Development Paths for Australian Biomedical Firms

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Introduction[1]

The purpose of this paper is to examine possible development paths for Australia's indigenous biomedical industry. The Australian biomedical industry has a number of components. It includes some of the R&D and other activities of the major foreign owned pharmaceutical companies. It also includes some of the activities of Australian owned pharmaceutical companies. However, in terms of the number of companies, the largest component consists of substantially Australian owned companies undertaking drug discovery and development for human purposes and a further group of companies developing supporting technologies and other associated products and services. The focus of this paper is on the latter group of Australian drug development and technology companies although the section on alliances encompasses the broader range of activities of pharmaceutical companies in Australia.

With one or two exceptions the companies comprising the Australian industry are at an early stage of development. The development prospects of the total industry reduce to the choices made by these young companies on how they obtain the necessary resources and how successfully these resources are applied to transform their early stage product pipelines into marketable drugs and other products.

By improving our knowledge of development paths we seek to better understand how small companies grow and progress their product pipelines. Focussing on the growth and development of small Australian companies is not to ignore the role of large companies. Despite the increasing importance of the relatively small biotech companies, the largest 10-20 pharmaceutical companies have a pivotal role in determining the future direction of the global industry. The relationship between these large companies and small biotechs is a vital part of industry development.

There is one set of policy issues about how the early stage biomedical companies can be encouraged to grow. There is another distinct but overlapping set of issues about how to increase the involvement of large multinational pharmaceutical, or for that matter large biotech companies, in Australia. The subject of this paper however is an examination of some of the business growth strategies of small companies which sometimes coincidentally involves large companies.

The development paths for these companies are complex. They depend on the companies' stage of development, their chosen market segment, the market potential of their products and so on. The development path depends on a mix of business strategies generally chosen sequentially but sometimes concurrently. They encompass choice of technology, research focus, product development, recruitment of expert personnel, but also include decisions about how the

[1] The authors gratefully acknowledge the assistance of Dr Asoka Wetasinghe and Alison Welsh in compiling the company databases on which much of this research is based.

necessary financial resources and substantial external expertise are to be acquired. Drug development is a lengthy, complex, expensive and uncertain process. The marshalling of the necessary resources to undertake successful product discovery, development and distribution requires formidable resources and organizational capabilities.

The focus of this paper is on the business and financial rather than technical choices along the development path – capital raisings, alliance formation and other strategies to provide the immense resources required. The paper begins with a discussion of the drug development process followed by a review of the Australian industry and the state of development of its drug product pipeline. The next section explores development strategies chosen by Australian biomedical companies to date such as raising capital and forming alliances. Because of its importance, then follows a section on the nature of alliances formed by Australian biomedical companies.

New Drug Development Technologies

The Australian industry is in many ways a creature of the state of the global industry – for instance the high cost and uncertainty of drug development, the pressures to improve the productivity of the drug discovery and development process, the emergence of new drug development technologies including the growing importance of biotechnology etc. This section highlights the most important of these including an outline of the new technologies before introducing the principal elements of the Australian industry's capabilities.

The pharmaceutical industry differs from most others in that it is highly dependent on a small number of products with large markets and these products take at least 10-12 years to develop. The industry depends heavily on the size and quality of its research program, but the results of this research are often hard to predict. The research pipeline is subject to considerable failure at each stage. The cost of drugs to a large extent reflects the enormous research effort involved in their development, rather than the manufacturing costs which are usually minor in comparison.

Despite the size of the research program, there has been considerable concern over a number of years about the productivity of the drug development and pipeline both in terms of the number of new drug candidates being developed and their ultimate chances of success. A commonly cited ratio is that for every drug that is finally approved by the regulatory authority for sale, 5 enter Phase I testing, and 250 enter preclinical testing after 5,000-10,000 have been tested in the discovery stage (PhRMA 2001). For every 3 drugs that enter the market, only one will prove profitable, in terms of recouping its cost of development.

In addition, the traditional pharmaceutical industry, which has concentrated on the development of small molecular weight compounds as new drug candidates, has also seen the rise over the past 20 years of biotechnology companies which are developing drugs based on naturally occurring larger scale biological molecules.

The pharmaceutical industry has therefore been forced firstly to adopt new technology, including some of those that traditionally belong in the biotechnology industry, and secondly to acquire new drug candidates and drug discovery technologies, again often from biotechnology companies and research groups.

One reason put forward for the difficulties with research productivity is that the 'easy' disease targets have been addressed and that disease areas of unmet need, such as cancer and degenerative disorders, are less tractable to the traditional approach to developing drugs.

This forces companies to seek out research groups and innovative companies that are developing different approaches to discovering ways of treating disease.

An earlier paper (Sweeny 2002) reviewed the technologies that are being mobilised by both traditional pharmaceutical companies and biotechnology companies to improve productivity and to improve success rates for drug candidates.

To reduce the cost of all aspects of the drug pipeline, companies have introduced technologies that speed up the discovery of drug candidates and their subsequent testing in preclinical and clinical stages.

Drug companies have relied heavily on **libraries of compounds** that could prove efficacious as drugs to treat disease. These libraries are quite extensive and a lot of effort has been put into exploiting new sources of compounds, typically from biota outside North America and Europe.

Combinatorial chemistry is a technique to make millions of variants of a single compound in a short period of time, which can then be tested for their efficacy. This has required a parallel development of automated **high throughput screening** techniques in which large numbers of compounds can be tested against a drug target using robotic machinery and automated testing and analysis.

As the amount of material, typically proteins, to be tested can often be quite small, these technologies have relied heavily on techniques originally developed in the semiconductor and microtechnology fields.

While significant gains have been made in the technologies to generate and test potential new drugs, the most difficult problem associated with new drug discovery is the identification and characterisation of the most appropriate target within a disease pathway.

