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In this edition...
Mayne Pharma is the beneficiary of good news, with this the UK's MHRA reversing its earlier decision to not approve its antifungal drug SUBACAP. Mayne conducted a six month dialogue with the agency, proving among other things that argument and persistence pays off. Success with the MHRA has the potential to speed up SUBACAP's path to market in the US. Wireless tracking technology company Bluechiip has secured its first sales, with biological samples storage outfit ATCC ordering an not immaterial but undisclosed number of products. Benitec is exploring therapeutic development opportunities in six areas, which is an encouraging sign of interest in its gene silencing technology. Patrys has obtained funds to support activities to the end of 2013.
Companies Covered: BCT, BLT, MYX, PAB

	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

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

Mayne Pharma's SUBACAP Approved in the UK

Mayne Pharma (MYX: $0.38) has had an earlier decision (in December 2011) by the UK's Medicines and Healthcare products Regulatory Agency to not approve Mayne's anti-fungal drug SUBACAP reversed.

The decision means the drug is approvable in the UK, subject to some further discussion regarding labelling and provision of stability data but no further clinical work is needed.

Mayne will now take the drug through a decentralised process to gain approval in Germany, Spain and Sweden.

The decision follows six months of work by Mayne Pharma in which the company submitted additional information about SUBACAP (itraconazole) to the MHRA. More specifically, the company provided pharmacokinetic *and* pharmacodynamic data which showed that the SUBACAP 50mg delivered the same therapeutic dose as Sporanox 100mg (the branded reference formulation of itraconazole), based on AUC/MIC ratios. This ratio divides the area under the curve (the amount of drug in the blood for a given period) into the minimum inhibitory concentration (minimum amount of drug that kills the pathogen). In other words the ratio combines a time dependent effect with a concentration dependent effect.

Mayne Pharma also showed that SUBACAP 50mg delivers a therapeutic effect (based on the AUC/MIC ratio) with or without the taking of food. This is significant because Sporanox 100mg must be administered with food ("a full meal"). Finally, Mayne demonstrated that SUBACAP 50 mg is less variable (in patients) than Sporanox, with about 90% of the drug being absorbed compared to 50% for Sporanox.

After gaining European approvals, the company will seek a TGA approval in Australia. The company will also discuss the data it has submitted to the MHRA with the FDA. If the FDA accepts these arguments then Mayne could submit a dossier for registration next year, possibly avoiding the need to conduct a Phase III trial of SUBACAP in the US. The trial is currently the subject of discussion for regulatory progression through a Special Protocol Agreement.

Mayne Pharma is capitalised at $58 million.

Bioshares recommendation: **Speculative Buy Class A**

Survey of Benitec's Programs Demonstrate Breadth of Application

Benitec (BLT: 1.7 cents) has provided the market with an update on the progress of its R&D programs. Benitec is commercialising a unique form of RNAi therapy. The 'C' word is rarely used in the pharmaceutical industry. But Benitec is upfront in that it believes its technology offers not only a potential therapy for a number of chronic diseases, but in fact a potential 'cure'.

Benitec's technology is being applied in six different disease areas. These are in:

– Neuropathic pain in patients with cancer
– Drug resistant lung cancer
– Hepatitis B
– Oculopharyngeal Muscular Dystrophy
– HIV/AIDS
– Hepatits C

The difference between the Benitec approach to RNAi and the other RNAi approach is that Benitec uses a double strand of oligonucleotides (so DNA) compared to a single strand of oligonucleotide (RNA). Benitec calls this DNA directed RNA interference (ddRNAi). With Benitec's approach, the idea is that it introduces the DNA into the target cell nucleus, thereby programming the cell to produce specific RNA. This specific RNA is matched to bind with the messenger RNA of interest, thereby blocking the protein manufacture of interest.

The advantage, and disadvantage, of the Benitec approach is that by introducing a change to the DNA of that cell, that change is permanent, thereby offering a potential cure. The downside is that the therapy is not reversible.

Another advantage for Benitec is that there are delivery systems available for getting its therapy into the cell, namely inactivated/benign viruses for which there is considerable experience in using. Trying to deliver a single strand of RNA into cells has proven very challenging for researchers, and is one of the main impediments to progression of RNAi therapies.

