The Role of Pharmaceutical Alliances

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Introduction

Alliances in business have a long history, but over the past couple of decades they have become an important feature of business organisation to such an extent that Dunning, a prominent researcher of multinational enterprises since the 1950's, has described this new trend which gives increased emphasis to cooperation as well as competition between firms as 'alliance' capitalism. In his view this has been brought about by globalisation and a series of landmark technological advances (Dunning 1995).

The pharmaceutical industry provides a good example of these developments. It has been subject to rapid technological change and significant restructuring. Pharmaceutical companies have been a prominent agent of globalisation, partly through international mergers but just as importantly in establishing global sales programs for their products. In addition the pharmaceutical industry, in which R&D is a core activity, has experienced breakthrough technological advances in biotechnology.

Dunning outlines five reasons for the growth of alliances arising from the impact of technological advances, several are particularly relevant to the pharmaceutical industry. 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.

Breakthrough advances in biotechnology has had a significant impact on core pharmaceutical technologies. Bioinformatics has resulted from the convergence of the distinctive technologies of biotechnology and IT. The impact of the shortening of the market exclusivity period has been to effectively truncate the product life of many new drugs. This both increased the pressure for additional drugs from pharmaceutical company product pipelines and intensified the search for new compounds from the biotechnology companies. The alliance framework seems an obvious structure to satisfy the objectives of the research rich but cash poor biotechs and the better resourced but discovery hungry pharmaceutical companies.

Accordingly academic consideration of pharmaceutical alliances has focused on strategic technology partnering (see for instance Narula and Hagedoorn 1999) between the funder of R&D typically a large pharmaceutical company and the biotech or university suppliers of technology.

In the view of Arora and Gamberdella (1990) technology alliances arise as a the result of:

> 'The increasing complexity and multi disciplinarity of resources required for innovation, and of the stock of knowledge itself [which] tend to make technological innovations the outcome of interactions and cooperation among fundamentally autonomous organisations commanding complementary resources.' (p. 362)

Alliances had become such a feature of technology driven industries that in a more recent paper (Arora et al. 2000) remarked on the rise of 'markets for technology' in which smaller high tech firms supply specialised technologies to larger established companies using various forms of alliance structures.

The framework of incomplete contracts has been used to examine technology alliances (see Aghion and Tirole 1994) in which the relationship between a research unit and a customer for the research is analysed. 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 research capability – a position increasingly found in the pharmaceutical industry.

Lerner and Merges (1997) 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 the Aghion and Tirole framework, is that the biotechs ceded the greatest proportion of the control rights when their financial position is weakest. The study also examined which party was likely to control particular aspects of the alliances. This indicated that the pharmaceutical company was most likely to control the marketing and manufacturing aspects as well as the power to terminate the alliance. The biotech was more likely to retain control over the patents and related litigation.

While this work undoubtedly offers important insights into the nature of pharmaceutical alliances, there are some possible difficulties with this analytical approach. The first is that alliances are formed for many reasons, not just to transfer technology.

Reflecting this the OECD has defined alliances in the following terms:

> '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.' (OECD 2001)

Two surveys of alliances published in the early 1990's reported that while sales and marketing alliances were 41% and 38% of all alliances respectively, R&D alliances accounted for only 11% and 13%. (Narula and Hagedoorn 1998). Indeed it might be expected that R&D activities would be too cloaked in secrecy, the IP considered too valuable, to trust to collaborative arrangements. The fact that R&D alliances appear to

have grown rapidly since the 1980s indicates that some of these inhibitions have been overcome.

Moreover alliances are occurring within a broader context – one in which global firms have been shedding 'non core' activities along and between their value chains as they concentrate on their 'core' competencies. Large multinational companies, which for decades have pursued various types of integration strategies, have found defining the boundary between core and non-core functions a difficult process. It has required careful consideration of the advantages and disadvantages of outsourcing each function. Large global pharmaceutical companies have been as involved in this evaluation process as any of the large corporations. It 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 and that, not only research, but other functions such as sales and marketing should be outsourced using alliance and other structures (Kay 2001).

For all these reasons this study adopts a broad definition of alliances. It is important in considering Australia's future role in the global pharmaceutical industry that while technology development and transfer is an important part of the industry's development path there may be other potential roles for Australian capabilities potentially facilitated through alliance structures.

The second 'complication' with the alliance model between large pharma and small biotech is that as will be shown in this paper the most rapid growth in alliance numbers has been between biotech companies rather than between pharmaceutical and biotech companies. This paper will examine the different features of these two types of alliances.

This has particular relevance to the Australian situation. Despite lacking global scale pharmaceutical companies, indigenous concerns such as CSL, Faulding etc have taken on increasingly international roles through alliances and other arrangements. At the same time a number of indigenous biotechs, some listed on the Australia Stock Exchange, have emerged owning the patent to a new compound of potential interest to the global pharmaceutical industry. To transform the patented discovery to a marketable drug requires a daunting amount of money and expertise (Di Masi 2001) which is likely to be beyond the capabilities of the Australian firms and capital markets. Accordingly alliances with global players represent the prime development path for Australia's fledgling biotechs and research institutes.

Geographically the Australian industry is far removed from the centres of pharmaceutical and biotech research activity, namely the United States and Europe. Are alliances with international companies realistic given this remoteness? A study of research collaboration in the Swedish biotechnology / pharmaceutical sector (McKelvey, Alm, Riccaboni 2002) is encouraging. Although Sweden has a more significant and longstanding pharmaceutical industry than Australia – two of its pharmaceutical companies have only recently participated in international mergers to form Astra Zeneca and Pharmacia, the

study shows that research collaborations on a firm-to-firm basis tend to be international while the links between firms and universities tends to be more strongly local.