Genomics seeks to exploit the findings from the sequencing of the human and other genomes to find new drug targets, by identifying faults in genes that contribute to diseases. Most major pharmaceuticals and biotechnology companies now have access to genomic and SNP databases which they are using to identify suitable gene targets.

Proteomics is the study of the proteome i.e. the ensemble of proteins found within a system (sometimes referred to as structural genomics or functional genomics). While there are may be some 35,000-50,000 genes in the human genome, they are responsible for the production of 500,000-1,000,000 proteins. Proteins are closer to disease processes and drug action than genes, as most drug targets are proteins. In addition, proteins now form a significant proportion of drugs, as recombinant proteins such as monoclonal antibodies.

All of the techniques described above generate or use large volumes of data. This data is often then tested against large libraries of other data to find matches or patterns that might suggest potential drug targets or lead compounds. **Bioinformatics** is the technology developed to managing and analyse this data and has lead information technology companies such as IBM and Oracle to become involved in alliances with biotechnology and pharmaceutical companies in the drug discovery and development process.

Australian Capabilities

While Australia has some capabilities in all aspects of the drug discovery and development process, its strengths have historically been concentrated in only a few of the stages. Australia is acknowledged for the strength of its basic research in medicine, biology and biotechnology and has developed a strong presence in clinical trials (principally in Phase III) as a result of this strength.

The Australian pharmaceuticals and biotechnology industry consists of the Australian operations of a range of large multinational pharmaceutical companies, a few Australian-based pharmaceutical wholesalers and manufacturers and a number of smaller Australian biotechnology companies.

Many of the Australian subsidiaries of the multinational pharmaceutical companies have been here for a long time and have well established distribution and marketing operations. Some such as Merck, Sharp & Dohme and GlaxoSmithKline have significant formulation and manufacturing plants while others such as Eli Lilly have made significant investments in clinical trials. Their research programs in Australia are largely conducted through Australian university and medical research institutes.

The larger Australian operations – Fauldings (now part of Mayne Health), Sigma Pharmaceuticals and Australian Pharmaceutical Industries, are principally wholesalers though Fauldings and Sigma manufacture generic drugs both on their own account and on contract. The largest manufacturer of generics in Australia is Alphapharm. The involvement of these companies in technology development is generally small.

The Australian biotechnology sector consists of both listed and unlisted companies.

Appendix One lists the companies in the Deloitte's index with market capitalisation at April 2002. The list is dominated by CSL, which is primarily a blood products company with some presence in the vaccine distribution market and with a portfolio of research projects targeting peptic ulcers, genital warts, cervical cancer, melanoma, periodontal disease, and glandular fever.

The 'Medical Devices' group of 15 companies has a collective capitalisation of about $6.0 billion, of which Resmed and Cochlear are together worth $4.7 billion. They make devices for sleep apnoea and profound hearing loss respectively.

The 'Research Biotechnology' group includes 47 companies with a total worth of about $2.3 billion, or an average worth of $49 million. There are 16 biotechnology companies with a capitalisation greater than $50 million, and 38 with a capitalisation exceeding $10 million.

Those listed companies whose operations are most closely related to the drug discovery and development business, therefore are small by international standards, even allowing for the fact that the cost of doing biotechnology R&D in Australia is half that in the USA. A recent review by Deloitte shows that listed Australian biotechnology firms are on average less than a tenth the size of Canadian firms (Deloitte 2002)

While most focus in Australian biomedical research is on understanding disease pathways and identifying suitable targets for drugs, a number of organisations are active in developing **libraries of lead compounds** and using high throughput screening to identify promising drug candidates.

Australia has a unique and diverse biota, the country accounting for instance for about 10% of global plant biodiversity (Quinn 1999).

This resource has been recognised by researchers and industry as a potentially valuable source of drug lead compounds and a number of organisations have compiled libraries of natural compounds for this purpose.

AstraZeneca has entered into an agreement with the State of Queensland that gives the company first rights of refusal to develop compounds based on the State's biota, i.e. plants and other organisms unique to the State. In return the company is helping the State to complete its survey of the biota and providing screening facilities at Griffith University to screen for potential new drug candidates.

BioProspect Limited is a listed company based in Western Australia that has a licence granted by the Western Australian Government giving it access to plant species collected by the WA Herbarium. It provides profiled plant extracts to drug discovery companies from this library as well as screening services, in conjunction with partners such as Southern Cross University and

Royal Perth Hospital. The library has produced compounds with promise as a human sedative and an organic pesticide.

Cerylid Biosciences Ltd was founded in January 2000 when as an offshoot of Amrad Corporation. It has a number of microbial and plant and marine macro-organism libraries sourced from a number of Australian States and territories as well as Papua New Guinea and Sarawak in Malaysia. It offers screening services and bioassay development using extracts from these libraries. In addition it operates an internal drug discovery and development program concentrating on drugs for multiple sclerosis, endometriosis and type I diabetes.

Other companies are working on developing new forms of lead compounds, Starpharma, for instance, is commercialising new polyvalent compounds called dendrimers for action against a broad range of viruses and other human diseases, including HIV/AIDS and cancer.

Of the 'Research Biotechnology' companies listed in Appendix One, IDT manufactures active ingredients while Clover Corporation manufactures lipid-based nutrients. Biotech Capital, Circadian Technologies, Genetic Technologies and Medica Holdings are essentially investment companies that have supported a range of instrument companies such as Axon Instruments, Proteome Systems, Optiscan Imaging . To identify the listed companies working primarily in drug discovery these other companies were removed to form the list of companies in the following table.

