

**Innovation and Industry Structure
In the Biomedical Industry:
Some Preliminary Results**

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Innovation and industry structure in the biomedical industry: Some preliminary results¹

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Introduction

Innovation in the pharmaceutical industry raises structural questions for the participants about their future roles. New technologies, and especially biotechnology, have made the industry structure more complex. Broadly speaking these technologies have been directed at two problems. One is increasing the range of drugs available to treat disease and the other is improving the efficiency of the drug discovery process – so called platform technologies. Some technologies have assisted in both areas.

These new technologies have been largely developed by specialist start up companies rather than emerging from within the large pharmaceutical companies. Access to the new technologies by large pharmaceutical companies has been through alliances, service contracts and occasionally outright purchase. A handful of the new biotechnology companies has been successful in transforming themselves into large integrated companies, not dissimilar to the large pharmaceutical companies. Other companies have attempted to survive by developing different business models – contracting their research expertise to large pharma, forming alliances amongst themselves to acquire complementary technologies and offering their platform technologies on a fee for service basis. These new business models are yet to prove their viability.

This new landscape raises issues for the participants across a number of dimensions. There are a group of issues relating to firm structure. What is the future of these specialist biotechs? Will large pharmaceutical companies retain their dominant role in the industry or will it be diminished by projected product pipeline deficiencies or a trend to personalised medicine? Will they outsource an increasing proportion of their functions to take advantage of the specialised products and technologies developed by smaller biotech and platform technology companies, and so enhance the role of such companies?

A further set of issues relate to the geographical location of the various industry segments and in particular to the interaction between the national and global innovation systems. Although the industry is in many ways globally integrated, many of its activities are highly concentrated in the United States. Not only are the majority of large pharmaceutical companies headquartered there, but also it is where much of the innovation, especially in the biotechnology sector, occurs. Historically of course, Europe was the centre of the industry. What role does Europe now have in shaping the future of the industry? European governments have been active in developing policies to promote the biotechnology industry and through a process of consolidation a number of European headquartered companies still feature amongst the top 10 pharmaceutical companies. These companies have large R&D budgets that fund much biotech development work. Japan, on the other hand, has retained a focus on

¹ The enthusiastic research assistance of Alison Welsh is gratefully acknowledged.

traditional pharmaceutical activities and efforts in the biotechnology industry appear to be modest.

Finally what role do peripheral players such as Australia have in this pharmaceutical world view, where at least some of its provincial governments aspire to developing a significant biotechnology sector and have been investing sizeable amounts of money in pursuing these goals. In Australia's case, its pretensions are based on a view that its science punches above its weight and that its limited success to date has been due to the failure of effective commercialisation strategies. Is this realistic given the dominance of distant European and American decision makers?

Some Theoretical Considerations

Some theoretical developments in economics and management can assist a better understanding of the changing firm structure of the industry and perhaps help to predict its future.

The impact of innovation on firm structure is multitudinous, but three factors are of central importance. One is its role in the creation of the large fully integrated pharmaceutical company, with its need to finance and manage, significant, high risk R&D expenditures on drug development. The second is the establishment of specialist start up companies to exploit particular innovations. Much of the innovation has been developed by these new specialist companies rather than emerging from within the large pharmaceutical companies. The third is that access to the new technologies by both large pharmaceutical companies and other specialist biotechs has often been through alliances, service contracts and occasionally outright purchase.

Innovation and the development of the vertically integrated firm

Chandler (1990) describes the growth in large powerful firms in the US and Germany between about 1860 and 1920 as being motivated by the ability to achieve economies of scale and scope through investment in new industrial technologies. The massive investment in new capital intensive large-scale technologies and processes in the US required the development of joint stock and holding companies to finance new railroads, steel plants, power generation and telephone companies. Henderson and Cockburn (1996) and Cockburn and Henderson (2001) have demonstrated the importance of scale and scope for pharmaceutical research and development indicating the advantages of size for pharmaceutical companies.

Recent developments in the theory of the firm help provide theoretical reasons for the development of large firms. For instance, transaction cost economics provides a theoretical justification for the vertically integrated firm. 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 history of the structure of the modern vertically integrated, multidivisional, multinational firm (Williamson 1971, 1981). He explains vertical integration in terms of achieving economies arising from information exchange and an improvement in the quality of information. He also argues that the integration harmonises interests, reduces opportunism and permits an efficient (adaptive, sequential) decision process (Williamson 1971).

The importance of economising on the cost of information has been described by Demsetz (1991) as being 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 (p173). Demsetz argues 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 it without themselves being knowledgeable in its production. 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. For instance, it may be more efficient for a pharmaceutical company to pay for a biotech with specialised knowledge, which is expensive to acquire, to discover and develop a drug to treat a particular disease, than develop it itself.

Another perspective provided by transaction cost economics is through the notion of asset specificity - 'that is the degree to which an asset can be redeployed ... without sacrifice of productive value' (Williamson 1989, p142). 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. Williamson demonstrates, in an otherwise neoclassical framework, that when asset specificity has a significant cost reducing impact on the production of a given product, internal organisation is favoured over market acquisition of the product (Williamson 1989). This result is of particular importance to pharmaceutical companies where transactions involve high levels of asset specificity – such as employees with high levels of tacit knowledge, or technologies that are unique, would tend to favour strategies that internalised such transactions, providing a rationale for the fully integrated pharmaceutical firm.

In the context of the pharmaceutical industry, the concept of 'residual property rights' (Grossman and Hart 1986; Hart and Moore 1990) provides further insight into reasons for the fully integrated model. 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 in which opportunistic behaviour can be used to considerable advantage. For instance the supplier of a product may engage in 'hold up', where it withholds supply until the terms of the contract are renegotiated in its favour. The buyer may prefer in these circumstances to buy the asset and so acquire the residual rights.

Pharmaceutical company managers regularly face the choice between in-house drug development and various forms of external development. In-house development utilises assets owned by the company and all surpluses arising from the successful development accrue to the company. However if a judgement is made that the size of the total drug development surplus is likely to be larger as a result of the use of an external development team with greater or specialist expertise, then the pharmaceutical company management may be tempted to contract with that team for the supply of a particular drug. In these circumstances important residual property rights rest with the contracted external R&D team, who may engage in opportunistic behaviour to extract a higher proportion of the surplus.