The purpose of this paper is to provide a broad overview of the extent and nature of alliances. It seeks to answer some basic questions about alliances. Are alliances as extensive as the discussions and anecdotal evidence suggests? How have their number and character changed over time? Who are the participants? Are the most common alliances between big pharma and little biotech? How are they structured and how much money is involved? Is licensing the main game or are there other aspects of structuring alliances that are important? Are alliances concentrated in particular kinds of technologies or therapeutic groups? How do Australian alliances compare with the patterns in the rest of the world? Does it seem realistic to expect Australian companies to develop their operations through alliance formation?

ReCap Database

The work on alliances has been assisted by a number of commercial databases that have been established to facilitate alliances by providing potential partners with detailed information about previous alliances (see www.recap.com, www.windhover.com and the MERIT CATI database at www.nsf.gov/sbe/srs/seind00/frames.htm pp. 2-56, 57) These databases provide valuable historical information about the alliances – their nature, the types of parties involved, their value and their purpose.

This paper reports on the analysis of one such database established by Recombinant Capital (ReCap)[1] which has been used by both academics (Lerner and Merges 1997; Tapon and Thong 1999) and financial market participants (e.g. Lehman Bros) as a source of comprehensive information about pharmaceutical alliances. ReCap was chosen because of its focus on pharmaceutical and biotechnology alliances, its accessibility and flexibility.

Alliances in ReCap are broadly defined and include asset purchases and acquisitions as well as partnerships that involve licensing, joint ventures joint development, distribution, marketing and manufacturing. While acquisitions and asset purchases may fall outside the OECD definition of an alliance, their inclusion in the database is helpful in gaining a complete picture of corporate realignments. The database includes information about alliances that involve biotechs, pharmaceutical companies and universities (including research institutes). It is particularly concerned with alliances involving biotechnology

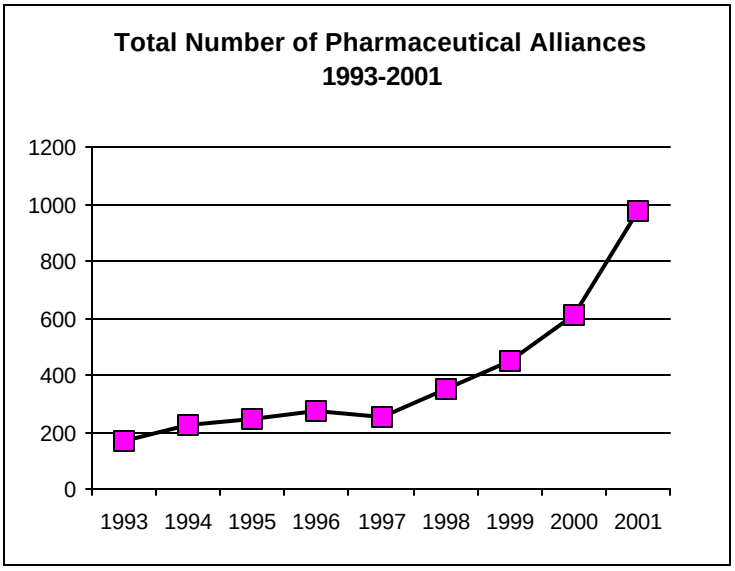
[1] The ReCap database was established in 1988. It attempts to collect comprehensive, worldwide alliance information from press releases, SEC filings and company presentations. The information is limited to those alliances that are announced publicly and the details that those announcements contain. Sometimes this means that the more commercially sensitive information is withheld. On other occasions information is not reported until there are some positive results. For these reasons the information must be regarded as indicative and not necessarily comprehensive. However public disclosure rules generally require listed companies to announce information which is price sensitive. In other cases companies find it in their interests to release information about alliances as a sign of progress towards their strategic goals. For this reason it can be expected that information about most significant alliances is released and therefore available to ReCap.

companies, but also collects information about alliances between pharmaceutical companies and with relevant medical device companies.

Alliances are categorised in various ways: nature of the alliance, parties, size ($), purpose etc. Typically the source material eg press release is also available on the database so that details of the alliance can be readily obtained to illuminate an aspect of the classification or other alliance details.

Number of alliances

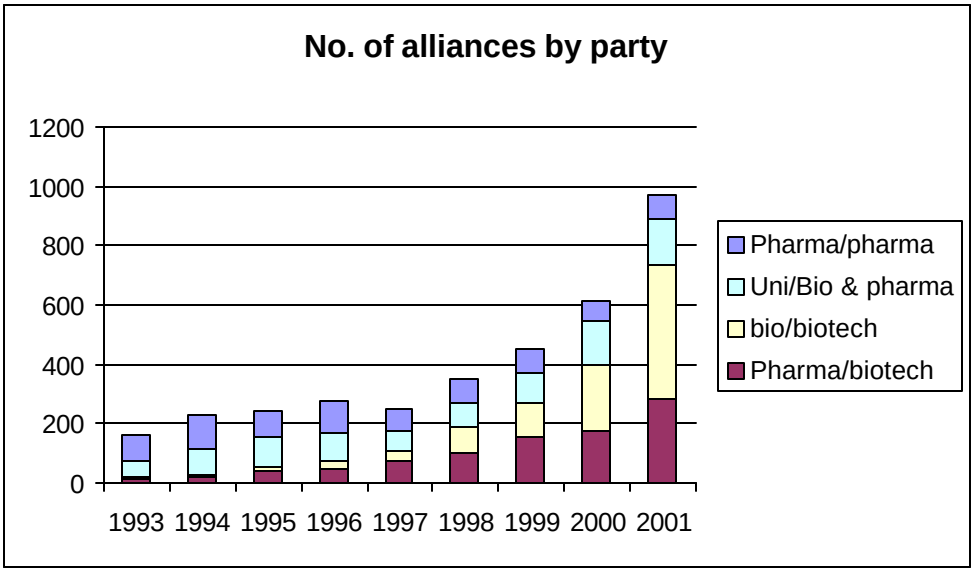
While pharmaceutical alliances have been under discussion and academic study for more than a decade it is only in the last few years that their number has increased to a significant level. The number of alliances has increased almost fourfold since 1997. The largest increase, 59.4% has occurred in 2001 to about 1000. For the large pharmaceutical companies this means entering into one new alliance about every month, although one company, Glaxo was on average announcing two new alliances every month in 2001.[2]



