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In this edition...
Pharmaxis announced results of its first Phase III cystic fibrosis trial for Bronchitol and the results were good. Not all data was released but the trial results indicate that Bronchitol was comparable to Genentech's Pulmozyme registration data.
And speaking of Genentech, we also include a succinct analysis of how workplace culture has been arguably decisive in creating the powerhouse that Genentech became, prior to its acquisition by Roche. The question is will that culture be maintained.
We also take note of strong and consistent demand for Cogstate's cognition tests. Virotherapy company Viralytics is in a capital raising mode and looks to be the first biotech to adopt an options rights issue as a fund-raising technique.

The Editors
Companies Covered: CGS, PXS, VLA

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.0%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.3%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.3%
Year 9 (May '09 - Current)	5.0%
Cumulative Gain	**104%**
Av Annual Gain (8 yrs)	**14.7%**

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Bioshares

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

Excellent Result For Pharmaxis Phase III Cystic Fibrosis Trial

Pharmaxis delivered its most important clinical result to date: data from its first Phase III Cystic Fibrosis (CF) trial in 324 patients with its lead therapeutic product Bronchitol. The result was excellent and consistent with previous data. Overall a 6.6% improvement in lung function (FEV1 level) was achieved, which was sustained at 26 weeks of treatment.

The main competing drug for Pharmaxis is **Genentech**'s Pulmozyme, which in 2007 generated global sales of US$440 million. According to Roche's Pulmozyme Product Information document, over 24 weeks Pulmozyme delivered once daily by nebuliser delivered an average 5.8% improvement in lung function (FEV1).

A requirement of the trial was that patients being enrolled into the trial would continue existing therapies. As a result around 55% of patients in both the control and the Bronchitol arm continued to receive Pulmozyme throughout the trial. In the group of patients on Pulmozyme therapy, their lung function improved by 5.2% from baseline after six months. In the patients not taking Pulmozyme, their lung function improved by 8% after six months from baseline.

Any result over 5% represents a meaningful commercial therapy for patients. That this was achieved in both patients taking Pulmozyme therapy and those not on Pulmozyme improves the commercial application of this drug.

Of the participants in the trial, 7% were excluded due to an intolerability to the drug (linked most likely to undiagnosed asthma). The most common adverse event was a cough.

Data not included

The results will be presented at a CF conference in France in June and at another meeting in Minneapolis in October. The data released did not include secondary endpoints such as antibiotic use, and the quoted figures are over baseline, not over the placebo, where it would appear around a 1% improvement in lung function was observed. The quoted

Cont'd over

figures also refer to the improvement in lung function at the end of the trial, not the average or mean change during the trial period although the results look reasonably consistent across the trial period. Of positive interest is that Bronchitol effect was sustained at week 26, where there was around a 3% fall away in lung function in the last 20 weeks in the control arm taking Pulmozyme treatment.

The results for Bronchitol are consistently good. The 8% improvement in lung function in patients not on Pulmozyme is a very strong result. Even with a 5.2% benefit in patients taking Pulmozyme, there is now a strong argument for Bronchitol to be administered in conjunction with Pulmozyme.

Will Bronchitol take market share away from Pulmozyme?

Given the ease of delivery of Bronchitol (in a hand held puffer) compared to the restrictive and time consuming delivery of Pulmozyme (through a nebuliser), and given the 8% headline improvement in trial participants not on Pulmozyme, Pharmaxis' Bronchitol will almost certainly take some market share away from Genentech's Pulmozyme once approved for use.

Path to Market

This trial should be sufficient for Pharmaxis to file Bronchitol for use in the treatment of cystic fibrosis in Europe by the end of September. If all goes well, to which we assign a high probability that it will, then the drug should gain approval within 12 months in Europe.

There is a second Phase III trial underway which is required to gain regulatory approval in the US. This trial is seeking to enroll 300 people with CF with 100 enrolled to date. Enrolment is expected to be completed by mid year. Pulmozyme use is higher in the US, in around 70% of people with CF. This predominantly US-based trial will be a similar design to the first Phase III trial.