If transaction cost economics provides sound theoretical support for a highly vertically integrated pharmaceutical industry, then how does one explain the plethora of small specialist drug discovery and platform technology companies? Are such companies simply destined to fail or be absorbed into large pharmaceutical companies?

The viability of small specialist biotechs and platform companies

Such companies appear to perform a particularly critical role in the development of new technologies, but are their business models viable? The resource based view of the firm provides some explanation of the reasons for their creation.

The development of the resource based view, with its emphasis on intangible assets, competencies, learning and accumulation of hard-to-imitate assets, is particularly relevant to the analysis of technology based firms. Indeed just as the neo classical firm is an abstraction of a simple nineteenth manufacturing plant, the resource based view is increasingly directed to describing and analysing late twentieth century high tech firms, which depend on the profitable output of their R&D labs.

Teece, Pisano and Shuen (1997) provide a comprehensive statement of the resource based view, elaborating on the concepts underpinning the theory, emphasising the path dependant nature of competitive advantage, and the importance of firm specific managerial and organisational processes and routines. They 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 (p515).

This view suggests that a small firm, whose most important resource is a nimble team of highly expert scientists and specialised technologists, might have substantial advantages in specialist areas of R&D over a fully integrated firm constrained by more formal decision making processes. This helps to explain the emergence of so many small scale biotechs and general platform companies specialising in R&D. On the other hand, transaction cost economics is valuable in explaining why such firms might struggle in undertaking global sales and marketing of their products compared with a large integrated pharmaceutical company.

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, how does one predict what is a unique and valuable resource other than that it is owned by a successful firm. Or in other words, successful firms have unique resources that are valuable because the firms are 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 be made between firms to help identify those of particular importance.

Something of this approach is found in Cockburn, Henderson and Stern (2000), who develop 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 and the view that it is determined by 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 patents and publications. 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.

Nonetheless, some of the difficulty about the ex ante identification of a unique and valuable resource remains. If the resource is unique how is its value ascertained other than by the ex post performance of the firm? The review of various strategies selected by specialist general platform companies and some biotechs, presented later in this paper, suggest that they share this uncertainty and that most are seeking to adopt the fully integrated pharmaceutical company model.

Alliances to acquire the new technologies

Alliances between pharmaceutical companies and biotechs and between biotechs themselves have become a feature of the pharmaceutical industry and the biotechnology sector. Alliances fund drug discovery and development and provide a mechanism for transferring platform technologies and access to global distribution networks. They certainly offer a lifeline to biotech companies otherwise dependent on the rigours of venture capitalists or the vagaries of the stock market. They also offer large pharmaceutical companies cost saving technologies and potential new products. This represents something of a market in technology.

Arora, Fosfuri and Gamberdella (2001) outline the difficulties in the development of such a market but also describe how progressively many of these have been overcome to permit the development of a market in technology. The difficulties in the development of a such a market are highlighted by the transaction cost economics approach to the theory of the firm and the resource based view, discussed in part above. Transaction cost economics emphasises the cost economies, the value of controlling residual property rights under conditions of incomplete contracts and the reduction in opportunism, which occurs by conducting transactions such as technology and other knowledge intensive transfers within the firm. The resource based view emphasises the value of the path dependant nature of knowledge development, the importance of firm specific managerial and organisational processes and routines in technology transfers within the firm, which seriously constrains transfer outside the firm (Kogut and Zander 1992). Indeed Kogut and Zander (1993) suggest that ‘technology transfer lies at the heart of the growth of firms ... Firms grow on their ability to create new knowledge and to replicate this knowledge so as to expand their market. Their advantage lies in being able to understand and carry out this transfer more effectively than other firms’ (p639).

These limitations on knowledge transfer are in addition to the appropriability problem raised by Arrow (1962) in which information once disclosed is costless to the user. Patents act satisfactorily in the pharmaceutical industry to reduce appropriability as a problem. Although the nature of a discovery is disclosed, its use is protected for a period during which the patent holder has exclusive market rights. Accordingly patents allow the rights to drug discoveries to be efficiently transferred.

Arora, Fosfuri and Gamberdella (2001) identify a series of changes in the markets for technology that have improved the ease with which technology can be transferred. Some of these are particularly relevant to the biotechnology industry. 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.

Recent developments in biotechnology, and particularly in bioinformatics, have greatly improved the transferability of platform technologies, which are directed

at improving the efficiency of drug discovery processes. Innovations such as ‘gene chips’ contain much embodied genomics knowledge and technology but are sold as a product. Similarly, bioinformatic software tools designed to synthesise and analyse the vast amount of data generated through the drug discovery and development process can be sold as products. These innovations have generated specialist companies which develop and market these products for use under various kinds of licence arrangements. Alliances between specialist companies have been used creatively to combine complementary knowledge stocks such as between software specialists and life sciences companies (Houghton and Rasmussen 2002).

Arora, Fosfuri and Gamberdella (2001, p67) 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’. This relationship between upstream technology suppliers and downstream producers has been facilitated by the much increased use of various types of alliances that range from joint ventures to co development to licenses. Whether these specialist companies represent a stable source of supply remains an open issue. As will be discussed in the next section the aspiration expressed in the strategies of most of these firms is to become a fully integrated pharmaceutical company. This suggests that for such firms to be fixed in the value chain as upstream suppliers would seem to them to be an unsatisfactory outcome.

The next section looks in more detail at the emerging industry value chain and the way in which the industry’s technological innovations are reflected in the creation of new institutional actors.

The pharmaceutical industry value chain

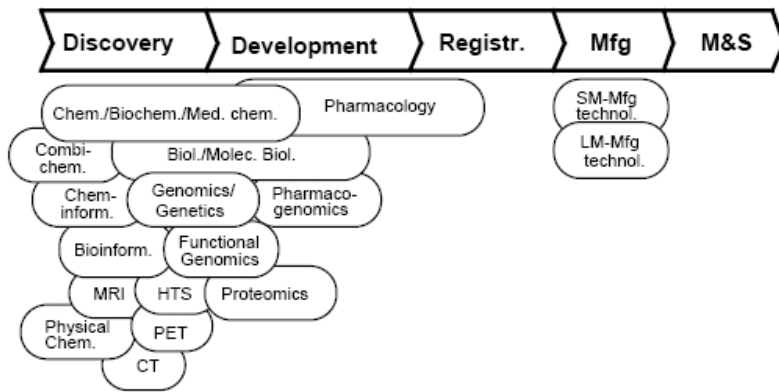
The concept of the value chain was introduced by Porter (1985), as ‘a systematic way of examining all the activities a firm performs and how they interact’ (p33). It has been extended to analysis of industry structure². The pharmaceutical industry value chain is highly structured, being governed to a large degree by the drug approval regulatory process in which drugs are ‘moved’ from discovery through development to marketing and sales.

In the pre biotechnology period fully integrated pharmaceutical companies (FIPCOs) conducted this entire process in-house, with relatively minor assistance from external parties such as university research institutes. In the post biotechnology period this value chain has become much more complex with the application of many specialised technologies to the drug discovery and development process.

A version of this value chain is shown in Figure 1, sourced from Granberg and Stankiewicz (2002), which illustrates some of the main innovations in the drug production process such as combinatorial chemistry, genomics, proteomics at the drug discovery and development phase. Rather than originating within the large pharmaceutical companies, each of these new innovations has spawned a new set of specialist start up companies (Figure 2).

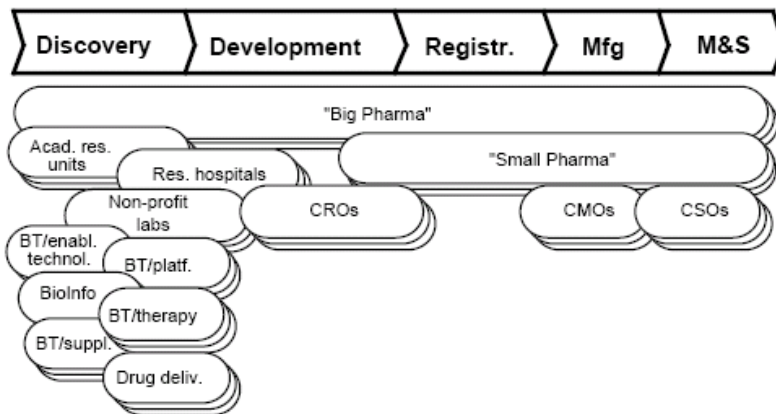
² Porter (1985, p34) refers to the integration of firm value chains into the industry ‘value system’.

Figure 1. Pharmaceutical Value Chain: Major Specialisations



Source: Granberg and Stankiewicz (2002).

Figure 2. Pharmaceutical Industry Value Chain and the Set of Institutional Actors



Source: Granberg and Stankiewicz (2002).

These companies range from those focusing on drug discovery and development (product biotechs) to those providing platform technologies – genomics, bioinformatics, proteomics etc. (These latter are referred to as GPT companies). In addition specialist companies in clinical trials (CROs), contract manufacturing (CMOs) and sales organisations (CSOs) have also emerged. There is therefore a significant challenge in developing an appropriately integrated structure, through which all these specialist tasks may be incorporated into the value chain. Alliances have a central role in this process.

Empirical Evidence of Changing Industry and Firm Structure Based on Alliances

This section presents some of the results of empirical work undertaken to shed light on aspects of changing industry and firm structure. It deals with four issues. The first is the growth in the number of alliances over the last decade, the changes in the

nature of the parties to those alliances and the reasons for these changes. The second is the geographic distribution of the alliance partners and the insight that provides into the interaction between global and national innovation systems. The closely related third issue is the nature of the technology transfer facilitated by these alliances. The final issue relates to the evolving industry value chain structure and the role of product biotechs and GPT companies.

While the pattern of alliances, and particularly their technology basis, is important for this analysis, this final issue is also discussed in terms of the results derived from a closer examination of aspects of these companies' business models. In particular it examines the proposition of Arora, Fosfuri and Gamberdella discussed above, about the future participation of the product biotechs and GPT companies in the industry value chain. As much remains to complete the analysis of the data sources, some aspects of this work, are still very much 'in progress'.

A great deal of the empirical work presented here is based on an analysis of biotech/pharmaceutical alliances drawn from the Recap database³, which attempts to be a comprehensive global source of information about such alliances. It has its shortcomings, eg it 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, from our cross checking, it does appear to be remarkably comprehensive. The other principal source of information, used to analyse biotech value chains and business models, is the SEC 10K reports filed by US listed companies, supplemented by company reports and web material.

Number of alliances

As suggested by Arora, Fosfuri and Gamberdella (2001), the alliance offers a mechanism by which large pharmaceutical companies can gain access to new product and specialist technologies provided by product biotechs and GPT companies respectively. For product biotechs, the alliance generally involves a licensing arrangement in which, in return for upfront and milestone payments the specialist company develops a drug, which is then trialed and marketed by the pharmaceutical company through its global distribution system. In addition, with a successful drug, the biotech will receive royalty payments. For the GPT companies, the arrangement may be different, depending on the technology and particularly on the level of commoditisation of the technology. The alliance may range from a co-development arrangement, not unlike that for a product biotech alliance, to a non-exclusive fee for service.

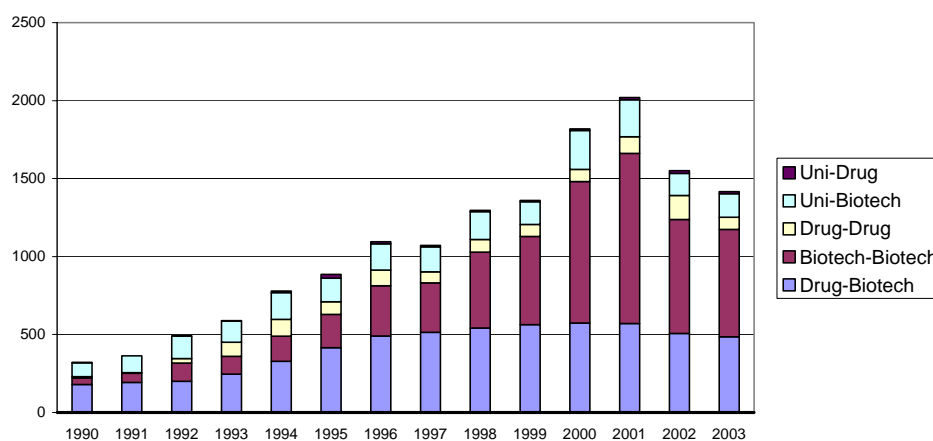
While such alliances have been important in meeting the needs of large pharmaceutical companies, what is clear from an analysis of alliance numbers is that the greatest increase has occurred in alliances between biotechs. As would be expected from developments in the pharmaceutical value chain discussed above, these alliances appear to be focussed on the transfer of complementary technology services, by which specialist companies combine their expertise to develop a new product or technology. A large part of this growth is a result of new drug discovery technologies. The largest of these are those associated with genomics, but others such as screening and combinatorial chemistry have also been important.

³ Recominant Capital see www.recap.com

The number of biomedical alliances recorded on the Recap database by date of commencement is shown in Figure 3, classified by the parties involved. The Recap database classifies alliances by three parties – pharmaceutical companies (drug), biotechs and universities, including institutes, research departments and government. GPT companies are included as biotechs. Pharmaceutical companies range from the large global companies to smaller regional or more specialist firms.

Figure 3 shows the significant increase in the number of alliances being formed in the period since 1990. As noted, the decline in 2002 and 2003 may be due to incomplete data for those years but may also reflect the influence of the industry cycle. The process of identifying and adding alliances to the database takes some time. This is illustrated by some 240 alliances for 2001 being added to the Recap database since May 2003.

Figure 3. Number of Biomedical Alliances, 1990 to 2003



Source: Recap Feb 2004.

Note: Data for 2002 and 2003 may be incomplete.

There are a number of remarkable aspects to Figure 3. The first is the growth in the number of alliances, which totalled 321 in 1990 and reached 2019 by 2002. This growth has two aspects. The first is the rapid growth between pharmaceutical companies (drug) and biotech companies from 180 to 490, after which the number broadly stabilised. The second is the rapid growth in the number of alliances between biotechs throughout the period. This is shown in more detail in Table 1 below.

Table 1. Number and Annual Growth in Biomedical Alliances, 1990-2001

	Drug-Biotech		Biotech-Biotech		Other		Total
1990	180		40		101		321
1996	490	18.2%	322	41.6%	283	18.7%	1095
2001	571	3.1%	1090	27.6%	358	4.8%	2019

Source: Recap Feb 2004.

The growth in all alliances over the first half of the period from 1990 to 1996 was high (22.7% pa) from a relatively low base, especially for biotech biotech alliances. In the second period from 1996 to 2001, the number of new drug biotech alliances, grew only modestly from 490 to 571 (3.1% pa), while biotech biotech alliances continued to grow rapidly from 322 to 1090 (27.6% pa). The growth in other alliances, such as those between pharmaceutical companies (drug drug), also moderated in the second period, after growing rapidly in the first.

The growth in alliances between biotechs and pharmaceutical companies in the first period is a product of the pressures being felt by the pharmaceutical companies to maximise the productivity of their pipelines and the complementary need for funding by the emerging biotech companies. 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 and improve the productivity of their pipelines through the application of new discovery technologies. The issue raised by this data is why the growth in alliances between pharmaceutical companies and biotechs tapered off between 1996 and 2001. Was it due for instance, to more selective strategies employed by large pharma, such as a focus on a smaller number of later stage alliances, or fewer biotechs seeking funding from large pharma in a more receptive financial market?

The dominant driver for the growth in alliances between biotechs is their need to exchange their new technologies. This reflects the fragmented nature of the technological development in specialist start-ups. Often complete products required the combined expertise of a number of specialist companies to produce a single marketable product. These issues are dealt with in more detail in the later section on alliance technologies.

Another feature of the Figure 3 is the relatively modest growth in alliances with universities or research institutes. This probably reflects a university commercialisation process that begins with the formation of a company, 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 large pharmaceutical companies is very small, an average of about 10 per annum over the period.

Geographic distribution of alliances

One aspect of the alliance is to provide a mechanism to integrate the activities of specialist companies and to transfer across different stages of the value chain specialist technologies and products. Another is to perform this integration function across geographic space. In this way an alliance is one of the instruments of the formation of local clusters, of regional and national innovation systems. It is one of the mechanisms by which a global innovation system is formed. Alliances are an indicator not only of how powerful national markets in technology and related pharmaceutical services have formed, but also the globalisation of the markets for biomedical products and technologies. Analysis of the Recap database demonstrates not only the extent of this global innovation system, but also the relative size of the most powerful national biotechnology innovation system, the United States. For several countries the number of alliances with the United States exceed the number of alliances formed within their country. In other words, for these countries, participation in the global innovation system may be more important than participation in their national innovation system.

Figure 4 attempts to capture some of the complex inter-connectedness of alliance formation between major biomedical countries. It shows alliances for the top six countries/regions involved in alliance formation. All European countries have been grouped together. Germany, Switzerland and France dominate but Denmark, Sweden, Netherlands and Italy make important contributions to the total. It also shows the number of 'internal' alliances for each country. That is alliances between companies with a common country of domicile.

The Recap alliances are not classified by country. That exercise has been undertaken in the Centre, by cross-referencing company information on Recap with a global company database. Each party to the alliance has been classified by country of domicile of the company corporate headquarters. This means that alliances formed by wholly owned subsidiaries would generally be classified by domicile of the parent company.

As discussed earlier in this paper, alliances have a range of purposes, which reflect the roles of the alliance parties in the value chain. These include technology transfer, product development, clinical research, manufacturing and distribution. About 75% of alliances on Recap involve technology transfer or specialist product development. In most alliances there is a 'client', which directs and pays for the work done and another party, which we will call the 'developer' which undertakes the work and receives payment. Some alliances have high degrees of cooperation, where these distinctions are less clear or where payment is mostly 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 the purposes of explaining the alliance linkages in Figure 4, alliances are assumed to follow the simpler format in which there is client and a developer with the client paying for work done by the developer. As noted above most alliances involve technology transfer or specialist product development.