Australian Listed Drug Discovery Companies: Product pipeline

Preliminary

Companies	Market cap	Technology base	Diseases targeted	Pre.	Phase I	Phase II	Phase III	Reg.	Total
Agenix	72.5	Agen immunoassays, vaccines	Medical diagnostics, vaccines		1				1
Amrad	109.7	Virology and cytokines	Nerve damage, hepatitis B, severe pain, cardiovascular disease, stroke	3	1	3			7
Anadis	26.6	Bovine colostrum	Diarrhoea, osteoporosis, H pylori	1		3			4
AntisenseTherapeutics	10.6	Antisense (mRNA) technology	Psoriaris, MS,	1	1				2
Australian Cancer Techn	11.9	Antibodies to P53 cancer gene	Colon, breast cancer	2	1				3
Autogen	28.4	Genomics for novel therapeutic targets	Obesity, type II diabetes	4					4
Bionomics Ltd	23.0	Genomics	Breast cancer, epilepsy, angiogenesis	3					3
Biota	44.3	Rational drug design	Influenza, rhinovirus, cancer, Alz	7					7
Biotron	8.8	Various	Viruses, heart, stroke, epilepsy	6					6
Bresagen	53.4	Interleukin GF, human GF, cell therapy	Leukaemia, rheumatoid arthritis, asthma, solid tumours	2		2	1	1	6
Epitan	10.2	alpha - MSH molecule	Skin cancer		2	2			4
Gropep	74.7	Biologics manufactureIn-licensing candidates for development	Diabetic neuropathy, venous ulcers, oral mucositis, osteoporosis	4		5			9
Meditech Research	36.0	Hyaluronic acid as anti-cancer drug delivery	Skin cancer, bowel cancer, breast cancer	2	5				7
Metabolic	124.2	Human growth hormone	Obesity, type II diabetes	1		1			2
Norwood Abbey	49.4	Mainly laser-based drug delivery, GnRH analogues	Immune based diseases	3	1				4
Novogen	262.1	Development of isoflavinoids	Osteoporosis, inflammatory diseases	4	3				7
Peplin	33.4	Pharmaceuticals from plants	Skin cancer, solid tumour cancer	4		2			6
Peptech	426.3	Tumour Necrosis Factor antibodies Polyunsaturated fatty acids	Inflammatory diseases	3					3
Prana Biotechnology	32.8	Oxidation proteins	Alzheimer's disease	5		1			6
Progen Industries	31.2	Biologics manufacture, inhibitors of carbohydrate-protein interactions	Cancer angiogenesis inhibitor, anti-thrombotic inhibitor	1	1	1			3
Provalis	61.9	Vaccines	Pneumonia, ear infection, streptococcus	6	1	1	3		11
Psivida	20.5	Biomatrials, nanostructured porous silicon	Drug delivery	3	2	1			6
Virax Holdings	14.7	Immunotherapy vaccines	HIV/AIDS	1		1			2
VRI Biomedical	15.3	Biopharmaceuticals, mucosal system	Diagnostics	7	7				14
Xcell Diagnostics	6.5	Cancer detection	Skin cancer	2					2
Total Selected Organisations				**75**	**26**	**23**	**4**	**1**	**129**

Sources:
Market cap (Deloittes, April 2002)
Technology base (CSES)
Diseases targetted (CSES)
Pipeline (CSES review of websites)

This table still includes some companies whose main activities are in biologicals manufacture, diagnostics, and drug delivery which would reduce the list of pure drug discovery and development companies still further. It does however exclude companies that produce supporting technologies for drug discovery and development. The principal companies in this area are Axon Instruments, Gradipore, and Proteome Systems.

The table lists the companies' technology base, diseases targeted and the current status of their drug development pipeline. With drugs already developed for the relatively 'easy' disease targets, as with other biotech companies, these Australian companies are primarily targeting disease where there is still an unmet need such as skin cancer, solid tumours, obesity, osteoporosis, HIV/AIDS, Alzheimer's disease and other inflammatory diseases.

The product pipeline is an attempt to gain an overall picture of the size and significance of the output of the larger (listed) drug discovery companies. This pipeline has been gleaned from the web sites and annual reports of individual companies. It is therefore only as complete as that information. The total pipeline of 129 drugs is relatively modest and skewed heavily in the direction of drugs in early stage. It compares with the total global pipeline of about 10400 drugs (IMS Health 2002). As previously suggested the drug development process is highly uncertain and only a small proportion of drugs at early stage survive to reach market. Some measure of the significance of the pipeline can be gauged by the application of average probabilities of success to this portfolio as shown in the table below. This indicates that the total effort of these companies may produce 20-25 new drugs. This compares with about 1600 projected successful drug outcomes from the global pipeline (PAREXEL 2001).

Total product pipeline: Listed Australian drug discovery companies

	Clinical Phase				Reg	Total
	Pre	I	II	III		
No of drugs	75	26	23	4	1	129
Industry average success rates*	10%	18%	28%	66%	91%	
Est. drugs to market	7.7	4.8	6.5	2.6	0.9	**23**

* *The Pharmaceutical R&D Compendium*, CMR International and *Scrip's Complete Guide to Trends in R&D* 2000, cited in PAREXEL 2001, p. 195.

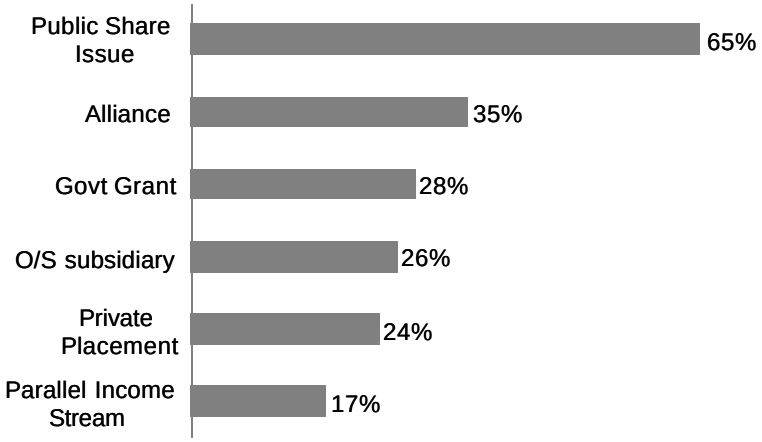
The total for the Australian drug discovery industry will of course be higher. There are a large number of companies that are not listed and the records from which this data are collected are likely to be incomplete. Nonetheless most of the major companies are listed. If an allowance for the unlisted companies and incomplete records represented a further 50% this would take the Australian total to about 2% of the world – reflecting an industry with an average share for Australia of the world output, but not one at this stage 'punching above its weight'.