Bronchitol has been granted orphan drug status in Europe and the US, and as a result will be given up to 12 years and seven years market exclusivity in those regions respectively if approved. Positively, there is also a question mark over how generics will enter the market with this product without completing their own trials given that pharmacokinetic (blood absorption profile) data cannot be gained, as the body does not absorb Bronchitol. (Bronchitol is an inert powder than draws water across 'faulty' lung tissues in people with CF through osmosis).

Bronchiectasis

While there are around 75,000 people in the world with CF, it is estimated there are over 600,000 people worldwide seeking treatment for a degenerative lung condition, termed bronchiectasis. Pharmaxis has completed one Phase III trial in bronchiectasis, with a second Phase III trial expected to start shortly and to be completed in 2010, after which the company should file for approval in Europe and the US. Bronchitol was filed for regulatory approval last year in Australia to treat this condition.

Summary

On the back of the company's most important clinical trial data received to date, Pharmaxis is well placed to bring its product onto the second largest pharmaceutical market in the world, in Europe. Given the strong links within the global CF community, direct distribution with its own sales force or local third party distributors is possible.

Bronchitol is manufactured by Pharmaxis in Sydney. The plant has a capacity to treat 40,000 people a year with CF, or just over half of all the people in the world with CF. At a price of US$13,000, the product would bring in around US$500 million a year for Pharmaxis at full capacity. At a multiple of 8 – 10 times sales, Pharmaxis has the potential to become a multi-billion dollar company based on the CF application alone.

Pharmaxis is capitalised at $508 million with $85 million in cash at the end of March.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Strong & Consistent Demand Continues For Cogstate Service

Cogstate continues to deliver a consistent result from operations. The company is now generating annual revenue of just under $7 million a year ($6.88 million trailing 12 months). It has become a profitable business. And we expect strong sales growth to continue that could exceed $10 million in financial year 2010.

Cogstate provides cognitive testing services to pharmaceutical companies running clinical trials using its proprietary software system. Demand for its services continues to be strong and has not been affected by the global economic slowdown, which the company cautiously warned previously might occur. For this financial year the company expects to record a net after tax profit of between $1.5 – $1.75 million (with only a small amount of tax payable from the use of some unrecouped tax losses totaling $6.9 million at the end of June last year).

Net cash flow for the first quarter of this year was just positive for the second consecutive quarter, at $30,000, although adding the change in debtors for the period (the company has no bad debts this financial year so it can be assumed these additional funds will be received), the figure is just under $160,000. Cash flow for the first nine months of this financial year was $535,000 (or $1.2 million including the increase in debtors from nine months ago).

The lower Australian dollar has had a significant impact on profitability for the company. The company may look to hedge its foreign currency exposure as revenue increases and becomes more predictable. The company is also working on delivering cost efficiencies into its service over the next 12 months.

The growth in the business is coming from expanding the company's customer base and increasing market share from competitors. The market continues to grow as more pharmaceutical companies move from pencil-and-paper type cognitive tests to more advanced electronic testing procedures. In April alone, the company signed an additional $1.12 million in contracts. Cogstate has at least two major competitors that also supply electronic cognitive testing products and services.

We estimate sales for this financial year will be around $7.5 million which will double the previous year. We expect the strong sales growth to continue into FY2010 exceeding $10 million in revenue with a profit after tax of between $2 – 2.5 million (with further use of unrecouped tax losses).

Cogstate is capitalised at $14 million with $2.7 million in cash. Based on the company's forecast earnings for FY2009, the company is trading on a PE of between 11 – 13. There is a strong consistency building in the Cogstate business. We expect Cogstate to continue to deliver strong growth in sales and net profit that should remain relatively unaffected by a slowing world economy.

Bioshares recommendation: **Buy**

Viralytics' Options Rights Issue

Viralytics (VLA: 3.5 cents) is developing an approach to treating cancer that makes use of a property of viruses to lyse (break apart) cells. The company has established IP over strains of a wild-type picornovirus, the coxsackie virus A (CVA), types 13, 15, 18 and 21. The virus typically causes mild upper respiratory tract infections, often typified as the common cold. However, the virus CVA21 binds to two cell surface receptors (ICAM-1 and DAF) that are over-expressed on cancer cells. When the virus binds to the cancer cell it infects and lyses the cell, in this way, killing the cancer cell.

