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In this edition...
This is the 500th edition of Bioshares. We have taken the opportunity to review the sector over the time this report has been published and to post some thoughts and reflections on the practise of biotech investment.

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - current)	-9.0%
Cumulative Gain	**214%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

26 April 2013
Edition 500

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.

500

The first edition of Bioshares was mailed to subscribers in April 2000. The first 12 editions were printed in hardcopy and released quarterly. In 2003, the switch to a weekly release by email was made in response to readers' wishes for more timely analysis.

Much has taken place in Australian biotech in the intervening 13 years. Many companies, such as Medicine Quantale, Q-Vis, SSH Medical, Denx and Chemeq have come and gone. Many mergers have taken place and several notable acquisitions have occurred, starting with Axon Instruments in 2004 and latterly with Cellestis, Peplin and ChemGenex Pharmaceuticals. ASX listed life science companies have received close to $6.6 billion in equity funding over the 13 years. One company, Acrux, set the benchmark for investment returns when it paid a $100 million dividend in 2011.

Failure has been a consistent feature as one would expect from a high risk sector. The sources of failure continue to be studied and debated often years after the event.

In some ways the last 13 years has been a set of investment experiments, in several instances, very bold experiments. Australian investors can now point to models, strategies and business practises that yield better chances of success in contrast to approaches that have been found wanting.

When looking at failure, there is a tendency to throw the baby out with the bathwater. Investors should not forget the havoc that the GFC played and continues to play on investments across the board and specifically with many biotechs. A long term consequence, perhaps positive, is that the price of risk capital has risen to more realistic levels.

In our 500th Anniversary edition of Bioshares, we look back on the last 13 years of listed biotech in Australia to consider the lessons learned. No doubt the next few years will supply more lessons. However, investors with a bent for learning will be the ones that profit, even in the world of speculative biotech investing.

Looking Back on 13 Years of Biotech in Australia

by Mark Pachacz, Research Principal, Bioshares

In this review of the last 13 years of biotech investing in Australia, I discuss 'Lessons Learnt in Australian Biotech', look at who can be counted as 'Biotech's Money Makers', identify 'The Best Listings', note the trend in 'The Number of ASX-listed Biotechs', estimate "Value Creation' (in aggregate) and conclude with a 'Review of Biotech M&A'.

Big Lessons Learnt in Australian Biotech

Looking back over the last 13 years at the biggest losses in the Australian biotech sector is a very sobering and useful task. The global financial meltdown can not be overstated for its impact on companies. However, there are three main reasons why most of the companies in the table on the next page have experienced major setbacks which has caused devastating losses in value on funds invested.

The major disasters in this sector have occurred because of (a) technology development failure (b) poor market research (c) or poor commercialisation by management.

Technology Failure

In some cases technical difficulty has been the reason for company failures. Biosensor technology group Ambri falls into this category, with the hurdles of developing a durable and accurate biosensor using antibodies just proving too difficult. Over a decade, Ambri accumulated losses of $96 million until it gave up on the program and changed business activities.

Fermiscan, which tried to develop a test for breast cancer by analysing hair samples in a synchrotron, also hit technology hurdles as a well as having a business model for supplying its test to the market that just wasn't feasible. Fermiscan built up accumulated losses of $59 million and changed its business activities in 2009.

Metabolic Pharmaceuticals couldn't get its anti-obesity drug to pass major clinical hurdles, and has accumulated $81 million in losses to date, with a net decrease in value of $56 million of funds invested (taking into account its current $25 million market value). It is now focusing on wound leading applications with its Polynovo assets and has been renamed Calzada.

Poor Commercialisation

A total of $189 million was invested in mechanical heart group Ventracor before it went into voluntary administration in 2009. Ventracor was a victim of the Global Financial Crisis. However, arguably poor management contributed to the downfall of the company, with another heart pump company Heartware able to successfully move through the challenging GFC period.

The failures at Progen Pharmaceuticals was a result of disputes between shareholder factions and poor drug development in its oncology products. The company has raised $151 million with a market value now of only $4 million to show for it.

If Acrux was an example of how to commercialise a drug delivery technology well, then Norwood Abbey was a case of drug delivery gone wrong. The company generated accumulated losses of $111 million, unable to find successful markets for its products.

Poor Market Research

Chemeq made its way through $149 million before it went into administration in 2007. Chemeq was developing an antimicrobial for use in the poultry and pork industry. However a poor understanding by management of the markets for its products was largely to blame.

Proteome Systems and Life Therapeutics (formerly Gradipore) both developed protein separation products. While they both had products that made it to market, there was insufficient demand from end users to build significant sales from large scale applications. Proteome Systems consumed $106 million and Life Therapeutics spent $100 million.