However as the next chart shows, for every one new alliance announced involving a drug company, there were in 2001 more than twice that number involving biotech companies. By far the largest single category of alliance and the fastest growing was between biotech companies. Until 1997 this had been an insignificant category. The majority of alliances were with universities or between pharmaceutical companies. From 1997, alliances involving biotech companies grew rapidly to dominate in numerical terms. Alliances by

[2] As mentioned above other databases (eg MERIT and Windhover) collect information about alliances from public announcements. Attempts to cross check the results from the Recap database are frustrated by conflicting definitions and limited public access. The information that is publicly available from these other sources appears to confirm the broad order of magnitude of the Recap results and also, to the extent that recent data are available, the strong increase in alliances in 2001. However where differences appear to emerge is that these other sources suggest a higher number of alliances in the mid 1990s.

contrast between pharmaceutical companies declined. Even those involving universities showed little growth, perhaps suggesting that increasingly biotech companies are taking on the role of commercialising university research.



Trends in alliances in Australia

The trends in the number of alliances and the parties involved appear to be remarkably similar to 'global' trends reported above.

The ReCap database does not provide details of the nationality of the alliance parties. To gain a picture of the position for Australia a list of potential parties was compiled based on the biomedoz.com.au database of Australian owned biotechs and research institutes supplemented by any missing listed biotechs taken from the Deloittes Biotech Index. This was tested for completeness against a number of other directories. The total list was 205 companies, institutes, universities and major hospitals. Each name was searched on the ReCap database. As a result, 143 alliances were identified. This includes pre-1993 alliances but excludes several concerned with veterinary applications.

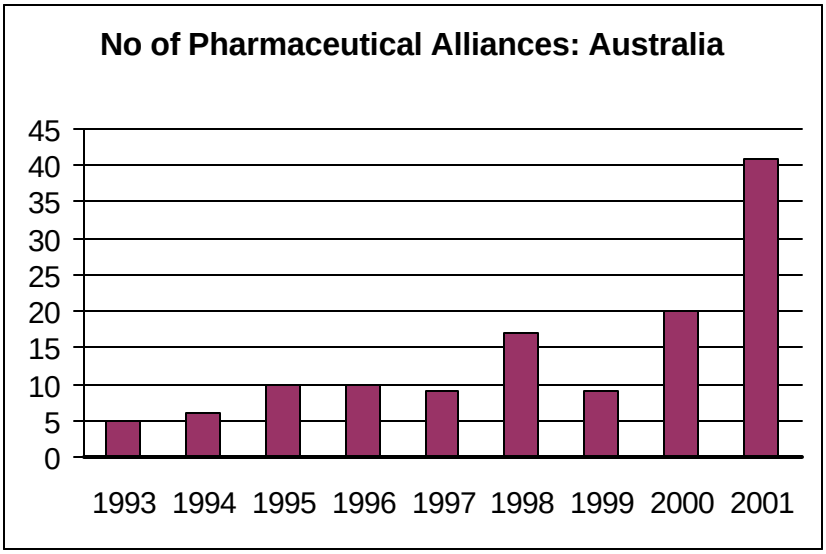
The same qualifications apply to this Australian list as for the 'global' one. It includes only announced alliances. While doubtless many alliances remain secret there is nonetheless the same pressure to report progress and for listed biotechs to release price sensitive information under the 'continuous disclosure provisions' in Australia as in the US and other countries. As discussed above the database may have a US bias because SEC filings are a major source of alliance information.

Nonetheless the ReCap sourced list seems to be remarkably complete when checked against Australian biotech company web sites for alliance information. A search through

archival press releases on these sites failed to turn up any significant missing alliances. A couple with universities had been not been included.[3]

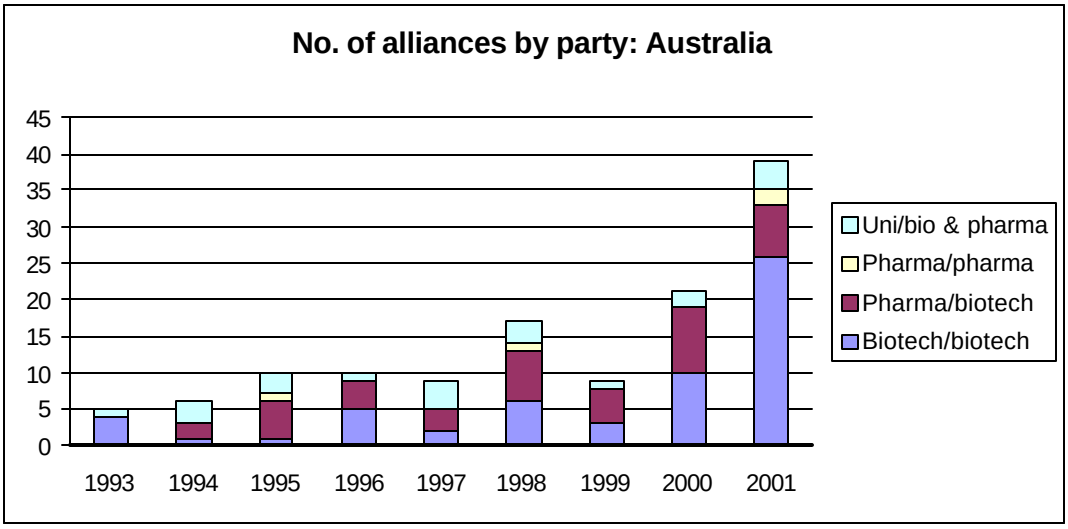
As for the total alliance chart above the number of alliances involving Australian parties grew rapidly in 2001. The 40 alliances recorded in the 2001 is many times the level of the early 1990's. As for the total number of alliances, the last two years and the late 90's were very active in terms of alliance formation.

Compared with the total database of almost 1000 alliances in 2001, 40 is a modest total. Nonetheless it is higher than that based on our share of world GDP and demonstrates encouraging activity levels in the biotech sector.



In parallel with overseas trends, Australian alliances were predominately driven by biotechs. Given the limited number of local pharmaceutical firms – it is not surprising that few alliances have been between pharmaceutical companies. However as in the United States alliances between pharmaceutical companies and biotechs have remained at relatively low levels. Alliances with universities (including research institutes) have also remained at modest levels.

[3] Research collaborations with universities may be more generally understated in the Recap database because they may not warrant a press release. Information on company web sites tends to suggest a larger array of research collaborations than turns up in company press releases. Presumably the failure to specifically announce these collaborations is due to their preliminary and exploratory nature.



Although over 200 Australian organisations were surveyed on the ReCap database only a small number had a significant number of alliances recorded. Those with the largest number are set out below.

Organisation	Alliances listed on ReCap
Faulding (incl. Soltec)	29
Amrad (incl. Cerylid)	24
Proteome Systems	16
Biota	12
CSL	10

Source: ReCap February 2002.
Note: Some joint alliances double counted.

Several companies not included above have been very active in the last year or two. These include BresaGen (6), Axon Instruments (7) and Agen Biomedical (9, 4 in two years).

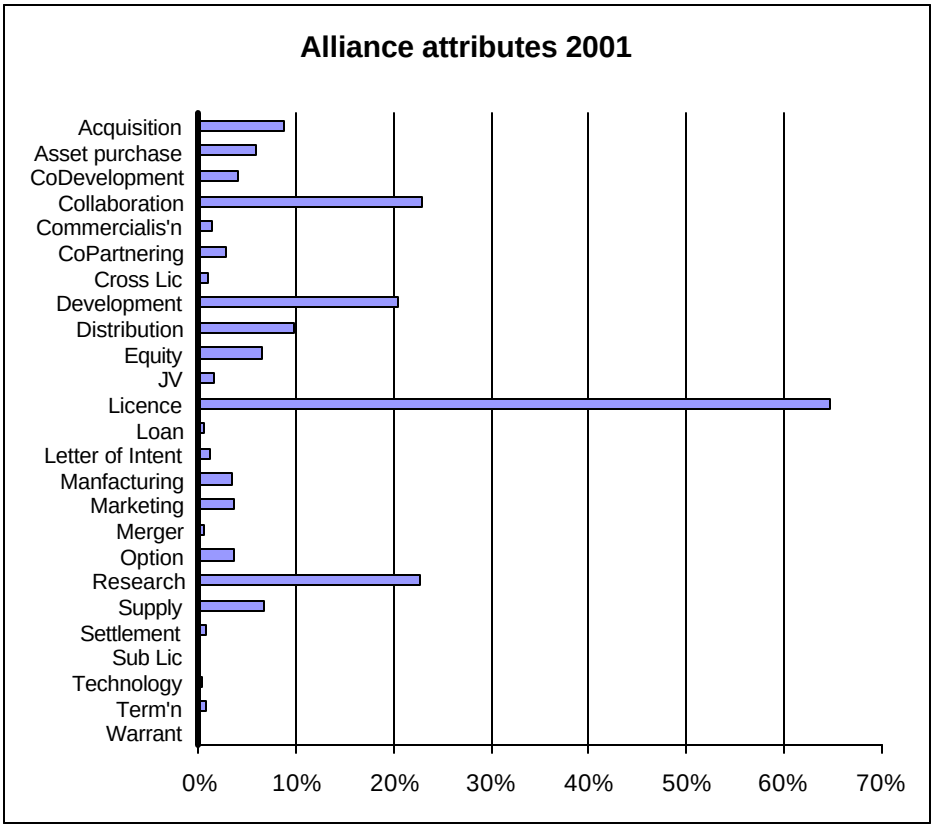
The Nature of Alliances

The ReCap database categorises the characteristics of each alliance announced according to about 30 attributes. These include licensing, research, development, distribution, marketing, merger, asset purchase and acquisition. Each alliance may be categorised as having a number of these attributes. The more complex alliances for instance may involve some combination of licensing, distribution and an equity injection.

By far the dominant attribute as shown below is licensing. About two thirds of alliances contain some form of licensing. Research, development and collaboration are also important.

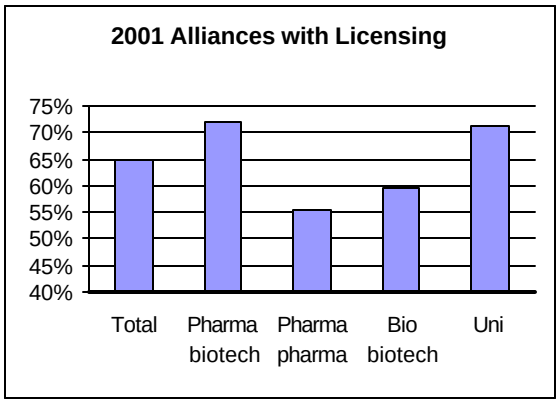
As previously discussed, the inclusion in the database of acquisition and asset purchase transactions may go beyond the common concept of an alliance. An acquisition may in

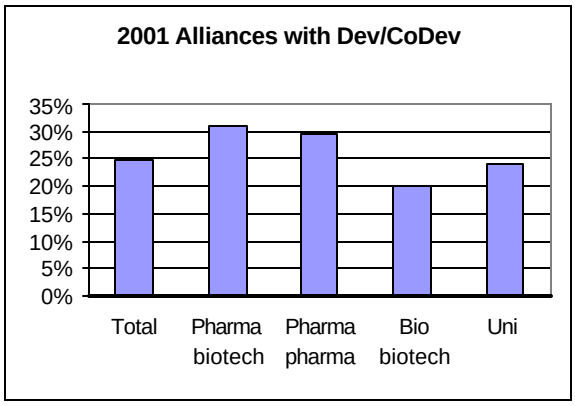
fact be the termination of an alliance and its substitution by ownership. However it is also a matter of degree as to when an equity injection, as part of an ongoing collaboration, becomes an acquisition. For completeness it is useful to have these transactions in the database. Nonetheless for some purposes, e.g. the payout analysis below it is preferable to exclude such transactions.