In addition being a targeted therapeutic, Cavatak also has rapid onset of action, with cells infected in a time period of six to ten hours. Another aspect of the therapy is that it utilises a wild-type virus and is not engineered, conferring stability through the production process and potentially a greater degree of comfort with drug approval agencies.

The virus is generally found in about 10% of the population, which have seroconverted, that is, they have developed antibodies to the virus. Although this might suggest a limitation to the therapy, in fact it indicates that the coxsackie virus, while relatively common, is generally benign. In non-seroconverted patients the goal is to deliver a dose that is lethal to cancer cells but not to normal cells. This can be achieved because of the relative over abundance of ICAM-1 and DAF on cancer cells.

To date, the company has dosed 17 cancer patients, with no adverse effects reported. In five melanoma patients dosed in a two patient pilot study and a three patient Phase I study, some reductions in tumours were observed, with no product related adverse effects. In a second melanoma patient Phase I dose ranging study, similar outcomes were reported.

A challenge with developing oncolytic viral therapies is determining the effective therapeutic dose. Although a particular dose might be administered, the process of replication that follows can see orders of magnitude increases in viral load. Robust assays that measure potency are required in order to determine the effective dose, and agreement on this aspect of trials that fall under an FDA IND approval process will be crucial for the clinical development of the technology for the US market.

Limitations?

The therapy is limited to ICAM positive cancers and to patients who have not developed antibodies to the coxsackie A 21 virus. The potential of the therapy may be limited by routes of administration. If direct injection into tumours is found to be the most efficacious route of administration, then therapeutic approach may be limited, dependent on the ability of oncologists to locate and access tumours. This may be less of an issue as increasingly sophisticated imaging technologies emerge. Viralytics has begun to evaluate the intravenous administration of Cavatak in prostate, breast and melanoma patients.

Phase II trial

There is clinical appeal to the Viralytics therapeutic approach because of its emerging safety profile which is related to its selectiveness to cancer cells. However, as with many novel approaches to treating cancer, the efficacy of the approach can't be properly ascertained until Phase II trials of the therapy are conducted (in trials with sufficient patient numbers) and in trials that compare the effectiveness of the therapy against standard of care. Viralytics has developed plans for a Phase II trial which would enroll 60 patient in a cross over design, randomized to standard of care as the control.

A Phase II trial will also be useful in determining if antibodies that neutralise Cavatak are produced in sufficient quantity to render the therapy ineffective after administration. (Earlier studies report that neutralizing antibodies were produced 10 days after a first injection.)

Capital Raising

Viralytics is currently conducting a capital raising with an initial tranche of funds to be obtained through an options rights issue. The company hopes to raise $3 million (minimum $1 million) through the issue of 302 million 1 cent options that have a 29 June 2010 exercise price of 4 cents. If all the options under the options rights issue were taken up, and if all options from this new class were exercised, the company could raise a further $12.1 million.

The purpose of the fund raising is to support the pre-Phase II development Cavatak, including the manufacture of product from contracted GMP standard facilities and to complete three Phase I trials planned or underway.

The plan by Viralytics to use an options rights issue is novel and is an approach not yet tried by a biotech company. Rights issues are attractive to shareholders who wish to maintain their proportional shareholding in a company. As such an options rights issue does the same thing but in effect allows for a greater portion of the funding to be contingent and deferred. If the company gets the go-ahead to progress to Phase II trials under an FDA Investigational New Drug application filing, then there is a greater likelihood of a positive share price response.

Summary

In the event of being unable to raise sufficient funds through its options right issue, Viralytics faces an uncertain future. The company's cash balance as of March 31, 2009 stood at $976,000. However, the company has steadily advanced its Cavatak therapy in the clinic and has had several patents granted (including an important foundation patent in the US). The current funding plan at least allows the company to ensure that necessary elements of its Phase II plan under an FDA IND application are in place.

Viralytics is capitalised at $11 million.

Bioshares recommendation: **Speculative Hold Class C**

Genentech's Culture

by Jocelyn Ng, Ph.D.