Business Strategies for Australian Medical Biotechs

As has been demonstrated in the previous sections the Australian biotech industry is at a fledgling stage. It has a modest product pipeline and has produced only a small number of drugs for market of which Relenza, developed by Biota, is perhaps the best known. The larger more successful companies such as CSL, ResMed, and Cochlear occupy niche segments that tend to disqualify them as 'true' biotechs.

This section focuses on the business development strategies that have been pursued by Australian medical biotechs. The companies surveyed in this section include those listed companies in Appendix but are a broader group so as to include a reasonably comprehensive number of unlisted biotechs. The starting point for establishing an appropriate list of companies are those Australian owned biotechs listed on the BIOMEDOZ website. These names have been supplemented by those companies listed on the ASX and included in the Deloittes Biotech index. The resulting list has been culled to exclude those pharmaceutical companies that are largely wholesale, retail or vitamin supplement suppliers or generic manufacturers, as well as predominantly medical device companies such as Resmed and Cochlear. This has resulted in a list of about 100 Australian biomedical companies. The web sites and annual reports for these companies have been searched to find evidence of the various development strategies adopted and where possible to quantify those employed. About half a dozen different strategies are discernable. In no way does the adoption of one preclude the selection of another, but a number may be taken up sequentially. The various development strategies are shown in the chart below.

Australian biomedical development strategies 1998- 2002



Numerically almost two thirds of the companies have undertaken a public share issue and 35% formed an alliance. Twenty eight per cent have obtained a government grant. An overseas subsidiary has been established by 26% of the companies, sometimes as part of an alliance or marketing strategy but in other cases as a precursor to an overseas capital raising. Only 24% reported undertaking a private placement suggesting some under reporting. Most companies

accessing the public markets could be expected to have undertaken prior private placements. To lessen their reliance on the capital markets a small number of firms has sought to establish parallel revenue streams – product sales to generate a cash flow that can be used to support research expenditure.

It might be expected that these strategies would occur sequentially with a government grant as a starting point to fund or help fund the basic laboratory research. As activity levels and costs rise this would be followed by a private share placement, often involving a venture capitalist with an IPO to follow. As has been suggested in the literature (see Nicholson, Danzon and McCullough 2002), the formation of an alliance may provide expert external endorsement of the commercial value of the discovery and help support the valuation on which the IPO is based.

From our admittedly small sample, the sequence is if anything the other way around with twice as many companies undertaking an IPO before forming their first alliance. Thirty per cent of those undertaking an IPO record receiving a government grant but there is little evidence of a staged approach. Many companies appear to adopt the various development strategies in an opportunistic and 'out of sequence' fashion. For instance in examining the question 'does a government grant lead to, or is it associated, with further company development strategies' of those companies in receipt of a government grant, a high proportion (85%) had also raised capital via a public or private issue. In some noteworthy cases such as Proteome Systems, the grant preceded the first capital raising by some years. In other cases the first capital raising and the awarding of the government grant occurred contemporaneously. It is difficult therefore, on the data reviewed, to conclude that the award of a grant is necessarily a catalyst for further corporate success although doubtless there are examples of that outcome.

The two most numerous strategies were public issue and alliance Raising capital helps the company retain ownership of its technology The public issue has the advantage of widening the investor base and increasing the pool of capital making larger raisings possible at a high price if conditions are favourable. However it can also be destabilising. It puts the company under the sometimes harsh scrutiny of the public market and can introduce a high level of volatility into the share price. Short term strategy to placate the market can become a preoccupation of the board and management at the cost of long term strategy. Future placements are priced off the public market which might underprice the stock during periods of adverse sentiment towards biotech stocks. The proportion of those recording undertaking a private placement (24%) seems to be understated. Our data base relies on press releases and annual reports to record such events. It could be expected that the majority of companies would undertake a private placement. This has clear advantages for small companies. It taps a ready, if not always, willing market of venture capitalist and institutions as investors including those who might bring complementary commercial skills but typically leaves the founding management in charge.

On the other hand a drug development alliance typically involves the sale of the rights to the technology in return for an upfront and milestone payments and a royalty share of the sales should the drug proceed to market. This has the advantage of bringing forward an uncertain

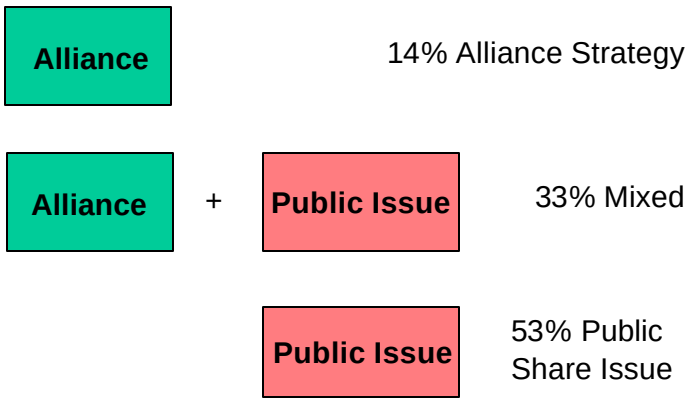
revenue stream as well as introducing complementary skills. Although it has the disadvantage of forgoing the big rewards of a successfully marketed drug, it may nonetheless be a prudent response to the highly uncertain outcomes of the drug development process for a small company with only a few drugs in its pipeline. It provides some return on the discovery while retaining ownership and control of the business.

There is an increasing literature about choosing the optimal stage at which to form an alliance. Typically the more developed the drug, the better the alliance terms. On the other hand the accumulated expenditure is larger and the likelihood of total loss higher.

Does an alliance provide support for a capital raising, particularly an IPO, or is it an independent strategy. Is it, as has been suggested above, a useful vote of confidence in a company's technology to be obtained pre float or should alliance formation be regarded as a way of raising funds and obtaining other in-kind support while avoiding the harsh gaze of the public equity markets?

The chart below summarises the results of a review of the strategies of almost 70 companies drawn from our list that had formed alliances or undertaken a public raising over the period 1998 to June 2002. It therefore only captures strategies adopted in this period.

Development strategies adopted by Australian biomedical companies 1998-2002



From the data recorded over the last 4 years, 53% of the companies have undertaken a public issue but not formed an alliance. 33% have adopted a mixed strategy and the remaining 14% have formed an alliance without worrying the public markets. These results no doubt reflect the relatively generous environment for biotech IPOs in the period and a willingness of this group biomedical companies to grasp these opportunities as they are offered. It is somewhat surprising that the alliance only strategy wasn't more prominent given the growth in alliance numbers overseas. Perhaps this will become more important as our companies move their products further down the pipeline.

Equity Capital Raising by Australian Bio Medical Companies

Estimates of total equity raisings, private placement and IPO's, were obtained for the same list of companies as above. Again this data were compiled from company announcements, annual reports and other information available from their web sites. It is essentially for the period 1998/99 to 2001/02 although some data were available for prior years. The data for 2001/02, collected in August 2002, may still be incomplete.

The table below shows a rapid increase in capital raising activity in 1998/99 from $60m to $379m and reaching particularly high levels of $721m in 2000/01. This included a raising of $320m by CSL which tends to overwhelm the activities of the smaller companies. The decline to $150m in 2001/02 mirrors the fortunes of the technology sector on the ASX, but is nonetheless significantly higher than 1998/99. As noted earlier the figure for private placements is likely to be understated.

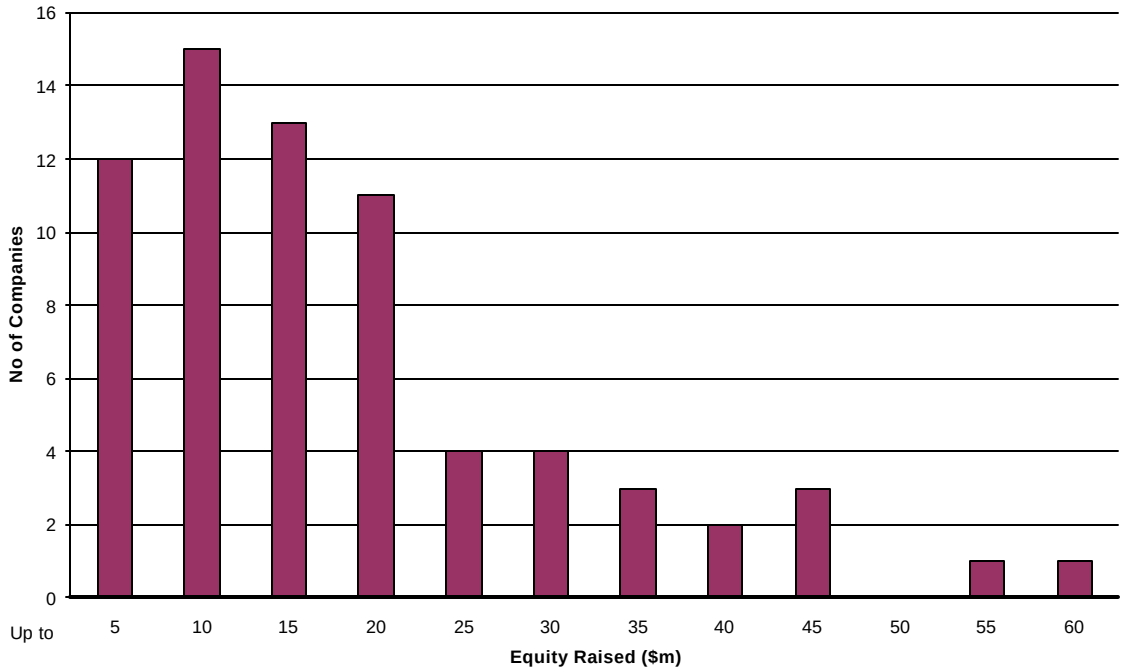
Selected Australian biomedical capital raisings

	1998/99	1999/00	2000/01	2001/02
Total number				
Private Placement	4	17	6	3
Public	8	27	35	20
Total	12	44	41	23
Total Amount ($m)				
Private Placement	17.5	114.3	28.2	5.5
Public	42.4	265.2	693.4	145.2
Total	59.9	379.4	721.6	150.7
Average Amount ($m)				
Private Placement	4.4	6.7	4.7	1.8
Public	5.3	9.8	19.8	7.3
Total	5.0	8.6	17.6	6.6

The average amount raised has been modest peaking in 2000/01 at $17.6m but for most of the period the average has been in the range $5-10m. This is small by any measure, but especially so given the huge cost of developing a single successful drug, including the cost of failure, estimated to be of the order of US$800 million (DiMasi 2001).

To gain a better understanding of the aggregate amount raised by each company over the period the chart below provides a distribution of the total amount raised by each company over the period 1998/99 to 2001/02.

Total equity raised 1998-2002



This shows that most companies raised amounts of up to $20m. This reflects the modest capacity of the local market. It may also reflect the relatively modest demands, given the early stage of their pipelines, of most of the companies in the market. The Pharmaceuticals Industry Action Agenda (DITR 2002) provides estimates of the cost of drug development at each stage (excluding the cost of failure). This puts the total at A$300m, about $60m to the end of Phase 1 and twice that to complete Phase 2. The amounts recorded as being raised in this period may provide part of early stage funding of a single drug per company. It is difficult on this basis to contemplate the Australian capital markets funding the full cost of later stage development. For the full development of potential drugs an alliance with a well funded partner appears to be the main way forward.

Australian Alliances

An overview of Australian pharmaceutical alliances in the global context was provided in an earlier paper in this series (Rasmussen 2002). This showed, both for Australia and the rest of the world, the recent rapid growth in alliances, particularly between biotech companies.

This earlier work was based on the summary information available from the ReCap database. Many questions remained about the nature of the alliances, their purposes, the role of the alliance partners, the countries of the companies involved etc. To seek to answer these questions this more detailed analysis has been undertaken using information drawn from the press releases announcing the formation, or further development, of alliances listed on ReCap. Many of these releases are available from the ReCap database. However to ensure that the analysis was as complete as possible, the web site of each Australian biotech company and in some cases that of its overseas alliance partner, was searched to obtain a copy of the press release for each Australian alliance listed on ReCap. This search process was also used to check for any announced alliances missing from ReCap. Only a very small number of additional research collaborations were discovered as part of this process. Given the limited number and their uncertain status as alliances, it was decided not to include these additional arrangements in our database. This had the advantage of retaining the definitional integrity of the ReCap database.

A reasonably complete set of press releases could be assembled for the period 1996-2001 – 90 out of the total number of alliances of 107. Accordingly this analysis focuses on this five-year period. The purpose of collecting the additional detail about each alliance available from press releases was to determine the following characteristics about each alliance:

- the role of the alliance partners. In most alliances there is one party which is the client and funding source, and the other party which is primarily undertaking the R&D;
- the alliance partner's country of origin;
- the source country of the technology or other knowledge being used through the alliance;
- an estimate of payments to be made under the alliance i.e. 'payouts'; and
- broad purpose of the alliance. For example:
  - drug discovery or development
  - development of platform technologies
  - product distribution.

The parties to the alliances and their role

Almost half of the alliances were between biotechs (51 of 107), about one third (33) were between biotechs and pharmaceutical companies and 15% involved universities mostly with biotechs. The sharpest growth over the period occurred in those between biotechs. There were

25 alliances between biotechs in 2001 compared with 10 in 2000. Almost all alliances between biotechs and pharmaceutical companies involved the biotech providing the R&D, with the pharmaceutical companies acting as the funding source. As might be expected the universities were the research party in alliances with biotechs.

Alliance payouts and trends in the number of alliances: 1996-2001

Partners	1996	1997	1998	1999	2000	2001	Total 1996-2002 Alliances	Payouts ($m)*
Bio/Biotech	5	2	6	3	10	25	51	126
Pharma/Biotech	4	3	7	4	9	6	33	145
Biotech/uni	0	4	2	1	2	3	12	9
Other	1	0	2	2	1	5	11	0
Total	10	9	17	10	22	39	107	280

* Excludes payments made for acquisitions.

The number of alliances reporting payouts was small – only 14, so drawing firm conclusions are difficult, even though the results are interesting.[2] Of the total of $280m reported, over half ($145m) was for payments made to biotechs by pharmaceutical companies. However almost all of the remainder was for alliances between biotechs ($126m), with payouts to universities from biotechs totalling $9m. While the prominent role played by the pharmaceutical companies is as expected, the magnitude of the biotech payouts to other biotechs is perhaps surprising. This must be qualified to the extent that one of the largest biotech alliance payouts ($43m) involved a biotech company which was in the process of becoming a subsidiary of a pharmaceutical company. Nonetheless this data suggests that biotechs are increasingly involved in providing funding through alliances.

The small number of transactions reported means that the results tend to strongly reflect the activities of a small number of companies. Of the total payout value of $280m, $187m relates to alliances involving AMRAD. Whether this properly reflects AMRAD's relative position or an under reporting by other companies, is a little difficult to judge. Undoubtedly there are some alliances in which the payments are confidential. However this and the small number of companies involved in alliances is a further example of the limited size of the Australian biotech sector.

Main purpose

Most alliances reviewed in detail fell into one of three categories:

- drug discovery or development;

[2] The data for payouts is derived from the value disclosed in press release or other documentation announcing the alliance. It is generally a lump sum incorporating an upfront payment (e.g. licence fee) together with expected near term milestone or other payments.

- development of platform or other supporting technologies; and
- product distribution .

A significant proportion (23%) were concerned with drug development. This is the traditional purpose of an alliance discussed in the literature (see for instance Lerner and Merges 1997), typically between a pharmaceutical company and a research house – a biotech or university with a patented compound with potential for trial. In the table below, where the first named alliance partner is the client, there are only 4 alliances of this traditional kind. Most of the 'development' alliances have a biotech as the client and either another biotech or university as the research house. These results provide further evidence of the more influential role being adopted by biotechs in alliance structures.

The number of alliances by main purpose: 1996-2001

Main Purpose*	Bio/biotech	Pharma/biotech	Biotech/Uni	Other	Total
Development	9	4	7	1	21
Distribution	4	9	0	1	14
Technology	24	12	4	2	42
Other	7	5	0	1	13
Total	44	30	11	5	90

* Includes only alliances announced by press release.

By far the largest category was where the main purpose of the alliance was the exchange, or a collaboration with a company to further develop, platform or other supporting technologies. To a degree this reflects the nature of the Australian companies forming its biotech sector. Led by instrument developers and manufacturers, Proteome Systems and Axon Instruments a high proportion of Australian company alliances are concerned with the development and enhancement of advanced instrumentation for the biotech sector or the development of diagnostic tests rather than the development of drugs per se. Some of these alliances involve the acquisition or development of Australian technology for use by or incorporation in an overseas company's product line. In other cases the alliances appear to contemplate a genuine partnership in which different specialisations are to be combined to produce a new prototype product which is to be marketed by both alliance partners. Alliances between biotechs are the largest sub category within the 'technology' category, 24 out of 42, although the number with pharmaceutical companies (12) is also significant.