The number of internal alliances reported for each country is shown in Figure 4 within the space representing each country. The size of the area reflects to some extent the number of internal alliances, although it is not to scale. For instance the relative importance of the US with 1684 internal alliances formed in the period 2001 to 2003 is shown by having by far the largest area. Australia, with 13 internal alliances formed over the same period, has the smallest area.

The arrows in Figure 4, show the alliance linkages between each pair of countries – one the 'developer' country and the other is the 'client' country. The direction of the arrow represents the intended flow of funds under the alliance from the client country to the developer country. For most countries a single line represents a two-way flow of funds between companies in each country. The direction of the arrowhead represents the potential or intended flow of funds into that country under the alliance. The number at each arrowhead on the perimeter of the country space is the number of alliances involved in receiving (or potentially receiving) funds from companies in the associated 'client' country. For instance over the period 2001 to 2003, 275 alliances were formed by US 'client' companies funding (or potentially funding) European 'developer' companies. There were 462 alliances formed in which European 'client' companies were funding (or potentially funding) US 'developer' companies.

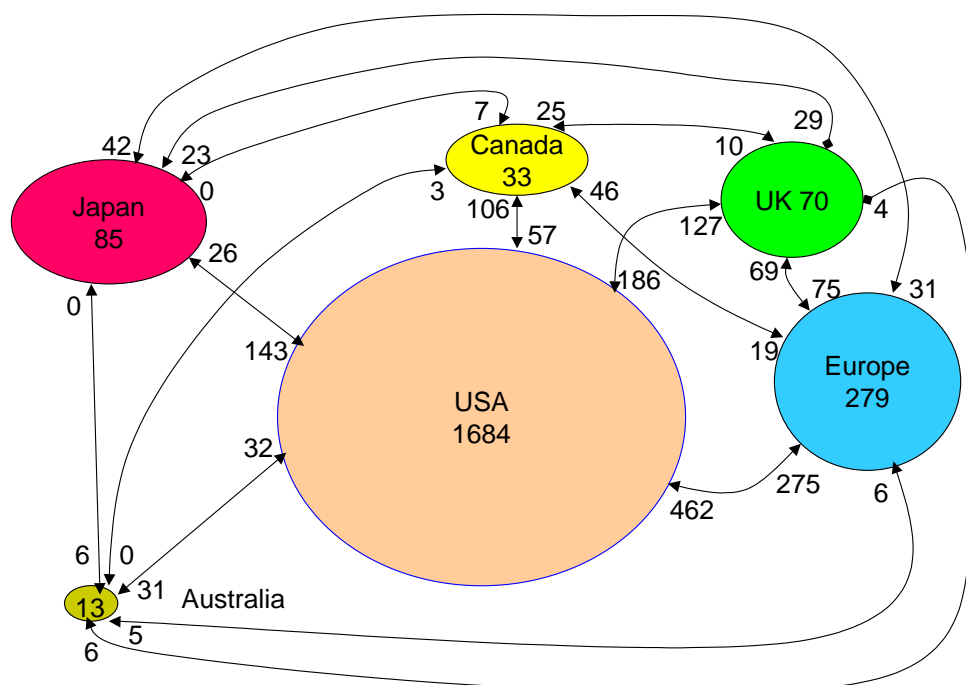
The relative concentration of the industry in the United States is illustrated both by the large number of alliances internal to the US, 1684 formed over the three-

year period, as well as the number of international alliances involving US companies. Of the total alliances formed and listed on Recap in the three years to 2003, 55% involved a company domiciled in the United States.

While US companies are extremely active in their home market, the data indicate that US companies as the ‘client’ are using alliances to make substantial product and technology or other acquisitions from Europe, UK, and Canada. Together, the number of US alliances with these three countries was 508, about 30% as many as those internal to the US.

Figure 4 also indicates that the US is a significant source of technology and product development for other countries. European, UK and Japanese ‘client’ companies have a total of 791 alliances with US ‘developer’ companies –462 European, 186 UK and 143 from Japan. This total significantly outnumbers internal alliances for those countries (434).

Figure 4. Biomedical Alliances Formed, 2001 to 2003: Top 6 Countries/Regions



Note: Direction of the arrows represents flow, or potential flow, of alliance funds
 Source: CSES, Recap Jan 2004.

Canada, as ‘developer’ appears to be undertaking an important role as a centre for biomedical research and development on behalf of client companies in Europe, US and UK with a total of 177 alliances with those countries. This is consistent with Canada’s relatively favourable R&D cost structure.

As a small player in the biotech industry, being involved in about 2% of global alliances, Australia represents an interesting case, in that the number of client and developer alliances is about equal. This reflects not only the role of Australian biotechs as a source of product with 48 alliances as developer, but also the requirements of Australian companies for complementary technologies as shown by the number of alliances in which they are the client (45). In such a small market with limited capabilities these technologies are acquired from overseas, most prominently

from the US with 32 alliances. This compares with only 13 alliances formed internally over the same period. In Australia's case it would appear that participation by companies in the global innovation system is at least as, if not more, important as participation in the national innovation system.

A further analysis of the country data (Table 3) by alliance party reveals the US focus on biotechnology, with 65.6% of biotech biotech alliances, and 43.3% of drug biotech alliances where the US is the client country. In contrast 34.1% and 31.4% of Japanese and European alliances respectively are between pharmaceutical companies (drug drug) illustrating a much greater emphasis on traditional pharmaceutical industry arrangements. Although the total numbers are small, alliances between universities and biotechs are highly concentrated in the US, again emphasising its relative focus on biotechs.

Table 2. Percentage Share of Alliances by Alliance Party, 2001 to 2003*

Client Country	All Alliances	Bio-Bio	Drug-Bio	Drug-Drug	Uni-Bio
Australia	1.5	2.1	0.4	1.1	2.3
Canada	2.9	4.8	0.6	0.4	4.5
Japan	7.7	2.5	11.5	34.1	2.5
Europe	21.8	16.5	31.5	31.4	9.9
UK	9.8	8.6	12.6	11.5	5.9
US	56.4	65.6	43.3	21.5	74.9
Total	100.0	100.0	100.0	100.0	100.0

Source: Recap, Analysis CSES.

*Top 6 Countries/regions only.