Out-licensed Applications

Benitec has out-licensed the application of its technology in the area of hepatitis C and HIV/AIDS.

Hepatitis C - Tacere Therapeutics (target: hepatitis C genome, delivery: adeno-associated virus)

Tacere Therapeutics is progressing the technology to develop a therapy for Hepatitis C. In *in vitro* studies and also in *in vivo* studies in non-human primates, Tacere showed production by the cell nucleus of its RNA molecules, which it calls shRNA (sh = short hairpin, because the RNA is initially looped into a hairpin structure). It is using a triple cassette, which delivers three independent short hairpin RNAs targeting the HCV genome.

Tacere previously had a major research/licensing deal with **Pfizer** for this program. However with Pfizer closing down one of its UK R&D facilities, Tacere is looking for a new partner. Benitec believes the program could move into the clinic in 2013. However it may be dependent on Tacere finding a new partner.

HIV/AIDS – Calimmune (target: HIV gene, delivery: lentivirus)

In February this year, the company sub-licensed its technology for the area of HIV to US-based biotech **Calimmune** for targeting up to three HIV genes. Through the **City of Hope National Medical Center** in the US, researchers have successfully achieved an RNAi therapy in three of four patients, incorporating the Benitec technology with a lentiviral vector to get the RNA into the cell.

Researchers at City of Hope stated that they had saved the lives of three of four patients, by reprogramming the patients' stem cells using shRNAi to change patients' stem cells to produce HIV resistant blood cells. (An issue with this approach however was that it was very complicated to deliver the therapy, which used a combination of novel technologies.)

All of the patients had suppressed HIV loads and after two years, two for the four patients still showed persistent expression of Benitec's shRNA. There was no significant toxicity linked to the therapy.

Calimmune is seeking to start its own clinical trial with the Benitec RNAi technology this year. The aim of this therapy is potentially to deliver permanent or long lasting HIV control.

In-house Programs

Cancer associated pain (target: PKCgamma gene, delivery vehicle: lentivirus)

The most advanced of Benitec's in-house programs is the potential for using its RNAi technology for the treatment of cancer-associated neuropathic pain, aptly called Project Nervarna. The potential of this therapy is that a single injection of the therapy into the spinal cord might deliver a long lasting pain relief. The program is using a lentivirus vector to deliver the ddRNAi constructs.

Proof-of-concept data has been achieved *in vivo* by others and Benitec will be seeking its own prove-of-concept data in animal studies in rats this year. The company will then conduct toxicology studies next year and is aiming to start Phase I clinical studies at the end of 2013.

The company is working with **TetraQ** at the University of Queensland to conduct the preclinical studies, and with a US-based research group.

Drug resistant lung cancer (target: betaIII-tublin gene, delivery: Jet-PEI polymer delivery vehicle)

This program is seeking to provide a therapy that overcomes chemotherapy resistance in patients with non-small cell lung cancer. The target is the betaIII-tubulin gene. The role of this gene in lung cancer has been well described by researchers at the **University of NSW** with whom Benetic is working. The betaIII-tubulin protein is not expressed on healthy cells but is on lung cancer cells, where it is believed to cause resistance to chemotherapy.

The company achieved some early success in mice studies and is seeking to confirm that result in larger numbers this year. A Phase I clinical trial could start in the second half of 2014.

Bluechiip Seals First Commercial Sales

Bluechiip (BCT: 22.5 cents) is commercialising a novel wireless tracking technology. The first area of application is for labelling hundreds of millions of biological samples that are cryogenically stored in commercial freezers throughout the world. This week the company made its first commercial sales of its products, to ATCC, a US-based biological materials storage facility.

ATCC stores around 10 million biological samples. The first sale with ATCC will see Bluechiip supply an undisclosed number of products, which CEO Brett Schwarz said is not immaterial. This deal more importantly represents the start of commercial use of the Bluechiip technology, and helps commercially validate the technology for other potential users.

ATCC has ordered the storage tubes incorporating the Bluechiip chips, the readers and the software. Bluechiip will purchase the tubes from a third party supplier, and fit the chips to the tubes. Further along, and what is the preferred model, Bluechiip would like to have agreements in place with storage equipment manufacturers to have the Bluechiip chip embedded in the vessels when they are manufactured.

Schwarz is confident ATCC will continue to integrate the Bluechiip technology into their storage facilities. