sciences information. A narrower and typically undisputed definition of bioinformatics is the application of information technologies to the processing of molecular biology datasets (BioLateral and BIOTF 2002, p. 5). The definition adopted in this chapter is closer to the narrower definition. This focuses attention on the genomics origins of the technology's development. Bioinformatics is a product of the explosion in data and data management requirements arising from the genomics revolution and in particular the Human Genome Project.

Further Tollman et al. (2001) have suggested that the genomics wave is technology-driven, formed by the integration of new high throughput techniques with powerful new computing capabilities. They characterize genomics:

> … as the confluence of two interdependent trends that are fundamentally changing the way R&D is conducted: industrialization (creating vastly higher throughputs, and hence a huge increase in data), and informatics (computerized techniques for managing and analyzing those data). The surge of data – generated by the former, and processed by the latter – is of a different order from the data yields of the pre-genomics era. (p. 11)

In this way bioinformatics is at the convergence of IT and biotechnology, combining the two technologies to produce solutions mainly for the biopharmaceutical sector, but also in agribusiness and environmental management. Most of the firms that provide bioinformatics services are in the software business with an intimate understanding of

[28] Much of this early section is taken from Houghton and Rasmussen (2002).

genomics, although its development has also involved firms that have designed specialist instruments and high powered computers for the sector.

Bioinformatics as a Strategic Asset

In Chapter 2, as part of the discussion of the resource based view, strategic assets were defined as:

> … the set of difficult to trade and imitate, scarce, appropriable and specialised resources and capabilities that bestow the firm's competitive advantage. (Amit and Schoemaker 1993, p. 36)

In this context, *resources* is defined to include 'know-how that can be traded (e.g. patents and licences)', and *capabilities* refer to a firm's capacity to deploy *resources*, usually in combination, using organisational processes to effect a desired end (Amit and Schoemaker 1993, p. 35). Strategic assets then are a subset of resources and capabilities that are firm specific, durable and scarce which generate economic rents for the firm. Examples include, the firm's technological capability, fast product development cycles, favourable cost structure and R&D capability (Amit and Schoemaker 1993, p. 36). A capability of a firm to research and develop one of the key biopharmaceutical platform technologies, such as bioinformatics, in such a way as to generate economic rents, must qualify as a strategic asset. Thus the resource-based view would lead us to expect that one of the requirements of new start-up bioinformatics firms is that they would create a competitive advantage by establishing a technology leadership position in bioinformatics and seek to protect it against imitation.

Indicators of technological value

By itself intellectual property may not be a strategic asset. However it is likely to be an important component of a strategic asset in R&D or in a technological capability. Ownership of high value intellectual property is likely to be a good indicator of ownership of such a strategic asset. Intellectual property associated with bioinformatics has many dimensions such as lines of code, algorithms, data content and structures and user interfaces. There are several ways in which bioinformatics IP can be protected – copyright, patent and trade secret. Of these, patent protection is of greatest assistance in protecting most forms of IP associated with bioinformatics (Harrison 2003). This includes lines of code and algorithms that relate to an

application, data structure and the user interface. Data content is not protectable by patent.

Patents have been long used as indicators of technological value (see for instance Griliches 1981, 1990; Narin et al. 1987) and although their shortcomings are well known (Griliches 1990), they represent the best indicator of technological value for bioinformatics.

Bioinformatics patent database

The patent results presented in this paper are based on an analysis of the bioinformatics patent database drawn from the US Patent Office (USPTO). There is no single and unique classification for bioinformatics patents. Rather a series of methodologies have been applied to extract bioinformatics patents from the USPTO patent database:

i. Extraction of patents belonging to US Patent Sub classes 382/129, 702/19, 702/20, 702/21, 703/11 and 703/12 as identified by Patel (2003) as relevant bioinformatics sub classes.
ii. Undertaking a multiple key word search of the patent title and abstract of the group of patents selected in (i) above to include only those which satisfied both the biotechnology and information technology content of bioinformatics.
iii. Manual review of patents selected in (ii), including the patent claims and other patent details to ensure consistency with the Woodward US PTO definition of a bioinformatics patent (Woodward, n.d.) [29].

This resulted in a database of 364 bioinformatics patents.

Patents are used in this section as an indicator of the value of the initial bioinformatics technology held by individual inventors and their assignee organisations. As a radical innovation based on significant new knowledge, bioinformatics has been sufficiently revolutionary to drive the creation of new companies. The patent data can be used to identify those start-up companies with significant bioinformatics IP. It is suggested

[29] Cockburn (2005) uses a somewhat similar approach to identify bioinformatics patents. He uses a word search for patents with a 'software' and 'molecular biology' component to obtain a set of patents which are further refined by manual review.

that those firms with the highest value technology are best placed to develop a strategic asset in the development of bioinformatics.

Trends in bioinformatics patents

The majority of bioinformatics patent applications were received in a period of just five years from 1998 to 2003. Figure 13.1 shows the broadly upward trend in the number of bioinformatics patents *issued* annually over the period 1997 to 2005. However this trend in patents issued conceals quite a different trend in patent *applications*. From the analysis of bioinformatics patents, successful patent applications appear to have peaked in 2000 and have been falling ever since.

Figure 13.1 Bioinformatics patents by year of application and issue

Source: USPTO; author analysis.

Estimating the trend for *successful* patent applications suffers from a truncation problem (Hall et al. 2000) and the trend can only be constructed with a significant lag. The application date is included on the patent and becomes available for *successful* patents once it is issued. The number of known applications, by year of application is shown in the chart above for patents issued prior to the end of 2005. From an analysis of patents issued for the earlier part of the period, it is possible to estimate the shape of the lag structure between patent application and issue. This indicates that bioinformatics patents are issued with a lag of up to 6-7 years, although more than half are issued within four years of application. This means that although most of the successful applications up to year 1999 are known, there are still patents to be issued

from the application years since then. An estimate of those still to be issued is based on the lag structure that applied for the period prior to 2000. For instance it can be expected that a further 20% of patents applied for in 2001 are yet to be issued. An estimate of the total number is arrived at by adding this number to those already issued. Less certainty attaches to the more recent years where the proportion of those yet to be issued is higher. Nonetheless the downward trend in patent applications is by then already well established.

The significance of the shape of the of the applications chart is that it indicates that the vast majority of patentable bioinformatics IP was developed over the course of a decade, from about 1995, with a particularly intense period of patenting between 1998 and 2003. The decline in the number of patent applications raises potential issues about the sustainability of the level of innovation in the technology. Does it indicate, that after such an intense burst of patenting activity there remains little 'white space' left in the patent coverage of the fundamental technology, so as to prevent further innovations being be patented, as has occurred with some other platform technologies (Lux Research 2005a)? Or does it indicate a more fundamental problem with the continuing development of the technology? Perhaps the returns to investment in the technology are insufficient to justify continuing R&D in bioinformatics. Does it reflect a problem with the business model of those firms involved in its commercialisation. The paper will return to discuss these issues further in a later section.

Concentrated holding of initial bioinformatics IP

This section seeks to show the high level of concentration in the holdings of bioinformatics patents by a relatively small group of organisations. For start-up firms, the resource based view would suggest that companies with a disproportionate share of bioinformatics patents and therefore bioinformatics IP would have the best chance of establishing a strategic asset to develop bioinformatics technology.

The vast majority of patents are assigned by their inventor to the organisation that finances or supports their patent application. Typically this is the inventors' employer. In the database 93.2% of all patents were assigned to an organisation – a company, university, research institute or government department. Individuals hold the

remainder. There are a total of 195 organisations and individuals on this database with patent holdings.

The organisations holding bioinformatics IP have been ranked in order of the value of their patent portfolios. There are a number of options to measure this value. One is to rank simply by the number of patents. However by themselves patents have been found to be a poor indicator of economic value (Trajtenberg et al. 1997; Harhoff et al. 1999; Hall et al. 2000). One method of distinguishing those of greater value is to compare the number of citations, i.e. the number of times the patents are referred to in other successful patent applications (a forward reference) (Hall et al. 2000; Trajtenberg et al. 1997). A patent is required to acknowledge the 'prior art' on which it is based or from which it is to be distinguished. Typically those patents more frequently cited represent the foundation patents for the technology.

Another option therefore is to rank the organisations according to the number of citation adjusted patents. This has been found to be not only a good predictor of value (Harhoff et al. 1999) but also a likely basis of firm formation (Shane 2001). Trial use of this as an indicator tended to elevate in the rank order, some companies that had only one or two relatively highly cited patients, which were either incidental to or proved to be of insufficient scale for the companies' future business development. This may suggest that portfolios require a minimum size to form an effective basis for commercialisation. Patenting strategies are partially defensive and a larger number of patents may add defensive value to a portfolio by broadening their cumulative scope, all which helps to create sustainable competitive advantage (Jaffe 1999).

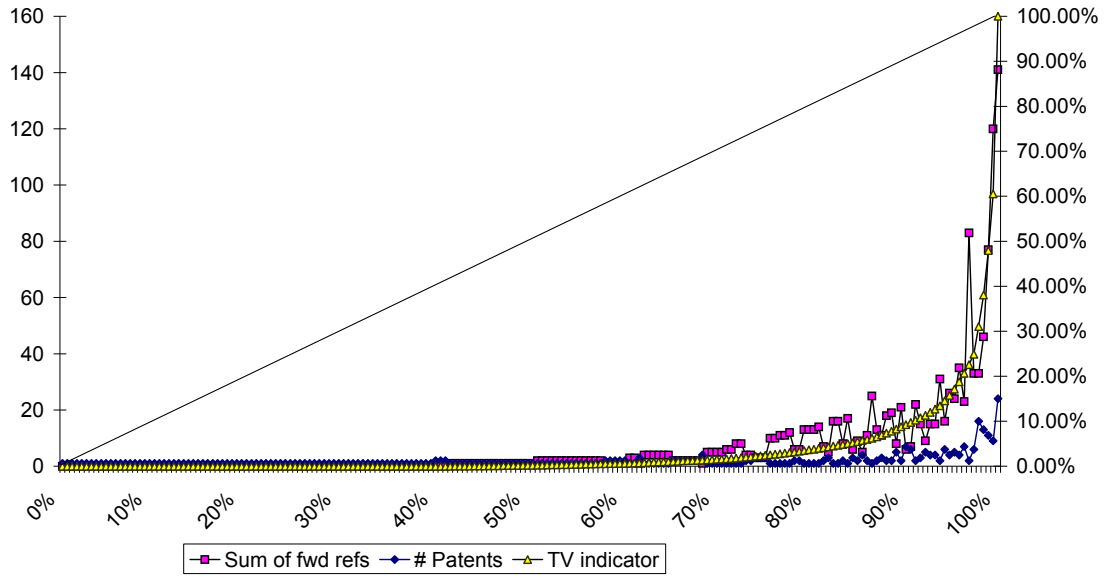
For this reason an indicator of the relative value of the patent portfolio for each organisation has been constructed by using both the number of citations and number of patents in each organisation's portfolio. This takes the form:

$$TV_j = \frac{p_j c_j}{\sum_{j=1}^{n} p_j c_j}$$

where TV_j is the index of estimated technology value for the j^{th} organisation, and p_j and c_j are the number of patents and the number of citations (sum of the forward references) respectively for the j^{th} organisation.

A chart for the patent holdings of each organisation and individuals ranked by TV_j is shown in Figure 13.2. It incorporates both the citation data and the number of patents for each organisation. It demonstrates the extreme skewness of the technology value indicator (*TV*).

Figure 13.2 Bioinformatics patents issued, 1997 to May 2005



Source: USPTO; Delphion.

The top 10% of organisations hold 90.8% of the value of the total bioinformatics patent database according to the technology value index (TV_j). The number of citations is also heavily skewed with 61% of total citations with the top 10% of organisations. The number of patents is less heavily skewed with almost 40% of patents in the top 10%. As a measure of technology concentration the Gini coefficient was estimated for both the technology value indicator and the number of citations. At 0.84 for the technology value indicator and 0.80 for the number of citations, the Gini coefficient confirms what is evident from the chart, which is the very unequal distribution or high concentration of valuable bioinformatics patents.

This establishes that a small number of organisations, and in particular a small number of companies, are in a highly privileged position in undertaking the commercialisation process, by virtue of the high relative value of their patent portfolio. The remainder of this section will focus on the progress of this small number of bioinformatics 'pioneers'. The top 10% of organisations, representing over 90% of 'technology value' and 60 % of citations is a manageable group to analyse.

Of the 20 organisations listed in Table 13.1, the top four, Affymetrix, Curagen, Incyte and Rosetta occupy a dominant position, collectively accounting for over 30% of citations and almost 70% of the TV index. In addition Curagen and Incyte have particularly high average citation count per patent, attesting to the quality of their patent portfolio. Of the universities, the University of California with 33 citations, 16 patents and 6.2% of the TV index is the most important by a substantial margin over CalTech and John Hopkins University. University patents have relatively low average citation counts indicating perhaps that they are of lesser commercial interest.

Table 13.1 Top 10% assignee organisations ranked by TV indicator

	No. of citations	No. of patents	Av. citation per patent	TV indicator
Affymetrix	141	24	5.9	39.47%
Curagen Corporation	120	9	13.3	12.60%
Incyte	77	11	7.0	9.88%
Rosetta Inpharmatics	46	13	3.5	6.98%
University of California	33	16	2.1	6.16%
Hitachi	33	6	5.5	2.31%
IRORI	83	2	41.5	1.94%
IBM	23	7	3.3	1.88%
Oxford Glycosciences	35	4	8.8	1.63%
Biodiscovery	24	5	4.8	1.40%
Vialogy Corporation	26	4	6.5	1.21%
California Institute of Technology	16	6	2.7	1.12%
Medical Science Systems	31	2	15.5	0.72%
Visible Genetics	15	4	3.8	0.70%
Tripos Associates	15	4	3.8	0.70%
Fujitsu Limited	9	5	1.8	0.52%
Pharmacopeia.	15	3	5.0	0.52%
US Dept. Health & Human Services	22	2	11.0	0.51%
Johns Hopkins University	7	6	1.2	0.49%
Agilent Technologies	6	7	0.9	0.49%
Total top 10%	777	140	5.6	91.2%

Source: USPTO; Delphion.

IBM and Hitachi are two of the large non-biomedical companies to be included in the top 10% list. Both have relatively large but somewhat low value patent holdings consistent with companies developing an 'absorptive capacity' rather than contemplating a start-up business based on in-house technological excellence. Agilent, a broadly based technology company, spun-off by Hewlett Packard, with a strong scientific instrumentation business also has 7 patents but each is relatively low value.

Two companies, IRORI and Medical Science Systems each have two highly cited patents, which is the reason for their inclusion. Of the remaining specialist companies, Visible Genetics, Tripos and Pharmacopeia, have each used their bioinformatics IP to build bioinformatics components as part of their mainstream product offerings. Visible Genetics specialised in pharmacogenomics before being taken over by Bayer in 2002. Tripos was established in 1979 and was spun off by the Evan and Sutherland Computer Corporation in 1994 to focus on combinatorial chemistry. It offered computational software packages and access to compound libraries as part of its product suite. Pharmacopeia was established to discover new drugs and developed proprietary data management software to support its drug discovery activities.

On the basis of this analysis of bioinformatics patent portfolios, the four companies, Affymetrix, Curagen, Incyte and Rosetta which account for some 70% of the TV index, could de described as having the greatest potential to create a strategic asset in bioinformatics technology.

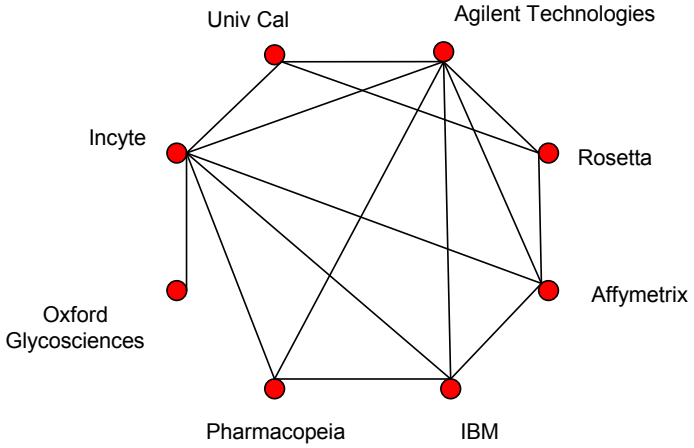
The Bioinformatics Network

A number of previous chapters have discussed the importance of a networked approach to innovation. The open innovation paradigm discussed in Chapter 3 suggests that the commercialisation process requires complementary assets through licensing and other alliance structures. The value network is an important component of the business model. Chapters 9 and 10 have each illustrated the importance of alliances for biopharmaceutical firms in the transfer of technologies and know-how. The analysis presented in those chapters demonstrated some of the complexity of this alliance formation. A common assumption of a hierarchical relationship between large and small specialist firms was shown to be only partly true (Arora, Fosfuri and

Gambardella 2001b, p. 67). Many alliances were formed, particularly by platform technology companies, between specialist firms reflecting the need for complementary assets to assemble final products and services. Both the hierarchical and horizontal alliance patterns are evident in the development of bioinformatics.

The first set of network relations examined is between the bioinformatics organisations themselves. A strong 'internal' network was formed between the top 10% IP organisations in order to share technological knowledge through licensing and other forms of collaboration (see Figure 13.3). The purpose of this network is directed towards the acquisition of complementary technologies (Teece 1986). For instance the main product developed by Affymetrix is a 'gene chip', a disposable DNA probe array containing gene sequences on a semi conductor chip suitable for high through put screening. Its development involved many 'non-bioinformatic' features, such as screening and microarrys as well as incorporating 'software to analyse and manage genetic information' generated by the high through put screening process (Affymetrix 1996). Another example is Rosetta, which has accessed though licensing arrangements, 25 patents held by Affymetrix.[30] None of these relate to bioinformatics patents. Many of them involve the manufacture and processing of microarrays. Bioinformatics software is required to manage and analyse the information generated.

Figure 13.3 Networks formed by R&D alliances between the top 10% bioinformatics IP organisations



Source: Recap; author analysis.

[30] Including eleven originally assigned to its parent Affymax.

This particular network demonstrates the cohesiveness of relations between this group of leading IP firms. In addition to the interlocking alliances between the start-up companies, IBM, Agilent Technologies and the University of California are also important participants in this technology network. Agilent in particular is a prominent participant, with direct relations with each of the organisations except Oxford Glycosciences. As well as having a bioinformatics capability, it is a diversified technology company and provides instrumentation for a number of the bioinformatics systems products developed by the start-ups.

A high proportion of the companies in this R&D network are Californian based. Only the ubiquitous IBM and the somewhat peripheral Oxford Glycosciences are non-Californian, indicating that geography also has had a role to play in the establishment of this network (Saxenian 1994; Cooke 2001). The absence of the East Coast based and leading IP firm, Curagen from this network is also noteworthy in this context. The local network enables firms to capture geographically bounded information spillovers through access to rich informal networks (Owen-Smith and Powell 2004). The formal participation of the University of California in this network is likely to strengthen spillovers as well as more formal technology transfers to the start-up companies. Eight University of California staff members were amongst the top 20 publishers (citation adjusted) of bioinformatics papers but were not so prominent as patent holders.

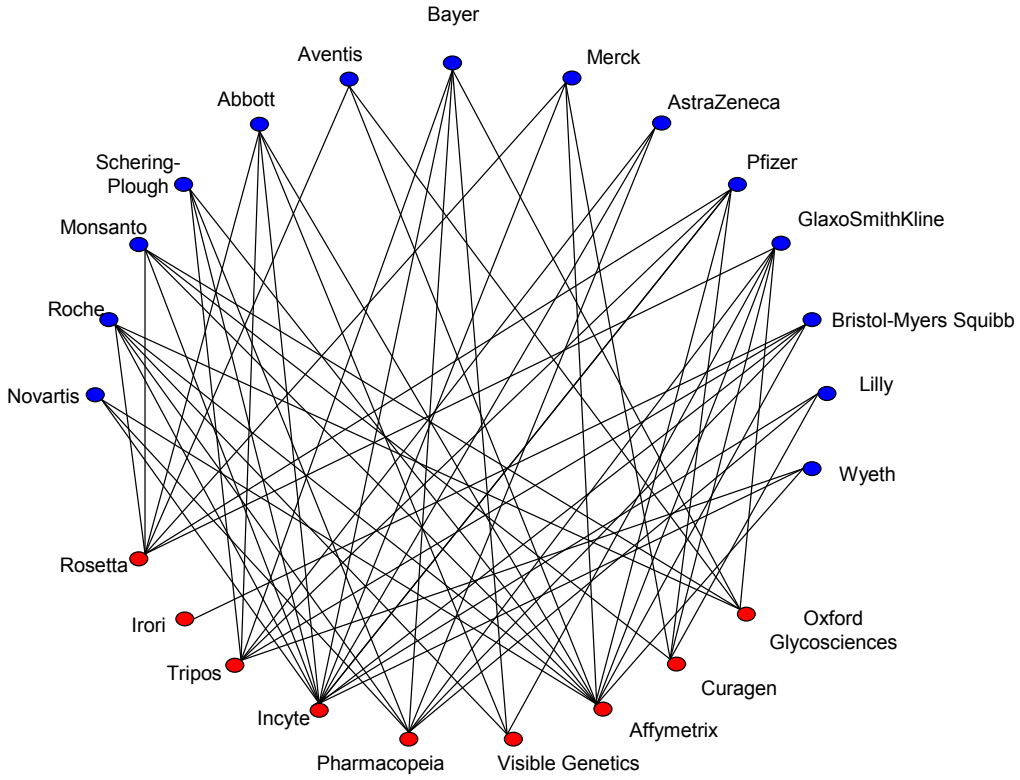
A second set of important relations are those formed between the specialist bioinformatics companies listed in the top 10% and an array of large pharmaceutical companies. In their role as 'client' pharmaceutical companies contribute to the R&D costs of the bioinformatics companies as collaborating customers and also occasionally as shareholders. For instance GSK owned a 38% share of Affymetrix at the time of its initial public offering (IPO).

With the exception of Johnson & Johnson, each of the top dozen global pharmaceutical companies are involved in alliances with up to six of these specialist companies (see Figure 13.4). Similarly the bioinformatics companies have established multiple links with the major pharmaceutical companies. Affymetrix has alliances with each of them. These alliances are shown in the Figure 13.4. Most of the

bioinformatics product development has taken place in close consultation with these potential users.

In addition to these two important sets of alliances, the companies were also involved in a diverse set of alliances with firms outside these two groupings in order to acquire a range of non bioinformatics platform technologies.

Figure 13.4 Alliances between specialist bioinformatics companies in the top10% and pharmaceutical companies as the client



Source: Recap; author analysis.

These sets of alliances reflect the complex nature of the task involved in bringing bioinformatics products to the market. The development of most bioinformatics products is a complex multi firm integration of multiple components. For this reason they have much in common with complex product systems (CoPS) characterised by Hobday (1998) and Hobday et al. (2000). CoPS are typically multi-firm projects with high levels of user involvement. The products are highly customised to meet particular user requirements and this feeds into the innovation process, which has multiple feedback loops as user and supplier seek to optimise the product offering.

The need to constantly redevelop and enhance product offerings to meet user requirements however has taken a heavy toll of these bioinformatics companies. Few of the emerging bioinformatics companies have gained any relief from the constant R&D investment in new and enhanced product. As will be demonstrated in the case studies below, even as revenues rose strongly this was generally matched by a demand for additional R&D expenditure, a cycle from which most companies failed to escape.

The innovation process adopted by the specialist developers of the bioinformatics technology is consistent with the open innovation paradigm. This section has demonstrated the importance of the networks established by the bioinformatics specialists with each other and with the pharmaceutical companies. This analysis demonstrates the significance of small start-up companies as the originators of the innovation process (Langlois 2003; Rothwell 1994), the partnerships established between them to share insights into a new technology and to provide the components to form complex product systems. The role of the pharmaceutical companies is essentially as downstream customers participating in the innovation process through shaping the products of the specialists to their requirements and providing some of the necessary R&D funding.

It can be inferred from the intensity of this networked relationship that joint assets are created by the network participants. The larger issue, not easily settled from this data however, is how the relational rents are distributed. In particular how the relational rents are distributed between the pharmaceutical companies and the bioinformatics specialists. Does the nature of the business model adopted by the bioinformatics companies affect this distribution?

An essential component of the open innovation paradigm is the importance accorded to the selection of the business model through which the innovation process is pursued. The process through which the firm realises the value of the new technology, which provides it with a sustainable and profitable revenue stream is essential to the survival of the firm. The next section examines more closely the development of the bioinformatics start-ups as they select their business models and determine their business strategies.

The Business Models of the Bioinformatics Start-ups

This section traces the evolution of the business models of the companies identified above as the leading specialist developers of bioinformatics IP. The data on which this section is based is from company filings to the US SEC or similar documents for the non-US companies supplemented by web searches. As previously explained, the structure of the annual filing of the 10-K report to the SEC requires companies to outline their business strategies and explain major changes to those strategies. This analysis employs the Chesbrough and Rosenbloom (2002) business model framework developed in Chapter 4. This is one that divides the functions or components of the business model into its value proposition, market segment and revenue model, value chain and value network, cost structure and profit potential and corporate strategy.

This group of start-up companies has been motivated by a common *value proposition*, that bioinformatics could radically improve the efficiency with which drug candidates could be identified and developed. The technology had a capacity to manage the vast quantity of data generated by the adoption of genomics based drug discovery techniques. This could be extremely valuable to pharmaceutical and biotechnology companies seeking to discover and develop new drugs. However the manner in which this proposition was translated into a business model differed markedly between the firms.

Three bioinformatics business models

The leading bioinformatics IP firms appear to have adopted one of three business models, some transitioning from one to the other over time. The first two are platform technology business models, one specialist, the other blending bioinformatics with other technologies, while the third is the 'hybrid model. The first is a relatively specialist bioinformatics business model, closely aligned to the definition of bioinformatics provided by Tollman et al. (2001), quoted earlier in this chapter. This brings together the computerised techniques for managing and analysing data and the 'industrialised' drug search techniques of high through put screening. Specialist companies adopting this model have offered a range of such bioinformatics services to pharmaceutical and biopharmaceutical companies largely on a fee for service basis

[31]. The second is where the bioinformatics technology has been blended with other platform technologies, most notably photolithography in the case of Affymetrix, to create a new range of products or services sold to pharmaceutical and biopharmaceutical companies. The third is where the firm's expertise in bioinformatics is not only offered to a range of external clients, generally larger pharmaceutical companies, but is also used to develop an in-house drug discovery and development business.

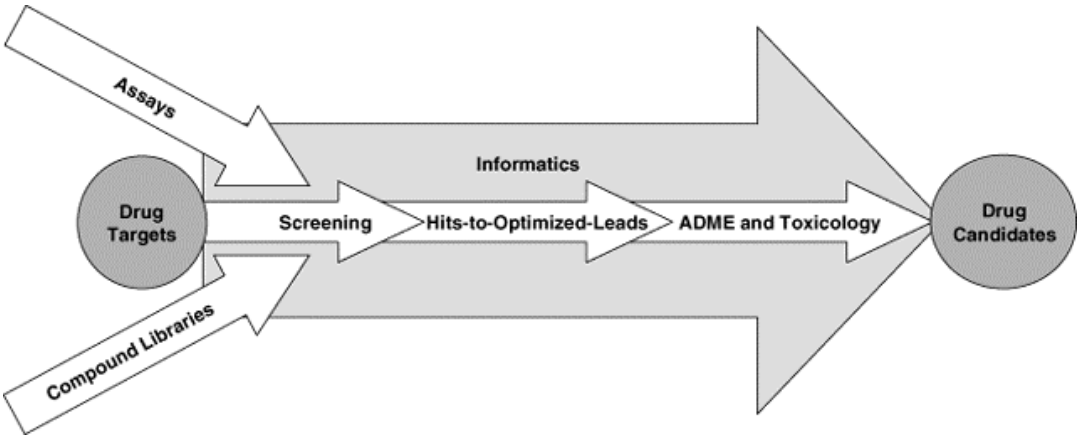
The following sections discuss examples of each of these business models, as adopted by four start-ups with leading positions in bioinformatics IP, Affymetrix, Curagen, Incyte and IRORI, renamed Discovery Partners International in 1998. Together the companies are assignees of 64% of the patentable IP as measured by the Technology Value indicator. Each of these companies became publicly listed and therefore 10-K reports are available to provide the information for the following analysis.

The 'pure' bioinformatics business model: Discovery Partners International (IRORI) and Incyte

Both Discovery Partners International (DPI) and Incyte at incorporation adopted the 'pure' bioinformatics business model based on the *value proposition* of improving the efficiency with which drug candidates were identified. DPI offered a bioinformatics package consisting of improved target validation, more efficient use of proprietary compound libraries, faster high through put screening and more advanced computational tools in order to speed up and improve the efficiency of the identification of drug candidates at the preclinical stage (DPI 2000).

[31] Within the 'pure' bioinformatics model Cockburn (2005) distinguishes between companies which are essentially software companies, those that are application service providers and those providing services to third parties to integrate and streamline disparate databases. Of the companies identified as being amongst the 'IP pioneers', only the second group, application service providers is relevant.

Figure 13.5. Role of bioinformatics in identifying drug candidates



Source: Discovery Partners International, Inc. (2001).

Incyte developed a similar range of products, although it had a greater genomics focus. In its 1996 *Prospectus* it claimed to be:

> … a leader in the design, development and marketing of genomic database products, software tools, and related services'. [It created] 'a portfolio of database products [which] integrated bioinformatics software with both proprietary and publicly available genetic information to create information-based tools used by pharmaceutical companies in drug discovery and development. (Incyte Corporation 1996, p. 3)

The *market segment* targeted by both companies was pharmaceutical and biotechnology companies, particularly the former as indicated by the following quote from the DPI *Prospectus*:

> Since inception in 1995, we have sold products to and conducted projects for over 100 customers, including Aventis, Bayer, Bristol-Myers Squibb, SmithKline Beecham and Warner-Lambert. (DPI 2000, p. 6)

Incyte adopted 'a fee for service' *revenue model*. Incyte outlined its revenue model in the following terms:

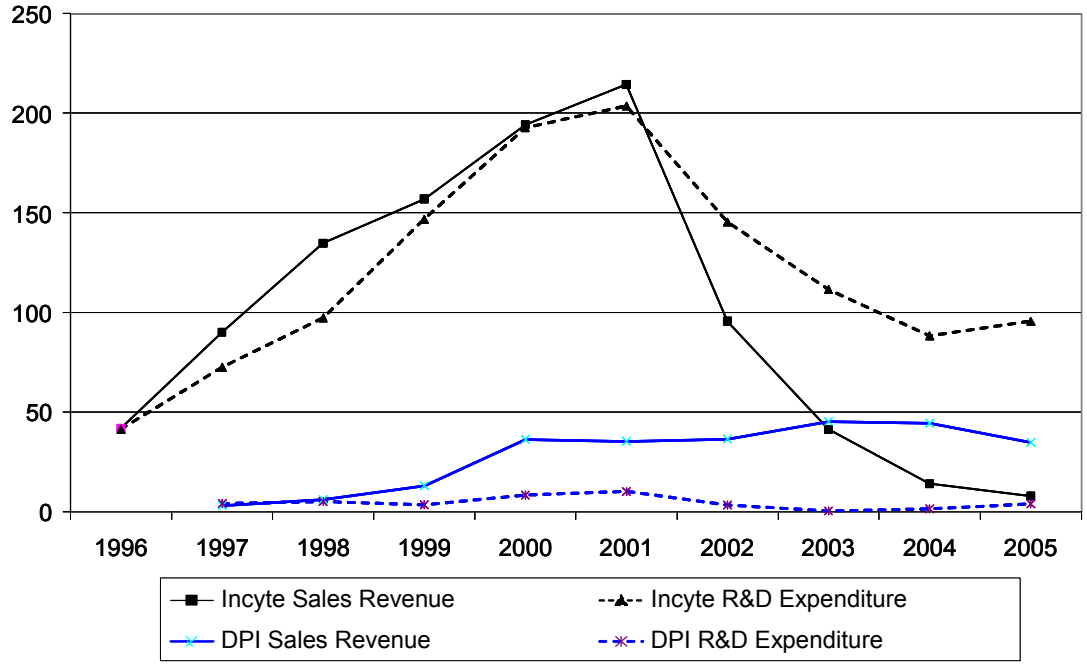
> The Company's current pharmaceutical customers subscribe on a nonexclusive basis. Revenues from these customers generally include database subscription fees and may include additional fees for specific sequencing services, such as satellite database services. The Company's agreements with its customers also provide for milestone payments and royalties from the sale of products developed with Incyte technology and database information. (Incyte Corporation 1996, p. 3)

Its revenues have been predominately non exclusive database subscription and access fees. There has been an intention to capture some of the future upside of value generated, in the form of future drug revenues, but this was still very much in prospect at the time of the *Prospectus*. The DPI revenue was somewhat different, with a combination of fees for services and the sale of libraries of compounds, analytical and computational tools.

As with other platform technology companies discussed in chapters 11 and 12, both Incyte and DPI have conducted their activities across the whole *value chain* from research and development through to marketing and distribution and supported by the bioinformatics *value network* outlined in the earlier section. Incyte's alliance structure was complex, incorporating alliances with both peers and pharmaceutical companies, whereas DPI was relatively stand alone.

The *cost structure and profit potential* of technology companies particularly in their early years was largely driven by the relationship between sales revenue and R&D expenditure. The lag between R&D and sales revenue for platform technology companies is much shorter than for drug discovery companies, so profitability can be achieved earlier providing a reasonable margin between the two can be achieved. The chart below shows the sales revenue and R&D expenditure for Incyte, for the period 1996 to 2005 and for DPI from 1997, the earliest data available, to 2005. As is shown in Figure 13.6, only DPI achieved a sizeable margin of sales over R&D. This was sufficient to provide profitability for 2003 and 2004.

Figure 13.6 Incyte and DPI sales revenue and R&D expenditure, 1996 to 2005 ($ million)



Source: Incyte and DPI SEC filings of its *Prospectus* and 10-K reports.

For Incyte, despite the rapid growth in sales to 2000, it was never sufficient to break the shackles of increasing R&D expenditure. Between 1996 and 2001, Incyte's revenues grew from $41.9 million to $214.3 million. However this revenue growth was almost exactly offset by increasing R&D expenditures and was not sufficient to cover selling and admin costs. This inability to move revenues ahead of expenditure on R&D appears to have been a fundamental problem, leaving it vulnerable to any downturn in revenues.

Corporate strategy

Both companies had begun operation as leaders in the 'design, development and marketing of genomic database products, software tools, and related services' (Incyte Corporation 1996). This leadership was based not only on technological expertise, but also on the management of a fully integrated value chain. Based on previous discussions of business models this should have been a winning formula. The technological leadership in a platform technology, which apparently delivered considerable value to its customers, was an important strategic asset and, as has been previously argued, the development of the fully integrated value chain is the most successful business model structure. However as demonstrated in the section above

the profit potential was eroded by the high cost of ongoing R&D relative to sales revenue. This forced a radical change in corporate strategy.

In 2001, the business climate began to change and Incyte bought a small drug discovery company for a nominal sum and began to divert resources to drug discovery. Revenue for 2002 plummeted from over $200m to $95.5 million as expenditure by its client base of over 100 pharmaceutical and biotech companies declined as the information libraries moved increasingly into the public domain. Over the period to 2004, the company was engaged in a radical restructuring program, including cessation of various bioinformatics product lines, as revenues declined further to $14.1 million. By 2005 Incyte had ceased all activities in information products including closure of its initial Palo Alto, California facilities. Reflecting on this experience, the company reported in its 2005 10-K report:

> … in recent years, consolidation within the pharmaceutical and biotechnology sectors and a challenging economic environment led to reduced demand for research tools and services. This trend, together with the public availability of genomic information, significantly reduced the market for and revenues from, our information products. (Incyte Corporation 2005, p. 7)

DPI suffered a similar fate. After achieving profitability in 2003 and 2004, revenues in 2005 began to fall as contracts to supply information based products were not renewed. In its 2005 10-K report filed in March 2006, the company was even more pointed in its comments about its market position than Incyte:

> … it has become evident during 2005 that the basic business sector in drug discovery contract research and services was undergoing a major and quite unfavorable market shift. Worldwide improvements in communications and shipping, coupled with entrepreneurial efforts in rapidly developing locations such as India, China and Eastern Europe, enabled the highly skilled scientists in those areas to build companies providing a similar range of products and services to us and our peer group, but at significantly lower prices. New guarantees of protection of intellectual property in these locations has offered the necessary assurances to the biotech and pharmaceutical industry that the decision to outsource basic drug discovery offshore has become driven by low price. This shift has essentially resulted in the loss of our ability to consummate synthetic chemistry library contracts, the principal basis of our business in preceding years. (DPI 2005, p. 4)

As part of the company's reorganisation, the original IRORI bioinformatics product line was sold to Nexus Biosystems for the relatively nominal sum of $1.9m in a management buy out by the former Chief Technical Officer. In 2006, its Directors contemplated sale or closure of the whole business (DPI 2005).

The experience of Incyte and DPI, each beginning from a position of considerable IP advantage, suggests that a pure form bioinformatics business model is unlikely to be viable. The cost of redeveloping product offerings, reinvesting in new compound libraries involves high and ongoing R&D expenditure. Both these companies have struggled to earn sufficient revenue from sales of information products and fee income to provide a profitable return on funds employed. Sale of what is essentially a set of information services and related products suffers the fundamental problem outlined by Varian and Shapiro (1999) that the generation of information services have high sunk costs (Baumol and Willig 1981; Sutton 1991, 1998) and almost zero marginal costs. Designing pricing regimes that recover the costs of providing such services appears to be challenging. Appropriability emerged as a significant issue as many of the databases fundamental to the bioinformatics services became publicly available. The more recent radical shift in demand and competition from low cost countries has been in a sense a 'final straw' for a struggling business model.

Other bioinformatics business models

Curagen and Affymetrix adopted different business models from the 'pure' bioinformatics business model with different *value propositions*. Affymetrix's prime business was the gene chip for which bioinformatics was a component. As it announced in its IPO, it intended that:

> … its GeneChip system [become] the platform of choice for acquiring, analyzing and managing complex genetic information in order to improve the diagnosis, monitoring and treatment of disease. The Company's system consists of disposable DNA probe arrays containing gene sequences on a chip, instruments to process the probe arrays, and software to analyze and manage genetic information. (Affymetrix 1996)

Curagen on the other hand adopted the 'hybrid model'. It had always intended that its technology platform would serve both an external market and internal drug discovery program. As stated in its IPO:

> CuraGen‘s goal is to establish its fully-integrated technologies and GeneScape operating system as the preferred platform for genomics and to pursue, *both internally and through collaborations*, a broad portfolio of research programs for drug discovery, drug development and pharmacogenomics. (author emphasis) (Curagen Corporation 1998)

Two of Curagen’s collaborators, Biogen and Genentech, each committed to purchasing 5% of its stock at its IPO and other collaborators included Abgenix (which also became a shareholder) and Bayer.

In an interview in 2002, its CEO Jonathan Rothberg outlined Curagen’s strategy:

> CuraGen was born out of the convergence between the information technology and the genomics revolution. It has been our goal from the start to meld those two disciplines into a high-throughput system that would allow CuraGen scientists to discover and develop a sustainable pipeline of pharmaceutical products. CuraGen’s business strategy consists of three parts: First, develop and continuously enhance technologies to streamline the drug discovery and development process; Second, apply that technology platform with leaders in the pharmaceutical and biopharmaceutical industry to better understand how to make drugs, how to prioritize drugs, and how to give the right drugs to the right patient; and Third, apply that platform and expertise to the development of our own drug pipeline. (*The Wall Street Transcript* 2000)

Thus the initial *value propositions* of these two companies were quite different from the ‘pure’ bioinformatics companies, Incyte and DPI. Affymetrix’s proposition was that its ‘gene chip’ system, consisting of disposable DNA probes, other instruments and software, was to become ‘the platform of choice’. Curagen on the other hand had a different proposition. It offered its technology platform as ‘the preferred platform for genomics’ (Curagen Corporation 1998) to pharmaceutical and biotech companies, while at the same time using it to develop its own drugs in house. In the short term this was little different in reality to Incyte’s proposition, but for investors it gave a stronger statement of intention that in the longer term its revenues would come from drug sales and that it should be valued as a hybrid of a drug discovery and platform technology company.

Curagen's *value chain* combined the integrated value chain typical of a platform technology company in which it developed and marketed its technology platform to final customers, while at the same time developing a drug discovery value chain, which in time would require consideration of development and distribution activities.

As was discussed in the section above, the *value networks* of the two companies were quite different. While Curagen developed strong links with the large pharmaceutical companies (see Figure 13.4) it did not form alliances with the other leading bioinformatics firms (Figure 13.3).

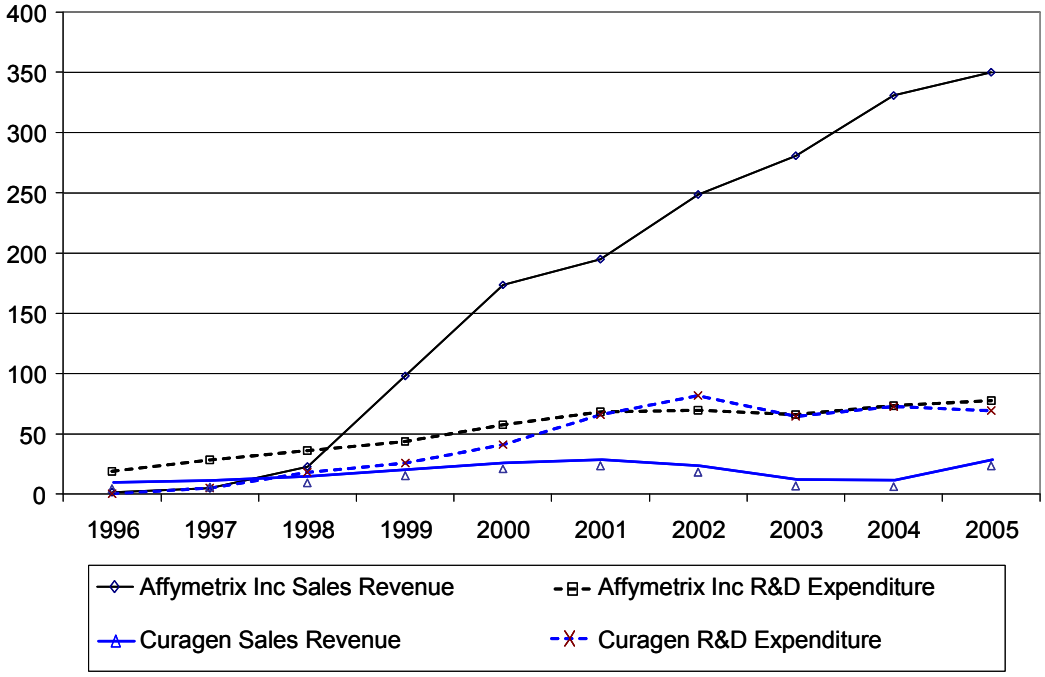
Affymetrix on the other hand developed a *value chain*, typical of a platform company, which incorporated all the stages in the value chain from development to distribution of its 'gene chip' system. As was discussed in Chapter 11 and shown in Figure 13.3 above, it also developed a highly complex *value network* of complementary platform technology companies to provide it with genomics, bioinformatics and instrumentation expertise. As shown in Figure 13.3, it had alliances with IBM, Agilent Technologies, Incyte and Rosetta from amongst the top 10% of bioinformatics IP organisations as listed in Table 13.1. It also formed alliances with most of the large pharmaceutical companies.

The *market segment* for the two companies was also quite different. Affymetix's customer base was quite diverse. Almost any pharmaceutical and biopharmaceutical firm engaged in drug discovery had a demand for the convenience of the 'gene chip' system, whereas Curagen was dependant on persuading a relatively small group of large bioechs and pharmaceutical companies to use its bioinformatics-based discovery platform. The *revenue models* were correspondingly different. Curagen charged database subscription fees to access its technology platform. Affymetrix on the other hand, by embedding much of its technology in the gene chip product, didn't depend on database access or other subscription fees but rather received revenue from product sales.

The *cost structure and profit potential* of the two companies is sharply contrasting as shown in Figure 13.7. For most of the period, sales revenue for Affymetrix had exceeded R&D expenditure and since 2002 it has been profitable. In contrast Curagen

has maintained R&D expenditure well above sales revenue for the whole period, presumably reflecting, not only its investment in building its technology platform, but also its expenditure on its in house drug discovery program.

Figure 13.7 Affymetrix and Curagen sales revenue and R&D expenditure, 1996 to 2005 ($ million)



Source: Affymetrix and Curagen SEC filings of *Prospectus* and 10-K reports.

These contrasting financial outcomes produced different *corporate strategy* responses. By 2000, the burden of this R&D expenditure had produced a reassessment of the ongoing platform investment, when a separately funded subsidiary, 454 Life Sciences was established to develop a platform for rapidly analysing entire genomes. By 2005, Curagen's strategy appears to have shifted entirely to achieving profitability through drug discovery and development:

> We are striving to become profitable by commercializing a subset of therapeutics stemming from our development pipeline, and establishing partnerships with pharmaceutical and biotechnology companies for the development and commercialization of other therapeutics from our development pipeline. (Curagen 2005)

Certainly its revenue stream remained relatively modest, compared with its R&D expenditure. In 2005 its revenue was $23.5 million, largely from alliance payments and instrument sales, compared with R&D of $97.5 million. It had a number of

potential drugs in phase II clinical trial. Its success will now depend on the outcome of the trials for its drug pipeline and not on sales of its initial range of bioinformatics products.

On the other hand Affymetrix appears to have established itself successfully. It has been profitable since 2002 and in 2005 its net income was $57.5 on total sales revenue of $376.7 million. R&D expenses were $77.4 million or 21.1% of revenues. This ratio had fallen steadily from 30.3% in 2001. It had a healthy product gross margin of 72%. Gene Chip probe arrays remain the major source of sales revenue.

These case studies suggest that the 'pure bioinformatics' business model has not proved to be viable. Both leading IP companies which adopted this model have abandoned it. Incyte has closed its bioinformatics operations and is attempting to become a drug discovery company while DPI has sold off the original IRORI bioinformatics product line and the future of the whole company is being seriously reconsidered. Consistent with these outcomes, Curagen has also abandoned its bioinformatics platform services to devote its attention entirely to drug discovery. Again it appears that the same appropriability issues may apply. Curagen has worked closely with a number of pharmaceutical company shareholders which perhaps reaped a disproportionate share of any relational rents. The only clearly successful model is that developed by Affymetrix which has created a 'gene chip' system in which its bioinformatics expertise is embedded in, and is perhaps subsidiary, to a consumable DNA probe. The product based nature of its revenue model provides it with a source of ongoing revenue, with the rents less easily appropriated by its pharmaceutical customers. Of these case study companies, only Affymetrix appears to have used its leading position in bioinformatics IP to create a strategic asset that forms a basis of ongoing competitive advantage.

Implications for the other bioinformatics 'pioneers'

How generalisable are these conclusions to the rest of the group of companies with leading positions in bioinformatics IP? Table 13.2 sets out the broad strategy of each of the bioinformatics 'specialists' in the top 10% of organisations ranked by the TV index, firstly at establishment and secondly its current strategy. A number of companies are no longer independent, making it difficult or impossible to determine

their current strategies. Three business models are distinguished. The so called pure bioinformatics model of which Incyte and DPI are examples labelled as 'bioinformatics'. The use of expertise in bioinformatics for in-house drug discovery is labelled 'hybrid' and companies blending bioinformatics with other platform technologies, but remaining as platform technology companies, such as Affymetrix, are labelled as 'other platform technology (OPT)' companies.

It is apparent from Table 13.2 that in general those companies with a dominant bioinformatics IP position commenced as specialist bioinformatics companies, whereas those lower ranked became OPT companies. This may be consistent with the resource based view that gaining a leadership position in the bioinformatics IP created a short term strategic asset, which delivered an immediate competitive advantage as a bioinformatics specialist. There are clearly exceptions to this proposition.

Table 13.2 Strategies of bioinformatics start-up companies

Company	Company strategy at start	Company start	Current strategy (2006)
Affymetrix	OPT ('gene chip')	1992	OPT ('gene chip')
Curagen	Hybrid	1991	Drug discovery
Incyte	Bioinformatics	1991	Drug discovery
Rosetta Inpharmatics	Bioinformatics	1996	Acquired by Merck 2001
IRORI (renamed Discovery Partners Int.)	Bioinformatics	1995	Assets acquired by Nexus 2005
Oxford GlycoSciences	OPT (Proteomics)/ drug discovery	1988	Acquired by Celltech 2003
Biodiscovery	Bioinformatics	1997	Bioinformatics
Vialogy	OPT (microarray signals resolution)	1999	OPT (microarray signals resolution)
Medical Science Systems (renamed Interleukin Genomics)	OPT (genetic tests)	1986	OPT (genetic tests)
Visible Genomics	OPT (genetic tests)	1993	Acquired by Bayer 2002
Tripos	Bioinformatics	1994	Bioinformatics (sale and liquidation announced November 2006)
Pharmacopeia	OPT (combinatorial chemistry)	1993	Software component spun off to form Accelrys in 2001

Source: SEC 10-K reports and company web sites.

Affymetrix had the prime position in bioinformatics IP. Yet it chose to develop a product system based in part on bioinformatics but also drawing on many other technologies. Its revolutionary genomics product the 'gene chip' has owed much of its development to the photolithographic techniques used in computer chip manufacturing. Affymetrix, as part of its product system, provides special purpose

bioinformatics software to users to help manage and analyse the data generated by the gene chip assays. Affymetrix has been by the far the most successful of this group of companies and perhaps the very complexity of its technological base has made it difficult to imitate. Its origins as a company were complex. It was established with a high level of pharmaceutical company support through Glaxo which owned 38% of its equity at the time of the IPO (Affymetrix 1996).

The position of Tripos is also somewhat anomalous. Its bioinformatics IP position placed it at the bottom of this table, in yet it chose to pursue a classic pure bioinformatics business model. However Tripos is not strictly a start-up. It was a spin-off from an established software company. It perhaps had other pre-existing IP resources available to it that gave it competitive advantages as a bioinformatics company not reflected in its bioinformatics patent position. Up until 2005, its business model was showing signs of success, with small profits or breakeven being achieved from 2001 to 2005. However in 2006 it appears to have succumbed to the same problems as Incyte and DPI and, in November 2006, it announced its intention to sell its 'discovery informatics' business and assuming that transaction, 'dissolve and liquidate' the company (Tripos, Inc. 2007).

Of the dozen companies listed above, six were established to provide, specialist bioinformatics services to pharmaceutical and biotech companies to improve the efficacy of drug discovery. Rosetta, one of the more prominent bioinformatics companies of the late 1990s was acquired by Merck in 2001 for $600 million, placing a significant value on its IP and other resources. As discussed, the IRORI IP was recently sold as part of a company restructure (DPI 2005) and Curagen and Incyte have transformed themselves into drug discovery companies.

Table 13.3 sets out key financial statistics for the bioinformatics start-ups for which such information is available for 2001 and 2005. This results in the exclusion of those privately owned or acquired by another company. The table presents sales revenue, R&D expenditure and operating profit for eight companies. These show wide disparities in the scale of the companies with three companies Affymetrix, Incyte and Pharmacopeia achieving sales in excess of $100 million by 2001, while Interleukin

Genetics had negligible sales. Only Tripos reported an operating profit in 2001 of $2.4 million, while Incyte had a loss of $187 million.

Table 13.3 Bioinformatics start-ups: Key financial statistics, 2001 and 2005

	2001			2005		
Company	Sales rev.	R&D exp.	Op. profit	Sales rev.	R&D exp.	Op. profit
Affymetrix Inc	194.9	68.2	-40.6	350.2	77.4	57.4
Curagen	23.5	65.8	-61.2	23.5	69.1	-73.9
Incyte	214.3	203.5	-187.2	7.8	95.6	-100.7
Discovery Partners Int. (IRORI)	35.2	10.0	-14.5	34.8	3.9	-16.0
Interleukin Genetics (Med Sci Sys.)	0.2	2.7	-4.8	0.0	3.1	-6.1
Tripos	46.1	8.9	2.4	55.4	10.9	-4.3
Visible Genetics	13.6	10.8	-40.7	n.a.	n.a.	n.a.
Pharmacopeia Accelrys (1)	122.3	32.5	-14.7	102.4	45.7	-25.8

Note: (1) Combined results for 2005 may not be strictly comparable with 2001.
Source: SEC 10-K reports.

In the period to 2005, Affymetrix has been the only company to achieve a profit – a significant one of $57.4 million, on an 80% increase in sales. A number of companies were restructured and their business models radically realigned. Curagen, Incyte and Discovery Partners International (IRORI) abandoned or sold off their bioinformatics businesses. Both Incyte and Discovery Partners International (Irori) reported in their 10-K reports that competition from low cost countries such as India, China and Eastern Europe[32] and the public availability of much of the data libraries made the business uneconomic. Curagen had always intended that its technology platform would serve both an external market and internal drug discovery program. By 2005, Curagen's strategy had shifted entirely to drug discovery and development. Pharmacopeia had spun off its software business as Accelrys and retained the drug discovery business. However Accelrys has continued to generate heavy losses. Tripos recently announced is intention to sell what assets it can and dissolve the company.

This analysis suggests that the maximum value lay in using bioinformatics as an adjunct to other business opportunities rather than offering it as a specialist service. For some companies, bioinformatics was simply one component imbedded in a much larger product offering or product system. Other companies used their knowledge of

[32] 'Worldwide improvements in communications and shipping, coupled with entrepreneurial efforts in rapidly developing locations such as India, China and Eastern Europe, enabled the highly skilled scientists in those areas to build companies providing a similar range of products and services to us and our peer group, but at significantly lower prices' (Discovery Partners International 2005, p. 4).

bioinformatics largely for internal drug discovery. A number of companies later switched from bioinformatics specialists to drug discovery companies.

The revenue model also varied. Some companies adopted a 'fee for service' model while others developed a 'product sales' model. In some instances these differences resulted in major departures in cost structure and profit, and therefore competitive strategy. Of particular importance to the cost structure was the level of R&D expenditure necessary to sustain competitive advantage in the product or service offering.

Implications of business model choice

The only clearly successful business model of this group of companies is that developed by Affymetrix. It appears to be sustainable. R&D expenditure is a reasonable proportion of revenues and it has been profitable for a number of years. Its market capitalisation as at 30 June 2006 was $1.8 billion, one of the highest for a biopharmaceutical company. Its value proposition, and consequently value network, was quite different from the other companies. It created a product, the gene chip, based on clear technological leadership protected by far the most valuable patent portfolio of all bioinformatics companies. The gene chip is the core of a product system that includes scientific instruments and bioinformatics software. Revenue is derived from product sales to pharmaceutical companies and biotechs, not from term contracts that provide access to bioinformatics services or compound libraries. Appropriability is high with patents and other forms of protection working adequately. Affymetrix established a different value network at its inception. It merged the technological contributions of a number of specialist technology companies and maintained close links with pharmaceutical companies. However having established its product it was less susceptible to appropriation of its share of the value created by collaborating partners (Gans and Stern 2003).

Conclusions and Observations

Affymetrix has structured its business model effectively. Its value proposition is both compelling and structured, at least initially, to make imitation difficult. It drew on a high proportion of other companies with leading positions in bioinformatics IP. In addition it formed many alliances with firms with expertise in microarray and gene

expression technologies such as bioMerieux as shown in the case study in Chapter 11. It also formed alliances with most of the large pharmaceutical companies with which it placed its initial product systems for testing and validation. Doubtless significant 'relational rents' (Dyer and Singh 1998) were created from this value network. However its share of such rents has been more than sufficient to finance its on-going R&D program, at least in part, because of its pre-imminent IP position. Arguably it has created strategic assets in bioinformatics and related technologies that have delivered sustainable competitive advantage. There is no evidence however that the business model has been structured to offset a weak appropriability position. It began with a strong appropriability position and designed its business model to buttress its strengths.

If Affymetrix is becoming successful, why then the failure of so many of the other firms with leading positions in bioinformatics IP? The business models adopted by the 'pure' bioinformatics companies were vulnerable in various ways. The value proposition was a powerful one. Bioinformatics services have been effective in greatly improving the efficiency of the drug discovery process. The enthusiasm with which alliance partnerships were formed with pharmaceutical companies suggests that the services provided were indeed highly valuable. However the revenue received by the bioinformatics companies from these contracted services was not sufficient to support the R&D and other expenditure necessary to sell and maintain the value of their products and services. In these cases, perhaps the relational rents created by the partnership with the pharmaceutical companies were largely appropriated by the pharmaceutical companies. The strong IP positions in bioinformatics patents, given the information intensive content of the service offered, was not sufficient protection against such appropriation.

Ultimately the inimitability of the inventions failed to protect the revenue streams from lower cost competitors or from the release into the public domain of previously proprietary genomic data. As a consequence, the companies failed. This appears to be an example of an innovation process that failed to create viable specialist companies, more because the business model failed, than that the innovation was of little value.

Indeed the reaction of a number of the companies (such as Curagen and Incyte) to close down or dispose of their external bioinformatics service divisions, and to internalise their technological expertise to assist with in-house drug discovery, suggests that they continue to see significant value in the underlying technology. However a new strategy, the hybrid model, is required to capture the value of the bioinformatics technology through the value of patentable drugs discovered by the company. This illustrates one of the limitations of the open innovation model for platform technologies such as bioinformatics. The revenue generated for the specialist companies needs to be sufficient to provide a sustainable basis for an ongoing business. The value of the technology in the case of bioinformatics has been too vulnerable to being bargained away by partners and the appropriability regime for the services offered proved to be too weak (Gans and Stern 2003). The reaction has been to internalise this capability and use it to help build core competencies in drug discovery in order to gain competitive advantage. In other words, having tried the open innovation model, these firms are returning to a model of innovation closer to that described by the resource based view, in which strategic assets are used to discover and develop inimitable drugs, not platform technologies.

PART E.

VALUE CREATION AND CAPTURE: IMPLICATIONS

Chapter 14. Single Firm Case Study: Starpharma[33, 34]

Introduction

The apparent retreat from the highly networked approach to innovation, as advocated by the open innovation paradigm, evident in the strategies adopted by a number of the case study companies, to one in which alliances are more selectively used suggests that the open innovation approach has its limitations. The changed strategy is more consistent with the resource based view, which stresses the importance of internally owned strategic assets to provide the basis of sustainable competitive advantage.

This chapter presents an example of a start-up biopharmaceutical company, which adopts a selective approach to alliance formation, in part, so as retain strategic control of its leading IP position in a technology platform. By adopting a single company as the unit of analysis, a number of shortcomings of the earlier case studies can be overcome. Firstly it is possible to pay greater attention to the historical genesis of the company and the contribution of individual actors to its development. Secondly the impact of particular alliances formed, or not formed, can be assessed. Greater attention can also be paid to funding sources and how this may influence the need for alliances.

In particular it is possible to gain a greater understanding of the role of IP in the development of the firm's strategic assets. One of the problems with the analysis of the case study companies in the previous chapter is that the patent statistics provide only a partial analysis of the companies IP position. Such an analysis identifies the initial assignee, but provides no information about subsequent patent transfers. The documents dealing with the individual firm often provide a more complete picture of the patents acquired, licensed or otherwise made available to the firm through alliances. This more complete picture is achievable through a single company case study.

[33] An earler version of this chapter was published as Rasmussen, B. 2007, 'Is the commercialisation of nanotechnology different? A case study approach', *Innovation: Management, Policy and Practice*, vol. 9, no. 1.
[34] All dollars in this chapter are Australian dollars unless otherwise indicated

This case study seeks to juxtapose the open innovation paradigm and the resource based view and tests their respective relevance to the business model adopted by the case study company. Which is more important, the networked approach to innovation or the development of internally owned and controlled strategic assets?

The case study traces the development of an Australian biopharmaceutical company, Starpharma, which has assumed a dominant IP position in the pharmaceutical application of dendrimers, one of five fundamental nanomaterial platforms. Starpharma has used its dendrimer expertise to develop a microbicide for HIV and genital herpes, currently in clinical trial. The clinical trials have received significant financial support from the National Institute of Health (NIH) and the approval process has been 'fast tracked' by the US Food and Drug Administration (FDA). It is one of the first uses of nanotechnology to synthesise a new drug.

The Dendrimer Nanotechnology

Nanotechnology is the latest in a series of general purpose technologies (GPT) (Helpman 1998), earlier examples of which, have transformed household life, industry structure and firm performance (Jovanovic and Rousseau 2003). They are characterised by their economic pervasiveness and technological dynamism (Bresnahan and Trajtenberg 1995). Earlier examples include electricity, information technology and biotechnology. The application of nanotechnology is expected to be similarly transformative (The Royal Society 2004; European Commission 2004; Roco and Bainbridge 2005). It has been suggested that the convergence of nanotechnology with other general purpose technologies, such as biotechnology, will be particularly synergistic (NSF 2002). To a degree the application of nanotechnology to the discovery and development of pharmaceuticals is analogous to the application of the various platform technologies already discussed. However the qualities of nanotechnology mean that the impact on medicine is likely to be far more revolutionary, than simply one of efficiency and effectiveness gains in the drug discovery and development process.

Nanotechnolgy has no universally agreed definition. The following definition provided by the US National Institutes of Health describes its scope but provides little insight onto its potential:

> Nanotechnology involves the creation and use of materials and devices at the level of molecules and atoms. (NIH 2007, 25 April)

The dimensions of nanotechnology are generally considered to be in the range 1 to 100 nanometres. The diameter of DNA is in the 2.5 nanometre range while red blood cells are about 2500 nanometres (NNI 2007).

The main reason for the interest in the nanoscale is that:

> … [nano]materials can have different or enhanced properties compared with the same materials at a larger size. The two main reasons for this change in behaviour are an increased relative surface area, and the dominance of quantum effects [which] can significantly change a material's optical, magnetic or electrical properties. (The Royal Society and The Royal Academy of Engineering 2004, p. 5)

For instance at the nanoscale, gold can appear to blue or red, depending on the size of the gold particle. Materials at the nanoscale may be significantly lighter and stronger than at the macro scale.

The application of nanotechnology to medicine (nanomedicine) has followed several paths. These are drug delivery, drugs and therapy, in vivo imaging, in vitro diagnostics, biomaterials and active implants (Wagner et al. 2006).

The first two of these, drug delivery and the development of drugs and therapies, are most relevant to the case study. To date the development of nanopharmaceuticals has followed three paths. The first has been to reformulate existing drugs as nanoparticulates. The second is to use the properties of nanomaterials as drug delivery vehicles for existing approved drugs. The third is to create new pharmaceuticals. Dendrimers are expected to have a major role in both the creation and delivery of new drugs (see for instance Whelan 2006).

Dendrimers are synthetic nanoscale structures (1-10 nm) that can be tailored for many pharmaceutical applications. With specialist chemistry techniques, they can be constructed 'from the bottom up' in a precise manner, to create a core and branch like structure, that can be given unique functionality. Starpharma has used the polyvalent

(multibranch) structure of the dendrimers to create drugs with powerful, simultaneous and multiple binding properties (Starpharma 2005a).

While the microbicide for HIV and genital herpes, known as VivaGel, is its lead product, Starpharma is working on dendrimers as angiogenesis inhibitors and the application of dendrimers to a range of viral respiratory, tropical and exotic diseases. Through its subsidiary, Dendritic NanoTechnologies, it also has a significant investment in the development of the technology more generally, particularly to develop lower cost dendrimer manufacturing techniques.

Starpharma Development History

Relationship with BRI

Starpharma grew out of the Biomedical Research Institute (BRI), a joint venture established at the initiative of the Strategic Research Foundation (SRF),[35] with CSIRO, Australia's largest public research organisation. The SRF was formed by the Australian state government of Victoria to establish large-scale collaborative research initiatives in economically strategic areas of technology (SRF 1991).

BRI was established as a company limited by guarantee in 1990. Dr Peter Colman[36] from CSIRO was appointed to the executive role of Director in 1991. Importantly SRF contributed both money and technology management skills. Dr John Raff previously SRF Biotechnology Project Manager became BRI's General Manager. Money from SRF was used by BRI to purchase a super computer and an extensive suite of molecular analysis equipment. CSIRO made in-kind contributions of staff and accommodation (CSIRO 1994).

From its commencement, BRI was established on a significant scale in Australian terms. By 1992 its labs housed a complement of 55 CSIRO staff scientists (SIRF 1992). This contribution was of particular significance, because it gave BRI access to a long intellectual tradition, as well to essential equipment and laboratory space. CSIRO in-kind payments for these staff amounted to about $3.3 million per annum.

[35] Renamed Strategic Industry Research Foundation (SIRF) in 1993.
[36] Dr Peter Colman is the inventor of the anti-flu drug Relenza, until recently the only Australian invented drug approved by the FDA.

Initially at least, this was matched in cash by SIRF (SIRF 1992) but over the course of the decade this fell away. By 2000 CSIRO's beneficial interest in BRI had increased to 60% (CSIRO 2000).

BRI's research program focused on the design of pharmaceuticals to counteract viruses particularly influenza and AIDS (SIRF 1991). In 1992 the BRI Synthetic Chemistry Group embarked on a research program to develop pharmaceuticals utilising the principle of polyvalency. Key staff members were organic chemists with a greater interest in pharmaceuticals than polymer chemists.[37] This led to research into dendrimers (Starpharma 2000a).

BRI filed for and obtained a number of dendrimer patents. A filing was first made in Australia in 1993 and subsequently in the US in 1996, with the patent being granted in 2001. There were further filings in the US over the period from 1997 to 2001 with three patents being granted between 2001 and 2004. These patents secured BRI's IP in dendrimers.

Starpharma was spun off from BRI in 1997. It entered into a Technology Agreement with BRI under which it licensed the commercialisation rights to the dendrimer technology on an exclusive basis. It agreed to pay a royalty of 25% of the future net earnings received by Starpharma through its exploitation of the technology (Starpharma 2000a). It also entered into research contracts with a number of Australian and overseas research organisations to further develop the technology. Starpharma's stated intention was to 'fund and develop these projects to the point of proving efficacy in humans (phase II clinical trials) prior to licensing to a pharmaceutical company' (Starpharma 2000a, p. 16).

The relationship with BRI during this period was particularly close. BRI was retained under contract from 1997 to provide a range of R&D services at a cost of $1 million per annum (Starpharma 1999). Dr Peter Colman was both a director of Starpharma and Managing Director of BRI. Dr John Raff, in September 1996, left BRI to become CEO of Starpharma (Starpharma 2000a) and was appointed to the Board in April

[37] Anonymous referee.

2000 (Starpharma 2000b). Other key BRI/CSIRO staff members to join Starpharma during this foundation period included the co-inventors of the BRI technology, Dr Barry Matthews and Dr George Holan, who became Research Director and Senior Scientific Consultant respectively at Starpharma (Starpharma 2000a).

Fund raising

Much of Starpharma's funding in the period to 2000 was from government grants. Under the Federal Government's START program it received two grants totalling $5.65m (Starpharma 1999) and it was also successful in obtaining a small grant from the US National Institute of Health (NIH).

From 1997 however a series of capital raisings provided an increasing share of Starpharma's funds for its development program. As shown in Table 1, Starpharma has raised a total of $47.1 million in equity capital raisings and received government grants of $7.1 to fund R&D expenditure of $31.3 million.

An initial private placement of $5 million was undertaken in 1997 to establish the company. At the same time founders' shares, representing 60% of the company's equity, were issued to directors and management. Despite dilution to about 20-25%, this has allowed a group of initial stakeholders to retain practical control over the affairs of the enterprise helping achieve a consistent business strategy. The largest institutional shareholder is Acorn Capital Ltd, a passive microcap manager with about 8% (Jackson 2005).

Table 14.1 Starpharma revenue sources and R&D expenditure, financial years ending June 1998-2005 ($'000)

Year ended 30 June	Govt grants	Other revenue	Total revenue	Capital raising*	R&D
1998	796	262	1058	5000	990
1999	738	159	897	0	1183
2000	1344	266	1610	7280	2632
2001	886	1078	1964	20823	4005
2002	383	945	1328	217	6228
2003	839	671	1510		5713
2004	703	688	1391	13788	4119
2005	1409	640	2049		6410
Total	7098	4709	11807	47108	31280

Note: *Net proceeds.
Source: Starpharma Annual Reports and Prospectuses.

Starpharma undertook an IPO in September 2000, raising $20.8 million and has returned to the capital markets several times, most recently in November 2005 for $15 million. These subsequent raisings have been a mixture of institutional private placements and rights issues to existing shareholders. Details of the capital raisings, including the issue price are set out in Table 2. Since the initial raising, issue prices have ranged from a high of $0.85 to a low of $0.51 reflecting market conditions and the market assessment of the company's prospects. Indeed the pricing of the most recent raising may be considered disappointing, given the substantial de-risking of the project, following significant progress in human trials. In order to gain greater access to US capital the company established an ADR program in January 2005, which has progressively received increasing levels of support (Raff 2005).

Table 14.2 Starpharma capital raisings, 1997 to 2005

Date	Shares ('000)	Price ($)	Amount ($'000)
03/09/1997	50000[(1), (2)]	0.25	5000
24/09/1999	12500[(1)]	0.625	7813
20/09/2000	26400	0.85	22440
10/09/2003	13335	0.52	6934
18/03/2004	9000	0.84	7560
14/11/2005	29412	0.51	15000

Notes: (1) Adjusted for 4:1 split.
(2) Includes 30 million founders shares issued at no consideration (Starpharma 1998, 1999).
Source: Starpharma Annual Reports and Prospectus.

It is noteworthy that in its early stages, the company unlike its US counterparts, has never entered into an association with a venture capital company (VC), in which the VC provided expertise, as well as finance. In general, biotechs in Australia are more likely to go to the public markets at an earlier stage than US biotechs (Herpin et al. 2005) rather than seek private equity from a VC. Vitale (2004) has commented that government policy has encouraged company formation, but many companies have difficulty getting funding from venture capitalists or other private investors.

The early listing has contributed to instability in the sector, as companies have faced the pressure of managing the uncertainty of an early stage R&D program, under the public scrutiny required by ASX disclosure requirements. In Starpharma's case, it is

perhaps significant that it was able to enlist the technology management skills that had been developed in BRI, thus obviating the need for such assistance from a VC.

Alliances, collaborations and product development

Since its establishment, Starpharma has formed a large number of research and other collaborations in Australia, the US, Canada and Europe. One of these was an alliance with Viradae, a small Canadian clinical services company but also with operations in the US, with the objective of introducing the microbicide application of the dendrimer technology to the US regulators (Starpharma 1999). The project succeeded in obtaining a US SBIR grant from the NIH of $0.6 million to advance its antiviral applications to Phase 1. These plans changed however and the work was completed elsewhere in the US.

PanBio, a Queensland diagnostics firm, is credited with introducing Starpharma to Dr Donald Tomalia, widely regarded as the inventor of dendrimers. Dr Tomalia was a former scientist at Dow Chemical, where he had patented a number of large dendrimer technology inventions. In September 2001 PanBio and Starpharma announced that they would invest $2.2m in a new joint venture company with Dr Tomalia. However in March 2002 PanBio decided not to proceed with this investment and Starpharma took a 49.9% position in the joint venture company, Dendritic NanoTechnologies (DNT) with Dr Tomalia. DNT had a portfolio of some 30 patents. The company was nominally headquartered in Melbourne but its operations were located in Michigan at the Central Michigan University (Starpharma 2001; PANBIO 2001).

In January 2005, DNT was restructured, with Dow Chemical depositing all of its 196 dendrimer patents plus associated royalties with the company in return for a 31% equity in the company (InPharma Technologist.com 2005). Starpharma, in return for an additional cash equity, obtained exclusive rights to all pharmaceutical applications of the IP (NanoInvestorNews 2005) and retained its largest shareholder status with a 33% holding in DNT (Uldrich 2005). In October 2005, Starpharma terminated its Technology Agreement with BRI, acquiring outright ownership of its core technology (including three patents) in exchange for 6.4% equity in the company (Starpharma 2005c). In October 2006 Starpharma bought DNT outright through the issue of

Starpharma shares. This gave it total control of the sizeable Dow dendrimer patent portfolio. Combined with its own patents and those sourced from DNT, these transactions place Starpharma in a powerful position with respect to the application of dendrimer technology (Lux Research 2005b).

Although Starpharma is researching a range of pharmaceutical applications of dendrimer technology, its lead product is a topical microbicide known as VivaGel for the prevention of sexually transmitted diseases (STDs) including HIV and genital herpes. Preclinical trials were completed in 2003 and the drug was approved by the FDA in July 2003 for human trials. This was the first dendrimer nano-drug to be approved for human trial by the FDA. The Phase 1 human safety trial was successfully conducted by the Institute of Drug Technology Ltd at the CMAX facilities in Adelaide.

In October 2005, Starpharma received a US$20.3 million funding award from the US National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to further develop the product. The grant reflected the strong US and international interest in solutions to the problem of STDs. The novel nature of the dendrimer technology probably also had a role in attracting NIH interest. Although the reasons for NIH awards are not on the public record, the NIH CRISP database provides an abstract of successful grant applications. From these it is fair to conclude that the novel nature of the technology has played a part in the success Starpharma has achieved with NIH (2008a).

The clinical studies are to be carried out in the US and Kenya and in conjunction with several Australian medical research institutes including the Burnett Institute in Melbourne and the Thai Red Cross AIDS Research Centre in Bangkok (Starpharma 2005a, 2005b, 2007).

There are several competing products to VivaGel. Both the Populations Council's Carraguard and Cellegy's Savvy are microbicide gels that appear to be somewhat more advanced than VivaGel. Both have been subject to special guidance from the FDA, which has permitted a combined large scale PhaseII/III trials to test for efficacy

in humans, rather than the standard path of Phase II proof-of-concept trials followed by large scale efficacy Phase III trials (Intersuisse Limited 2004).

Manufacturing dendrimers has represented a challenge for Starpharma. One issue is the uniformity of the size of the dendrimer nanoparticles and the other is the cost of production. Both of these appear to have been addressed by DNT, which announced in May 2005 the development of a new class of dendrimers, which are scaleable precision nanostructures that can be manufactured in high volumes at lower costs (DNT 2005).

Expertise in Dendrimer Technology: Creation of a Strategic Asset

The empirical work presented in this thesis, particularly for a number of the bioinformatics companies reviewed in the previous chapter, has provided evidence to suggest that some platform technology companies are less aggressively pursuing the networked approach to innovation, advocated by the open innovation paradigm, and instead retreating to a strategy that builds on their technology leadership to create a strategic asset in drug discovery.

Starpharma's competitive opportunity has been in the development of dendrimers, and it has put most of its resources into using this technology platform to develop in-house therapeutics. It has not sought to use its expertise in dendrimers to provide others with a platform for drug development. All its effort has gone into using this expertise to create a strategic asset that provides it with a basis of sustainable competitive advantage. It appears not to have been attracted by alliances that may have undermined its strategic position, but rather focussed on partnerships that have buttressed its competitive advantage.

This history of the development of Starpharma, outlined above, has highlighted the features of this strategic asset building process. The first was to develop its own expertise in dendrimers. The second was the establishment of a formidable position in dendrimer IP for pharmaceutical applications and then to acquire full ownership of the key patents supporting the dendrimer technology platform. Lastly was the decision to

use dendrimer to address a target market of great need, with a topical therapeutic that avoided some of the regulatory issues of an ingested drug.

Starpharma's own expertise

The successful commercialisation of biotechnology is heavily dependent on the excellence of the basic science (McKelvey et al. 2004, etc.) and its transformation into useful technology (McKelvey 1996). In its early stages, Starpharma was successful in assembling a team of scientists and other actors with high levels of competencies in an area with significant market potential. Such foundation resources have been found, more generally, to be critical in the success of biotechnology commercialisation.

Starpharma's 'star scientists' (Zucker et al. 1998a, 1998b) Drs Holan and Mathews, co-inventors of the BRI dendrimer technology and Dr Peter Colman, not only the Director of BRI, but also a viral drug expert and the inventor of Australia's first FDA approved drug,[38] became involved in Starpharma through its antecedent organisations, BRI and its JV partner CSIRO. These initial resources and competencies inherited from BRI were later complemented by Dr Donald Tomalia, the dendrimer pioneer, through the joint venture with Dendritic NanoTechnologies (DNT). As the inventor of much of the Dow patent portfolio he was the undoubted dendrimer 'star scientist'. Dr Tomalia's involvement not only supplemented Starpharma's own position in dendrimer IP but also brought to the project a leading scientist with an active interest in commercialising his inventions.

For instance, according to Zucker et al. (1998a, 1998b), the star scientist emerging from the research labs, with significant and unique skills, has been a critical success factor for the commercialisation of biotechnology in the US. This work suggests that the science-based knowledge from universities did not simply 'spillover' due to proximity, but depended on the excludable transfer of tacit knowledge, from lab to start-up, by the 'star scientist'. The role of Starpharma's 'star scientists' would appear to conform to this model, in which the general diffusion of knowledge to the scientific community is tightly controlled by both IP protection and personal incentives offered to the key scientists.

[38] Relenza is an anti-viral flu drug.

Along with scientific expertise, the original JV between CSIRO and SIRF, a Victorian Government agency, also provided significant technology management skills and experience in the form of Dr John Raff, General Manager of BRI. The importance of such capabilities is supported both theoretically and empirically. The dynamic capabilities approach of Teece et al. (1997) for instance, emphasises the role of strategic management in the adaptation and integration of competencies to match the changing environment. Managerial skills and the ability to recognise commercial applications of technology were ranked second and third respectively, behind quality of the product, as the factors that affect business performance of biotechnology firms, in a major survey of such firms (Bagchi-Sen et al. 2004).

Starpharma's IP position

Starpharma has put considerable effort into securing control of the key dendrimer patent portfolio. Starpharma's entry into dendrimer IP was relatively modest. The Starpharma team, when working at BRI, successfully filed for three dendrimer patents in the area of pharmaceutical preparations, firstly in Australia in the period 1993 to 1996 and subsequently in the US. It was not until it formed its joint venture company, Dendritic NanoTechnologies (DNT) with Dr Donald Tomalia, that it had access to Tomalia's portfolio of some 30 patents. These covered both pharmaceutical and other applications. The next step was when Dow became a shareholder in DNT and deposited all its dendrimer patents with the company. Starpharma, then became a minority shareholder in DNT and gained access to these patents only through a licensing agreement. By acquiring DNT, Starpharma took complete control of these patents. In addition it has secured total control of the BRI patents through an equity issue to BRI. The equity deal also terminated BRI's rights to royalties from future earnings.

Acquiring this patent portfolio has not been achieved without cost. Although the cash outlay has been modest, acquiring DNT and therefore the Dow portfolio, gave Dow 8.6% of Starpharma and a Board seat. While that association may bring long term benefits, it reduces the grip on the company of the original stakeholder group, who prior to the DNT and BRI transactions, owned 20-25% of the company and through management and their Board seats, largely directed the company's strategy.

Has this been worthwhile? In the bioinformatics case studies discussed in Chapter 9, the experience of these companies, which all began with strong patent portfolios, has been mixed. A number found that their IP positions were ultimately of little value in attempting to market bioinformatics information services. At least one other, Affymetrix, has built a prosperous business on its IP foundations. For those bioinformatics companies that have turned to in-house drug discovery and development, it is still perhaps too early to place a value on their bioinformatics IP foundations.

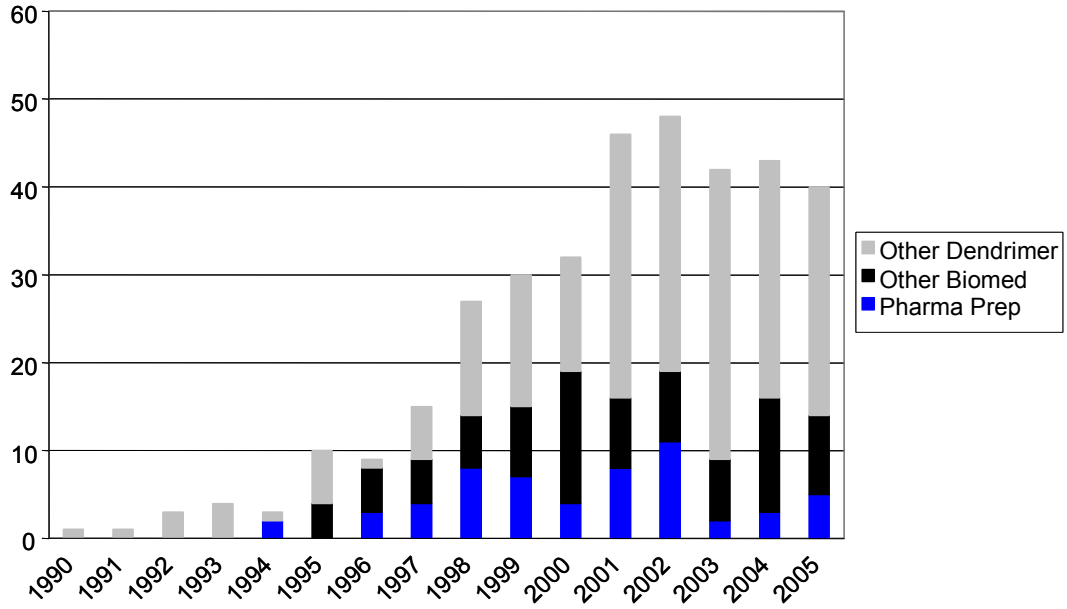
While some of the literature on the value of patents has in various ways questioned the effectiveness of patent protection (see for instance Penrose 1951; Griliches 1990; Heller and Eisenberg 1998; Jaffe 1999; Winter 2000; Lerner 2002; Grabowski 2002; Jaffe and Lerner 2004; Lanjouw and Schankerman 2004), others such as Winter (2000), Grabowski (2002), and Lanjouw and Schankerman (2004) have demonstrated the importance of patents for the pharmaceutical industry, where the level of R&D investment is high and the cost of imitation is relatively low (Grabowski 2002), compared with other industry sectors.

The work of Lanjouw and Schankerman (2004), for instance, has demonstrated the relatively high usage of patents in the pharmaceutical industry, compared with other high technology sectors, per million dollars of R&D expenditure. The number of pharmaceutical patents per unit of R&D is approximately twice that of other 'high tech' sectors such as chemicals, electronics and other health. Winter (2000) quotes surveys of patent effectiveness, which indicates the high relative effectiveness of drug patents compared with the other sectors surveyed. This suggests that patents are an effective way to protect pharmaceutical IP, although the survey refers to drugs rather than platform technologies. In Starpharma's case its patenting is directed to protecting both its drug discovery efforts and the use of the underlying dendrimer platform for drug development, suggesting that such a strategy is more likely to be worthwhile.

Patenting in dendrimers grew rapidly in the later part of the 1990s. As shown in Figure 14.1, the number of dendrimer patents granted by the USPTO increased significantly from 1994 to 2003. As a platform technology, dendrimers have a range of uses in basic and applied chemistry, as well as in biomedicine. For the period since

1990, patents granted for biomedical purposes have represented about 40% of all dendrimer patents granted in the period since 1990, and for the period 1996 to 2000, the proportion was more than half of the total. Of these biomedical patents, 39% related to pharmaceutical preparations, the largest single sub grouping classified. The majority of these patents were issued in the period 1998 to 2002, indicating a period of highly productive research output, after allowing for the lag between patent application and issue, in the second half of the 1990s.

Figure 14.1 Number of dendrimer patents issued by the USPTO, 1990 to 2005



Source: USPTO, keyword search using Delphion.

Of the biomedical patents relating to pharmaceutical preparations, Dow is the largest assignee and most heavily referenced, indicating both a sizeable and strategically valuable portfolio. Table 14.3 shows that it has the largest portfolio of any organisation with 7 patents. In terms of the technology value indicator developed to assess the value of bioinformatics patents in Chapter 13, it represents over three quarters of the value of the total dendrimer patents relating to pharmaceutical preparations.

Table 14.3 Measures of relative patent value: Dendrimer patents relating to pharmaceutical preparations

Assignee	Patents	Fwd refs	TVI
Dow Chemical Company	7	195	77.3%
University of California	5	6	1.7%
Schering Aktiengesellschaft	4	14	3.2%
Nycomed Salutar, Inc.	3	35	5.9%
BRI/ Starpharma	3	4	0.5%
Burstein	3	7	0.7%
Other	35	155	10.7%
Total	60	416	100.0%

Source: USPTO. Key word search using Delphion.

Dow's dendrimer patent portfolio extends beyond pharmaceutical preparations, to include other biomedical uses and dendrimers in general. Not only is Dow the largest assignee in these other areas, but the patents are also the most highly referenced. This makes the Dow portfolio of patents an extremely valuable one to own, or to which to gain licence access. All of these patents were transferred to DNT and have therefore now been acquired by Starpharma as part of the purchase of DNT.

This analysis suggests that with the acquisition of DNT, Starpharma has obtained exclusive control of the most valuable dendrimer patent portfolio developed to date. Therefore the acquisition of the Dow patent portfolio has been a very important strategic move for Starpharma. At once it has secured the IP basis of its own dendrimer based drug development program and closed out the potential for competitors to use the platform without its approval.

This view has been independently confirmed by Lux Research (2005b), which has conducted a detailed study of nanotechnology patents. Its report indicates that there is little 'white space' in Starpharma's patent portfolio, held directly and indirectly, meaning that there are few openings for competitors to successfully lodge patents that would challenge Starpharma's exclusive access to this technology.

Value of the dendrimer technology

There is little point to these advantages, if the technology has no value. In its quest to create a strategic asset of its primary position in dendrimer IP and its own pharmaceutical expertise, Starpharma has chosen to apply these resources and capabilities to the development of a human therapeutic to tackle genital herpes and

HIV. The world epidemic in HIV/AIDS means that its microbicide is directed to tackling one of the areas of greatest unmet medical need. Despite the development of an anti viral cocktail of AIDS drugs, HIV/AIDS is projected to be one of the larger and most rapidly growing causes of death and disability for the next 20-30 years (see for instance Mathers and Loncar 2006). According to the World Health Organisation, 15-20% of the adult population of US (45 million) and Europe have genital herpes. Forty million people worldwide are said to have HIV (Starpharma 2005b), a high proportion of whom are in third world countries.

The Vivagel microbicide has the advantage of a lower development risk, being a topical gel that is external to the body and its manufacturing costs are said by Starpharma to be low. There are a number of product extensions, such as a condom coating, which increase the size of the potential market and may bring forward its commercialisation (Starpharma 2007).

With successful human trials of Vivagel and its approval by the FDA, current estimates of the market size for Vivagel fall in the range $700 million to $1400 million per annum (Starpharma 2007). This would represent a significant return for investors in Starpharma. Although an early Phase I trial was successful, the FDA has required larger tests for safety to be held in the US and a developing country (Kenya), so human trials remain in an early phase and therefore the risks of failure are still high.

By a number of counts, Starpharma has created a strategic asset, but will it deliver sustainable competitive advantage? Starpharma's expertise in dendrimers and its patent portfolio represent a set of resources and capabilities that are 'difficult to trade and imitate, scarce, appropriable and specialised' (Amit and Shoemaker 1993, p. 36) but whether it will deliver sustainable competitive advantage depends on the outcome of the human trials for its lead product, Vivagel. Nonetheless Starpharma has created enough of a strategic asset to have been able to continue to raise capital from its investor base as indicated in Table 14.2. Perhaps this is all that can be asked of a drug discovery company at this stage of its development.

Starpharma and the Open Innovation Paradigm

The section above has evaluated the extent to which Starpharma had been successful in creating a strategic asset and therefore the degree to which the resource based view might be relevant to its business strategy. The resource based view and the open innovation paradigm emphasise different aspects of the innovation process (Christensen 2006). The former is focussed on the competitive advantage accruing to internally owned strategic assets, while the latter sees most of the dynamics of the innovation process arising from active participation in alliances and networks with other companies. To what extent is the open innovation paradigm relevant to Starpharma's business strategy?

The growing propensity of biopharmaceutical companies to form alliances to gain access to fundamental technologies has been demonstrated in chapters 9 and 10. The complexity of the network in the biomedical sector has been documented by Powell et al. (2005) who traced the development of the network established, over the period 1988 to 1999 by 482 organisations, categorised into five types of actors – dedicated biotechnology firms (DBFs), public research organisations, government, pharmaceutical companies and venture capital companies. This showed not only the increased complexity and density of the network over the study period, but also the transition in the nature of the alliances within the network. In particular it illustrates the transition from predominately R&D and commercialisation alliances between biopharmaceuticals and pharmaceutical companies to a much increased number of finance alliances with venture capital companies. Central positions in this network were occupied by several government funding bodies, most notably the NIH, the major pharmaceutical companies, an increasing number of DBFs and some of the venture capital companies.

In a number of ways Starpharma's use and integration into this network follows the model established by this US-based empirical research. A key development for Starpharma was the announcement in October 2005 of NIH funding for further clinical trials. Starpharma's capacity to attract funding from the NIH aligns this aspect of its business strategy with that of its US counterparts. The work of Powell et al. (2005) confirms the critical role performed by NIH in the biomedical innovation

system. Its work shows that the NIH is the single most important organisation in the biomedical network, with a central position in that network.

Starpharma's technology alliance with Dr Donald Tomalia, the creation of the joint venture company and indirectly, its relationship with Dow, have all been crucial to the development of the company. Starpharma has also formed collaborations with a number of medical research institutes in Australia (e.g. the Burnet Institute) and has up to a dozen such collaborations with institutes and universities overseas, mainly in North America (Starpharma 2000a, 2007). Company documents refer vaguely to a similar number of industry collaborators but no details are provided. The only Starpharma alliances listed on Recap are those involving DNT and its collaboration with BRI.

There are two types of actors, seen as critical to the success of biotechs – venture capital companies (Kenney 1986; Lerner 1994, 1995: Powell et al. 2002) and major pharmaceutical companies (Arora and Gambardella 1990; Powell et al. 1996; Galambos and Sturchio 1998; Rasmussen 2006), which are missing from Starpharma's list of collaborators. Venture capital (VC) companies are seen, not just as suppliers of early stage capital, but also as providing critical management expertise and commercial support for companies that may possess strong technical teams but little commercial experience. Their experience has also been found to have a positive impact on the success of biotech IPOs (Lerner 1994). This may explain the findings of Powell et al.'s (2005) work, which has demonstrated the increasing role of venture capitalists in the US biomedical network.

That Starpharma has bypassed VC involvement may reflect several factors. The first is that the role of VC companies particularly in the 1990s was been much smaller in Australia than the US. For most of those that do attract VC funding the amount can be very small. The median amount provided in the period 1996-2003 was only $0.5 million (Vitale 2004, p. 13). This reflects lower levels of availability of private equity, both from institutions and private sources. Just four companies provided half of the venture capital over the period (Vitale 2004, p. 15). Accordingly, Australian biotechs have been forced to access public markets at an earlier stage and for smaller amounts than their US counterparts (Herpin et al. 2005). Starpharma is consistent with this

pattern, going public with its third approach to investors only three years after establishment.

However even had VC funding been more available, it is entirely plausible that Starpharma would not have altered its funding strategy. Its relatively experienced management team would have found the need for VC commercial expertise much less pressing. Moreover VC participation would have diluted control and most likely introduced new conditions which, given the continued equity positions and active participation of many of the original stakeholders, would not have been accepted lightly. This is certainly consistent with other aspects of its business strategy, such as its IP strategy, where obtaining control has been an important objective.

In contrast, Starpharma has actively sought the involvement of a major pharmaceutical company (Starpharma 2005a) and as indicated in its 1999 Prospectus, its intention was to licence its leading products to a major pharmaceutical company to finance later stage human trials and market distribution. In 2003, it revealed that it had enlisted a specialist firm, Biocomm, to seek out a suitable partner (Starpharma 2003). This process has been made more difficult for Starpharma by its distance from the centres of biopharmaceutical research. Australia has no large domestic research pharmaceutical companies and the involvement of 'big pharma' in Australian R&D has been low (Rasmussen 2004). Their support must be obtained through intensive lobbying in the US or Europe.

The pressure to find a partner has been lessened somewhat by the US$20.3 million NIH grant which will finance human trials to Phase III (Starpharma 2005b). Successful trials to this point, at which probability of success increases to about 65% (see Chapter 6) will substantially improve Starpharma's bargaining position in any discussions with 'big pharma' about licensing arrangements. Capital for this product development phase remains difficult to raise in Australia.

A study by Lux Research (2005b) reports on the results of interviews with large pharmaceutical company corporate executives responsible for nanotechnology, which indicate that 'big pharma' companies are less focussed, commit fewer resources, people and R&D funding to nanotechnology than other industries. Lux Research

suggests that big pharmaceutical companies will ultimately pay a high price for this lethargy, as the cost of acquiring the technology increases sharply, which ultimately may work to Starpharma's advantage.

This suggests that Starpharma's inability to form an alliance with a major pharmaceutical company reflects both its remoteness from the centres of biopharmaceutical research and a cautiousness or indifference about the technology on the part of 'big pharma'.

Observations and Conclusions

Starpharma's competitive strategy has paid a great deal of attention to securing a dominant IP position in the pharmaceutical application of dendrimers. In this respect it conforms to the expectations of Teece's (1986) appropriability theory for an innovating firm. It is in a strong appropriability position with respect to the owners of complementary assets and is therefore in a good position to negotiate with the owners of such assets. Although, as Teece's theory predicts, it may have to concede some of its profits to access some complementary assets, such as global pharmaceutical company distribution capabilities, it is in a good position to participate in a wider value network without giving up significant relational rents.

To date however, Starpharma has been a cautious participant in the biopharmaceutical network. It has formed alliances and collaborations to develop, prove up and obtain technology but has always managed such interactions as the client, not as the R&D alliance party. It has not attempted to market its technology expertise to third parties and therefore it has not participated in the two way trade in technologies seen to be at the core of the open innovation paradigm. At no stage has it participated in a network involved in creating value in which relational rents needed to be shared. Its business model has remained a drug discovery one with a strong emphasis on in-house product development, even as it has strained to achieve IP dominance of the dendrimers platform technology.

This firm behaviour is more consistent with that predicted by the resource based view, in which a firm seeks to secure sustainable competitive advantage by creating internally owned strategic assets. Earlier in the chapter it was argued that Starpharma

had travelled much of the distance towards creating a strategic asset in dendrimers and using that platform to develop the Vivagel microbicide. Whether it has actually created a strategic asset depends however on the successful outcome of the human trials.

It is difficult to generalise from the Starpharma example. While its prospects appear to be good and the support received from the NIH and the FDA encouraging, it has adopted a business model which may yet be unsuccessful. At the same time its behaviour is consistent with that of some firms analysed in less detail in chapters 11 and 12. Its strategies resonate with those of bioinformatics companies studied in Chapter 13, that have drawn back from the highly networked platform technology company business model to one focussed on in-house drug development, in which they attempt to create a strategic asset based on their platform technology capabilities.

Chapter 15. Creating and Capturing Value in the Biopharmaceutical Sector

Introduction

The greater part of this thesis has focused on understanding the behaviour of biopharmaceutical firms, their alliances, the manner in which their business models are structured, and how they have evolved. Little attention has been paid to the implications of these findings for the biopharmaceutical sector.

As a technology expected to transform public health, biotechnology has received generous funding from governments around the world. A good proportion of the NIH's almost $30 billion annual budget has been devoted to biomedical research (NIH 2008b). Over 3500 companies, as discussed in Chapter 8, are engaged world wide in the biopharmaceutical sector. However as documented in this thesis, only a small proportion are profitable and of these only a handful are responsible for most of the profits generated. Has the development of biopharmaceuticals created value? If so, which types of companies have secured this value?

The Value of Biopharmaceutical Drugs

Number of drugs approved

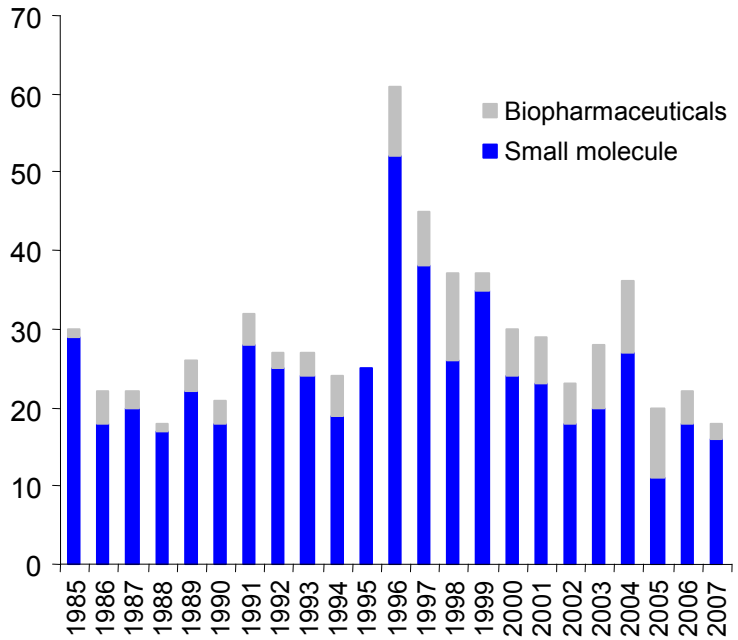
Biopharmaceutical drugs remain a relatively small but generally growing share of total drugs approved by the FDA. The definition of a biopharmaceutical drug in this section follows Walsh (2006) but excludes vaccines and blood products. The definition is based on the use of modern biotechnology in the drug's development and therefore excludes the earlier development of 'biologicals' (Walsh 2002).[39] Small molecule drugs are those non biopharmaceutical drugs approved by the FDA's Centre for Drug Evaluation and Research (CDER) which are generally the product of the older non biotechnology medical technologies. They remain largely the province of the pharmaceutical companies, although just as pharmaceutical companies are involved in producing biopharmaceuticals, so too are biopharmaceutical companies

[39] 'A biopharmaceutical is a protein or nucleic acid based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source' (Walsh 2002, p. 135).

sometimes involved in producing small molecule drugs.[40] Both definitions exclude vaccines and blood products.

While the number of drugs being approved each year has been falling from an average of 48 in the period 1996-98 to 20 in period 2005-07, as shown in Figure 15.1 the number of small molecule drugs generated by the major pharmaceutical companies remains dominant, despite the rising share of biopharmaceuticals. In the period 1990 to 2007, the ratio of small molecule drugs to biopharmaceuticals was over 5 to 1. In the last five years this has reduced to 3 to 1, but the trend has been highly variable. This continuing productivity of the small molecule drug technologies helps to explain the endurance of the pharmaceutical business model.

Figure 15.1 FDA new molecular entities (NMEs): Biopharmaceuticals and small molecule drugs

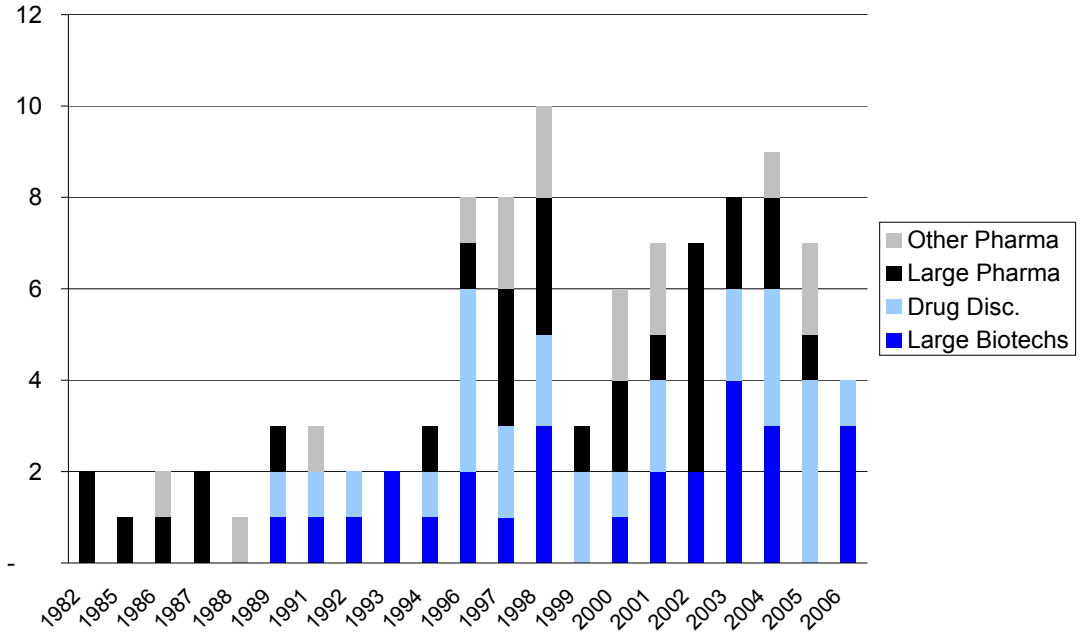


Source: Sources: FDA (2008a, 2008b), Gosse and Manocchia (1996), Leader et al. (2008), Reichert (2000, 2004, 2006), Reichert and Paquette (2003) and Walsh (2006).

[40] Although the impact on the number of drugs classified is small, there has been some difficulty in defining biopharmaceutical and non biopharmaceutical or small molecule drugs. This arises in part from technical issues but also from administrative and classification issues arising from transfers of responsibility between the FDA agencies, CDER and the Centre for Biological Evaluation and Research (CBER). However for the purposes of this thesis it is the definition of biopharmaceuticals which is of central importance and for that Walsh (2006) has been adopted as the authority.

Not all biotechnology based drugs have originated with biopharmaceutical companies. Pharmaceutical companies have also been active in developing biopharmaceuticals, both in house as well as through alliances. Figure 15.2 shows the number of biopharmaceutical drugs approved by the FDA by year of approval. According to the definition adopted here a total of 101 biopharmaceuticals have been approved. These have been classified according to the type of company which applied for the new drug approval (NDA) referred to by the FDA as the 'drug sponsor'. The applicant or 'drug sponsor' is 'the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the *Federal Food, Drug, and Cosmetic Act*.[41]

Figure 15.2 Number of FDA new biopharmaceutical approvals by year of approval and type of sponsor company*



Note: *Excludes vaccines and blood products.
Sources: FDA (2008a, 2008b), Parexel (2006) and Walsh (2006).

This provides an insight into the involvement of pharmaceutical companies in sponsoring biopharmaceutical approvals. Of the total drugs approved 45% of sponsors have been pharmaceutical companies. Two thirds of these companies have been 'Top Dozen' pharmaceutical companies ('Large pharma').[42] Of the remaining 55%, all

[41] http://www.fda.gov/cder/handbook/sponsor.htm
[42] In Chapter 10, Trends in Biopharmaceutical Alliances for the Key Business Models, the largest 10 pharmaceutical companies by pharmaceutical sales was adopted as the definition of 'large pharma'. There is a continuum of companies ranked by sales and any cut-off is somewhat arbitrary. The top 10

biopharmaceutical companies, half of the drugs have been sponsored by the six large biotechs. The value of biopharmaceutical drugs sold however demonstrates a very different outcome for pharmaceutical companies in general and large pharmaceutical companies in particular.

Sales of biopharmaceuticals

Of the 101 biopharmaceuticals satisfying the Walsh (2002) definition, 80 had sales for the period 2002 to 2006. Those without sales for this period included drugs which had been superseded by newer drugs, drugs approved too recently to have sales recorded in the period and some speciality drugs (e.g. imaging agents) for which data were not available. Table 15.1 shows the value of global sales for these 80 drugs for the five year period, 2002 to 2006, classified according the type of FDA sponsor. By 2006, total global sales had reached $44 billion having grown at an average of 28.4% per annum since 2002, almost three times the growth rate for total global pharmaceutical sales of 10.8% per annum. By 2006, 76% of total sales arose from drugs for which biopharmaceutical companies were the sponsor, with large biotechs responsible for 63.0% or $27.7 billion of the total. The growth rate for large biotechs was 31.0% per annum. Large biotechs, with only 31.6% of the drugs by number, had achieved a disproportionate share of the total sales value. On the other hand, large pharma was responsible for only 22% or $9.3 billion of total sales, although its growth rate of 36.8% per annum, was the highest of the four categories.

Table 15.1 Global sales of biopharmaceuticals by type of sponsor, 2002 to 2006 ($ billion)

Sponsor	2002	2003	2004	2005	2006	CAGR
Large biotechs	9.4	12.5	16.3	21.3	27.7	31.0%
Drug discovery	2.9	3.5	4.3	5.0	5.8	19.0%
Large pharma	2.6	4.1	6.0	7.7	9.3	36.8%
Other pharma	1.2	1.1	1.1	1.1	1.2	0.2%
Total	16.2	21.2	27.7	35.1	44.0	28.4%

Note: CAGR compound annual growth rate.
Source: IMS, SEC 10-K reports, annual reports and other company information.

The FDA sponsor, particularly where the sponsor is a pharmaceutical company, may not be the initial discoverer or developer of the drug. In many cases a

was chosen to be both representative and manageable analytically. For the analysis presented in this chapter, the top 12 by sales is adopted as the definition of 'large pharma' because the two companies that would otherwise be excluded, Roche and Abbott have developed several biopharmaceuticals with significant sales and to classify them as 'other pharmaceutical' would be misleading.

biopharmaceutical company may have had this role, before licensing or selling the drug to a pharmaceutical company during the development process. In an effort to establish the source of each biopharmaceutical approved, the origin of the each drug was traced through company information (SEC 10-K reports, annual reports and other company information) to determine whether the drug's discoverer, as distinct from its sponsor, was a biopharmaceutical or pharmaceutical company. In a small number of cases insufficient information was available to classify the drug. However for the vast majority of biopharmaceuticals, it was possible to determine whether the originator or discoverer of the drug was a biopharmaceutical or pharmaceutical company. This exercise was undertaken for each biopharmaceutical with sales in 2006, a total of 79 of the 101 biopharmaceuticals approved since 1982 (see Appendix A for list of 79 drugs and originator and sponsor companies).

Table 15.2 shows the total number of 79 biopharmaceuticals with sales in 2006 cross tabulated by developer and FDA applicant. The size of the portfolios as between large biotech, drug discovery and large pharmaceutical companies are of similar orders of magnitude, 25 for large biotechs, 20 for drug discovery and 23 for large pharmaceuticals. Fourteen out of the total of 23 drugs for which a large pharmaceutical firm was the applicant were sourced internally. Only 5 drugs originated with biopharmaceutical companies.

Table 15.2 Number of biopharmaceutical drugs on sale, 2006, by type of sponsor and originator

FDA sponsor	Originator			Total
	Biopharma	Pharma	Other/NEC	
Large biotechs	23	1	1	25
Drug discovery	16		4	20
Large pharma	5	14	4	23
Other pharma	6	2	3	11
Total	50	17	12	79

Source: IMS, FDA, SEC 10-K reports, annual reports and other company information.

Global sales of these biopharmaceuticals for 2006 are shown in Table 15.3. It shows that of the total value of biopharmaceuticals sold in 2006 of $44.0 billion, biopharmaceutical companies were responsible for originating drugs valued at $37.3 billion or 85% of the total. Almost three quarters of this amount (73.7%) was generated by large biopharmaceutical companies with sales of $27.5 billion. In total,

pharmaceutical companies sold a relatively modest amount of $10.5 billion of biopharmaceuticals of which $4.1 billion or 39% originated with biopharmaceutical companies.

Table 15.3 Global sales of biopharmaceuticals by type of originator and FDA sponsor, 2006 ($ billion)

FDA sponsor	Originator			Total
	Biopharma	Pharma	Other/NEC	
Large biotechs	27.5	0.0	0.1	27.7
Drug discovery	5.6	0.0	0.1	5.8
Large pharma	3.3	5.7	0.3	9.3
Other pharma	0.8	0.3	0.1	1.2
Total	37.3	6.0	0.7	44.0

Source: IMS, FDA, SEC 10-K reports, annual reports and other company information.

Returns to Innovation

While this picture of biopharmaceutical sales presents a useful picture of the sector and of the relative importance of the major types of contributing firms, further analysis is required to determine whether the investment in biopharmaceuticals by these firms has been worthwhile. That is, whether the investment in the cost of development is likely to be repaid by the past, current and future sales.

There is a large literature on the returns to R&D and the returns to innovation (see Martin and Salter 1996 for a survey). Much of this literature is directed at estimating the social returns to R&D. In particular it is concerned with whether the public investment in R&D has been worthwhile and therefore seeks to measure both private returns and broader public benefits. In the case of publicly funded biomedical research, for instance, the beneficial outcomes are not only the drugs discovered and developed, but also include the broader health benefits, savings in hospitalisation costs and labour productivity improvements. A number of approaches have been adopted, including econometric studies, case studies and industry surveys of the contribution of research to new products (Martin and Tang 2007).

A common approach of the econometric studies is to define a production function in terms of an accumulating, and depreciating, stock of knowledge which is created by investment in R&D. Calculating the total factor productivity growth attributable to the investment in R&D (typically a residual) provides a measure of the return to R&D

(Griliches 1979). A number of studies have measured returns to innovation at the industry level (Griliches and Lichtenberg 1982; Griliches 1986).

The annual return on the total stock of knowledge, to which both industry and publicly funded research has contributed, is defined as the social return to R&D or innovation. Toole (2000) adopts such an approach for the biomedical research by demonstrating the relationship between innovation, defined as the creation of NME's, and a stock of knowledge, created by the pharmaceutical industry R&D and publicly funded basic science. The distinction between innovation and R&D is made by Crepon et al. (1998) where innovation is modelled independently of production, either as a function of patents or innovative sales, before entering the production function as a factor of production.

This distinction between returns on R&D and returns to innovation is germane to the present analysis. As the Oslo manual states, R&D is but one step in the innovation process. Innovation includes not only R&D, but also the later stages of development for preproduction and production, new marketing and organisational methods (OECD 2005b). The availability of sales data for all biopharmaceuticals on sale in a particular year, affords an opportunity to value the returns to the investment in innovation on the not unreasonable assumption that all biopharmaceuticals included in the sales data are innovative. The full costs of researching and developing the drugs to approval stage is available from the DiMasi and Grabowski (2007) study discussed in Chapter 6. Approximate costs of production and sales are available from company annual accounts.

The methodology adopted here is quite different from the production function approach discussed above. In essence it is to calculate the present value of the historical and projected sales (net of production and selling costs) and express that as a ratio of the present value of the costs of developing the drugs. To a degree this approach reflects the available data. For instance an alternative approach would be to express the results as an *annual* return on investment if more detailed annual data for costs were available. The adopted methodology is dependent on DiMasi and Grabowski's (2007) present value estimate of the cost of developing a successful drug.

The approach used is a variant of the one adopted by Grabowski and Vernon (1994b) in that it relies on projections of cash flows of a cohort of drugs, rather than accounting measures of return on equity, but departs in several important respects. The purpose of this analysis is to measure the returns to the investment in innovation[43] of the total portfolio. There is no attempt to separate the returns for individual drugs or measure the returns from high selling drugs versus low selling drugs. Instead the purpose has been to measure and classify the contribution to the total value of biopharmaceutical drugs by the different types of companies. As discussed the methodology also reflects different data availability and the more recent analysis of the cost of developing biopharmaceuticals (DiMasi and Grabowski 2007).

Value of sales

Firstly an estimate is made of the present value of the sales of the 79 biopharmaceuticals on sale in 2006. The valuation of sales uses a different methodology for each of four time periods. In summary these are:

- 2007-18, future projections of sales for the portfolio based on econometric modelling,
- 2002-06, actual global sales data used for each of the 79 drugs for the five years,
- 1998-2001, data for sales by drug available for US, factored up to approximately equal global sales; and
- 1994 to 1997, estimated actuals of sales by drug for the period.

These are used to construct a time series of total annual sales for the portfolio of 79 drugs for the period 1994 to 2018. To ensure consistency between the present value of costs and sales, the present value of the drug portfolio, as at 2006, was then calculated using a discount rate of 11.5% as adopted by DiMasi and Grabowski (2007) in their estimate of the average development cost of a successful biopharmaceutical.

[43] In the remainder of the chapter this is called the returns to innovation while acknowledging the differences between the ratios of present value of sales to costs calculated here and the rates of return arising from the production function approach.

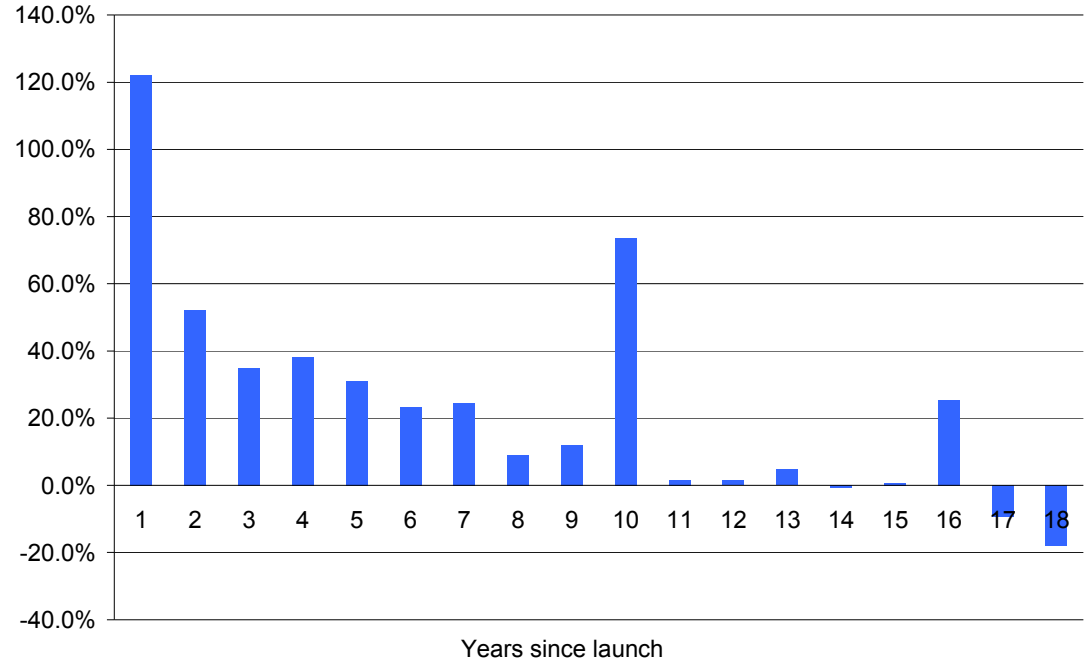
2007-2018 period

The first and least certain of the components of the estimate of sales is that for the period 2007 to 2018. Sales of individual drugs generally follow an S-shaped curve in which after an initial high growth phase, sales plateau and then fall as generic or follow on competitors enter the market (Grabowski and Vernon 1994b). Although the pattern varies between drugs, the growth rates are highly correlated with the years since launch.

The first task was to determine a set of growth rates for each year since launch date based on the sales history of the 79 drugs over the period 2002 to 2006. The five years of sales data for the period 2002 to 2006 for the total 79 drugs covers a wide range of launch dates, from one year to more than eighteen years since launch. The drug sales for the five year period were segmented into cohorts according to years since launch. A set of growth rates was calculated for sales of each drug according to its year of launch. These growth rates were weighted by sales for each drug, and a weighted average of drug sales for each year, one to eighteen, since launch was calculated.

These are shown in Figure 15.3. The highest growth rate is for drugs in the first full year after launch which has a weighted average growth rate of 122%. The growth rates decline rapidly with launch date falling to 29% 5 years after launch and are negative in years 17 and 18 after launch. There are also some anomalies. For instance the weighted average growth rate for drugs 10 years after launch is 73.7%, largely due to the rapid growth in sales of Genentech's Nutropin, which although launched in 1994 experienced sales of 177% between 2005 and 2004. However on the whole, growth rates follow an inverse exponential curve.

Figure 15.3 Weighted average annual sales growth rates for 79 biopharmaceuticals by years since launch based on sales data, period 2002 to 2006



Source: Sales data IMS.

To project the value of sales the relationship between growth and years since launch was used to estimate a set of growth rates over an eighteen year period. That is, the growth rate for the nth year after launch, $\rho_{n,}$ was assumed to be a function of the number of years, n since launch. Consistent with the expected S-shape of the underlying sales curve, an inverse exponential curve is the most appropriate to capture the decay in the sales growth rates in the years after launch. Thus the form of the equation is the following:

$$\rho_n = Ae^{-\beta n} + E \qquad (1)$$

A log linear form was used to estimate the coefficients, that is:

$$\ln \rho_n = \alpha - \beta n + \varepsilon \qquad (\ln A = \alpha) \qquad (2)$$

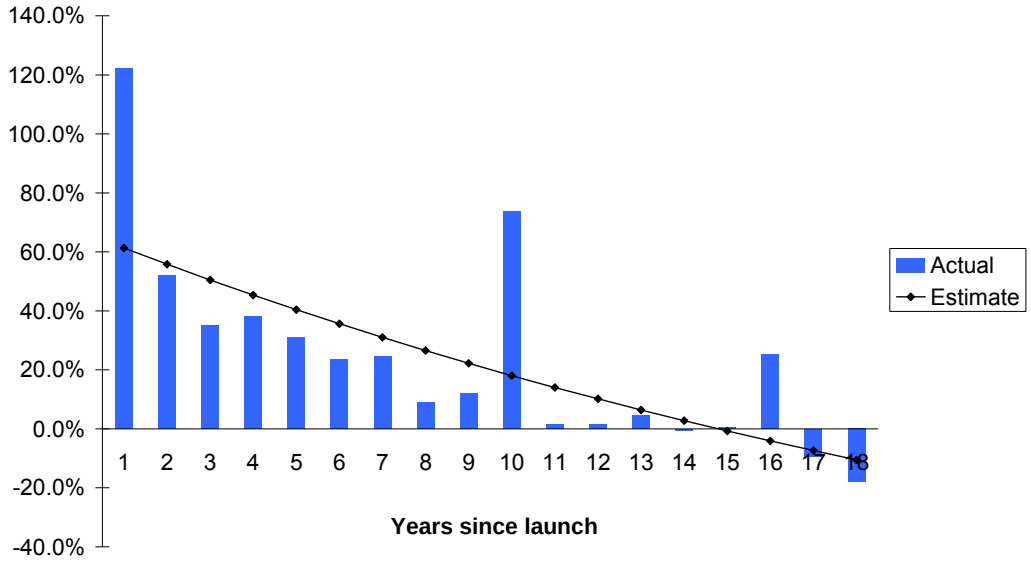
In estimating this relationship, the coefficients proved to be significant. The two variables, ρ_n and n were reasonably highly correlated with an adjusted R^2 of 0.558. Auto correlation does not appear to be a problem with a Durbin Watson statistic of 1.95. These results are shown in Table 15.4.

Table 15.4 Relationship between sales growth rates (ρ) and years since launch (*n*)

	Coefficients	Standard error	t stat	R sq	Adjusted R sq.	df	F statistic	D.W.
Intercept	0.513	0.0791	6.48					
Years since launch	-0.0347	0.00731	-4.74	.584	0.558	17	22.5	1.95

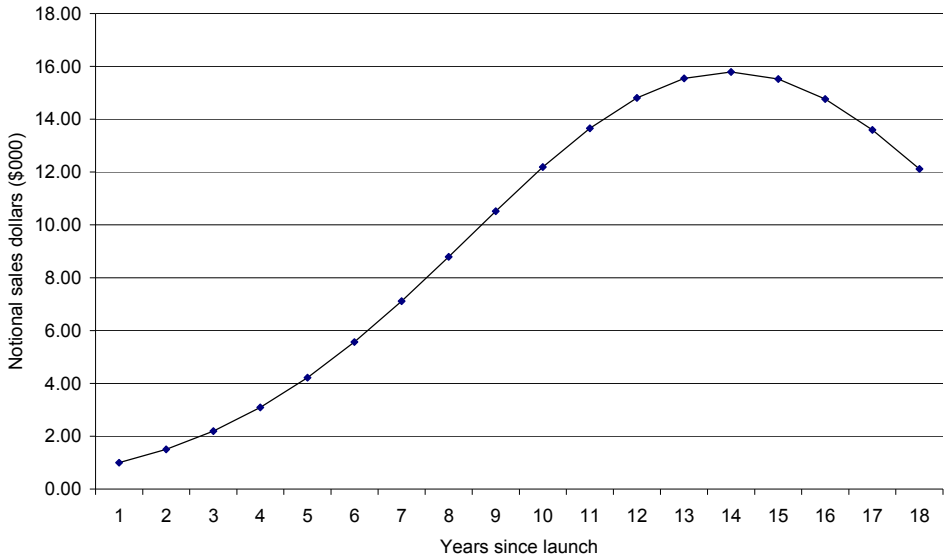
The relationship was used to estimate a set of projected growth rates for each year since launch. For instance the growth rate for drugs sales six years from launch, was estimated to be 35.7%, i.e. (exp (0.513 – 0.0347*6)). The following year it was expected to decline to 31.0% and so on. These estimated growth rates are shown in Figure 15.4 together with the actuals from figure 15.3.

Figure 15.4 Actual and estimated annual sales growth rates for 79 biopharmaceuticals by years since launch based on sales data, period 2002 to 2006



Applying these estimated growth rates to a notional amount of $1000 sales in the first full year from launch produces a notional sales curve for a single drug over a period of 18 years (see Figure 15.5). In projecting the sales of the 79 biopharmaceuticals forward beyond 2006, it is assumed that each drug will follow this path for the remainder of its life. For instance, it is assumed that drugs launched six years ago will follow this path from year seven and the sales for drugs launched thirteen years ago will peak and begin to decline and so on. In projecting the sales forward a critical issue is the expected average lifetime of drugs in the portfolio.

Figure 15.5 Notional sales profile of a single biopharmaceutical based on estimated average growth rates by year since launch



The historical data suggests that biopharmaceuticals have a life of at least 18 years from launch. However in projecting forward many uncertainties arise, not the least of which are mooted arrangements for the regulation of biogenerics or biosimilars and the proposed market exclusivity period for branded biopharmaceuticals.

Compared with small molecule drugs, biopharmaceuticals exhibit remarkable longevity. On average, sales growth has remained positive for the first 14 years after launch and in some cases beyond patent expiry. Two biopharmaceuticals, Epogen and Neupogen, approved more than fifteen years ago, are still achieving annual sales well in excess of one billion dollars. Although Europe and a number of other countries permit 'biogenerics' the United States is yet approve their introduction. The manufacturing of biopharmaceuticals is difficult and expensive, meaning exact replication is generally not possible and the FDA is concerned about the possible adverse effects of faulty generic biopharmaceuticals. Indeed Grabowski, Ridley and Schulman (2006) have argued that there is natural protection for branded manufacturers against the introduction of generics. They argue that the variability and high fixed costs of manufacturing biopharmaceutical drugs means that the price of generic biopharmaceuticals may be less than 20% lower than the branded product. Moreover proposed legislation in the United States would allow a market exclusivity period of 12 years, not far short of the bid by the US Biotechnology Industry Organization (BIO) for 14 years, to protect biopharmaceutical innovation. Both these

factors mean that current drugs are likely to maintain a growing level of sales for an extended period.

To construct the forward projections, it is necessary to make some assumptions about the average life from launch of each drug cohort. The maximum is provided by the available data, i.e. 18 years, while a possible lower limit is provided by the proposed market exclusivity period of 12 years. Although the end of market exclusivity would not prevent further sales being achieved, a decline can be expected. In addition long range projections become highly uncertain for a range of reasons, e.g. drug withdrawal or the introduction of a superior competitor. In accordance with these considerations, it was decided for the purposes of the projections, to adopt a phased approach to the shortening of drug lives to 12 years. No sales would be projected beyond 18 years from launch. Those launched in 2006 would have a 12-year life. Prior launches are assumed to have lives as shown in Table 15.5. between 12 and 18 years. The assumed life of drugs launched for periods in between is shown in Table 15.5. While essentially pro rata, the phasing assumes that the impact of the introduction of the market exclusivity period and other uncertainties during the period would be somewhat greater in shortening the average life of the newer drugs.

Table 15.5 Assumed sales life of biopharmaceutical by years of launch

Years since launch	Assumed life since launch
18-16	18
15-13	17
12-10	16
9-7	15
6-5	14
4-3	13
2-1	12

The growth rates shown in Figure 15.5, estimated using the regression results for equation (2), were applied to the 2006 sales figures for each launch year cohort, extending back to the 1989 cohort, the earliest year for which there were significant sales volumes. The results of these projections are included in figure 15.6 for the period 2007 to 2018.

1998-2001 period

The second component was based on US sales data that was factored up to a global equivalent. Overlapping data was available for 2002 and the ratio of global to US sales for each drug was applied to the US sales data for 1998 to 2001.

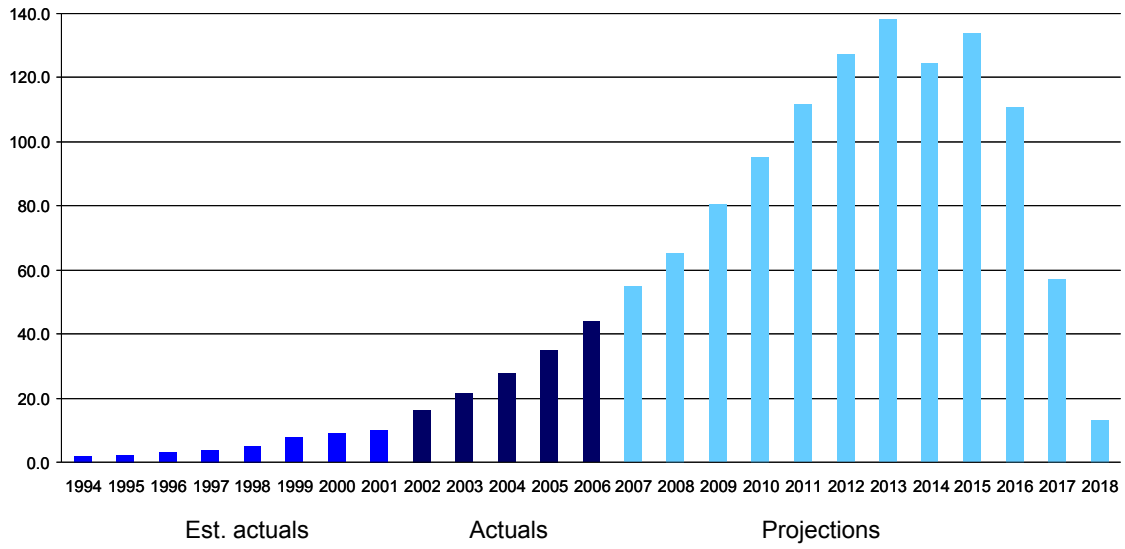
1994-1997 period

For this period the growth factors employed in the projections of sales to 2018 were used to produce estimated actuals for the period 1994-1997 based on the sales for 1998. The earliest year for which sales were estimated, 1994, was chosen on the basis of materiality. The period 1994-97 was the smallest component and a more extended period would not have made a material difference to the total values.

Total period

Estimated sales for the total period 1994 to 2018 are shown in Figure 15.6.

Figure 15.6 Estimated global sales for all biopharmaceuticals with 2006 sales, 1994 to 2018 ($ billion)



As previously indicated a discount rate of 11.5% was applied to the annual sales totals for the whole period to calculate a present value for 2006 of $ 812 billion.

Net value

This estimate provides a measure of the gross value of sales of this group of biopharmaceutical drugs. To obtain a value net of costs, estimates of the 'costs of sale' and 'selling and administrative expenses', covering most of the operating costs

incurred by pharmaceutical companies are required. The average ratios to sales for the large biotechs for 2006 were 15.7% for cost of sales and 26.6% for selling and administration expenses. Being considered reasonably representative of the total sample, these percentages were applied to the entire portfolio. The cost of sales and selling and administration expenses available for pharmaceutical companies was dominated, not only by the costs of producing small molecule drugs, but also a range of non pharmaceutical costs pertaining to other health products and therefore not representative of the costs of producing and selling biopharmaceuticals. Accordingly the ratios for large biopharmaceutical firms were considered a better measure of these costs. The reported costs for drug discovery companies are complicated by distribution arrangements with pharmaceutical companies and large biotechs.

It is acknowledged that these ratios are approximate estimates of the post development costs of innovation. Doubtless they include costs not closely related to innovation. However this would if anything make these conservative estimates of the post development costs of innovation. Applying these ratios for large biopharmaceuticals to the estimate of gross present value gave a result, for present value net of costs, of $469 billion based on 2006. The values for the individual components for each period are set out in Table 15.6.

Table 15.6 Present value of all biopharmaceuticals with 2006 sales (net of operating costs*) by period

Period	Net $ billion	Gross $ billion
1994-1997	20	34
1998-2001	38	67
2002-2006	100	173
to 2018	311	538
Total	469	812

Note: * i.e. cost of sales and selling and administration expenses.

While the table indicates that almost 60% of the value of the drugs is in the future period 2007-2018, the drugs have already delivered substantial value of $158 billion in present value terms. As will be discussed below, this compares favourably with the estimated costs of development.

Relative contributions to value

In order to determine the main contributors to this value, the valuation model was run for selected groups of drugs according to the type of FDA sponsor and type of originator, employing the same methodology for the four components described above. These results are shown in Table 15.7.

Table 15.7 Present value (net of operating costs) by type of applicant and developer* ($ billion)

FDA sponsor	Originator			Total
	Biopharma	Pharma	Other/NEC	
Large biotechs	284	0	1	285
Drug discovery	63	0	2	65
Large pharma	42	56	3	101
Other pharma	11	5	1	18
Total	400	61	8	469

Note: * Total may not add due to rounding errors.

Table 15.7 confirms the dominance of large biotechs illustrated by the earlier sales figures (Table 15.3) producing $285 billion in present value terms or 61% of the total value of these biopharmaceuticals. The large pharmaceutical firms are sponsors of 22% of the total value or $101 billion. This amount is split 42%/56% respectively between those drugs sourced from biopharmaceutical firms and those generated internally. Drugs sold by drug discovery companies account for 14% of the total or $65 billion.

This division of value by originator and FDA sponsor takes no account of royalty payments as a result of licensing arrangements. As demonstrated in chapter 10, large pharmaceutical companies, in particular, have committed significant amounts to alliances with biopharmaceutical companies. According to Recap data total alliance payout commitments for alliances formed by large pharmaceutical companies for 2005 was $10.8 billion (see Table 10.4). However as explained in chapters 9 and 10 these amounts are contingent on all alliance milestones being achieved. Actual payments by large pharmaceutical companies remain at more modest levels.

Recap provides estimates of actual alliance payouts for selected companies for some years. Total alliance payouts for the large pharmaceutical companies considered here total $736 million for 2004. Actual payouts by the top six biopharmaceutical firms

were only $50 million for 2004 indicating that alliance payments are not a significant factor for these companies. Alliance payouts include a mixture of payments, such as for development milestones and royalties. It is not possible to distinguish between the amounts paid out for the cost of drug development from the proportion of sales revenue paid in royalties for in licensed drugs. However some upper bounds can be established. If the *total* amount of alliance payments were for royalty payments by large pharmaceutical companies it would represent about 20% of current biopharmaceutical sales revenue derived from drugs sourced from biopharmaceutical companies. While significant, even an impost of this amount would not be enough to change the attractive economics of in licensed drugs for large pharma. This is discussed further below.

Relative costs of development

These values need to be placed in the context of the cost of developing these drugs. In Chapter 6, it was concluded that the best estimate of the capitalised cost of developing a successful biopharmaceutical was $1.241 billion in 2005 dollars, including the cost of failures (DiMasi and Grabowski 2007). To convert this estimate from 2005 to present values at 2006 it was capitalised for one year at 11.5% giving a result of $1.384 billion. This estimate of average cost is used to calculate the costs of developing, both the total drug portfolio and segments by type of applicant and developer. This would imply that the cost of developing the total portfolio of 79 drugs would have been $109 billion. Of course the costs of developing individual drugs will vary from this average, but particularly for the larger portfolios these variations will tend to be averaged out.

The costs of development in total and by each segment are given in Table 15.8.

Table 15.8 Cost of development by type of applicant and developer

FDA sponsor	Originator			Total
	Biopharma	Pharma	Other/NEC	
Large biotechs	31.8	1.4	1.4	34.6
Drug discovery	22.1	0.0	5.5	27.7
Large pharma	6.9	19.4	5.5	31.8
Other pharma	8.3	2.8	4.2	15.2
Total	69.2	23.5	16.6	109.3

Source: DiMasi and Grabowski (2007); author analysis.
Note: Totals may not add due to rounding.

This estimated cross tabulation of total sector cost by type of originator and FDA sponsor shown in Table 15.8 does not take into account inter firm alliance revenues and expenditures, which may affect the total cost of development for in licensed drugs, in particular those in licensed by large pharmaceutical companies. While the cost of in licensing individual successful drugs may be higher than average, the total cost may nonetheless compare favourably with in house production because of the reduced cost of failures. It is beyond the scope of this thesis to deal with this issue in any detail and while it is an area of additional uncertainty for the estimates, its likely impact on the results is considered to be modest.

A further issue is whether the DiMasi and Grabowski (2007) estimates fully account for the investment in platform technologies. The estimate is based on the cost of development incurred by biopharmaceutical firms in the course of the development process. Although there is some evidence of under recovery of the investment in platform technologies, to the extent that these costs are properly charged to drug discovery firms, they will be included in the estimate of drug development cost.

Returns to innovation

Both the costs of development and the value of sales are expressed in present value terms based on year 2006. Both are calculated using as a common discount rate of 11.5% per annum, which is the cost of capital for biopharmaceutical firms as estimated by DiMasi and Grabowski (2007). If the present value of the sales equals the present value of the costs, the sales have been sufficient to cover the cost of capital but not provide a return to innovation. Only if the present value of sales exceeds the present value of costs, or their ratio is greater than one, could it be said that there has been a return to innovation. This is consistent with the 'production function' approach discussed above where the return to R&D is the estimated residual after returns to other factors production, such as labour and capital.

Table 15.9 shows the ratio of present value of sales provided in Table 15.7 to the cost of development from Table 15.8. Ratios in excess of one represent positive returns to innovation.

Table 15.9 Returns to innovation, ratio of present value of sales to development costs by type of applicant and developer

FDA sponsor	Originator			Total
	Biopharma	Pharma	Other/NEC	
Large biotechs	8.9	0.0	0.9	8.2
Drug discovery	2.8	0.0	0.4	2.3
Large pharma	6.1	2.9	0.6	3.2
Other pharma	1.4	1.9	0.3	1.2
Total	5.8	2.6	0.5	4.3

The results presented in Table 15.9 are notable for four things. The first is that drugs developed by biopharmaceutical firms, whether sponsored by large biotechs, large pharmaceutical companies or by drug discovery companies, are expected to achieve substantially positive returns to innovation. The ratio of present value to cost of development is 4.3. This would appear to provide sufficient margin for error to conclude that the biopharmaceutical sector is in the process of creating significant returns on the drug development costs invested in the sector. While these returns have been distributed unevenly, each type of sponsor has at least achieved a return equalling the cost of capital.

The second is the very high ratio, 8.2 obtained by the large biotechs for sales of biopharmaceuticals that have been either developed in house or in licensed from other biopharmaceutical firms.

Thirdly from a relatively small number of drugs (5), the ratio of present value of sales to costs from drugs sourced from biopharmaceutical firms by large pharmaceutical companies is 6.1, well above average and significantly higher than the ratio from their own internally developed biopharmaceuticals which are a relatively modest 2.9. There was discussion above about the possible impact of royalty payments by large pharmaceutical firms with an upper bound of about 20% being suggested by current data. A 20% reduction in the net present value of sales from in licensed biopharmaceuticals as result of royalty payments would reduce the ratio of the present value of sales to costs to 4.9, a still satisfactory result for large pharmaceutical firms.

The fourth notable result is that despite the large losses currently being incurred by drug discovery companies, the portfolio of their drugs currently on sale are expected to achieve a positive return, with a ratio of present value to costs of 2.3, from future

sales growth in the existing portfolio of drugs. This ratio would be increased to the extent of royalty payments.

Caveats

The principal purpose of this analysis has not been to estimate the specific returns to innovation but firstly to test the hypothesis that there has been a positive return to innovation from the development of this large cohort of biopharmaceuticals and secondly to obtain an estimate of relative contribution to the total by different types firms. There are a number of caveats relevant to these estimates.

Firstly this analysis makes extensive use of averages to reach its conclusions, despite a recurring theme of this thesis and the work of others such as Scherer (2000) that the pharmaceutical industry is one where outcomes are highly skewed. Averages are used, to estimate the costs of development, for the growth rates in sales and for the market exclusivity period.

With respect to the cost of development it was suggested above that given the size of the portfolio, the use of an average would be appropriate since the variations in actual costs about the mean would be reasonably unbiased. The growth in total sales is dominated by a relatively small number of drugs, so the value of the portfolio depends disproportionately on these sales. Of the 79 drugs making up the total portfolio, thirteen have sales in excess of one billion dollars and account for 72% of the total sales in 2006. To take account of this skewness, the growth rates used to project sales are averages weighted by the value of sales and therefore sensitive to variations in the sales of the blockbuster drugs. One other average is the assumed sales life of the drugs. A good deal of variability can be expected due to the entry of follow on drugs or the failure of existing drugs. The approach adopted here is to phase in an assumed sales life of 12 years, even though the historical data suggests a longer period has been the norm. This provides a conservative bias to afford a ‘buffer’ against the uncertainty of the future sales life for each drug. This is one of the uncertainties tested in the sensitivity analysis below.

Sensitivity analysis

The implications of these key assumptions are tested by sensitivity analysis. Table 15.10 sets out the results of sensitivity analysis using different assumptions for the main variables; sales growth rates, blockbuster failure, sales life and the average cost of development.

Although as shown in Table 15.6 a significant proportion of the total value is already 'locked in', changes to the growth rates would nonetheless be expected to have a significant impact on the value of the total portfolio. To illustrate, the impact of a 50% reduction in the estimated growth rates reduces the present value to $338 billion, a decline of 28% compared with the base of $469 billion. It could be argued for a number of reasons that the historical sales margins are not sustainable due to increasing competition and cost containment. Suppose the future sales margin (assumed to be 58%) was reduced by one third, the estimated present value would be reduced to $348 billion. Rather than an across the board reduction in growth rates another potential risk is the failure and withdrawal of several blockbusters. This possibility was tested by assuming the withdrawal in 2009 of three blockbusters totaling sales of $7.5 billion in 2006, released in the period 2002-04 and therefore having a maximum impact on sales to 2018. The impact on values was not so marked as the 50% across the board reduction in growth rates. The present value fell to $406 billion, a reduction of 13%.

Table 15.10 Sensitivity analysis

	PV (net of operating costs)*	Ratio of PV of sales to development cost	
		Ratio PV to base cost	Ratio PV to base cost plus 20%
Growth rates reduced by 50%	338	3.10	2.58
Future sales margin reduced by one third	348	3.19	2.66
3 blockbuster failures	406	3.72	3.10
Sales life reduced to 5 yrs	216	1.98	1.65
Sales life increased to 18 yrs for all drugs	503	4.61	3.84
Development cost increased by 20%	131		
Base value estimate	469	4.30	3.59
Base development cost estimate	109		

Note: *Net of operating costs, i.e. cost of sales and selling and administration expenses.

The sales life of the drugs represents an uncertainty for the growth projections which could affect individual drug sales or sales of all drugs. Two scenarios where tested. An extension to 18 years for all drugs in line with historic data as shown in Figure 15.6 and a reduction to 5 years, consistent with possible improvements in manufacturing technologies (and lower fixed costs) or less generous legislative protection than that currently proposed. An increase to 18 years increases present value by 38% to $503 billion, and a reduction to 5 years reduces the present value by 41% to $216 billion.

The third sensitivity test is for the cost of development. DiMasi and Grabowski (2007) provide no guidance on the uncertainty of their estimate, although in contrast to the projections of value, the development cost is historic so there is less uncertainty about its value. However there are clearly many assumptions about individual variables on which the total estimate depends. One issue raised above is whether the estimate sufficiently reflects the cost of the contribution of platform technologies. The R&D expenditure by 'pure' platform companies represented 11% of total R&D expenditure in 2002 by the 143 companies analysed in Chapter 12. R&D expenditure by hybrid platform technology accounted for a further 26%, but a large proportion of that would be expected to have spent on drug development. Another issue raised in Chapter 6 is that the cost of capital used by DiMasi and Grabowski (2007) may be too low. To allow an assessment of the possible impacts of these factors on the estimates of the returns to innovation, the sensitivity analysis tests for an increase of 20% in average development costs to $1.661 billion.

Overall, these tests indicate that the portfolio is likely to yield positive returns to innovation even with significantly reduced assumptions about growth rates or sales life or somewhat increased assumptions about development costs. Of course if these factors were to occur coincidently at the level assumed they would have a greater negative impact on the returns to innovation. For instance, events such as the failure of one of the blockbuster drugs and significant reduction in sales life due to a decreased market exclusivity period would have a large impact on the value of the total portfolio. On the other hand the projections include some assumptions that could be considered conservative. For instance it is unlikely that there would be no sales of the branded product beyond the market exclusivity period.

While a range of plausible assumptions could produce considerably lower results, the estimates nonetheless indicate that significant returns to innovation, and therefore economic rents are likely to be generated by sales of this group of biopharmaceuticals. The historical data to 2006 indicates that the value of sales ($158 billion) already exceeds the cost of development ($109 billion). There are therefore good reasons for believing that this group of biopharmaceuticals will return more than the cost of capital.

Perhaps the most interesting feature of the analysis is the relative returns from the drug portfolios developed and sponsored by the various types of firms. The return on innovation for the large biotechs is extremely high by comparison with that achieved by other types of firms. For large pharmaceutical firms the yield from a relatively small number of in licensed drugs is also high with a present value of sales to costs ratio of 6.1, or 4.9 if a 20% royalty was to apply, considerably higher than the 2.9 achieved for biopharmaceuticals developed in-house. The return for drug discovery companies is also significantly above the cost of capital. However the companies producing two of the largest selling drugs, Centocor, the producer of Remicade and Medimmune, the producer of Synagis have since been acquired by large pharmaceutical companies, Johnson & Johnson and Astrazeneca respectively eliminating the possibility of creating independent and successful biopharmaceutical firms. Imclone Systems was the only independent drug discovery company with significant drug sales in 2006.

The conclusion of this analysis that the biopharmaceutical sector will generate considerable value is at variance to some emerging views that the sector's financial performance has been disappointing after the expectations generated by the continuing technology breakthroughs (see for instance Pisano 2006).

This sense of disappointment understandably arises from the poor profitability of the vast majority of biopharmaceutical firms noted earlier in this thesis and the failure of the sector to generate many new successful companies. However this assessment fails to take account of a number of factors.

One is that the implications of the highly skewed returns to drug development need to be properly factored into any assessment of the biopharmaceutical sector. It is in the nature of drug development and the structure of firms in the sector that most firms will not be profitable and indeed many will fail. Although both the successes and failures need to be taken into account, the sector needs to be judged more by the outstanding success of a small number of firms, than the failure of the majority. It is these successful firms which deliver the returns to innovation.

The second reason is that an estimate of future sales needs to be factored into any evaluation of the sector. However difficult or uncertain that estimate may be, there is every reason to expect significant future sales revenues from drugs already in the market. Firstly, there is good historical sales experience for biopharmaceuticals showing positive growth over many years. Secondly current marketing arrangements and the costs of producing generics or follow on drugs can be expected to protect future revenue streams.

The third reason is that almost a quarter of the sales revenues generated by biopharmaceuticals are received by pharmaceutical firms. Of these, 39% are sourced from drugs developed by biopharmaceutical firms. Whether the assessment being made is the value of the application of the technology through biopharmaceutical firms, or the application of the technology to the industry more generally, this represents a substantial addition to the total value of biopharmaceutical sales. While its impact on profitability of particular biopharmaceutical firms may be quite modest, its contribution to the value added by the sector is substantial.

A related point is that successful biopharmaceutical firms are constant prey to acquisition by pharmaceutical firms, which eliminates their sales contribution from any analysis which focuses only on biopharmaceutical companies. The recent acquisition of Medimmune and Centocor are examples of successful firms plucked from the pool of emerging biopharmaceutical firms by large pharmaceutical firms, lowering the average performance of independent biopharmaceutical firms.

Conclusion

The purpose of this chapter has been to determine, firstly whether the biopharmaceutical sector has created value and secondly if so, which types of the companies have captured this value.

The estimates of value presented in this chapter suggest that the biopharmaceutical sector has produced considerable value. The returns to innovation from the biopharmaceuticals on sale in 2006 are estimated to be more than four times the cost of development including cost of capital. However these returns have been captured disproportionately by the large biotechs and to a lesser extent, by the large pharmaceutical companies. If the sales of the drugs produced by the two companies discussed above, Centocor and Medimmune, which have been acquired by large pharmaceutical companies since FDA application, are transferred from the 'drug discovery' category to 'large pharmaceuticals', then the total value capture by large biotechs and large pharmaceuticals is approximately 90% of the total value.

Chapter 16. Implications for Industry Structure

Introduction

What are the likely implications of the results presented in this thesis for the structure of the industry? Chapter 7 discussed the advantages of retaining the large vertically integrated business model for pharmaceutical firms despite the challenges of biotechnology. It suggested that the major modification to the model was the formation of a more complex value chain and value network to access a range of complementary assets. Chapters 9 and 10 verified the intensity of alliance formation to access new platform and drug discovery technologies. In other respects the advantages of the large vertically integrated firm, such as economies of scale and fully integrated value chain, remained. Although the large biotech business model has not been examined to the same extent, in most respects the arguments favouring a large fully integrated structure for large biotechs are the same. It is perhaps not surprising then that the valuation estimates of sales by type of firm presented in the previous chapter, suggest that about 90% of the value has been captured by a small number of large pharmaceutical and biopharmaceutical companies.

While this thesis suggests that pharmaceutical companies have adjusted well to the challenges presented by biotechnology, many industry observers appear to be less sanguine about the longer term prospects of the business model. These concerns centre on a declining product pipeline, a bunching of patent expiries for some of the highest selling drugs and more stringent cost effective evaluations adversely effecting drug reimbursements (TUFTS CSDD 2007; PWC 2007; US GAO 2006; Rasmussen 2004). The previous chapter has demonstrated the powerful position occupied by large biopharmaceutical companies in the rapidly growing biopharmaceutical sector. However despite their success large biopharmaceutical companies are a fraction of the size of the largest pharmaceutical companies.

Comparison of Large Biopharmaceutical and Pharmaceutical Firms

Table 16.1 shows, that while large biotechs may dominate the biopharmaceutical sector they are, with the possible exception of Amgen, yet to match the large

pharmaceutical companies according to a range of size measures. The table shows sales, expenditure on R&D and operating profitability for each of the six large biotechs and top 12 pharmaceutical companies by sales.

Table 16.1 Comparison of key financial performance measures: Large biotech and Top 12 pharmaceutical companies, 2005 ($ million)

Company	Sales	R&D expenditure	Operating profit
Large biotechs [1]			
Amgen	12,022	2,314	4,848
Biogen Idec	1,617	748	236
Chiron Corp.	1,421	434	150
Genentech	5,488	1,262	1,922
Genzyme Corp.	2,453	502	601
Average	4,600	1,052	1,551
Standard deviation	4,458	777	1,975
Pharma Top 12 by pharma sales [2]			
Pfizer	44,280	7,440	11,534
Glaxo	39,430	5,709	12,513
Sanofi-Aventis	32,340	4,789	2,741
Novartis	24,960	4,484	6,141
Astrazeneca	23,950	5,356	6,502
J&J	22,320	6,312	10,411
Merck	22,012	3,848	4,631
Wyeth	15,320	1,262	3,656
BMS	15,250	2,746	3,000
Lilly	14,645	3,026	1,978
Abbott	13,990	1,821	4362
Roche	12,900	3,792	7375
Average	23,450	4,215	6,237
Standard deviation	10,383	1,836	3,565

Notes:

(1) Excludes Gilead Life Sciences, which although classified as a biotech by Recap, derives most of its sales from small molecule drugs

(2) Operating profit for the pharmaceutical companies includes non-pharmaceutical activities.

Source: Pharmaceutical Executive May 2006, SEC 10-K reports and annual reports.

Comparing the averages of the two groups shows that, sales of large pharmaceutical companies are almost six times and expenditure on R&D and profitability four times, the average for the large biotechs. Not all of the results for R&D and profitability are directly comparable, as non pharmaceutical activities for some of the pharmaceutical companies are significant. Moreover as indicated by the standard deviations, there is a wide dispersal within the two groups and therefore some overlap between them. For instance although Amgen, the largest of the large biotechs, is outside the ranking of the top 12 pharmaceutical companies based on sales, its profit of $4.8 billion in 2005 places it well within the range of the top 10 pharmaceutical companies, comparable with Sanofi-Aventis, for instance. The level of R&D expenditure by the large biotechs

is, on average, substantially lower than the top 12 pharmaceutical companies. Only Amgen with an R&D program of $2.3 billion and Genentech with $1.3 billion have programs comparable to those of the top 12 pharmaceutical companies.

Pharmaceutical companies therefore retain a very prominent position in the industry structure, with substantial momentum derived from their traditional drug business. Small molecule drug approvals, dominated by the large pharmaceutical companies, remain a declining but nonetheless much larger component of total drug approvals than biopharmaceuticals as shown in Figure 15.1 in the previous chapter. The global sales of the top 12 pharmaceutical companies totalled $280 billion in 2005. Total sales of biopharmaceuticals are a small but fast growing segment of total sales. The large pharmaceutical companies, through alliances and selective acquisition, have demonstrated a capacity to gain access to a significant proportion of the sales of the more successful biopharmaceuticals. With the acquisition of Centocor and Medimmune by large pharma, no biopharmaceutical drug amongst those analysed in the previous chapter, with sales above $1 billion, remained outside the large pharmaceutical and biopharmaceutical firms.

Future of the Business Models

Looking forward it would seem that the large pharmaceutical firms have the resources to continue to dominate the pharmaceutical industry. They have shown a willingness to adapt their business model to the impact of the new drug discovery and platform technologies and to acquire through alliances or outright purchase access to the most rapidly growing biopharmaceuticals. Accordingly, the major firms can be expected to derive an increasing proportion of their sales from in-licensed biopharmaceuticals. As Pisano (2006), has argued, in an industry much fragmented by the specialist nature of the knowledge base, the large pharmaceutical companies have a distinct advantage in playing the role of the well informed integrator. This could become a specialist role with the main burden of drug discovery and early stage development taken by the drug discovery companies (Kay 2001). However their likely continuing role as small molecule drug developers militates against this.

The large pharmaceutical companies face many challenges, not the least of which include, a declining trend in drug approvals, a bunching of patent expiries over the

next decade and countervailing power from the pharmaceutical benefit managers and government agencies around the world being applied to prices. A possible reduction in the importance of the blockbuster model, with a greater trend towards personalised medicine, may also lessen some of the advantages of the large integrated model. Nonetheless their massive financial resources and the adjustments they have already made to their business model imply an ongoing capacity to adjust to these pressures.

The large biotechs, which built their fully integrated business models in the early phase of the biotechnology revolution, have for the most part captured increasing value from more recently launched biopharmaceuticals, to retain a primary position in the biopharmaceutical sector. They have a dominant share of the most rapidly growing segment of the total pharmaceutical market. They have a stronger knowledge base, reducing their need for platform technology alliances. However they remain significantly smaller than the large pharmaceuticals companies. While to date the pharmaceutical companies have generally preferred to acquire the more recently emerging drug discovery companies, as the Novartis acquisition of Chiron in 2006 illustrates, the large biotechs are always at risk should they be financially weakened at any stage, such as by a drug withdrawal or other regulatory difficulties.

Much of the focus of this thesis has been on the business models of the drug discovery and platform technology companies. They have been the engines of innovation in this sector. It has been noted that the drug discovery companies do not appear to be content to adopt the role of contract research firms for upstream pharmaceutical companies. With one exception, all of those reviewed in Chapter 12 have developed in-house drug development capabilities, with the apparent intention of taking these drugs through to the approval stage as the best strategy for maximising the value of the firm. However this analysis demonstrates how difficult building an independent business along the lines of the large biotechs is likely to be, with most firms with a successful drug being acquired by one of the existing large pharmaceutical or biopharmaceutical firms.

The prospects for emerging drug discovery companies depend firstly on successful clinical trials, regulatory approval and reasonable sales. To date companies that have achieved this have been prone to acquisition and it appears difficult for such

companies to establish a business model that secures sustainable competitive advantage. The advantages possessed by fully integrated incumbents appear difficult to resist. This does not mean that such companies have not delivered value to their shareholders for the investment made, but ongoing independence has not been achieved.

There has been no attempt to place a value on the contribution of platform technology companies to the sector. It has previously been noted that more than half such firms had adopted a hybrid business model and a tendency for many of the case study companies to close their platform technology operations to focus on drug discovery. The prospects for such companies are analogous to the drug discovery companies. Those platform technology companies with an appropriable product or service, such as the case study companies, Affymetrix and Qiagen, appear to have established successful, vertically integrated, business models with sustainable competitive advantage based on their leading edge specialist technologies and products.

The evidence presented in this thesis indicates that the adoption of the vertically integrated business model appears to be important for success in this industry. For drug discovery companies this requires a significant investment in marketing and manufacturing infrastructure which needs high volume sales to sustain. Maintaining the firm through this vulnerable period appears to have been largely beyond the capabilities of drug discovery companies with successful drugs, given the willingness of acquirers to pay increasingly high premiums. On the other hand there does appear to be a sustainable role for platform technology companies with appropriable products and well structured fully integrated business models.

Appendix A

Table A.1 List of 79 Biopharmaceuticals on Sale 2006

Drug Name	Active ingredient	Originator	Sponsor
Orencia	Abatacept	Bristol Myers Squibb	Bristol Myers Squibb
Reopro	Abciximab	Centocor Inc	Centocor Inc
Humira	Adalimumab	Cambridge Antibody Technology	Abbott
Fabrazyme	Agalsidase Beta	Mount Sinai School Of Medicine	Genzyme
Proleukin	Aldesleukin	Chiron	Chiron
Amevive	Alefacept	Biogen	Biogen
Myozyme	Alglucosidase Alfa	Genzyme	Genzyme
Activase	Alteplase	Genentech	Genentech
Kineret	Anakinra	Amgen	Amgen
Elspar	Asparaginase	#N/A	Merck
Simulect	Basiliximab	Novartis	Novartis
Regranex	Becaplermin	#N/A	OMJ Pharmaceuticals
Avastin	Bevacizumab	Genentech	Genentech
Botox	Botulinum Toxin Type A	Allergan	Allergan
Myobloc	Botulinum Toxin Type B	Athena Neurosciences	Elan Pharm
Fortical	Calcitonin Salmon Recombinant	Unigene Laboratories	Upsher Smith
Erbitux	Cetuximab	Rhône-Poulenc Rorer, Imclone Systems	Imclone Systems
Ovidrel W/Diluent	Choriogonadotropin Alfa	Serono	EMD Serono
Zenapax	Daclizumab	Protein Design Labs	Hoffman-La Roche
Aranesp	Darbepoetin Alfa	Amgen	Amgen
Ontak	Denileukin Difitox	Seragen	Seragen
Pulmozyme	Dornase Alfa	Genentech	Genentech
Xigris	Drotrecogin Alfa (Activated)	Lilly	Lilly
Raptiva	Efalizumab	Genentech	Genentech
Epogen	Epoetin Alfa	Amgen	Amgen
Enbrel	Etanercept	Immunex	Immunex
Neupogen	Filgrastim	Amgen	Amgen
Gonal-F	Follitropin Alfa/Beta	Serono	EMD Serono
Naglazyme	Galsulfase	Biomarin	Biomarin
Mylotarg	Gemtuzumab Ozogamicin	Celltech Group	Wyeth Pharms Inc
Glucagen	Glucagon Hydrochloride Recombinant	#N/A	Novo Nordisk
Glucagon	Glucagon Recombinant	#N/A	Lilly
Zevalin	Ibritumomab Tiuxetan	Idec	Idec Pharmaceuticals Corp
Elaprase	Idursulfase	Shire	Shire
Remicade	Infliximab	Centocor Inc	Centocor Inc
Levemir	Insulin Detemir Recombinant	Novo Nordisk Inc	Novo Nordisk Inc
Lantus	Insulin Glargine Recombinant	Aventis	Sanofi Aventis US
Apidra	Insulin Glulisine Recombinant	Aventis	Sanofi Aventis US
Humalog Mix	Insulin Lispro Protamine Recombinant; Insulin Lispro Recombinant	Lilly	Lilly
Humalog	Insulin Lispro Recombinant	Lilly	Lilly
Humulin 70/30	Insulin Recombinant Human; Insulin Susp Isophane Recombinant Human	Lilly	Lilly

Humulin U	Insulin Zinc Susp Extended Recombinant Human	Lilly	Lilly
Humulin L	Insulin Zinc Susp Recombinant Human	Lilly	Lilly
Humulin N	Insulin Susp Isophane Recombinant Human	Genentech	Lilly
Humulin R	Insulin Recombinant Human	Genentech	Lilly
Roferon-A	Interferon Alfa-2a	#N/A	Hoffman-La Roche
Intron A	Interferon Alfa-2b	Schering	Schering
Infergen	Interferon Alfacon-1	Intermune Pharms	Intermune Pharms
Alferon N	Interferon Alfa-N3	#N/A	Interferon Sciences
Avonex	Interferon Beta 1a	Biogen	Biogen
Rebif	Interferon Beta-1a	Serono	Serono Inc
Actimmune	Interferon Gamma-1b	Genentech	Intermune Pharms
Aldurazyme	Laronidase	Women's & Children's Hospital Adelaide Biomarin JV Biomarin With Genzyme	Biomarin
Refludan	Lepirudin Recombinant	#N/A	Bayer Health
Luveris	Lutropin Alfa	Serono	EMD Serono
Increlex	Mecasermin Recombinant	Tercica	Tercica
Iplex	Mecasermin Rinfabate Recombinant	Insmed	Insmed
Orthoclone Okt 3	Muromonab-Cd3	#N/A	Ortho Biotech
Tysabri	Natalizumab	Elan	Biogen Idec
Natrecor	Nesiritide Recombinant	Scios	Scios
Xolair	Omalizumab	Genentech/Tanox/Novartis	Genentech
Neumega	Oprelvekin	Wyeth Pharms Inc	Wyeth Pharms Inc
Kepivance	Palifermin	Amgen	Amgen
Synagis	Palivizumab	Medimmune	Medimmune
Vectibix	Panitumumab	Abgenix And Amgen	Amgen
Macugen	Pegaptanib Sodium	Gilead	OSI Eyetech
Oncaspar	Pegaspargase	Enzon	Enzon
Neulasta	Pegfilgrastim	Amgen	Amgen
Pegasys	Peginterferon Alfa 2a	Roche	Hoffman-La Roche
Somavert	Pegvisomant	#N/A	Pharmacia and Upjohn
Lucentis	Ranibizumab	Xoma	Genentech
Retavase	Reteplase	#N/A	Centocor Inc
Rituxan	Rituximab	IDEC/Genentech	Genentech
Leukine	Sargramostim	#N/A	Berlex Labs
Nutropin	SOMATROPIN [Rdna Origin]	Genentech	Genentech
Humatrope	Somatropin Recombinant	Lilly	Lilly
Streptase	Streptokinase	Aventis Behring	Aventis Behring
Tnkase	Tenecteplase	Genentech	Genentech
Forteo	Teriparatide Recombinant Human	Lilly	Lilly
Bexxar	Tositumomab; Iodine I 131 Tositumomab	Coulter Pharmaceuticals	Smithkline Beecham
Herceptin	Trastuzumab	Genentech	Genentech

References

Achilladelis, B. 1999, 'Innovation in the Pharmaceutical Industry', in R. Landau, B. Achilladelis and A. Scriabine (eds), *Pharmaceutical Innovation: Revolutionising Human Health*, Chemical Heritage Foundation, Philadelphia.

Affymetrix Inc. 1996, *Prospectus*, US Securities and Exchange Commission, Washington DC.

Affymetrix Inc. 2001, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Afuah, A. and Tucci, C. 2001, *Internet Business Models and Strategies: Text and Cases*, McGraw-Hill Irwin, London.

Aghion, P. and Tirole, J. 1994, 'The management of innovation', *Quarterly Journal of Economics*, vol. 109, no. 4, pp. 1185-1207.

Alexion Pharmaceuticals Inc. 2001, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

American Chemical Society (ACS) 2000, *The Pharmaceutical Century: Ten Decades of Drug Discovery*, ACS, at: http://pubs.acs.org/journals/pharmcent/, accessed 11 October 2006.

Amgen Inc. 2001a, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Amgen Inc. 2001b, *Annual Report 2001*, at http://www.amgen.com/investors/inv_reports.jsp

Amit, R. and Shoemaker, P. 1993, 'Strategic assets and organizational rent', *Strategic Management Journal*, vol. 14, pp. 33-46.

Amit, R. and Zott, C. 2001, 'Value creation in e-business', *Strategic Management Journal*, vol. 22, no. 6/7, pp. 493-520.

Arora, A. and Gambardella, A. 1990, 'Complementarity and external linkages in biotechnology: The strategies of large firms in biotechnology', *Journal of Industrial Economics*, vol. 38, no. 4, pp. 361-379.

Arora, A., Fosfuri, A. and Gambardella, A. 2001a, *Markets for Technology: The Economics of Innovation and Corporate Strategy*, MIT Press, Cambridge, Mass.

Arora, A., Fosfuri, A. and Gambardella, A. 2001b, *The Economics of Innovation and Corporate Strategy*, MIT Press, Cambridge, Mass.

Arora, A., Gambardella, A., Magazzini, L. and Pammolli, F. 2007, 'A Breath of Fresh Air? Firm types, scale, scope and selection effects in drug development, *Journal of Management Science* forthcoming.

AstraZeneca 2001, 'AstraZeneca Approach to E-Business', presentation to analysts, New York.

Bagchi-Sen, S., Lawton Smith, H. and Hall, L. 2004, 'The US biotechnology industry: Policy and practice', *Environment and Planning C: Government and Policy*, vol. 22, pp. 199-216.

Barney, J. R. 1986, 'Strategic factor markets: Expectations, luck and business strategy', *Management Science*, vol. 32, pp. 1231-1241.

Barney, J. R. 1991, 'Firm resources and sustained competitive advantage', *Journal of Management*, vol. 17, pp. 99-120.

Baumol, W. and Willig, R. 1981, 'Fixed costs, sunk costs, entry barriers and sustainability of monopoly', *Quarterly Journal of Economics*, vol. 95, pp. 405-431.

Beeley, N. and Berger, A. 2000, 'A revolution in drug discovery', *BMJ*, vol. 321, pp. 581-582.

Berndt, E.R., Bui, L., Reiley, D.R. and Urban, G.L. 2001, 'Information, marketing and pricing in the US antiulcer drug market', *Information, Educating and Marketing in Health Care*, vol. 85, no. 2, pp. 100-105.

Biogen Idec Inc. 2002, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

BioLateral and the Bioinformatics Industry Opportunity Taskforce 2002, 'Bio informatics: Issues and Opportunities for Australia, Emerging Industries', Occasional Paper No. 15, Department of Industry, Tourism and Resources, Canberra, at: http://bioinformatics.org.au/files/documents/biot-report-final.pdf , accessed April 2002.

Blumberg, D. and Perrone, F. 2001, 'How Much are Marketing and Sales Capabilities Really Worth? A European Study on How the Capabilities Drive Performance', Accenture, www.acenture.com

Brealey, R.A. and Myers, S.C. 2003, *Principles of Corporate Finance*, McGraw Hill, New York.

Bresnahan, T.F. and Trajtenberg, M. 1995, 'General purpose technologies: 'Engines of growth'?', *Journal of Econometrics*, vol. 65, pp. 83-108.

Burgleman, R., Maidique, M. and Wheelwright, S. 2001, *Strategic Management of Technology and Innovation*, McGraw Hill, Boston

Cambridge Antibody Technology Group PLC 2003, 'Home', at: http://www.cambridgeantibody.com/, accessed 25 March 2003.

Carlsson, B. and Eliasson, G. 1994, 'The nature and importance of economic competence', *Industrial and Corporate Change*, vol. 3, no. 1, pp. 687-711.

Carlsson, B. and Stankiewicz, R. 1991, 'On the nature, function and composition of technological systems', *Journal of Evolutionary Economics*, vol. 1, pp. 93-118.

Casper, S. and Kettler, H. 2001, 'National institutional frameworks and the hybridization of entrepreneurial business models: The German and UK biotechnology sectors', *Industry and Innovation*, vol. 8, no. 1, pp. 5-30.

Centre for Drug Evaluation and Research (CDER) 2007, 'CDER New Molecular Entity (NME) Drug and New Biologic Approvals in Calendar Year 2007', Food and Drug Administration, Washington DC, at: http://www.fda.gov/cder/rdmt/InternetNME07.htm, accessed 26 May 2008.

Chandler, A. 1977, *The Visible Hand: The Managerial Revolution in American Business*, Harvard University Press, Cambridge, Mass.

Chandler, A. 1990, *Scale and Scope: The Dynamics of Industrial Capitalism, Harvard University Press*, Cambridge, Mass.

Chandler, A. 2005, *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries*, Harvard University Press, Cambridge, Mass.

Chesbrough, H. 2003, *Open Innovation: The New Imperative for Creating and Profiting from Technology,* Harvard University Press, Cambridge, Mass.

Chesbrough, H. 2006, 'Open innovation: A new paradigm for understanding industrial innovation', in H. Chesbrough, W. Vanhaverbeke and J. West (eds), *Open Innovation: Researching a New Paradigm*, Harvard University Press, Cambridge, Mass.

Chesbrough, H. and Rosenbloom, R.S. 2002, 'The role of the business model in capturing value from innovation: Evidence from Xerox Corporation's technology spin-off companies', *Industrial and Corporate Change*, vol. 11, pp. 529-555.

Chesbrough, H., Vanhaverbeke, W. and West, J. (eds) 2006, *Open Innovation: Researching a New Paradigm*, Harvard University Press, Cambridge, Mass.

Christensen, C.M. and Rosenbloom, R.S. 1995, 'Explaining the attacker's advantage: Technological paradigms, organizational dynamics and the value network', *Research Policy*, vol. 24, no. 2, pp. 233-257.

Christensen, J.F. 2006, 'Whither core competency for the large corporation in an open innovation world?', in H. Chesbrough, W. Vanhaverbeke and J. West (eds), *Open Innovation: Researching a New Paradigm*, Harvard University Press, Cambridge, Mass.

Coase, R.H. 1937, 'The nature of the firm', 4 *Economica* (new series) 386.

Cockburn, I. 2004, 'The changing structure of the pharmaceutical industry', *Health Affairs,* vol. 23, no. 1, pp. 10-22.

Cockburn, I. 2005, 'State Street Meets the Human Genome Project: Intellectual Property and Bioinformatics', in R. Hahn. (ed), *Intellectual Property Rights in Frontier Industries*, AEI-Brookings Joint Centre for Regulatory Studies, Washington, DC.

Cockburn, I. and Griliches, Z. 1988, 'Industry effects and appropriability measures in the stock market's valuation of R&D and patents', *American Economic Review*, vol. 78, no. 2, pp. 419-23.

Cockburn, I. and Henderson, R. 2001, 'Scale and scope in drug development: Unpacking the advantages of size in pharmaceutical research', *Journal of Health Economics*, vol. 20, no. 6, pp. 1033-1057.

Cockburn, I., Henderson, R. and Stern, S. 2000, 'Untangling the origins of competitive advantage', *Strategic Management Journal*, vol. 21, pp. 1123-1145.

Cohen, S., Chang, A., Boyer, H. and Helling, R. 1973, 'Construction of biologically functional bacterial plasmids in vitro', *Proceedings of the National Academy of Science*, vol. 70, pp. 3240-3244.

Cohen, W.M. and Levinthal, D.A. 1990, 'Absorptive capacity: A new perspective on learning and innovation', *Administrative Science Quarterly*, vol. 35, pp. 128-152.

Conner, K.R. 1991, 'A historical comparison of resource-based theory and five schools of thought within industrial organization economics: Do we have a new theory of the firm?', *Journal of Management*, vol. 17, pp. 121-154.

Cooke, P. 2001, 'Regional innovation systems, clusters and the knowledge economy', *Industrial and Corporate Change*, vol. 10, pp. 945-974.

Crepon, B., Duguet, E. and Mairesse, J. 1998, 'Research Innovation and Productivity: An econometric analysis at the firm level', *Journal of Innovation and New Technologies*, vol. 7, pp. 115-158.

CSIRO 1994, *CSIRO Annual Report 1994*, Canberra.

CSIRO 2001, *CSIRO Annual Report 2001*, Canberra.

Curagen Corporation 1998, *Prospectus*, US Securities and Exchange Commission, Washington DC.

Curagen Corporation 2005, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Danzon, P., Nicholson, S. and Pereira, N. 2005, 'Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances', *Journal of Health Economics,* vol. 24, pp 317-339.

De Carolis, D. and Deeds, D. 1999, 'The impact of stocks and flows of organizational knowledge on firm performance: An empirical evaluation of the biotechnology industry', *Strategic Management Journal*, vol. 20, pp. 953-968.

Deeds, D.L., De Carolis, D. and Coombs, J. 1999, 'Dynamic capabilities and new product development in high technology ventures: An empirical analysis of new biotechnology firms', *Journal of Business Venturing*, vol. 15, pp. 211-229.

Degami, S. and Van Brunt, J. 2003, 'Financial snapshot for December 2002: Down, but not out', *Signals: The Online Magazine of Biotechnology Industry Analysis*, January 2, at: http://www.signalsmag.com/signalsmag.nsf/657b06742b5748e888256570005cba01/2488575d6afc884388256ca2006d9af6?OpenDocument, accessed May 2006.

Degami, S. and Van Brunt, J. 2006, 'Financial snapshot for December 2005: Smaller stocks need to catch up', *Signals: The Online Magazine of Biotechnology Industry Analysis*, January 18, at: http://www.signalsmag.com/signalsmag.nsf/657b06742b5748e888256570005cba01/5de058858447e0f5882570f9000668e3?OpenDocument, accessed May 2006.

Deirickx, I. and Cool, K. 1989, 'Asset stock accumulation and sustainability of competitive advantage', *Management Science*, vol. 35, no. 12, pp. 1504-1511.

Demsetz, H. 1991, 'The theory of the firm revisited', in O.E. Williamson and S.G. Winter (eds), *The Nature of the Firm*, Oxford University Press, New York, pp. 159-178.

Dendritic Nanotechnologies Inc (DNT) 2005, 'Dendritic NanoTechnologies announces new low-cost family of precision nanostructures', press release, 18 May.

Dewer, R.D. and Dutton, J.E. 1986, 'The adoption of radical and incremental innovations: An empirical analysis', *Management Science*, vol. 32, pp. 1422-1433.

Dierickx, I. and Cool, K. 1989, 'Asset stock accumulation and sustainability of competitive advantage', *Management Science*, vol. 35, pp. 1504-1511.

DiMasi, J.A. and Grabowski, H.G. 2006, 'The cost of biopharmaceutical R&D: Is biotech different?', Tufts Center for the Study of Drug Development, Tufts University, Boston, Mass.

DiMasi, J.A. and Grabowski, H.G. 2007, 'The cost of biopharmaceutical R&D: Is biotech different?', *Managerial and Decision Economics*, vol. 28, no. 4-5, pp. 469-479.

DiMasi, J.A., Hansen, R. and Grabowski, H.G. 2003, 'The price of innovation: New estimates of drug development costs', *Journal of Health Economics*, vol. 22, pp. 151-185.

DiMasi, J.A., Hansen, R., Grabowski, H.G. and Lasagna, L. 1991, Cost of innovation in the pharmaceuitcal industry', *Journal of Health Economics*, vol. 10, pp. 107-142.

Discovery Partners International Inc. (DPI) 2000, *Propectus*, US Securities and Exchange Commission, Washington DC.

Discovery Partners International Inc. (DPI) 2005, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Dosi, G. 1982, 'Technological paradigms and technological trajectories: A suggested interpretation of the determinants and directors of technical change', *Research Policy*, vol. 11, pp. 147-162.

Drews, J. and Ryser, S.T. 1996, 'An innovative deficit in the pharmaceutical industry', *Drug Information Journal*, vol. 30, pp. 97-108.

Dunning, J. 1995, 'Reappraising the eclectic paradigm in an age of alliance capitalism', *Journal of International Business Studies*, vol. 26, no. 3, pp. 461-491.

Dyer, J. and Singh, H. 1998, 'The relational view: Cooperative strategy and sources of interorganizational competitive advantage', *Academy of Management Review*, vol. 23, no. 4, pp. 660-679.

Eliasson, G. 2000, 'The industrial potential of biotechnology: A competence bloc analysis', in J. De La Mothe and J. Noisi (eds), *The Economic and Social Dynamics of Biotechnology*, Springer, Heidelberg.

Ernst and Young 2005, *Beyond Borders: Global Biotechnology Report 2005*, Sydney.

Ettlie, J.E., Bridges, W.P. and O'Keefe, R.D. 1984, 'Organization strategy and structural difference for radical versus incremental innovation', *Management Science*, vol. 30, pp. 682-695.

European Commission 2004, *Communication from the Commission: Towards a European Strategy for Nanotechnology*, COM(2004) 338, Brussels.

European Commission 2005, *Biotechnology 2020: From the Transparent Cell to the Custom-Designed Process*, Brussells, at: ftp://ftp.cordis.europa.eu/pub/food/docs/biotech_2020.pdf, accessed October 2006.

Food and Drug Administration (FDA) 2008a, *CDER New Molecular Entity (NME) Drug and New Biologic Approvals in Calendar Year 2007*, at http://www.fda.gov/cder/rdmt/InternetNME07.htm, accessed 14 June 2008.

FDA 2008b, *Drugs@FDA Data Files*, United States Food and Drug Administration, at http://www.fda.gov/cder/drugsatfda/datafiles/default.htm, accessed 14 June 2008.

Feng, H., Froud, J., Johan, S., Halsma, C. and Williams, K. 2001, 'A new business model: The capital market and the new economy', *Economy and Society*, vol.30, no. 4, pp. 467-503.

Fisken, J. and Rutherford, J. 2002, 'Business models and investment trends in the biotechnology industry in Europe', *Journal of Commercial Biotechnology*, vol. 8, no. 3, pp. 191-199.

Foss, N.J. 1996, 'Knowledge-based approaches to the theory of the firm: Some critical comments', *Organization Science*, vol. 78, pp. 470-476.

Freeman C. 1987, *Technology Policy and Economic Performance: Lessons from Japan*, Pinter, London.

Galambos, L. and Sewell, J.E. 1995, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme and Mulford, 1895-1995*, Cambridge University Press, New York.

Galambos, L. and Sturchio, J. 1998, 'Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation', *Business History Review*, vol. 72, pp. 250-278.

Gambardella, A. 1995, *Science and Innovation: The US Pharmaceutical Industry During the 1980s*, Cambridge University Press, New York.

Gambardella, A., Orsenigo, L. and Pammolli, F. 2000, 'Global Competitiveness in Pharmaceuticals: A European Perspective', Report prepared for the Enterprise Directorate General of the European Commission, Luxembourg.

Gans, J.S. and Stern, S. 2003, 'The product market and the "market for ideas": Commercialization strategies for technology entrepreneurs', *Research Policy*, vol. 32, pp. 333-350.

George, P. and Perrone, F. 2001, 'How Much are Marketing and Sales Capabilities Really Worth? What Every Pharmaceutical Executive Should Know, the US Study', Accenture, www.acenture.com

Golec, J. and Vernon, J. 2007, 'Financial Risk in the Biotechnology Industry', NBER Working Paper 13604, National Bureau of Economic Research. Cambridge, Mass.

Gomes-Casseres, B. 1996, *The Alliance Revolution: The New Shape of Business Rivalry*, Harvard University Press, Cambridge, Mass.

Gosse, M.E. and Manocchia, M. 1996, 'The first bio-pharmaceuticals approved in the US, 1980-1994', *Drug Information Journal*, vol. 30, pp. 991-1001.

Grabowski, H. 2002, 'Patents and new product development in the pharmaceutical and biotechnology industries', Duke University, Durham, North Carolina.

Grabowski, H. and Vernon, J. 1994a, 'Innovation and structural change in pharmaceuticals and biotechnology', *Industrial and Corporate Change*, vol. 3, pp. 435-449.

Grabowski, H. and Vernon, J. 1994b, 'Returns to R&D on new drug introductions in the 1980s', *Journal of Health Economics*, vol. 13, pp. 383-406.

Grabowski, H. and Vernon, J. 2001, 'Pressures from the demand side: Changing market dynamics and industrial structure', in H. Kettler (ed.), *Consolidation and Competition in the Pharmaceutical Industry*, based on papers delivered at the OHE Conference, London 16 October 2000, Office of Health Economics, London.

Grabowski, H., Ridley, D. and Schulman, K. 2006, 'Entry and competition in generic biologicals', mimeo, Health Sector Management Program, The Fuqua School of Business, Duke University, Durham, North Carolina.

Granberg, A. and Stankiewicz, R. 2002, 'Biotechnology and the transformation of the pharmaceutical value chain and innovation system', paper presented at the

Medicon Valley BioConference, Medicon Valley Academy, Copenhagen, 8-10 October.

Granstrand, O., Patel, P. and Pavitt, K. 1997, 'Multi-technology corporations: Why they have "distributed" rather than "distinctive" core competencies', *California Management Review*, vol. 39, pp. 8-25.

Grant, R.M. 1991, 'The resource-based theory of competitive advantage: Implications for strategy formulation', *California Management Review*, vol. 33, pp. 114-135.

Griliches, Z. 1979, ''Issues in assessing the contribution of R&D to productivity growth', *The Bell Journal of Economics*, vol. 10, pp. 92-116.

Griliches, Z. 1981, 'Market value, R&D and patents', *Economic Letters*, vol. 7, pp. 183-187.

Griliches, Z. 1986, 'Productivity, R&D and basic research at the firm level in the 1970s', *American Economic Review*, vol. 76, no. 1, pp. 141-154.

Griliches, Z. 1990, 'Patent statistics and economic indicators: A survey', *Journal of Economic Literature*, vol. 28, pp. 1661-1707.

Griliches, Z. and Lichtenberg, F. 1982, 'R&D and Productivity at the Industry Level: Is There Still a Relationship?', NBER Working Paper No. 850, National Bureau of Economic Research, Cambridge, Mass.

Grossman, S. and Hart, O. 1986, 'The costs and benefits of ownership: A theory of vertical and lateral integration', *Journal of Political Economy*, vol. 94, no. 4, pp. 691-719.

Grossman, S. and Hart, O. 1986, 'The costs and benefits of ownership: A theory of vertical and lateral integration', *Journal of Political Economy*, vol. 94, no. 4, pp. 691-719.

Guedji, I. 2005, 'Ownership vs. Contract: How Vertical Integration Affects Investment Decisions in Pharmaceutical R&D', Mimeo, University of Texas at Austin.

Guedj, I., Scharfstein, D. 2004. 'Organisational Scope and Investment: Evidence from the drug development strategies and performance of biopharmaceutical firms', NBER Working Paper No. 10933, National Bureau of Economic Research, Cambridge, Mass.

Gulati, R. 1998, 'Alliances and networks', *Strategic Management Journal*, vol. 19, pp. 293-317.

Hagedoorn, J. 1993, 'Understanding the rationale of strategic technology partnering: Inter-organizational modes of cooperation and sectoral differences', *Strategic Management Journal*, vol. 14, pp. 371-385.

Hagedoorn, J., Link, A. and Vonortas, N. 2000, 'Research partnerships', *Research Policy*, vol. 29, pp. 567-586.

Hall, B.H. 1993, 'The stock market's valuation of R&D investment during the 1980s', *American Economic Review,* vol. 83, no. 2, pp. 259-264.

Hall, B.H., Jaffe, A. and Trajtenberg, M. 2000, 'Market value and patent citations: A first look', NBER Working Paper No. 7741, National Bureau of Economic Research, Cambridge, Mass.

Hansen, R.W. 1980, 'Pharmaceutical development costs by therapeutic categories', University of Rochester Graduate School of Management Working Paper No. GPB-80-6, March.

Harhoff, D., Narin, G., Scherer, F.M. and Vopel, K. 1999, 'Citation frequency and the value of patented inventions', *The Review of Economics and Statistics*, vol. 81, pp. 511-515.

Harrison, R. 2003, 'Protecting innovation in bioinformatics and in-silico biology', *Biodrugs*, vol. 17, pp. 227-231.

Hart, O. and Moore, J. 1990, 'Property rights and the nature of the firm', *Journal of Political Economy*, vol. 98, no. 6, pp. 1119-1158.

Hedman, J. and Kalling, T. 2002, *IT and Business Models: Concepts and Theories*, Copenhagen Business School Press, Copenhagen.

Heller, M. and Eisenberg, R. 1988, 'Can patents deter innovation? The anticommons in biomedical research', *Science*, vol. 280, pp. 698-701.

Helpman, E. (ed.) 1998, *General Purpose Technologies and Economic Growth*, MIT Press, Cambridge, MA.

Henderson, R. and Cockburn, I. 1994, 'Measuring competence? Exploring firm effects in pharmaceutical research', *Strategic Management Journal*, vol. 15, pp. 63-84.

Henderson, R. and Cockburn, I. 1996, 'Scale, scope and spillovers: The determinants of research productivity in drug discovery', *Rand Journal of Economics*, vol. 27, no. 1, pp. 32-59.

Henderson, R. and Clark, K. 1990, 'Architectural innovation: The reconfiguration of existing product technologies and the failure of established firms', *Administrative Science Quarterly*, vol. 35, pp. 9-30.

Herpin, T., Karuso, H. and Foley, J. 2005, 'Australian biotech companies: Navigating the maze', *Journal of Commercial Biotechnology*, vol. 11, no. 2, pp. 111-120.

Higgins, M. and Rodriguez, D. 2006, 'The outsourcing of R&D through acquisitions in the pharmaceutical industry', *Journal of Financial Economics*, vol. 80, pp 351-383.

Hobday, M. 1998, 'Product complexity, innovation and industrial organisation', *Research Policy*, vol. 26, pp. 689-710.

Hobday, M., Rush, H. and Tidd, J. 2000, 'Innovation in complex products and systems', *Research Policy*, vol. 29, pp. 793-804.

Houghton, J. and Rasmussen, B. 2002, 'The convergence of information technology and biotechnology: Bioinformatics developments and implications', CSES Working Paper No. 20-1, CSES, Victoria University, Melbourne.

Human Genome Sciences Inc. 2001, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

ICOS Corporation 2002, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

ImClone Systems Inc. 2001, 'Letter to Shareholders', in *Annual Report 2001*, pp. 2-6, at http://phx.corporate-ir.net/phoenix.zhtml?c=97689&p=irol-reportsAnnual

Incyte Corporation 1996, *Prospectus*, US Securities and Exchange Commission, Washington DC.

Incyte Corporation 2006, *Form 10-K*, US Securities and Exchange Commission, Washington DC.

In-PharmaTechnologist.com 2005, 'Dow spins out dendrimer portfolio to nanotech firm', *In-PharmaTechnologist.com*, 26 January, at: http://www.in-pharmatechnologist.com/news/ng.asp?id=57592, accessed November 2005.

Jackson, R.A. 2005, 'Starpharma raises another AUD $15M to support VivaGel', *NanoBiotech News*, 30 November, p. 9.

Jaffe, A. 1999, 'The US patent system in transition: Policy innovation and the innovation process', NBER Working Paper No. 7280, National Bureau of Economic Research, Cambridge, Mass.

Jaffe, A. and Lerner, J. 2004, *How Our Broken Patent System is Endangering Innovation and Progress and What to Do About It*, Princeton University Press, Princeton, NJ.

Jovanovic, B. and Rousseau, P.L. 2003, 'General purpose technologies', Department of Economics, New York University.

Kang, N.-H. and Sakai, K. 2000, 'International strategic alliances: Their role in industrial globalisation', STI Working Paper No. 200/5, Directorate for Science, Technology and Industry, OCED, Paris.

Kay, J. 2001, 'Changes in market structure: The economic issues', in H. Kettler (ed.), *Consolidation and Competition in the Pharmaceutical Industry*, Office of Health Economics (OHE), London.

Kenney, M. 1986, *Biotechnology: The University-Industrial Complex*, Yale University Press, New Haven, CT.

Kittredge, A. 2005, 'A shrinking target: Clinical trials are taking longer and costing more, as competition from patients heats up', *The Scientist*, vol. 19, no. 7, pp. 46.

Klaes, M. and Stent, E.M. 2005, 'A conceptual history of the emergence of bounded reality', *History of Political Economy*, vol. 37, no. 1, pp. 27-59.

Klein, B., Crawford, R.G. and Alchian, A.A. 1978, 'Vertical integration, appropriable rents and the competitive contracting process', *The Journal of Law and Economics*, vol. 21, pp. 297-326.

Kogut, B. 1988, 'Joint ventures: Theoretical and empirical perspectives', *Strategic Management Journal*, vol. 9, pp. 319-332.

Kogut, B. and Zander, U. 1992, 'Knowledge of the firm, combinative capabilities and the replication of technology', *Organization Science*, vol. 3, no. 3, pp. 383-397.

Kogut, B. and Zander, U. 1993, 'Knowledge of the firm and the evolutionary theory of the multinational corporation', *Journal of International Business Studies*, 4th quarter, pp. 625-644.

Lähteenmäki, R. and Lawrence, S. 2006. 'Public biotechnology 2005: The numbers', *Nature Biotechnology,* vol. 24, no. 6, pp. 625-634.

Landau, R. 1999, 'Introduction', in R. Landau, B. Achilladelis and A. Scriabine (eds), *Pharmaceutical Innovation: Revolutionising Human Health*, Chemical Heritage Press, Philadelphia.

Langlois, R.N. 2003, 'The vanishing hand: The changing dynamics if industrial capitalism', *Industrial and Corporate Change*, vol. 12, pp. 351-385.

Lanjouw, J. and Schankerman, M. 2004, 'Patent quality and research productivity: Measuring innovation with multiple indicators', *The Economic Journal*, vol. 114, pp. 441-465.

Laursen, K. and Salter, A. 2006, 'Open innovation: The role of openness in explaining innovation performance among UK manufacturing firms', *Strategic Management Journal*, vol. 27, pp. 131-150.

Leader, B., Baca, Q. and Golan, D. 2008, 'Protein therapeutics: A summary and pharmacological classification', *Nature Drug Discovery*, vol. 7, January, pp. 21-39.

Lerner, J. 1994, 'Venture capitalists and the decision to go public', *Journal of Financial Economics*, vol. 35, no. 3, pp. 293-316.

Lerner, J. 1995, 'Venture capitalists and the oversight of private firms', *Journal of Finance*, vol. 50, no. 1, pp. 301-318.

Lerner, J. 2002, 'Patent Protection and Innovation over 150 Years', NBER Working Paper No. 8977, National Bureau of Economic Research, Cambridge, Mass.

Lerner, J. and Merges, R. 1998, 'The Control of Strategic Alliances: An Empirical Analysis of Biotechnology Collaborations', NBER Working Paper No. 6014, National Bureau of Economic Research, Cambridge, Mass.

Lichtenberg, F. 1996, 'The Effect of Pharmaceutical Utilization and Innovation on Hospitalization and Mortality (HE PR)', NBER Working Paper No. 5418, National Bureau of Economic Research, Cambridge, Mass.

LION Bioscience AG 2002a, 'Business Model', at: http://www.lionbioscience.com/company/business-model accessed 25 March 2003.

LION Bioscience AG 2002b, 'R&D Report', in *Annual Report 2002*, Heidelberg, Germany.

Lundvall, B. 1992, *National Systems of Innovation, Towards a Theory of Innovation and Interactive Learning*, Pinter, London.

Lux Research 2005a, *The Nanotech Intellectual Property Landscape*, New York.

Lux Research 2005b, 'Statement of Findings: The Nanotech IP Landscape', New York.

Malerba, F. 2005, 'Sectoral systems of innovation: A framework for linking innovation to the knowledge base, structure and dynamics of sectors', *Economics of Innovation and New Technology*, vol. 14, no. 1-2, pp. 63-82.

Malerba, F. and Orsengio, L. 1990, 'Technological regimes and patterns of innovation: A theoretical and empirical investigation of the Italian case', in A.

Heertje and M. Perlman (eds), *Evolving Industries and Market Structures*, University of Michigan Press, Ann Arbor.

Malerba, M. and Orsenigo, L. 1993, 'Technological regimes and firm behaviour', *Industrial and Corporate Change*, vol. 2, no. 45-71.

Malknight, T. 1999a, 'Eli Lilly, 1998 (A): Strategic challenges', 9-399-173, Harvard Business School Publications and IMD International, Boston.

Malknight, T. 1999b, 'Eli Lilly, 1998 (B): Emerging global organization', 9-399-174, Harvard Business School Publications and IMD International, Boston.

Margretta, J. 2002, 'Why business models matter', *Harvard Business Online*, January, at: http://harvardbusinessonline.hbsp.harvard.edu/relay.jhtml?name=itemdetail&id=R0205F&referral=8636, accessed March 2003.

Martin, B.R. and Salter, A. 1996, *The Relationship between Publicly Funded Research and Economic Performance: A SPRU Review*, Science Policy Research Unit, University of Sussex, Brighton.

Martin, B.R. and Tang, P. 2007, 'The Benefits from Publicly Funded Research', SEWPS Paper No. 161, Science and Technology Policy Research (SPRU), University of Sussex, Brighton.

Mathers, C.D. and Loncar, D. 2006, 'Projections of global mortality and burden of disease from 2002 to 2030', *PLoS Medicine*, vol. 3, no. 11, pp. 2011-2030.

Mathews, R. and Robinson, D. 2008, 'Market Structure, Internal Capital Markets, and the Boundaries of the Firm', *The Journal of Finance*, vol, LXIII, No. 6, pp 2703-2736.

McKelvey, M. 1996, *Evolutionary Innovations: The Business of Technology*, Oxford University Press, Oxford.

McKelvey, M., Rickne, A. and Laage-Hellman, J. 2004, 'Stylized facts about innovation processes in modern biotechnology', in M. McKelvey, J. Laage-Hellman and A. Rickne (eds), *The Economic Dynamics of Modern Biotechnology*, Edward Elgar, Cheltenham, UK.

Mercer Management Consulting 2001, 'Where are the next profit zones in pharmaceuticals? The blockbuster model will begin to yield winners and losers', Boston.

Merck 2003, *Annual Report 2003*, New York.

Millennium Pharmaceuticals Inc. 2001, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Millenium Pharmaceuticals Inc. 2002, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Millenium Pharmaceuticals Inc. 2003, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Mosakowski, E. and McKelvey, B. 1997, 'Predicting rent generation in competence-based competition', in A. Heene and R. Sanchez (eds), *Competence-based Strategic Management,* pp. 65-85, John Wiley, New York.

Mowery, D. 1983, 'The relationship between intrafirm and contractual forms of industrial research in American manufacturing, 1900-1940', *Explorations in Economic History*, vol. 20, pp. 351-374.

Myers, S.C. and Shyam-Sunder, L. 1995, 'Measuring pharmaceutical industry risk and the cost of capital', in R.B. Helms (ed.), *Competitive Strategies in the Pharmaceutical Industry, American Enterprise Institute for Public Policy*, Washington, DC.

NanoInvestorNews 2005, 'Dendritic NanoTechnologies, Dow and Starpharma sign major three-way deal to commercialize nanotechnology', 25 January, at: http://www.dendrimercenter.org/images/downloads/DOWannouncement.pdf, accessed November 2005.

Narin, F., Noma, E. and Perry, R. 1987, 'Patents as indicators of corporate technological strength', *Research Policy*, vol. 16, pp. 143-155.

National Center for Biotechnology Information (NCBI) 2004, 'Microarrays: Chipping Away at the Mysteries of Science and Medicine', Bethesda, Maryland, at: http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html, accessed October 2006.

National Institutes of Health (NIH) 2007, 'National Roadmap for Medical Research: Nanomedicine, Overview', US Office of Portfolio Analysis and Strategic Initiatives, Maryland, at: http://nihroadmap.nih.gov/nanomedicine, accessed 20 May 2008.

National Institutes of Health (NIH) 2008a, 'ERA Commons: Computer Retrieval of Information on Scientific Projects', at: http://crisp.cit.nih.gov/, accessed June 2006.

National Institutes of Health (NIH) 2008b, 'The NIH Almanac: Appropriations', US Department of Health and Human Services, Washington DC, at:

http://www.nih.gov/about/almanac/appropriations/part2.htm, accessed 20 May 2008.

National Nanotechnology Initiative 2007, 'The scale of things: Nanometers and more', at: http://www.nano.gov/html/facts/The_scale_of_things.html, accessed 20 May 2008.

National Science Foundation (NSF) 2002, *Converging Technologies for Improving Human Performance: Nanotechnology, Biotechnology, Information Technology and Cognitive Science*, Arlington, Virginia.

Nelson, R. 1993, *National Innovation Systems: A Comparative Analysis,* Oxford University Press, Oxford.

Nelson, R. and Winter, S. 1982, *An Evolutionary Theory of Economic Change*, Belknap Press, Cambridge, Mass.

Organisation for Economic Cooperation and Development (OECD) 1999, *Managing National Innovation Systems*, Paris.

OECD 2000, *International Strategic Alliances: Their Role in Industrial Globalisation*, Paris.

OECD 2001, *Innovative Networks Co-operation in National Innovation Systems*, Paris.

OECD 2002, *Dynamising National Innovations Systems*, Paris.

OECD 2005a, 'Statistical Definition of Biotechnology', OECD, Paris, at: http://www.oecd.org/document/42/0,2340,en_2649_34537_1933994_1_1_1_1,00.html, accessed October 2006.

OECD 2005b, *Oslo Manual: Guidelines for Collecting and Interpreting Innovation Data*, Paris.

Orsengio, L. 1989, *The Emergence of Biotechnology*, Pinter, London.

Orsenigo, L., Pammolli, F. and Riccaboni, M. 2001, 'Technological change and network dynamics: Lessons from the pharmaceutical industry', *Research Policy*, vol. 30, pp. 485-508.

Owen-Smith, J. and Powell, W. 2004, 'Knowledge networks as channels and conduits: The effects of spillovers in the Boston biotechnology community', *Organization Science*, vol. 15, pp. 5-21.

PANBIO 2001, 'PANBIO joins the nanotechnology revolution', PANBIO Ltd, Brisbane, at:

http://www.panbio.com.au/download/nanotechnology%20revolution.pdf, accessed November 2005.

PAREXEL 2001, *PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2001*, Barnett International, Waltham, Mass.

PAREXEL 2005, *PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2005/2006*, Barnett International, Waltham, Mass.

PAREXEL 2006, *PAREXEL's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007*, Barnett International, Waltham, Mass.

Patel, P. 2003, 'UK Performance in Biotechnology-related Innovation: An Analysis of Patent Data', Final Report prepared for the Assessment Unit of the UK Department of Trade and Industry, SPRU, University of Sussex, Brighton.

Penrose, E. 1951, *The Economics of the International Patent System*, John Hopkins University Press, Baltimore.

Perry, M.K. 1989, 'Vertical integration: Determinants and effects', in R. Schmalensee and R.D. Willig (eds), *Handbook of Industrial Organization*, North-Holland, Amsterdam.

Pharmaceutical Executive 2006, May, pp. 75-84, at: http://pharmexec.findpharma.com/pharmexec/data/articlestandard//pharmexec/302008/531367/article.pdf

Pharmaceutical Research Manufacturers of America (PhRMA) 2006, *Pharmaceutical Industry Profile 2006*, Washington DC.

Pisano, G.P. 1991, 'The governance of innovation: Vertical integration and collaborative arrangements in the biotechnology industry', *Research Policy*, vol. 20, pp. 237-249.

Pisano, G.P. 2006, *Science Business: The Promise, the Reality and the Future of Biotech*, Harvard Business School Press, Cambridge, Mass.

Porter, M. 1985, Technology and competitive advantage', *The Journal of Business Strategy*, vol. 5, no. 3, pp. 60-78.

Powell, W. 1998, 'Learning from collaboration: Knowledge and networks in the biotechnology and pharmaceutical industries', *California Management Review*, vol. 40, no. 3, pp. 228-240.

Powell, W., Koput, K. and Smith-Doerr, L. 1996, 'Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology', *Administrative Science Quarterly*, vol. 41, pp. 116-145.

Powell, W., Koput, K., Bowie, J. and Smith-Doerr, L. 2002, 'The spatial clustering of science and capital: Accounting for biotech firm-venture capital relationships', *Regional Studies*, vol. 36, no. 3, pp. 291-305.

Prahalad, C. and Hamel, G. 1990, 'The core competence of the corporation', *Harvard Business Review*, May-June, pp. 79-91.

PriceWaterhouseCoopers (PWC) 2007, 'Pharma 2020: The vision: Which path will you take?', PWC, at: http://www.pwc.com/extweb/pwcpublications.nsf/docid/91BF330647FFA402852572F2005ECC22 accessed 20 August 2007.

Priem, R. and Butler, J. 2001, 'Is the resource-based "view" a useful perspective for strategic management research?', *Academy of Management Review*, vol. 26, no. 1, pp. 22-40.

Qiagen 2001, *Form 20-F: Annual and Transition Report of Foreign Private Issuers*, US Securities and Exchange Commission, Washington DC.

Raff, J. 2005, 'Starpharma Holdings (ASX: SPL)', paper presented at the 2005 Emerging Growth Capital Annual Australian Biotechnology Expo, held in conjunction with the Australia Stock Exchange, Sydney, 9 August.

Rasmussen, B. 2004, 'Alliance Opportunities for Aus Biotechs', Pharmaceutical Industry Project Working Paper No. 23, June, CSES, Victoria University, Melbourne.

Rasmussen, B. 2006, 'Innovation and industry structure in the biomedical industry: Role of alliances', in B. Grewal and M. Kumnick (eds), *Engaging the New World: Responses to the Knowledge Economy*, Melbourne University Press, Melbourne.

Reichert, J.M. 2000, 'New biopharmaceuticals in the USA: Trends in development and marketing approvals 1995-1999', *Trends in Biotechnology*, vol. 18, no. 9, pp. 364-369.

Reichert, J.M. 2001, 'Clinical development of therapeutic medicines: A biopharmaceutical versus pharmaceutical product comparison', *Drug Information Journal*, vol. 35, pp. 337-346.

Reichert, J.M. 2004, 'Biopharmaceutical approvals in the US increase', *Regulatory Affairs Journal Pharma*, vol. 15, no. 7, pp. 1-7.

Reichert, J.M. 2006, 'Trends in US approvals: New biopharmaceuticals and vaccines', *Trends in Biotechnology*, vol. 24, no. 7, pp. 293-298.

Reichert, J.M. and Paquette, C. 2003, 'Therapeutic recombinant proteins: Trends in US approvals', *Current Opinion in Molecular Therapeutics*, vol. 5, pp. 139-147.

Roco, M. and Bainbridge, W. (eds) 2005, *Nanotechnology: Societal Implications, Maximizing Benefit for Humanity*, Report of the National Nanotechnology Initiative Workshop, 3-5 December 2003, Subcommittee on Nanoscale Science, Engineering and Technology, National Science Foundation, Washington DC.

Rosenberg, N. 1990, 'Why do firms do basic research (with their own money)?', Department of Economics, Stanford University, Stanford, Calif.

Rothwell, R. 1994, 'Towards the fifth-generation innovation process', *International Marketing Review*, vol. 11, pp. 7-31.

Sampat, B.N. 2006, 'Patenting and US academic research in the 20th Century: The world before and after Bayh-Dole', *Research Policy*, vol. 35, pp. 772-789

Saxenian, A.L. 1994, *Regional Advantage: Culture and Competition in Silicon Valley and Route 128*, Harvard University Press, Cambridge, Mass.

Scherer, F.M. 1996, *Industry Structure, Strategy and Public Policy*, Harper Collins, New York.

Scherer, F.M. 2000, 'The pharmaceutical industry', in A.J. Culyer and J.P. Newhouse (eds), *Handbook of Health Economics*, Elsevier, Amsterdam.

Scriabine, A. 1999, 'Discovery and development of major drugs currently in use', in R. Landau, B. Achilladelis and A. Scriabine (eds), *Pharmaceutical Innovation: Revolutinising Human Health*, Chemical Heritage Press, Philadelphia.

Shan, W., Walker, G. and Kogut, B. 1994, 'Interfirm cooperation and startup innovation in the biotechnology industry', *Strategic Management Journal*, vol. 15, pp. 387-394.

Shane, S. 2001, 'Technological opportunities and new firm creation', *Management Science*, vol. 47, pp. 215-220.

Shapiro C. and Shapiro, H. 1999, *Information Rules: A Strategic Guide to the Network Economy*, Harvard Business School Press, Boston, Mass.

Sharpe, W.F. 1964, 'Capital asset prices: A theory of market equilibrium under conditons of risk', *Journal of Finance*, vol. 19, no. 3, pp. 425-442.

Simon, H.A. 1955, 'A behavioural model of rational choice', *Quarterly Journal of Economics*, vol. 69, pp. 99-118.

Simon, H.A. 1957, *Models of Man*, John Wiley, New York.

Starpharma 1998, *Starpharma Annual Report 1998*, Melbourne.

Starpharma 1999, *Starpharma Prospectus 1999*, Melbourne.

Starpharma 2000a, *Starpharma Prospectus 2000*, Melbourne.

Starpharma 2000b, *Starpharma Annual Report 2000*, Melbourne.

Starpharma 2001, 'PANBIO to join Starpharma as investor in Dendritic Nanotechnologies Limited', press release, 10 September, Melbourne.

Starpharma 2003, *Starpharma Prospectus 2003*, Melbourne.

Starpharma 2004, 'Starpharma announces institutional share placement', press release, 18 March, Melbourne.

Starpharma 2005a, 'Development of VivaGel™ significantly accelerated with $US20m funding from NIH', press release, 3 October, Melbourne.

Starpharma 2005b, *Starpharma Annual Report 2005*, Melbourne.

Starpharma 2005c, 'Starpharma secures full ownership of core technology', press release, 10 October, Melbourne.

Starpharma 2007, 'CEO Presentation to Nanobusiness 2007 Conference', 16 April, Melbourne, at: http://www.starpharma.com/data/070416%20Presentation%20Nanobusiness2007.pdf, accessed 12 May 2007.

Stein, J., 1997, Inter Capital Markets and the Competition for Corporate Resources, *The Journal of Finance*, vol LII, No 1, March 1997, pp 111-133.

Strategic Industry Research Foundation (SIRF) 1992, *SIRF Annual Report 1992*, Melbourne.

Strategic Research Foundation (SRF) 1991, *Annual Report 1990-91*, Melbourne.

Sutton, J. 1991, *Sunk Costs and Market Structure: Price Competition, Advertising and the Evolution of Concentration*, MIT Press, Cambridge, Mass.

Sutton, J., 1998, *Technology and Market Structure: Theory and History*, MIT Press, Cambridge, Mass.

Sweeny, K. 2002, 'Technology Trends in Drug Discovery and Development: Implications for the Development of the Pharmaceutical Industry in Australia', Pharmaceutical Industry Project Working Paper No. 3, March, CSES, Victoria University, Melbourne.

Teece, D.J. 1986, 'Profiting from technological innovation: Implications for integration, collaboration, licensing and public policy', *Research Policy*, vol. 15, no. 6, pp. 285-305.

Teece, D.J. 2006, 'Reflections on "profiting from innovation", *Research Policy*, vol. 35, pp. 1131-1146.

Teece, D.J. and Pisano, G. 1994, 'The dynamic capabilities of firms: An introduction', *Industrial and Corporate Change*, vol. 3, no. 3, pp. 537-556.

Teece, D.J., Pisano, G. and Shuen, A. 1997, 'Dynamic capabilities and strategic management', *Strategic Management Journal*, vol. 18, no. 7, pp. 509-533.

The Royal Society and The Royal Academy of Engineering 2004, 'Nanoscience and nanotechnologies: Opportunities and uncertainties', July, London, at: http://www.nanotec.org.uk/finalReport.htm, accessed November 2005.

The Wall Street Transcript 2000, 'Dr Jonathan Rothberg – Curagen Corporation: CEO Interview', 17 September, at: http://www.twst.com/ceos/crgn_sept17.html, accessed 29 May 2006.

Tollman, P., Guy, P., Altshuler, J., Flanagan, A. and Steiner, M. 2001, 'A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry', Boston Consulting Group, at: http://www.bcg.com/impact_expertise/publications/files/eng_genomicsgenetics_rep_11_01.pdf, accessed May 2002.

Toole, A. 2000, 'The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry', SIEPR Discussion Paper No. 00-07, Stanford Institute for Economic Policy Research, Stanford University, Stanford, Calif.

Trajtenberg, M., Henderson, R. and Jaffe, A. 1997, 'University versus corporate patents: A window on the basicness of invention', *Economics of Innovation and New Technology*, vol. 5, pp. 19-50.

Tripos Inc. 2007, *Form 10-K: Annual Report*, US Securities and Exchange Commission, Washington DC.

Tufts Centre for the Study of Drug Development (CSDD) 2003, 'Biopharmaceutical Development and Approval Times, 1982-2002', March, Tufts University, Boston.

Tufts Center for the Study of Drug Development (CSDD) 2007, 'Outlook 2007', Tufts University, Boston.

Uldrich, J. 2005, 'Starpharma: A "nano star" on the rise', *NanoNovus*, 17 March, at: http://nanonovusblog.blogspot.com/2005/03/starpharma-nano-star-on-rise.html, accessed November 2005.

US Government Accountability Office (US GAO) 2006, 'New Drug Development: Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development Efforts', Report to Congressional Requestors, GAO-07-49, Washington DC.

US Department of Energy, Office of Science 2008, 'Genome Programs', Washington DC, at: www.ornl.gov/hgmis, accessed 8 April 2008.

Vanhaverbeke, W. and Cloodt, M. 2006, 'Open innovation in value networks', in H. Chesbrough, W. Vanhaverbeke and J. West (eds), *Open Innovation: Researching a New Paradigm*, Oxford University Press, Oxford, pp. 258-281.

Verlinder, M.C. 2000, 'Eli Lilly: The Evista Project', in Harvard Business School Press, *From the Field: Inside Biotechnology and Pharmaceuticals*, HBSP No. 4924, Harvard, Cambridge, Mass.

Vitale, M. 2004, 'Commercialising Australian Biotechnology', Australian Business Foundation, Sydney.

Wagner, V., Dullaart, A., Bock, A. and Zweck, A. 2006, 'The emerging. nanomedicine landscape', *Nature Biotechnology*, vol. 24, no. 10, pp. 1211-1217.

Walsh, G. 2002, 'Biopharmaceuticals and biotechnology medicines: An issue of nomenclature', *European Journal of Pharmaceutical Sciences*, vol. 15, pp. 135-138.

Walsh, G. 2003, *Biopharmaceuticals: Biochemistry and Biotechnology*, Wiley, Chichester.

Walsh, G. 2006, 'Biopharmaceutical benchmarks 2006', *Nature Biotechnology*, vol. 24, no. 7, pp. 769-776.

Walton, J. 2001, 'Investors' views on Merger and acquisition, alliance and licensing activity in the pharmaceutical industry', in H. Kettler (ed.), *Consolidation and Competition in the Pharmaceutical Industry*, based on papers delivered at the OHE Conference, London, 16 October 2000, Office of Health Economics, London.

Weatherall, M. 1990, *In Search of a Cure: A History of Pharmaceutical Discovery*, Oxford University Press, Oxford.

Wernerfelt, B. 1984, 'A resource-based view of the firm', *Strategic Management Journal*, vol. 5, pp. 171-180.

Whelan, J. 2006, 'It's a small world: First generation nanomedicines are here and the arrival of polymer-based drug-delivery systems mean drugs can target specific points within a cell', *Chemical and Industry*, 20 February.

Wiggins, S.N. 1987, 'The cost of developing a new drug', Pharmaceutical Manufacturers Association, Washington DC, June.

Williamson, O. 1971, 'The vertical integration of production: Market failure considerations', *American Economic Review*, vol. 61, no. 2, pp. 112-123.

Williamson, O. 1975, *Markets and Hierarchies: Analysis and Antitrust Implications,* The Free Press, New York.

Williamson, O. 1981, 'The modern corporation: Origins, evolution, attributes', *Journal of Economic Literature*, vol. 19, December, pp. 1537-1568.

Williamson, O. 1989, 'Transaction cost economics', in R. Schmalensee and R. Willig (eds), *Handbook of Industrial Organization*, North Holland, Amsterdam.

Williamson, O. 1999, 'Strategy research: Governance and competence perspectives', *Strategic Management Journal*, vol. 20, pp./ 1087-1108.

Winter, S. 2000, 'Appropriating the gains from innovation', in G. Day and P. Schoemaker (eds), *Wharton on Managing Emerging Technologies*, John Wiley, New York.

Woodward, M. n.d. 'SNiPpetS and Bytes', Powerpoint presentation, US Patent and Trademark Office, Washington DC, at: www.uspto.gov/web/patents/biochempharm/documents/snippets.pps, accessed June 2006.

Xenova Group PLC 2003, 'Home', at: www.xenova.co.uk accessed 25 March 2003.

Zucker, L., Darby, M. and Armstrong, J. 1998a, 'Geographically localized knowledge: Spillovers or markets', *Economic Inquiry*, vol. 36, no. 1, pp. 65.

Zucker, L., Darby, M. and Brewer, M. 1998b, 'Intellectual human capital and the birth of us biotechnology enterprises', *American Economic Review*, vol. 88, no. 1, pp. 290-306.