On Thursday, March 12, 2009, Genentech finally accepted an offer from Roche to buy up the remaining 44% of Genentech shares that it did not own at US$95 per share, a price tag of US$46.8 billion. For eight months, Genentech rejected offers made by Roche. Genentech claimed Roche was undervaluing the biotech company but there was concern in losing their innovative culture, which Arthur Levinson, Genentech's chairman and CEO, has highlighted time and time again.

What makes Genentech impressive?

Everyone in biotech knows of the stature and reputation of the company within the industry. But Genentech's own Investment Community Meeting webcasted on 02 March 2009 highlighted the following points:

– on track to achieve or exceed their strategic objectives for 2010:

- No. 1 in Oncology sales in the U.S. (and they have been since 1Q 2006);
- 25% Non-GAAP earnings per share, EPS, growth rate, CAGR (EPS CAGR) for 2008 was 39% which is "faster than that of any other company with a market value of more than $50 billion, including Apple, Oracle and various oil producers."
- 20 new molecule entities, NME, in clinical development (actual numbers indicate 23 NME from January 2006 to December 2008)
- 15 Major New Products of Indications Approved (received 12 approvals - 1 new and 11 additional indications - by Q4 2008)
- Cumulative Free Cash Flow of $12 Billion ($6.8 Billion for 2006-2008 and a projected $7.9 Billion for 2009-2010 totals approximately $14 Billion)

– an enviable discovery and development pipeline: 19 in Phase I, 14 in Phase II, 12 in Phase III, four in FDA submission preparation, and three awaiting FDA action. Several of these are the same drug in different disease indications;

– 25 key collaborations with 17 different pharma and biotech companies that (will) feed into their discovery and development pipeline;

– six therapeutic areas including oncology, immunology, tissue growth and repair, infectious disease and neuroscience. (Note that the decision to expand into Infectious Disease and Neuroscience came only in January 2006.

How did Genentech achieve this track record?

The Strategic Overview of the company highlighted 4 guiding principles:

Scientific Excellence	People & Culture
Execution	Long-term Planning

One can interpret this as people and their performance – scientific excellence and people and culture – are key but have to be supported by management that can perform in terms of execution and long-term planning.

A number of reports have largely attributed Genentech's success to its innovative and entrepreneurial culture. The main argument is that there is an intimate link between scientific excellence and R&D productivity. This productivity is fostered through an open and fun environment that encourages initiative, creativity and innovation and which ultimately generates loyalty. Another key theme has been that retaining and motivating the most talented and productive employees contributes to the bottom line. Nevertheless, Genentech has been a well-run company that understands that the key factors to continued success are commercial execution, R&D productivity, financial discipline and effective use of cash.

How did Genentech achieve this innovative culture?

Levinson has said: "You can make it really complicated or really simple…. If you want an innovative environment, hire innovative people, listen to them tell you what they want, and do it."

From the recruitment stage, Genentech attracts talented employees, not just scientists. Nevertheless, the company makes sure it hires the right people through a rigorous process of possibly up to 20 interviews. Key research team leaders are highly credentialed: for example, ex-professors or Howard Hughes investigators or members/fellows of professional organisations like the National Academy of Sciences, the American Academy of Arts and Sciences or the Royal Society.

Once hired, people are entrenched in the culture. The organization is "extremely non-hierarchical". The most well known anecdote that illustrates this value is that even CEO Levinson himself may find it difficult to find parking in the morning. There is a "casual, free-spirited approach" to doing both business and science at every level. Genentech values an informal, enjoyable environment.

To encourage entrepreneurial leadership, researchers are encouraged to spend 20-25% of their time on projects that they choose themselves (industry average is 10%). Scientists are featured on the website similar to how professors in universities are featured with a paragraph or two describing their research interests and a link to their recent and relevant publications. Sabbaticals can be taken. Collaborations and post-docs programs are part of the scientific agenda, thereby accelerating discovery efforts. This culture is supported and underscored by consistent messages emanating from management.

Arthur Levinson was head of research before he assumed the job of CEO in 1995. Early on, he was able to allot half of Genentech's revenues back into research. Up until today, the company's R&D spend has been at 20% of revenues. Genentech funds basic research but in a targeted way. Employees take pride in being involved in such research and are themselves challenged by peri-

Cont'd over

odic reviews in front of a research committee that assesses whether research projects should be continued or not. The argument from the Genentech model is that it is the science that wins over an analysis of the market or on a return on investment. Scientific rigor does make for effective therapeutics: Herceptin is a blockbuster despite the fact that it targets only 25% of the breast cancer population. Furthermore, decision-making is an open, participatory process where both technical and business functions come together for discussion.

Culture has been the company's competitive advantage. The company has top ranking in a number of surveys over the past several years on the best company to work for, notably those conducted by *Fortune* magazine and the journal *Science*. Thus, Genentech is outstanding not only amongst other biotech or life science companies but across all other companies, regardless of industry. Has this recognition been an important factor in recruiting? Genentech has increased the number of therapeutic areas it expects to deliver in and, in parallel, built critical mass in their research programs with a rise in its number of scientists from about 500 in 2001 to almost 1200 in 2008. Their scientific output in terms of publication citations and issued patents does build pride and morale internally as well as continuing to attract talent.

Can innovative culture survive a takeover?

The full support of the management and board is needed to either sustain an effective culture in the work place or repair a damaged culture. When a new CEO comes in and wants to make a difference, he or she can change culture, killing off that which previously existed whether intentionally or inadvertently. To promote or uphold an existing culture means letting go and letting things be which is not easy to do for one whose responsibility it is to lead. At the board level, culture can be maintained and encouraged or changed as well. It is worth noting that Arthur Levinson is on the boards of both **Apple** and **Google**, two very innovative companies with distinct cultures.

Is Roche interested at all in preserving Genentech's culture? Roche Chairman Franz B. Humer told investors in July 2008 that the pharma company would work to maintain the biotech's culture. Humer said "The most important thing is that Genentech scientists can and will continue to maintain their own culture, their own independence, their own freedom to set priorities and review projects the same way they have done in the past."

Nevertheless, there are pressures that can slowly and subtly erode culture, if not outright end it. *BioWorld* argued that Genentech's innovative "culture will be difficult to maintain" and that "over the next decade, we'll see Genentech stars bail and get together to form their own companies or join management teams at existing companies." This would not be unexpected and would be consistent with the cycle of life in biotech.

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Bioshares Model Portfolio (8 May 2009)

Company	Price (current)	Price added to portfolio	Date added
ASDM	$0.30	$0.30	December 2008
QRxPharma	$0.50	$0.25	December 2008
Hexima	$0.52	$0.60	October 2008
Atcor Medical	$0.23	$0.10	October 2008
CathRx	$0.62	$0.70	October 2008
Impedimed	$0.75	$0.70	August 2008
Mesoblast	$0.82	$1.25	August 2008
Cellestis	$3.00	$2.27	April 2008
IDT	$1.59	$1.90	March 2008
Circadian Technologies	$0.85	$1.03	February 2008
Patrys	$0.06	$0.50	December 2007
Bionomics	$0.24	$0.42	December 2007
Cogstate	$0.23	$0.13	November 2007
Sirtex Medical	$3.25	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.33	$0.66	September 2007
Starpharma Holdings	$0.29	$0.37	August 2007
Pharmaxis	$2.62	$3.15	August 2007
Universal Biosensors	$0.84	$1.23	June 2007
Biota Holdings	$1.11	$1.55	March 2007
Probiotec	$1.69	$1.12	February 2007
Peplin Inc	$0.65	$0.83	January 2007
Arana Therapeutics	$1.38	$1.31	October 2006
Chemgenex Pharma.	$0.43	$0.38	June 2006
Cytopia	$0.12	$0.46	June 2005
Acrux	$0.71	$0.83	November 2004
Alchemia	$0.38	$0.67	May 2004

Portfolio Changes – 8 May 2009

IN:
No changes

OUT:
No changes

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.

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: Phylogica, Pharmaxis, Cytopia, Arana Therapeutics, Starpharma Holdings, Cogstate, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcygen Pharmaceuticals, Peplin, BioMD, Impedimed, QRxPharma, Patrys, Labtech Systems, Hexima, Tyrian Diagnostics, Mesoblast, Atcor Medical

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