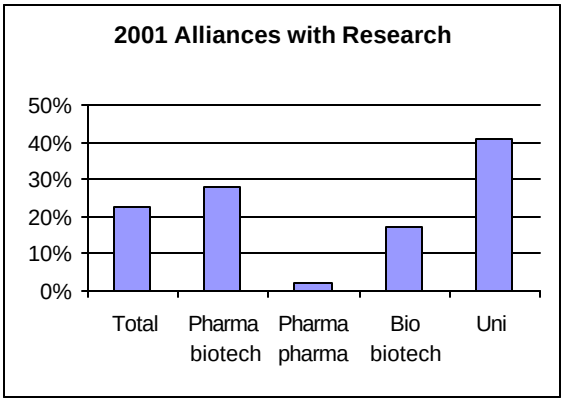
Many of the licensing arrangements concern new compounds. For instance Xenova and Millennium announced in December 2001 a licence agreement to develop Xenova's molecules for cancer treatment that had entered Phase 1. Millennium would acquire development and marketing rights in the US in return for a payment of US$11.5m. Others involve licensing arrangements for new technologies and information. For instance, Proteome Systems entered into an agreement with Johnson & Johnson to provide access to its newest databases for human genome research.

Alliance structures reflect the objectives of their partners. Although licensing is the dominant aspect of alliances, this varies between the parties. For instance alliances between pharmaceutical companies and biotech have a greater tendency to contain licensing arrangements (72%) than those between one pharmaceutical company and another (55%) or between biotechs (60%). Drug development has a greater tendency to drive alliances with pharmaceutical companies than between biotechs as charts below illustrate.





Alliances with universities not surprisingly are more likely to contain a research component (40%) than those between other parties. Such alliances also have a high proportion (36%) of university alliances described as involving collaboration.

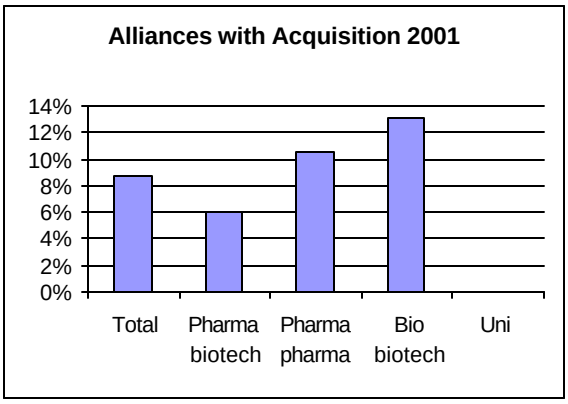


These charts begin to provide a guide to what motivates biotechs and pharmaceutical companies to enter into alliances compared with the drivers of alliances between biotechs or between pharmaceutical companies. Pharma/biotech alliances are more likely to be motivated by drug development than biotech/biotech alliances. The alliance is more likely to involve licensing as well as an equity injection, distribution and marketing than alliances between biotechs.

For biotech/biotech alliances the key motivations are research, drug development and distribution. Most alliances involve licensing agreements. Interestingly of those involving manufacturing (34), about two thirds are between biotechs, doubtless indicative of the worldwide shortage of biotech manufacturing capability. One major point of difference is the number of biotech/biotech alliances involving acquisitions.

As discussed above information about acquisitions is also included on the ReCap database. The likelihood of such alliances depends on the parties involved. Given their high profile it could have been expected that acquisitions involving pharmaceutical companies may have featured in a higher than average share of alliances. However acquisitions of biotech companies by other biotech's had the highest per cent and by far

the highest number. In 2001, 59 alliances between biotechs involved acquisitions compared with the total of 85 for all alliance parties. This reflects the level of corporate activity in the biotech sector.