Although Metabolic Pharmaceuticals couldn't get its obesity treatment drug to market, ironically an illegal market for an injectable form of the drug has emerged in sports and bodybuilding from drug supplied from China. This supports the argument that the drug should have been developed as an injectable, not in an oral tablet form.

Neuren Pharmaceuticals is continuing the development of its neuroprotective drug candidates, with Phase III trials underway. Investors there are $35 million under water at the moment, based on funds invested and current market value. The company's Phase III trial with Glypromate failed because the company selected the wrong patient population i.e. those undergoing coronary artery bypass surgery in fact don't experience much cognitive decline as thought. The company currently has a number of Phase II trials underway or in planning.

Avexa's HIV drug candidate showed every sign that it would work. However, when the company found it would have to double the size of its pivotal study, this put completion of the Phase III studies out of reach. Also having a twice a day drug did not fit in well with once a day HIV therapies. The company has acquired some mining assets and is still attempting to complete development of the HIV drug candidate. The company has a market value of $14 million ($11.9 million in cash) having raised $157 million in funds.

Pharmaxis

Pharmaxis has seen the greatest decrease in value of funds invested in a company. The company is continuing to commercialise Bronchitol (inhaled mannitol). It is on the market in Europe, although take-up has been disappointing to date. It has been knocked back by the FDA recently and together with a failure to meet the primary endpoint in the Phase III bronchiectasis trial has caused the stock to plummet.

What are the reasons for the setbacks? The most prominent rea-

Cont'd over

son has been poor patient compliance. This has resulted in an underperformance, particularly in the first Phase III study in cystic fibrosis. Poor patient compliance is also linked to the poor market performance of Bronchitol. This would suggest a failure in the market research work for the product.

Patient compliance might be improved with a more suitable inhalation device (in development) that would allow a more straightforward delivery of the 400mg (10 separate capsules currently, twice daily) of Bronchitol.

The company's problems can also be attributed to a technical failure in its Phase III trials in cystic fibrosis and bronchiectasis. There has been a $280 million drop in value from the funds raised at Pharmaxis to the current market price. The company is currently capitalised at only $43 million with $73 million in funds at the end of March. The company is continuing to commercialise its Bronchitol and Aridol assets but is seeking partner early stage drug development programs.

Selected Loss Making ASX Listed Biotechs 2000-2013

Company	Estimated Funds Raised (calculated as accumulated tax losses plus cash) ($M)	Current Value ($M)	Cash ($M)	Decrease in value of invested funds to date ($M)	Comments
Pharmaxis*	$323	$43	$73	-$280	Two products on market. Attempting difficult FIPCo model. Drug development failure with FDA to date
Ventracor	$189	$0	$0	-$189	Victim of the GFC and bad management. Went into administration in 2009
Chemeq	$149	$0	$0	-$149	Went into administration 2007. Poor market research and market estimate
Progen Pharmaceuticals	$152	$4	$4	-$148	Shareholder factions, poor development of drug development assets
Avexa	$157	$14	$12	-$143	Blow out in trial numbers in pivotal trial
Norwood Abbey #	$111	-	$0	-$111	Drug delivery gone wrong
Proteome Systems (later Tyrian Diagnostics)	$107	$1	$1	-$106	Poor market research
Life Therapeutics #	$100			-$100	Poor market research
Ambri #	$96	-	$4	$96	Biosensor technology too difficult
Fermiscan #	$59	-	-	$59	Pre-cancer diagnostic program too difficult
Metabolic Pharmaceuticals (now Calzada)	$81	$25	$4	-$56	Should have followed injectable path
Neuren Pharmaceuticals (NZ$)	89.2 (NZ$)	47.6 (NZ$)	6.5 (NZ$)	-$35	Phase II trials continuing. Poor selection of Phase III trial indication.
			Total	**-$1,161**	

* Funds raised excludes recent non equity funding and grants

Accumulated losses prior to change of business

Biotech's Money Makers

One of the metrics for determining the success of an emerging sector such as biotech is to look at whether key players in that sector have enjoyed financial success. In the table on the next page, we list some of the big financial winners from Australian biotech over the last decade.

Some of the gains in the table can still only be considered a paper gain. However 14 of the 21 people in this list have already crystalised substantial gains, either selling stock on market and with nine having prospered through acquisition of the businesses they held shares in.

Topping the list is Mesoblast founder and CEO, Silviu Itescu, with a total net worth of $412 million, with the majority of that held in company scrip. Second on the list is Sirtex Medical founder Bruce Gray, with a net worth of $149 million. Gray has already realised $50 million of that gain from sale of shares and maintains an 18% stake in the business.

In third and fourth places are David and Paul Duchen, who founded the generics business Arrow Pharmaceuticals which was sold to Sigma. The Duchens made in excess of $200 million from the business. Their timing was exquisite, their business plan was perfect and their execution was textbook.