Alliance payouts

The focus of this section has been on the geographic distribution of alliances by number. The Recap database also contains information about the financial size of alliances and related transactions, including mergers and acquisitions, where this information is publicly available. The financial structure of alliances can vary widely, and may incorporate equity investments and outright product purchases, as well as the more usual licensing arrangements. The dividing line between alliance and acquisition is not always clear. Nonetheless, we have filtered the database to remove mergers and acquisitions and similar transactions. The size of the alliance as reported, tends to be the total lump sum including upfront and milestone payments, so it is at best indicative. The data in Table 3, shows for each of the top 6 countries/regions, the total alliance payments to and from each country, as developer and client respectively.

While the results should be regarded as indicative only, Table 3 provides confirmation of a number of the industry features evident from the analysis of the number of alliances. The first is the importance of the US both as a client (source of funds), 52% of the total, and as a receiver of funds to develop new product and technology, 69% of the total. The second is the role of Europe as a client, particularly for US technology and product. There is a very substantial imbalance between European 'purchases' (\$11.7b) and supply (\$5.6b). More detailed analysis of this data, indicates that European companies 'spent' about \$7b over this period on US products and technology. Much of this comes from the major European pharmaceutical companies engaged in alliances with US biotechs.

Table 3. Alliance Payments by Top 6 Countries, 2001 to 2003

Country	Client		Developer	
Australia	185	0.5%	284	0.8%
Canada	834	2.2%	2095	5.6%
Europe	11749	31.4%	5644	15.2%
Japan	703	1.9%	21	0.1%
UK	4321	11.6%	3329	8.9%
United States	19597	52.4%	25834	69.4%
Total	37389	100.0%	37206	100.0%

Source Recap, CSES.

The table would suggest that Japan is a small player in funding alliances, but it could also reflect the different disclosure policies of the Japanese companies involved. The role of Canada, and to a much lesser extent Australia, as a net recipient of alliance funding is also shown in the table. Canadian companies attract support from a wide variety of large and small pharmaceutical companies as well as biotechs.

Alliance technologies

As previously discussed, technology transfer is a fundamental reason for alliance formation. The Recap database includes alliances formed for a variety of purposes, ranging from technology to manufacturing, distribution and marketing. Those with a technology focus are classified according to over 50 types of 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 methodologies such as monoclonal antibodies, oligonucleotide ligands, peptides and stem cell therapies.

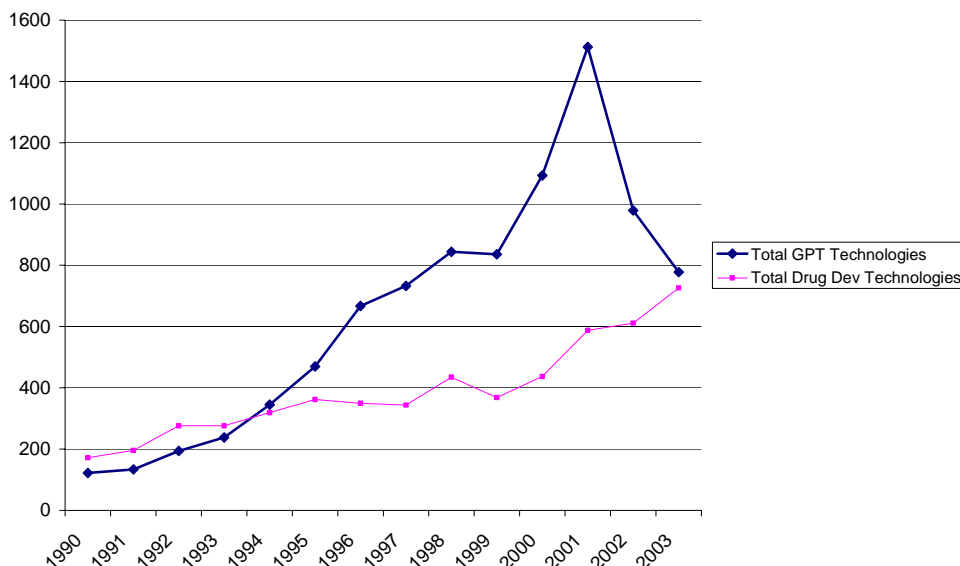
The formation of alliances focussing on particular technologies may to be a good indicator of the rise and fall in interest in new technologies. For instance, the number of genomic related alliances rose rapidly in the late 1990's. Alliances involving proteomics and bioinformatics are a feature of those formed in the last year or two. The charts below illustrate these trends and highlight in particular the rise in importance of alliances involving platform technologies. To focus on platform technologies we have divided the technology alliances between those relating more to platform technologies and those concentrating on drug development methodologies.

The trends in alliances related to these two types of technologies are shown in Fig 5. While the so-called 'drug development' alliances have exhibited steady growth over the period (11.7% pa), the number of GPT alliances grew spectacularly in the period to 2001, 25.7% pa. The decline in the number since then appears to be equally dramatic. This is associated with the apparent decline in interest in genomics related alliances. However, given the earlier qualifications about the timeliness of the data, this could in part be due to the absence of yet to be included alliances in the database.

In analysing further the growth of GPT related alliances, two phases may be identified. During the early phase, 1990–1996, alliances were formed to exploit the application of new technologies, such as screening, combinatorial chemistry, and micro assays, to the drug discovery and development processes. Most of these alliances (about two-thirds) were formed between pharmaceutical companies and

biotechs. This helps explain the growth in alliances between pharmaceutical companies and biotechs over this period shown in Figure 3.

Figure 5. Number of Alliance Technologies: GPT and Drug Development, 1990 to 2003



* Each alliance may have more than one technology.

Source: Recap Feb 2004, CSES.