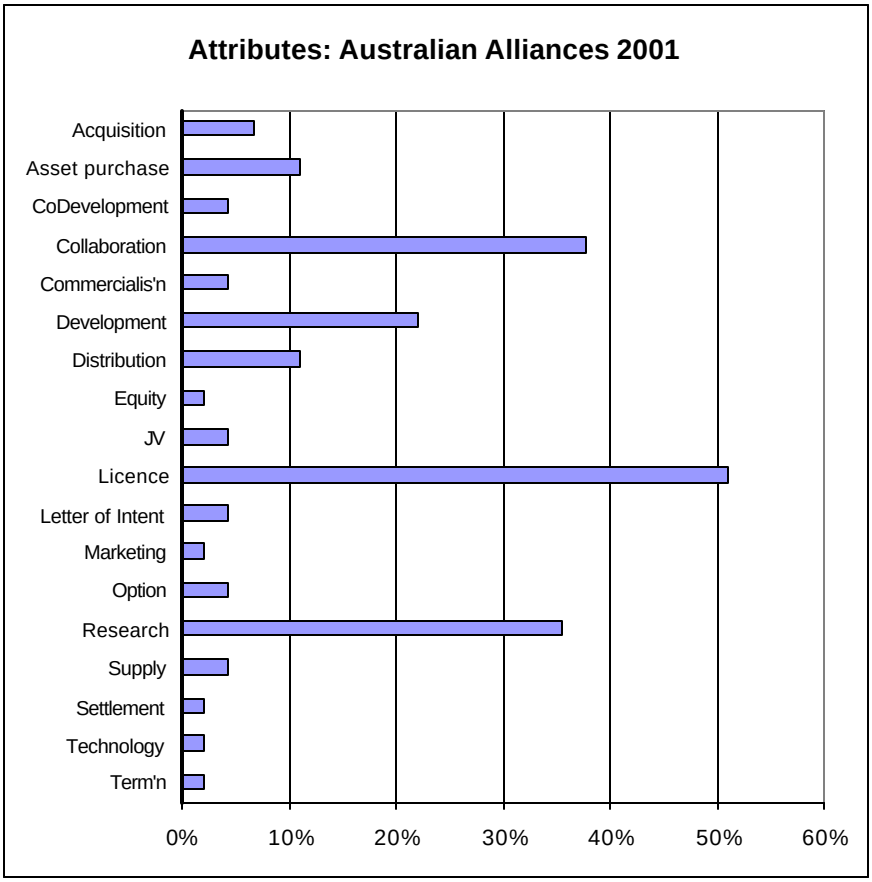
Australian alliance attributes

Perhaps reflecting the stage of maturity of the biotech sector in Australia, licences while prominent, featured in a significantly lower proportion of alliances than for the total database with only 51% of Australian alliances in 2001 involving licences compared with 65% for the total database. A check of earlier years indicated that this difference has been the case for some time. There were other signs of the relative immaturity of Australian alliances. The proportion involving early stage research and collaboration was higher in Australia and no alliances involved manufacturing.

One other difference was the higher proportion involving asset purchases and acquisitions. There was an abnormally high number of asset purchases and acquisitions in 2001. Faulding was involved in several of them, both buying and selling various product lines and part businesses in deals totalling over $1billion although one these did not proceed. CSL purchased the antibody collection and testing lab business from NABI and Biota purchased NuMAX Pharmaceuticals.

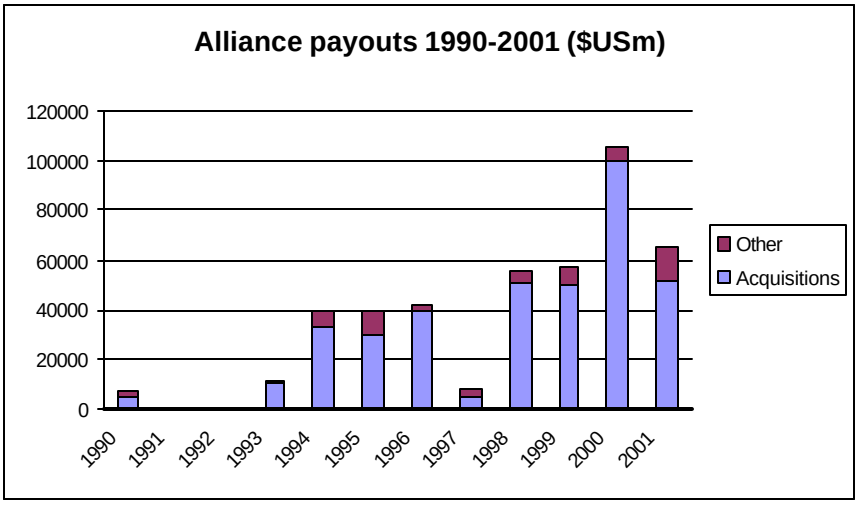
Otherwise there were strong similarities. The proportion undertaking research, development and distribution was about the same as the total database. This indicates that Australian companies and research institutes are participating in the global technology market place with a similar purpose as their peers in other parts of the world. The under representation of alliances with licensing is the greatest cause for concern.

Details of the Australian alliance attributes are shown in the chart below.

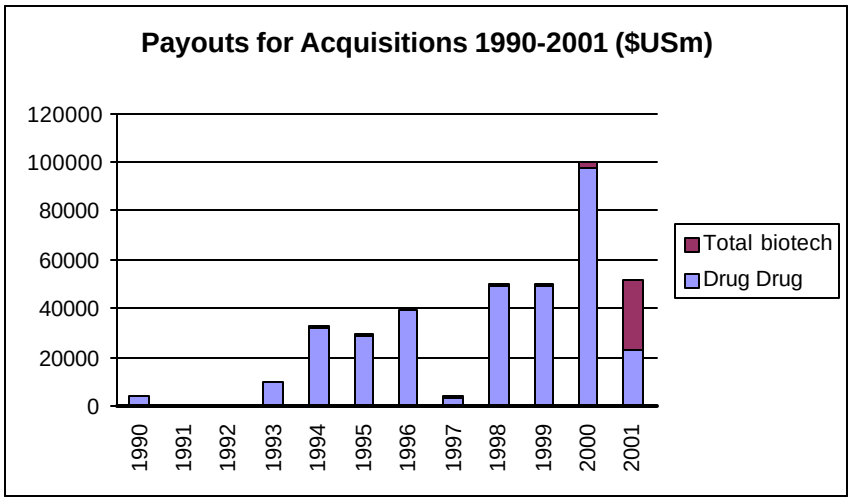


Alliance Payouts

The database provides information, where details are released, about the dollar value of the alliance. This may be a payment upfront for a licensing, marketing, or distribution arrangement or a payment for equity or outright acquisition. These payments are described by Recap as alliance 'payouts'. Not surprisingly payments made as part of acquisitions form the largest single component of alliance payouts as is shown by the chart below.

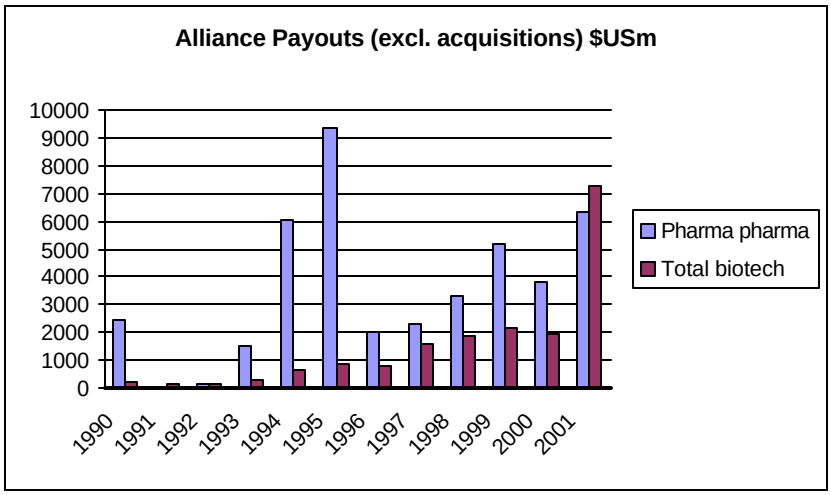


Up until and including 2000 the overwhelming majority of dollars spent on acquisitions was between pharmaceutical companies, the largest being the Pfizer merger/acquisition of Warner Lambert in 2000 totalling $US90b. However the character of acquisitions changed dramatically in 2001. More than half of the value of acquisitions involved biotech firms – between themselves or with pharmaceutical companies as shown in the chart below.



The largest biotech transaction is the announced acquisition of Immunex by Amgen totalling $16b, but there are many transactions exceeding $1b such as the $3.3b deal involving Medtronic and MiniMed and the takeover of Block Drug by Glaxo for $1.2b. Whether the 2001 experience represents a watershed or a one-off aberration only time will reveal, but the mixed fortunes of biotech companies and their need for partnerships provides a fertile ground for M&A activity.

The payouts for acquisitions however conceal the trend evident in the discussion above about the number of alliances and in particular the rapid growth in payouts involving biotech companies since 1997. By excluding the dollar value of acquisitions the increasing importance of alliances with biotech companies is revealed. As the chart below shows the size of alliance payouts involving biotechs has grown substantially over the last five years with those in 2001 particularly high. In other words the value of payouts give financial substance to the growth in the number of alliances announced.



Note: Also excludes payments to universities which are relatively small e.g. $95m in 2001.

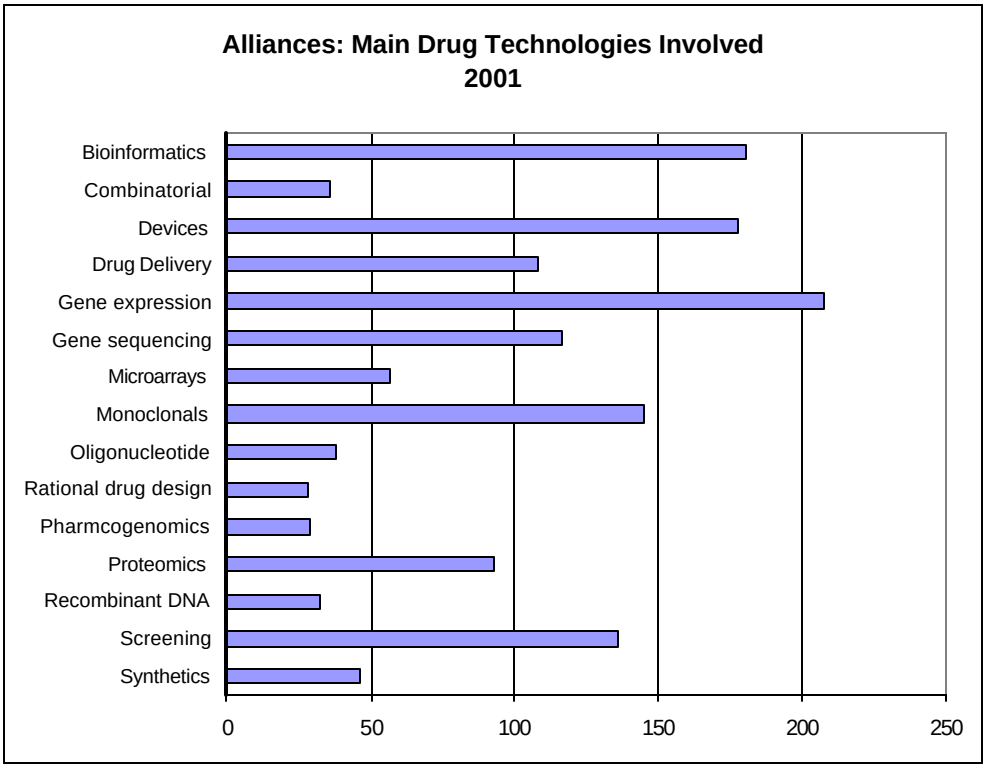
While the alliance payouts involving biotechs cover a broad range of types of collaboration – research, development, distribution etc, the payouts between the pharmaceutical companies, other than acquisitions, are for asset purchases – typically the purchase of a particular product line.

The number of Australian alliances with reported payouts was fairly small and therefore there is a need for caution in drawing conclusions. After excluding alliances involving acquisitions about 20 alliances reported alliance payouts totalling about $280m, generally in the form of licence fees and estimates of milestone payments made at the time of the alliance announcement. About 45% of this amount was for alliances between biotechs, with the proportion moving closer to 50% in 2001.

Alliance Technologies

It was suggested in the Introduction to this paper that one of the motivations for alliances is to gain access to new drug discovery and development technologies. The human genome project in particular has created firms with specialist sources of databases of information that can provide this on a commercial basis to other biotech and pharmaceutical firms. There are other technologies that can facilitate drug design or improving targeting. Others are supporting technologies. For instance gaining information (bioinformatics) is one of the fastest growing and most significant technology related reasons for entering into an alliance.

ReCap categorises alliances according to about 50 technologies. The database identifies the technologies involved in each alliance. As with other alliance attributes multiple technologies are possible for a single alliance. The main drug technologies involved in alliances for 2001 are shown in the table below. In addition to bioinformatics already mentioned gene expression and sequencing are both prominent. Various technologies relating to drug design are also important such as monoclonals.

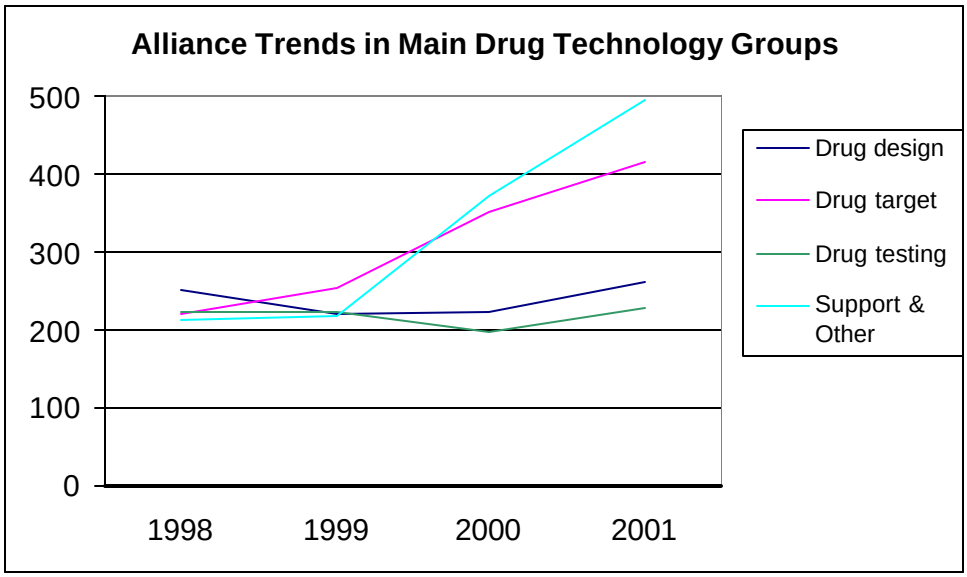


To gain an overall perspective of the recent growth in these principal drug related technologies, those above were grouped into four categories:

Drug target related	Drug design	Drug testing	Supporting and other technologies
Proteomics	Monoclonals	Combinatorial	Pharmcogenomics
Gene expression	Oligonucleotide	Microarrays	Drug delivery
Gene sequencing	Recombinant DNA	Screening	Devices
	Synthetics		Bioinformatics

As can be seen the four categories are indicative rather than prescriptive with a number of the technologies having applications in more than one category.

Alliances involving drug targeting and various supporting technologies have shown the most rapid growth over the last few years (see chart below). Supporting technologies include bioinformatics which has shown the most rapid growth. About 20% of alliances in 2001 involved bioinformatics. The category also includes alliances involving devices, some of which pertain to the drug discovery and development process, but in other cases involve less relevant diagnostic and other devices. The largest number of alliances involving drug targeting technologies are related to gene expression and sequencing – with about 20% of alliances in 2001 involving gene expression. In this category, alliances involving proteomics increased from about 10 in 1999 to over 90 in 2001. Overall the number of alliances involving drug testing remained fairly even through the period although alliances involving screening showed significant growth in 2001.



Conclusion

The results of this survey of the ReCap database indicate that while alliances have been much discussed for over a decade it is only in the last few years that they have grown to become significant in number. In 2001 about 1000 alliances were announced and recorded on the ReCap database compared with just over 600 in 2000 and the 200-300 recorded for much of the 1990s. This growth has been largely the result of the increase in the number of alliances entered into with biotech firms. The largest component of this growth was in alliances between biotech companies.

In terms of alliance attributes in 2001, 65% involved licensing arrangements, although it would appear that their purposes vary widely. Over 20% involve research, collaboration, or development, while 10% involve distribution. Only a small proportion involves equity or other payments.

The data suggests that alliances between pharmaceutical companies and biotechs are more serious business arrangements than those between biotechs. They are more likely than others to involve licensing and a higher proportion involve drug development, equity injections, distribution and marketing.

In this sense they are closer in form to those contemplated in the theoretical framework developed by Aghion and Tirole and tested by Lerner and Merges referred to in the introduction. However the framework appears to be less relevant to explaining the motivation and behaviour of the parties in the rapidly growing alliances between biotechs which appear not to involve large amounts of money, but where there are technological collaborations supporting advances in platform technologies.

Australian alliances, particularly given the small number recorded on the ReCap database, follow a remarkably similar pattern. There is some evidence however that they

are at an earlier stage of development to the average for the rest of the world. For instance a significantly lower proportion involve licensing (51% vs 65%).

An analysis of alliance payouts confirms the increasing importance of alliances with biotechs which was evident from the number of alliances. For much of the 1990s payouts (excluding those for acquisitions) were dominated by transactions between pharmaceutical companies. In contrast in 2001 payouts involving alliances with biotechs reached over $7billion exceeding payouts involving pharma/pharma alliances.

In terms of technologies involved in the alliances, those involving drug targeting and various supporting technologies particularly bioinformatics have shown the fastest growth. Of those involving drug targeting gene expression and sequencing is the most important. In the field of bioinformatics Australia is reasonably placed. Proteome Systems is prominent with 16 alliances recorded on ReCap.

The results presented in this paper indicate that the market place for pharmaceutical discoveries and technology through alliances is a significant part of the industry's development process and that its importance has grown remarkably in the last few years. Those Australian alliances listed on ReCap demonstrate a tentative participation in this marketplace by a small number of Australian biotechs and research institutes.

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