Former CSL CEO, Brian McNamee, is in fifth place. McNamee sold $17 million of shares in 2004 and at last record still holds just under $52 million in shares, giving him a net current value of $71.4 million. Axon Instruments founder and now Chancellor of Monash University Alan Finkel made an estimated net gain of around US$64 million from the sale of that business to Molecular Devices. This calculation assumes Alan held on to half of his Molecular devices shares for 2.5 years, when that company doubled in value because it was also acquired.

The gentlemen from Cellestis, Tony Radford and Jim Rothel, made a very tidy $47.9 million profit when their TB diagnostic business was acquired by Qiagen in 2011. Rothel and Radford partially have CSL boss Brian McNamee to thank for that, with the technology being spun out of from CSL.

The acquisition of diagnostic technology group Vision Systems has put three people on this list. They are CEO Jim Fox, who exited with $16.9 million, director Bruce Parncutt with $6.6 million and executive Finance Director Euan Pizzey with $6.3 million.

Not surprisingly Acrux has delivered some significant wealth for its inventors and management. Inventor Barrie Finnin has, we assume, largely exited with a net gain estimated at around $15 million. Former CEO Richard Treagus has increased his wealth by about $8.6 million, based on his last reported holdings. And inventor Tim Morgan cashed out his 8.8 million shares arguably a little early between 2005-2007, netting an estimated $7 million.

Nanosonics is set to increase the net wealth of a number of its management and investors. Chairman Maurie Stang is sitting on a scrip value of $11.5 million. His brother Bernard is doing slightly better at $11.6 million. Nanosonics investor Steve Kritzler is sitting on $9 million worth of shares.

Cont'd over

Genetic Technologies founder has just under $10 million of shares in that company. QRxPharma CEO and founder John Holaday has an $8.4 million stake in that business. Phosphagenics' Co-CEO and founder Harry Rosen has a shareholding worth $7.7 million.

And the scientist behind the successful biotech Peplin emerged with a $6.4 million gain.

Biggest Personal Winners from Australian Biotech Commercialisation, 2000-2013

Person	Company	Position	Notes	Value of shares sold to date ($M)	Estimated value of current and past holdings ($M)
Silviu Itescu	Mesoblast	Founder & CEO	*Includes $12.9 million of shares sold in 2007 at $2.15/share*	$12.9	$412.8
Bruce Gray	Sirtex Medical	Founder and inventor	*Maintains 18% holding in SRX*	$50.1	$149.0
David Duchen	Arrow Pharmaceuticals	Former Chairman & Founder	*Based on estmated exit prices from sale in Sigma shares*	$115.0	$115.0
Paul Duchen	Arrow Pharmaceuticals	Former CEO & Founder	*Based on estmated exit prices from sale in Sigma shares*	$88.0	$88.0
Brian McNamee	CSL	Former CEO	*Last reported holds 835669 shares in CSL*	$19.7	$71.4
Alan (& Elizabeth) Finkel	Axon Instruments	Former CEO	*Assumes held shares until Molecular Devices was acquired in*	$64.0	$64.0
Tony Radford	Cellestis	Founder and former CEO	*Sold in 2 tranches, first $4.2 million then remainder at $3.80 acquisition*	$47.9	$47.9
Jim Rothel	Cellestis	Founder and former Executive	*Sold in 2 tranches, first $4.2 million then remainder at $3.80 acquisition*	$47.9	$47.9
Jim Fox	Vision Systems	Former CEO	*Based on acquisition price of VSL of $3.75*	$16.9	$16.9
Barrie Finnin	Acrux	Inventor	*Estimate on shares sold between 77 cents and $3.50*	$15.4	$15.4
Bernard Stang	Nanosonics	Shareholder	*Based on current holding*	$0.0	$11.6
Maurie Stang	Nanosonics	Chairman	*Based on current holding*	$0.0	$11.5
Mervyn Jacobson	Genetic Technologies	Founder	*Based on current shares held of 127 million*	$0.0	$9.9
Steve Kritzler	Nanosonics	Shareholder	*Based on current holding*	$0.0	$9.0
Richard Treagus	Acrux	Former CEO	*Based on last known holding of 2.08 million shares*	$0.0	$8.6
John Holaday	QRxPharma	Founder & CEO	*Currently holds 7.6 million shares*	$0.0	$8.4
Harry Rosen	Phosphagenics	Joint CEO	*Currently owns 64.2 million shares*	$0.0	$7.7
Tim Morgan	Acrux	Inventor	*Estimate based on shares sold between 2005-2007 for 60-77*	$7.0	$7.0
JB Parncutt	Vision Systems	Former Director	*Based on acquisition price of VSL of $3.75*	$6.6	$6.6
James Aylward	Peplin	Inventor	*Based on acquisition price of $1.03*	$6.4	$6.4
CE Pizzey	Vision Systems	Former Executive	*Based on acquisition price of VSL of $3.75*	$6.3	$6.3

Best Australian Biotech Listings

The table below lists the best ever performing biotech listings on the ASX. There have been some stunning performances, however only 10 from the approximate 130 listings have seen their share price more than double over that time. Once again the impact on financial market conditions from the GFC can not be ignored. Approximately 40% of biotech companies that listed have either been delisted, changed business focus, or a have acquired a new biotech business development activity.