Australian firms particularly pharmaceutical companies establish alliances to distribute the products of overseas companies, generally in Australia, but sometimes overseas. The most common example is of an Australian pharmaceutical company (e.g. Faulding) entering a licensing agreement to market a pharmaceutical product in Australia. Fourteen of the total in the table above are distribution alliances. Other alliances include manufacturing, sales or acquisitions of product lines. For instance the sale of AMRAD Pharmaceuticals to Merck is included in 'other'.

In terms of growth of the individual categories the most rapid has been in 'technology' alliances – 16 in 2001 compared with only 3-5 in the 1990s. The increased number of alliances has been across the board however, with most other categories doubling in number between 2001 and 2000 as shown below.

Trends in the number of alliances by main purpose 1996-2002

Main Purpose*	1996	1997	1998	1999	2000	2001	Total 1996-2002	
							No.	%
Development	0	4	2	3	4	8	21	23%
Distribution	1	1	4	2	2	4	14	16%
Technology	3	4	5	3	11	16	42	47%
Other	0	0	1	1	4	7	13	14%
Total	4	9	12	9	21	35	90	100%

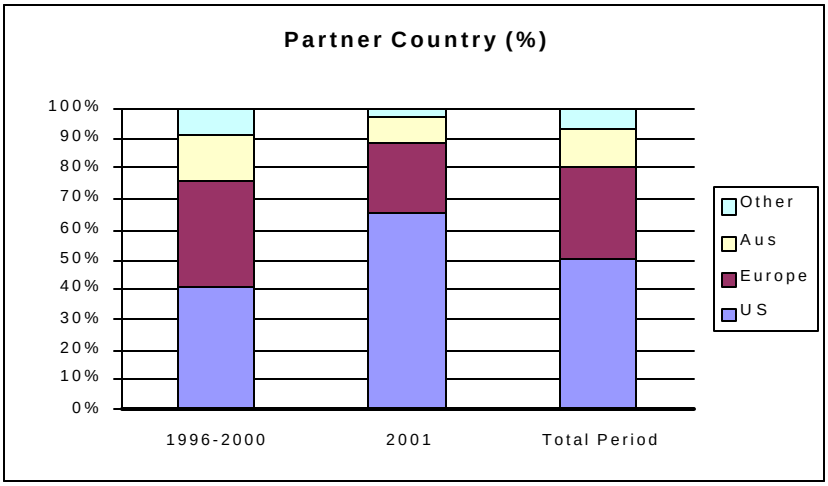
* Includes only alliances announced by press release.

Not only is the number, but also the value of payouts arising from of technology alliances important. Of the total $280m in alliance payouts, $115m relate to technology alliances. Given the small number of alliances involved in reported payouts it is difficult to generalise but each of the alliances involved licensing arrangements with overseas companies, both pharmaceutical and biotech, to access and develop Australian technologies in return for license fees, milestone payments and royalties.

Alliance partner countries

There have been suggestions (Hopper and Thornburn 2001, p. 13) that Australian companies have tended to partner disproportionately, given the technological dominance of the US industry, with European companies. Important partnerships have been formed with companies such as GlaxoSmithKline, AstraZeneca and Aventis. For the period 1996-2000, 35% of alliances were formed with European companies compared with 41% with US companies.

In 2001 this changed markedly with 66% of alliances being formed with US companies and the proportion with European companies falling to 23%. This reflects the rapid growth in alliances with biotechs and the concentration of such companies in the US. It may also reflect a greater willingness to seek out and engage with the overseas companies, rather than use the local subsidiaries of the larger pharmaceutical companies as the entree to alliance partnerships.



The press releases not only provided information about the country of the alliance partner but also the likely source country of the technology or discovery or other 'knowledge' contribution to the alliance. Sometimes the nature of the alliance prevented such a 'call' but in most cases it was possible to categorise each alliance according the source country of the technology. Reflecting the Australian technology content of most of the alliances, the source country for 55% of the alliances was Australia, 30% US and the remainder largely European.

In an attempt to better understand the rationale for the alliances, a cross tabulation was performed of country of alliance partner with source country of technology. This revealed that 66% of alliances with US companies sourced their technology from the US whereas in alliances with European companies almost exactly the reverse was the case – with 65% of alliances utilising or developing Australian technology as shown in the table below.

Proportion of alliances using Australian technology by country of alliance partner

Country of Alliance Partner	No. of alliances	% using or developing Aus tech
Australia	11	100%
United States	42	36%
Europe	26	65%
Total	85	54%

There are diverse reasons for this relatively low level of indigenous technology in US alliances. The alliances are a means of importing US technology and other forms of knowledge in a collaborative context. Most numerous in this alliance category, are Australian companies seeking alliances with US biotechs as a means of accessing complementary and enhancing technologies. Other significant reasons include licensing US pharmaceutical products for distribution in Australia and commissioning joint research projects involving US universities and institutes for drug development.

Conclusion

The traditional view of a pharmaceutical alliance is one in which the pharmaceutical company funds drug discovery and development carried out by a biotech or university. The pharmaceutical company eventually gains the revenue from sales of the drug having met most of its development cost. The biotech or university receives a licence fee, milestone payments and a royalty if the drug is successfully launched.

While there are alliances with Australian biotechs that are structured in this way, there are a larger number in which biotechs are in the 'client' role or funding source in a drug development or more likely, a technology alliance. While the number of companies providing alliance 'payout' information is limited, the financial importance of large pharma in alliances remains significant with over half of the funds committed in alliances being sourced from pharmaceutical companies.

There are a larger number of alliances concerned with the development of platform technologies or diagnostic tests, not with drug development per se. The degree to which the alliance represents a genuine technology collaboration, a pooling of different specialisations, or largely a technology purchase by one party from the other varies with the roles of the alliance partners[3].