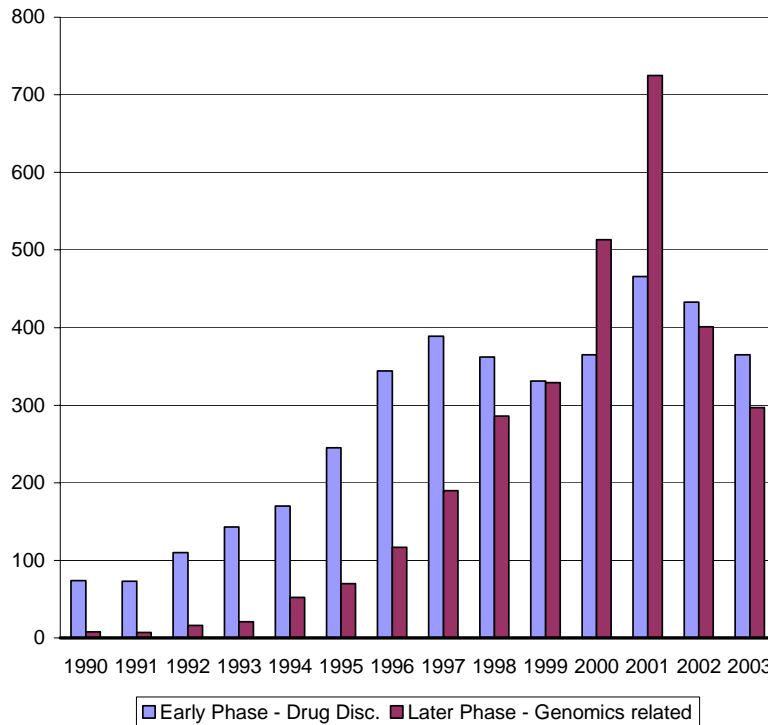
The later phase, 1998–2003, coincides with the focus on the application of genomics and related technologies to the development of the drug discovery process and to the development of related products and services. In this phase the majority (about 60%) of alliances were formed between biotechs, rather than with pharmaceutical companies.

The two phases are illustrated in Figure 6. The first shows the number of alliances formed involving screening, microarrays, combinatorial chemistry, immunoassays and drug delivery. The alliance formation activity grew rapidly from 74 in 1990 to 389 in 1997. It then plateaued for the remainder of the period. The second phase consists of genomics related technologies and includes gene expression and sequencing, bioinformatics and pharmacogenomics. Commencing in mid 1990's alliance formation involving these technologies grew from 21 in 1993 to 725 in 2001. In addition to the rapid growth of general platform technologies, Figure 6 shows the less rapid, but nonetheless steady growth of what are described as drug development technologies or methodologies. The focus of such alliances is on a particular target or lead technology, such as monoclonal antibodies or oligonucleotides. Over the course of the period the parties to these alliances changed from being predominately between pharmaceutical and biotech companies in the 'early' phase, to becoming mostly between biotechs in the 'later' phase.

The next section of this paper attempts to explore further the roles and objectives of biotechs, through an analysis of their business strategies, undertaken using SEC 10K reports and other company material. In particular the purpose of the next section is to return to some of the issues raised in the theoretical literature about

the role of product biotechs and GPT companies in the markets in product and technology.

Figure 6. Two Phases of Technology Adoption by Alliance Formation, 1990 to 2003



Source: Recap Feb 2004, CSES.

Biotech value chains

This section reports on one aspect of some broader work being undertaken to define the business models of the various pharmaceutical industry participants. One of the issues raised earlier was a suggestion that the industry was dividing between upstream developers of specialist technologies and new products, and downstream users and funders of these products and technologies. In this model alliances perform a key role by providing the mechanism through which this technology transfer takes place – a mechanism which permits the parties to trade without creating the diseconomies that would otherwise lead to vertical integration.

The upstream developers in this model are the product biotechs, which specialise in producing new drugs for the pharmaceutical company product pipelines, and GPT companies, focussing on new technologies that address broader issues of pipeline productivity improvement. 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.

An alternative interpretation of the current alliance structure between the product biotechs and pharmaceutical companies, is that the biotechs are using the alliances as a temporary funding mechanism, while on a development path toward the fully integrated pharmaceutical company model. Similarly, the GPT companies may

be providing access to their technologies on a fee for service basis in order to help fund their own drug development programs.

Analysing the value chains of these companies provides some evidence to determine which of these two models the companies themselves are seeking to pursue. In this exercise, the 2003 10K report for each of 150 US listed biotechs was reviewed to identify the activities being undertaken by each biotech as part of a simplified value chain. The following elements of the value chain were identified:

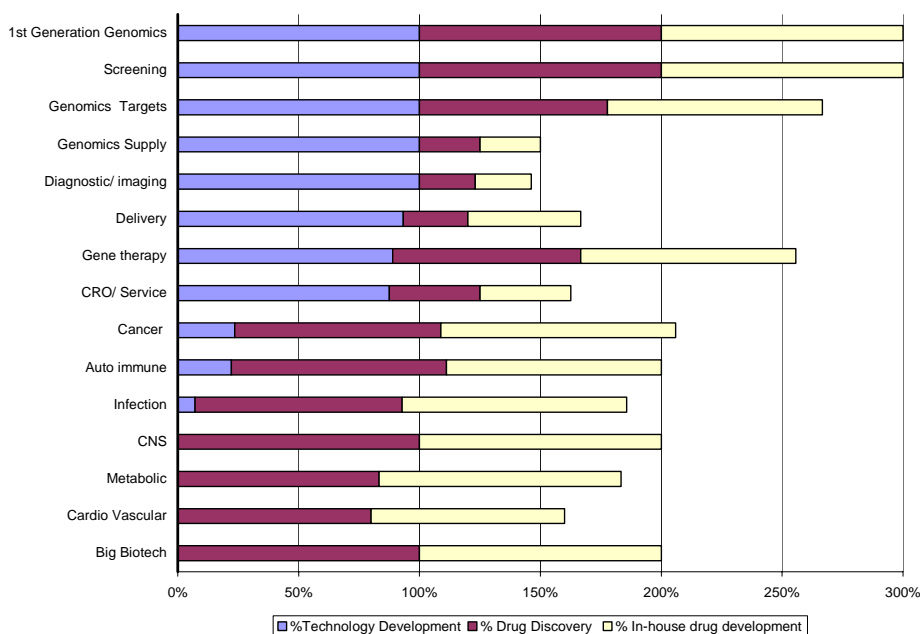
- Drug discovery
- Drug development – in-house and contract
- Platform technology development
- Clinical trials – in-house and contracted
- Manufacturing - contract and in-house
- Distribution – own marketing team

The focus of this analysis is on the first three activities and particularly on whether the drug discovery and development activity is only under contract or also ‘in-house’. By ‘in-house’ we mean that such activities are funded internally, rather than on behalf of another party under contract or through an alliance. Undertaking platform technology development is interpreted to include any such technology made available to other biotechs or pharmaceutical companies. It includes new drug discovery and development 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.