CSL has been the standout success in the sector, delivering almost an eight 80-fold gain from when the company listed in 1994. The consolidation of the blood products industry through two, large, well-executed acquisitions has delivered stunning success for the company.

Bionic ear company Cochlear has delivered an extremely impressive return for investors also since it listed in 1995. The company's share price has increased 25-fold over the last 18 years.

Cellestis, which was acquired in 2011, experienced a 1400% increase in share price during its time on the ASX. Mesoblast to date has recorded over a 1000% gain in price. Sirtex Medical has delivered just short of a 900% gain. Medical Developments to date has achieved a 540% increase from listing, with most of that gain having occurred in the last 12 months. And Heartware, Arrow Pharmaceuticals and Acrux have delivered shareholders a gain of between 300%-400% since listing.

Top Performing ASX Biotech Listings

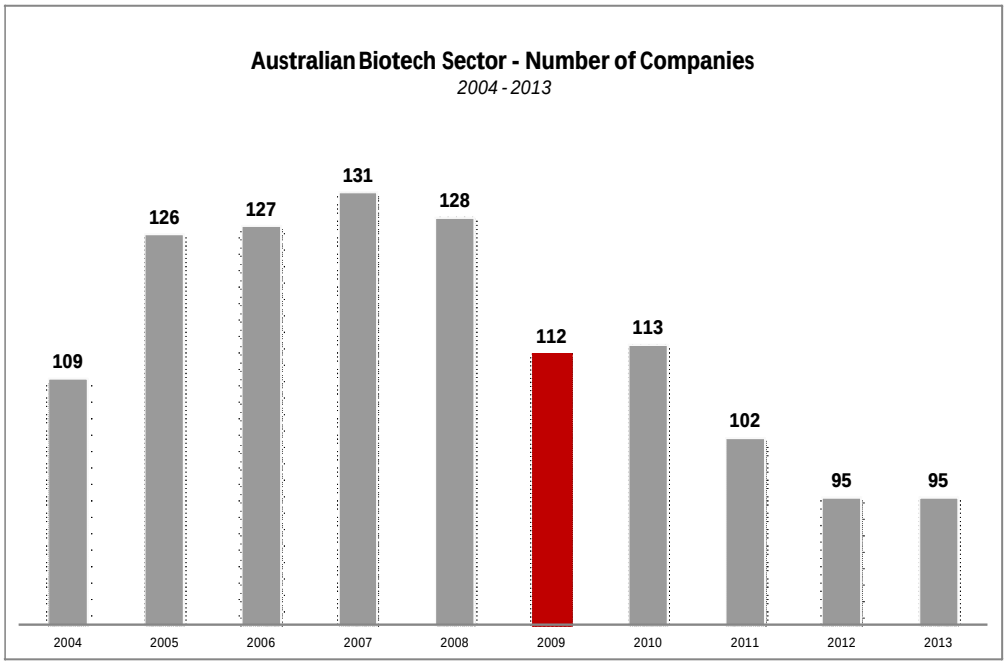
Date of Listing	Company	Listing Price	Current/ Final Price	Change	Current Value $1,000	Notes
1994	CSL	$0.77	$61.91	7975%	$80,752	Note 3 for 1 share split
1995	Cochlear	$2.50	$65.19	2508%	$26,076	
2001	Cellestis	$0.25	$3.80	1420%	$15,200	Acquired in 2011
2004	Mesoblast	$0.50	$5.82	1064%	$11,640	
2000	Sirtex Medical	$1.00	$9.82	882%	$9,820	
2004	Medical Developments	$0.25	$1.60	540%	$6,400	
2005	Heartware	$0.50	$2.36	372%	$4,720	
2002	Arrow Pharmaceuticals	$2.75	$11.60	322%	$4,218	Acquired by Sigma in 2005. Note five for one share split
2004	Acrux	$1.00	$4.12	312%	$4,120	
2000	Peplin	$0.40	$1.03	158%	$2,575	Acquired in 2009
2000	Axon Instruments	$0.20	$0.36	80%	$1,800	Acquired in 2004

The Number of ASX Listed Biotechs

The chart below shows the changes in the number of listed biotech companies whose shares trade on the ASX. At the end of March 2013 there were 95 listed biotechs on the ASX, down from the peak of 131 in 2007.

What is starkly clear is the direct impact that the global financial crisis has had on the biotech sector. Within two years the GFC wiped out 19 biotechs, compounded by the federal governments cessation of the Commercial Ready Start grant system.

Since 2007, there has been a 27% drop in the number of companies. However what has been impressive is the bounce back in the sector market capitalization, which fell by 54% in 2008 to $3.5 billion, to reach $9.0 billion at the end of March 2013. This excludes the $7.1 billion of acquisitions over the last eight years and the performance of the larger cap stocks CSL, Sigma, Cochelar and Resmed.

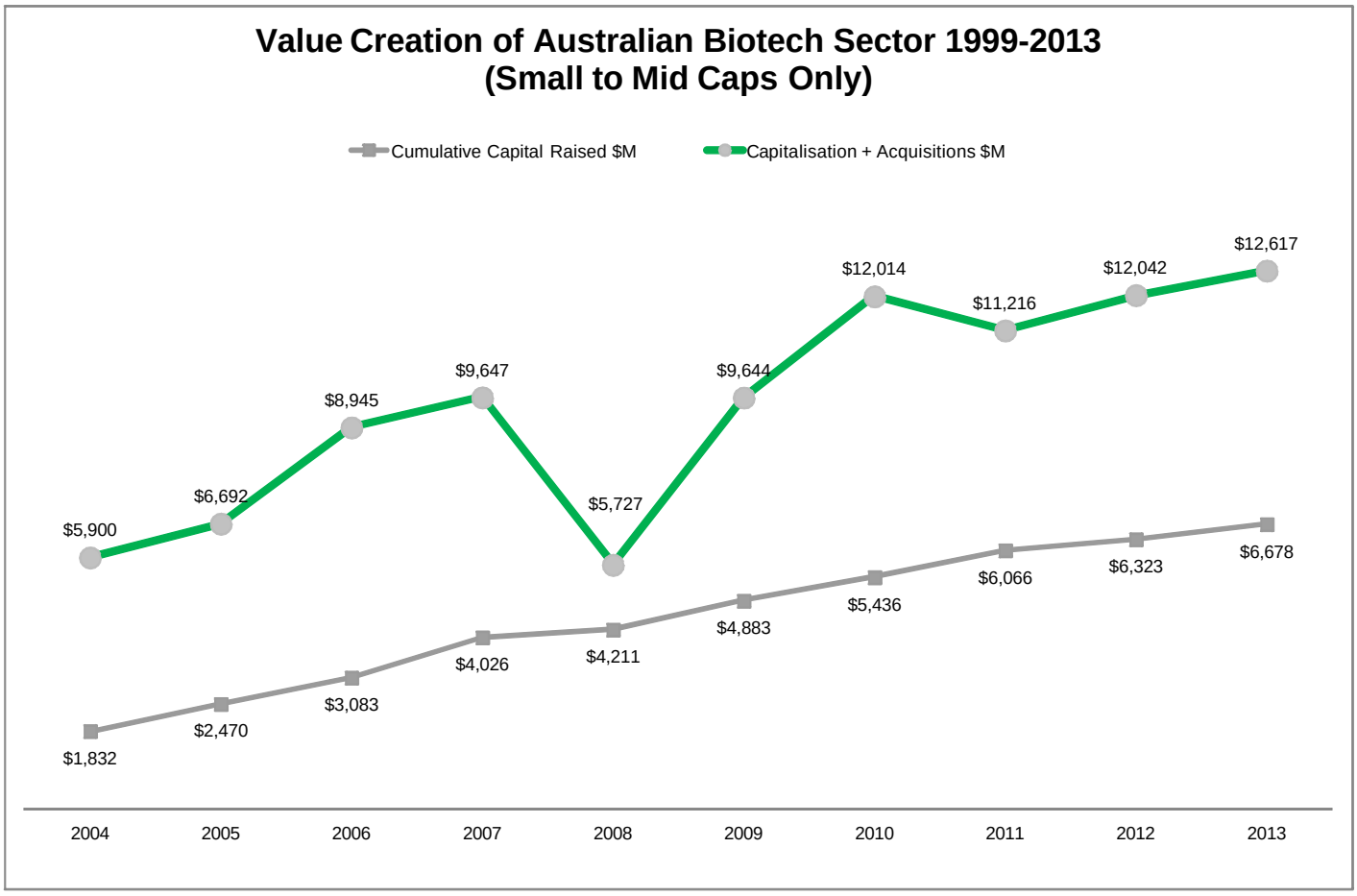


Value Creation from Australian Biotech

The chart below is a visual representation of the value that has been created from the Australian biotech sector from 1999 to 2013. The top line shows the changing market capitalization of the small-medium cap biotech companies, adding back in the value of any acquisitions that have occurred in previous years. The bottom line shows the cumulative level of funds that have been invested since 1999 (although only values from 2004 are displayed).

The chart excludes the acquisitions of the established pharmaceutical companies Mayne Pharma and Sigma's pharmaceutical assets. It includes only funds raised through public equity markets, so excludes those funds raised by companies prior to listing.

At the end of March 2013, the capitalisation of the small-medium cap biotechs plus the value of companies that have been acquired was $12.6 billion. This compares to the $6.7 billion in funds raised in the sector since 1999, representing a value creation over 14 years of $5.9 billion.



Bioshares Model Portfolio (26 April 2013)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	$0.260	$0.270	March 2013
Tissue Therapies	$0.135	$0.255	March 2013
Allied Healthcare	$0.030	$0.026	February 2013
Psivida	$2.12	$1.550	November 2012
Benitec	$0.014	$0.016	November 2012
Nanosonics	$0.405	$0.495	June 2012
QRxPharma	$1.10	$1.66	October 2011
Somnomed	$0.91	$0.94	January 2011
Cogstate	$0.380	$0.13	November 2007
Clinuvel Pharmaceuticals	$1.91	$6.60	September 2007
Universal Biosensors	$0.61	$1.23	June 2007

Portfolio Changes – 26 April 2013

IN:
No changes.

OUT:
No changes.

Review of Biotech M&A

Since 2005, there have been at least 19 Australian biotech companies that have been acquired for a total value of $7.1 billion. Of these acquisitions, 16 were made by overseas companies, delivering some excellent exits for investors and management.

The largest acquisition was of pharmaceutical group Mayne Pharma, with Hospira paying $2.6 billion for that business. Sigma sold its pharmaceutical business to Aspen Pharmacare for $900 million in a distressed sale to improve its capital position.

Standout successes in the sector include the sale of Vision Systems to Danaher Corporation for $791 million, which was announced in 2006 and completed in 2007. The generic drugs company Arrow Pharmaceuticals was sold to Sigma for around $733 million. The sale of Cellestis to Qiagen for $360 million was eventually accepted by shareholders in 2009 when Qiagen increased its bid to $3.80 a share (from $3.55). Chemgenex Pharmaceuticals achieved a successful exit from the sale of its oncology business to Cephalon, valuing the company at $255 million.

The disappointing exits in the sector include Arana Therapeutics, which was bought in the midst of the GFC by Cephalon for not much more than its cash and future royalty entitlements. The purchase of Cytopia by YM Biosciences was also a disappointment given the prominence now of Cytopia's compound CYT387 in the YM pipeline and the value creation that has occurred for YM as a direct result. Stem Cell Sciences which was bought for only $5 million generated little value for its shareholders.

Of interest is that a trend has emerged whereby every two to three years sees a raft of acquisitions in the Australian biotech sector. In 2006 there were six acquisitions in the sector, in 2009 there were four acquisitions, and in 2011 four local companies were bought. Given there have been no acquisitions now in this sector for two years suggests we may see some increased M&A activity over the next 12 months but only where M&A factors are in place. This may trigger an improvement in sentiment towards the Australian biotech sector.

Acquisition targets in the Australian biotech sector include the revenue generating companies Acrux, Sirtex Medical, Nansonics and Universal Biosensors, and Pharmaxis and Impedimed, which fall more into a distressed asset class. QRxPharma and Osprey Medical may be acquired if they successfully achieve pivotal development or registration milestones.

Acquisitions of ASX Listed Life Science Firms

Company	Acquirer	Year	Acquisition Price ($M)
Mayne Pharma	Hospira	2006	$2,600
Sigma (pharmaceuticals business)	Aspen Pharmacare	2011	$900
Vision Systems	Danaher Corporation	2006	$791
Arrow Pharmaceuticals	Sigma	2005	$733
Cellestis	Qiagen	2011	$360
Peplin	Leo Pharma	2009	$348
Arana Therapeutics	Cephalon	2009	$318
Chemgenex Pharmaceuticals	Cephalon	2011	$225
Axon Instruments	Molecular Devices	2004	$186
Evogenix	Peptech	2007	$156
Ascent PharmaHealth	Strides Arcolab	2011	$100
Amrad Corporation (Zenyth Therapeutics)	CSL	2006	$100
Gropep	Novozymes	2006	$96
Lipa Pharmaceuticals	Apil Healthcare	2007	$91
Enterix	Quest Diagnostics	2006	$57
PanBio	Inverness Medical	2008	$37
Bresagen	Hospira	2006	$21
Cytopia	YM Biosceinces	2009	$14
Stem Cell Sciences	Stem Cells Inc	2009	$5
			$7,138

Bioshares

Some Observations on Biotech Investing

by David Blake, Editor, Bioshares

To mark the 500th edition of Bioshares, I thought it timely to jot down some observations about investing in biotech. Some fit into the tips and tricks category of observations. Others are meant to encapsulate a way to think about investing in a specific asset class, and perhaps one or two are general and are not exclusive to biotech investing. These observations are not organised in any particular order.

1. Buying Patients

Drug development has been simplified as a process that proceeds from pre-clinical testing to a clinical development phase which sees drugs tested for safety and efficacy. Phase I studies involve small numbers of patients in which safety is studied. Phase II studies also evaluate safety and explore dosing and begin to explore efficacy. Phase III studies, which matter most when fronting drug regulators, necessitate larger numbers of patients in which groups are randomized to treatment arms and control arms. The control arm may involve the administration of a placebo or whatever is considered the standard or care.

That's the simple outline of the standard process but trials (or the requirements set by regulators) vary according to disease state, the number of patients that the disease effects and other characteristics of the patients.

A challenge for Phase III trials is to design them so that they are sufficiently powered. A properly powered studied will mean that the trial sponsor will avoid a result that appears to show a drug is ineffective when in fact it is effective. The way to attend to the risk of this error is recruit a greater number patients than might be necessary in the first instance. The catch is both time and money, complicated by the pool of patients suitable for recruitment and the degree of competition for those patients.

What's the investment point? Estimating a number for an entire clinical program and hence cost of patients that are necessary to maximize the chances of positive data sets to include in a submission to a drug regulator is a rough but first exercise for an investor to perform. If this figure exceeds the net present value of potential (net) revenues for the drug candidate then the flashy drug candidate AAA-001 is a dead'un.

The 'Buying Patients' simplification of what is really going on in the world of drug (and device) development is one of budgeting. Australian drug developers, it might be argued, have been less than successful because they have taken short cuts in the budgeting for patient numbers in clinical trials. A company's clinical strategy may need to be enlarged and adapted along the way to include additional trials that are designed to answer regulatory questions or to generate label claims that improve the competitive position of a therapy. What company has allowed for this budget demand? One that comes to mind is QRxPharma which added supplementary studies to its MoxDuo IR program.

As a footnote to this discussion, the reason why some drug candidates developed by small Australian biotechs don't get partnered to larger pharmaceutical companies is that they don't pass the cost of development and revenue tests applied by these larger firms.

2. Clinical Trials and the Enrolment Rate

One useful tactic for biotech investors to apply is to monitor recruitment rates in clinical trials. Delays and slowdowns can be construed to mean that the therapy is not preferred by clinicians or even patients, or that competitors have a lock on trial sites. The flip-side is that if a trial recruits on time or earlier, then it's a useful signal to buy the stock.

3. The General Manager as CEO

A problem I have observed with Australian biotech companies over the years is that of the CEO who acts as a general manager. The general manager mindset can work well for small private companies with few shareholders, such as VC backed companies.

However, it is more apt to cast the CEOs of listed biotechs as Chief Investor Relations Officer. There have only been few listed biotechs that have not needed to repeatedly return to the market for capital. The emphasis on investor relations requires a change in attitude for some who take on the CEO role if their career has had a business development, research or clinical focus. But it's a fundamentally necessary disposition to develop.

A consistent failure I have observed is that the CEOs bump up communications with the market when they need fresh capital and not before. Properly-focused CEOs take pro-active roles in cultivating new investor groups, maintaining links with existing investors, all the while applying cash in the bank to pay other executives to manage patent portfolios and contracts, oversee trials, and do the financials.

Is there an investment implication in all of this? Absolutely! A primary reason to divest a stock, more than technical and regulatory risk, is funding risk. A company without cash is a dead company, no matter how promising the assets. So whether or not a company orients itself towards investors, rather than away, can be read as a positive investment sign.

4. Manufacturing is 50% (of Drug Development)

A rule of thumb I have developed is that manufacturing accounts for at least 50% of risk and effort and value creation in drug development. This is in contrast to the emphasis placed on clinical development and progression through trials in human subjects. Clinical trials are important but so is the manufacturing of a drug or device.

The FDA places huge importance on manufacturing as a source of product risk. That organisation obtains considerable information about manufactured material and manufacturing processes when companies file Investigational New Drug applications. So when a company doesn't get a seal of approval for its IND or when it doesn't even think it should be attempted, take that as a sign that the company isn't serious about its business.

Apart from the safety side of manufacturing, there is also the

economics of manufacturing to consider. There is a vast difference between a drug that has six manufacturing steps and one that has more than 50, a lesson learned from Alchemia's experience with fondaparinux. Yes, the complex manufacturing stands as a barrier to entry but much time and money was spent to improve the manufacturing process with delays upsetting shareholder expectations for revenue flow.

5. Who Owns the Business?

Perhaps the most important insight I have made from analyzing biotech stocks is not in fact specific to that class (or sub class). It is the insight that investors must understand who the *other* owners of the business are in terms of their particular ownership or investment goals. It matters to know and understand who other share owners are to determine the potential for conflict, the degree of control or influence they hold and their investment horizon.