There is some evidence in this analysis that the year 2000 marked something of a 'sea change' for the Australian industry. Until then the bias was towards establishing alliances with European pharmaceutical companies with subsidiaries in Australia. Starting in 2000 and more pronounced in 2001, a significantly higher proportion of alliances were with US biotech partners. The purpose of the alliances also changed. They were more likely to be about gaining access to overseas, particularly US technology, rather than simply being a mechanism for financing the exploitation of an Australian discovery.

Concluding Observations About Development Paths

The early sections of this paper provided a commentary on the technical capabilities of the Australian industry in the context of the rapid changes in industry technologies and the pressures to improve drug development productivity. Australia has some relative advantages in its research base and in its unique biota as a source of new drugs. Its conspicuous successes have been at the margin of the industry such as CSL in blood products or the device manufacturers, Cochlear and Resmed. However in the mainstream drug discovery area its scale, despite recent growth, remains small. The total pipeline of the largest 20 listed companies is of the order of 130 compounds with the prospect of producing 20-25 drugs – a little over 1% of those likely to emerge from the estimated global pipeline.

[3] This trend at an international level is noted in Arora, Fosfuri and Gambardella (2001, p. 70).

The survey of over 100 companies suggests that the development paths for these companies fall into three groups – one pursuing alliances, another IPOs and a third somewhat smaller group following a 'mixed' strategy of both alliances and IPOs. Most companies obtain some of their initial capital from private placements. While the data indicate an encouraging capacity of the domestic market to finance drug development, with total capital raisings reaching $690m in 2000/01, the amounts are nonetheless modest in the context of the total cost of drug development. Perhaps the bargaining power of the local company is enhanced by delaying, through local capital raisings, the eventual sell down to a partner. However one suspects that at some stage alliance formation becomes the only development path to get Australian drugs to market.

The paper provides as much detail about alliances as can be gleaned from desk research. It confirms the earlier work showing the increasing, at least numerical, importance of alliances with biotechs while at the same time indicating that the pharmaceutical companies are important when it comes to gaining financial support. The trade in technology is also a strong motivation for alliances. The increasing number of alliances with biotechs are motivated by the need for Australian companies to acquire missing bits of technology rather than financial support. This has skewed an increasingly high proportion of alliances towards the US and away from the more traditional European based partnerships.

The evidence provided in this paper emphasises the likely importance of alliances in the development of the industry, given what appears to be a limited capacity of the capital markets to support an industry, at an early stage of development, with potentially high but uncertain returns.

Appendix One

Listed Australian biotechnology companies
April 2002

	Market Cap	Category
CSL	6,547,256,928	CSL
Resmed Inc	2,441,626,020	Medical Devices
Cochlear	2,254,881,228	Medical Devices
Peptech	426,257,368	Research Biotechnology
Axon Instruments	299,378,488	Medical Devices
Novogen	262,078,240	Research Biotechnology
Chemeq	163,485,898	Research Biotechnology
IDT	154,580,668	Research Biotechnology
MicroMedical Industries	128,346,920	Medical Devices
Metabolic	124,243,256	Research Biotechnology
Polartechnics	120,618,489	Medical Devices
Amrad	109,739,688	Research Biotechnology
Gradipore	108,923,436	Medical Devices
Circadian	98,682,187	Research Biotechnology
Compumedics	82,600,000	Medical Devices
Panbio	80,256,269	Research Biotechnology
Cellestis	78,450,225	Research Biotechnology
Gropep	74,670,728	Research Biotechnology
Optiscan Imaging	74,328,125	Medical Devices
Agenix	72,465,747	Research Biotechnology
Genetic Technologies	71,480,833	Research Biotechnology
Vita Life Sciences	64,829,418	Medical Devices
Ellex Medical Lasers	64,701,953	Medical Devices
Provalis	61,879,134	Research Biotechnology
Genesis Research & Development	59,959,392	Research Biotechnology
Ambri	55,247,753	Research Biotechnology
Bresagen	53,359,589	Research Biotechnology
Starpharma	52,862,456	Research Biotechnology
Norwood Abbey	49,384,321	Research Biotechnology
Biota	44,264,174	Research Biotechnology
Medica Holdings	43,496,060	Research Biotechnology
Meditech Research	35,977,529	Research Biotechnology
Sirtex Medical	34,312,261	Medical Devices
Peplin	33,414,818	Research Biotechnology
Prana Biotechnology	32,844,625	Research Biotechnology
Solbec Pharmaceuticals	32,650,305	Research Biotechnology
Progen Industries	31,221,592	Research Biotechnology
Biotech Capital	30,000,038	Research Biotechnology
Clover Corporation	28,584,974	Research Biotechnology
Autogen	28,362,878	Research Biotechnology
Anadis	26,571,312	Research Biotechnology

Bionomics Ltd	23,026,607	Research Biotechnology
Prima BioMed	22,117,417	Research Biotechnology
Psivida	20,543,694	Research Biotechnology
Pharmaction Holdings	16,019,149	Research Biotechnology
SSH Medical	15,780,384	Medical Devices
VRI Biomedical	15,321,927	Research Biotechnology
Virax Holdings	14,704,408	Research Biotechnology
Australian Cancer Technology	11,901,530	Research Biotechnology
Bioprospect	11,144,234	Research Biotechnology
AntisenseTherapeutics	10,565,625	Research Biotechnology
Epitan	10,175,977	Research Biotechnology
Brain Resource Company	8,839,063	Research Biotechnology
Biotron	8,753,500	Research Biotechnology
Genesis Biomedical	8,285,750	Medical Devices
Xcell Diagnostics	6,494,177	Research Biotechnology
Inovax	6,071,803	Distributor
Australian Vaccine Technologies	4,189,033	Research Biotechnology
Aquacarotene	4,021,512	Research Biotechnology
NSL Health	3,343,778	Medical Devices
Pi2	2,882,040	Research Biotechnology
Psiron	2,436,762	Research Biotechnology

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