The biotech companies have been classified by Recap according to their main purpose, eg principal therapeutic focus or main platform technology being sold or under development. The SEC requires each company in their 10K report to make a complete statement of its business strategy and activities, as well as provide comprehensive financial reports. A typical 10K report is of the order of 100 pages. Companies are required to report in a format useful to investment analysts.

Each company 10 K report was reviewed to determine the value chain activities in which each company was engaged. At this stage of the analysis, the focus was on recording whether a company engaged at all in any of three value chain activities – technology development, drug discovery and in-house drug development. Each company was classified, using the Recap classification, to one of the technology/therapeutic types listed in Figure 7.

Figure 7. Percentage of Companies in each Value Chain Activity by Company Category



Source: Recap, SEC 10K reports, CSES analysis.

The proportion of companies undertaking each of the three value chain activities, technology development, drug discovery and in-house drug development, in each Recap category, are shown in Figure 7. For instance 100% of the companies classified as ‘1st generation genomics’ were found to be engaged in each of the three value chain activities. In contrast, while all of the genomic supply companies were engaged in technology development, only a small proportion were engaged in either drug discovery or development. Indeed all of the company classifications that would be regarded as GPT companies had a high proportion engaged in technology development. However many of the companies engaged in these GPT categories were also engaged in drug discovery and development. For instance a high proportion of companies, classified as 1st generation genomics, screening, genomic targets and gene therapy, were also involved in drug discovery and development, as well as technology development.

On the other hand biotechs classified by therapeutic area (product biotechs), had little involvement in technology development. Only those classified as ‘cancer’ and ‘autoimmune’ biotechs had a significant proportion of companies involved in technology development (about 20%). So in this sense, the separation between the activities of GPT companies and product biotechs is quite clear. GPT companies are engaged in platform technology development, while product biotechs are not.

However Figure 7 indicates that of those classified as product biotechs most are engaged in in-house drug development, indicating that few are specialising as ‘contract drug developers’. These results for individual company categories are summarised in Table 4 for GPT and product biotech companies. The results indicate that most companies conduct a mixed business strategy.

Table 4. Proportion of Companies Engaged in each Value Chain Activity

Category	Drug discovery	In-house drug development.	Technology development
GPT	53%	60%	96%
Product biotech	86%	95%	15%

In addition to platform technology development, a large proportion of GPT companies (60%) are also engaged in in-house drug development. Equally, 95% of product biotechs are engaged in in-house drug development. This means that neither the majority of GPT companies nor the vast majority of product biotechs are willing to rely exclusively on fee for service, technology sales or contract revenues for their the longer term business revenues. Most are attempting in the longer term, to develop a drug from which they hope to receive substantial revenues, enabling them to make the transition to a fully integrated company. Of the companies included in this analysis six ‘big biotechs’ have made this transition.

Although the majority of GPT companies appear to be adopting a ‘mixed’ strategy, some 40% remain GPT only specialists at this stage. It is beyond the scope of this paper to provide a detailed analysis of this group of companies, but as might be expected they include GPT companies, such as Qiagen, Affymetrix and Nanogen, with well defined GPT products. Consideration of the sustainability of these business strategies is the subject of ongoing work.

This evidence indicates that the model suggested by Arora, Fosfuri and Gamberdella (2001), that the biotech industry is consolidating ‘toward a structure in which an upstream industry of specialised technology suppliers has become a *stable* (my emphasis) source of new products and technologies....to the downstream producers’, may not in fact emerge. It is the stated intention of most GPT and product biotechs to adopt the fully integrated company model and their comprehensive engagement with the value chain suggests that they are devoting resources to this end.

There are a number of new developments that may give them hope of success. Firstly a higher proportion of new drugs being approved by the FDA are biotech therapeutics –about 50 % in 2003 compared with only about 25% in 2002 (Van Brunt 2003). Secondly, there is an expectation that biologicals will have a lower development and approval time, because they target smaller patient groups. From our review of the biotechs’ 10K reports, there is a note of desperation in the conduct of their strategy, to retain ownership and develop the maximum number of drugs, while selling only what is necessary to stay afloat.

Conclusions and Implications

The theoretical literature provides powerful reasons for both the development of the fully integrated pharmaceutical company and the emergence of the specialist product biotech or GPT company. The integrated model follows from transaction cost economics, that firms seek to eliminate the diseconomies of market transactions by conducting such transactions in-house. On the other hand, the resource based view provides a rationale for the emergence of the path dependent, knowledge intensive, flexible, specialist biotech or GPT companies. These two somewhat competing models of the firm, are to an extent reconciled by the special qualities of an alliance,

which retains many of the advantages of contracting out, while providing a flexible structure in which to manage the inevitable diseconomies.

The empirical research presented in this paper provides ample evidence of the growth of the alliance, as a vehicle for achieving technology and product transfers between large pharmaceutical companies and specialist biotechs, as well as between biotechs. Alliance formation appears to be highly responsive to the need for the transfer of new technologies, as is demonstrated by the growth (and perhaps decline) of genomics related alliances. Alliances have also successfully bridged national boundaries and are an important mechanism for the development of a global innovation system. In particular international technology transfers provide other countries with access to US technology, and supplement US and European pipelines with foreign sourced product.

What is less clear is whether the specialist firms can form a stable relationship with one another and with the large pharmaceutical companies. The business strategies of many such firms indicate that they feel that such an upstream supply arrangement is not viable in the long term and that they need to develop their own drugs to achieve satisfactory long-term revenues. Although not much discussed in this paper, the large pharmaceutical companies, while retaining their powerful position as supply chain integrators, are known to have product pipeline deficiencies, and the product biotechs, have been helping to meet these deficiencies. Their role may be further enhanced by the shift to personalised medicine, which is more likely to be served by niche, rather than mass marketing, in which large pharma excels. In these circumstances perhaps the balance may shift in favour of the biotechs, so that alliances with large pharma do provide a viable, longer-term model for specialist biotechs. However it would certainly seem premature to suggest that these factors are prescient of the break-up of the fully integrated pharmaceutical company model.

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