Capital Career

This investment consideration is related to another very important concept for biotech investors, which is that companies without revenues are tasked with managing a capital career. A capital career describes the series of capital injections which firstly start the company, then to progress the commercialisation of a technology, and to support the sales and marketing of goods and services until free cash flows emerge and grow.

A successful capital career is one which sees transition in the share register as groups of investors (owners of the business) are replaced by new groups (owners of the business) with a new investment horizon, different appetites for risk and portfolio considerations.

Transitions occur ideally when one group of shareholders crystallise profits by selling shares to new investors who have formed a view that share price will continue to increase. Such transitions can occur when a company crosses a capitalisation threshold which puts the stock in the view of a new set of investors. These transitions can also occur when the risk profile of the stock changes (reduces) and if further upside is determined to exist.

One facet of register composition is the number of large shareholders and the aggregate shareholdings of the top two or three or even the top twenty. Companies with a concentrated ownership can have (with a smaller proportion of the company residing in the hands of smaller investors) a little free float, which means the supply of stock is limited. As with any good in short supply that faces a period of strong demand, the stock price can rise substantially in the face of little causative force.

The investment implication is this: look for stocks with a small 'free' float and time your entry into a stock with a group of investors, possibly institutional, so that you have alignment with some other shareholders.

6. Technologies in Search of Products in Search of Customers...

Technologies that can be used to create multiple products are known as platform technologies. They are attractive to investors because they deliver what is known in the trade as 'multiple shots at goal'. If one product fails for whatever reason, then others in development can take its place. Benefits flow to investors if certain early stage development steps don't need to be repeated, for example, clinical safety studies. And insights accumulated over time from one area of use might also be used to advance development in other areas. Another advantage with platform technologies is that income can be generated by products that are at the periphery of the platform. So in a variety of ways, platform technologies can offer the potential high reward accompanied by a decrease in various risks.

Companies in control of platform technologies act as portfolio managers, which is not always a feature welcomed by investors who prefer to make portfolio allocation decisions themselves.

However, where platform technology companies can fall down is when they look to develop products for markets or customers where there is no evidence of need, or validation of potential revenues, obtained from market and product research. It becomes an expensive effort in trying to put a square peg in a round hole.

More generally, what many Australian biotech companies have failed to do is to rigorously assess product candidates from an end-user, be it doctor, patient, nurse, or receptionist, and an end-payor perspective.

A related phenomena to 'technologies in search of products in search of customers' are companies that aim to 'never get out of Phase II'. Investors should look for the pattern in which a company moves from the failure of a drug in one setting into another and into another. Sometimes this is valid and sometimes it is not valid. There comes a time when a company should call it quits and stop spending shareholders money.

7. Information Asymmetry

The reality for investors in a biotech company is that they will only ever be appraised of a fraction of the relevant information that a company is capable of supplying and should supply. Actually, that's a reality that applies to pretty much any investor in any listed company. It is my personal opinion that listed companies act with much discretionary power when it comes to following the ASX's Continuous Disclosure rules.

The exemptions to Listing Rule 3.1 offers enormous latitude for companies to avoid disclosure. And a company can even make a statement about a material event of the highest order but essentially say nothing at all by being bland, vague and brief. Such an approach simply generates distrust.

One compensation biotech investors have when it comes to material information are the websites www.clinicaltrials.gov and the European Clinical Trials register, www.clinicaltrialsregister.eu. At least most companies feel compelled to post clinical trial design information to these centralised bodies.

Another help for investors has been the ASX Listing Rule 4B, which has required cash flow negative companies that have listed since 2000 to provide quarterly cash flow statements.

Cont'd over

Information asymmetry of another form occurs as a consequence of geography. Much of what Australian listed biotechs do is conducted or focused on offshore locations, especially in the US and Europe. It is more expensive for Australian-based investors to monitor and assess activities off-shore.

What is an appropriate investment strategy for investors to deal with problems of asymmetry? There are in fact several strategies available to investors. The first is the common and established approach to risk-weight stocks of interest and using those risk weightings to determine portfolio allocations. What biotech investors must aim to do is to get those risk weightings right.

A second strategy is to discover and study competitor companies and their products in detail and learn about the commercial context for a new product. It is much more difficult for the CEOs of biotech companies to dismiss information and data for rival products from discussions with investors.

8. It Goes Without Saying…

It goes without saying that the vast majority of life science stocks that are traded on the ASX are speculative.

Speculative means the risk of losing all of one's invested capital is very high.

This perspective can be lost by investors the more they attach themselves to biotech stocks and the longer they attach themselves to the sector, or even one stock.

While the speculative character of most biotech stocks might appear to be obvious, it worth remembering every time a cheque is written to buy shares after an enthralling meeting with a mercurial CEO.

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Pharmaxis, Starpharma Holdings, Cogstate, Bionomics, Biota Holdings, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phosphagenics, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Bioniche, Atcor Medical, Invion, Circadian Technologies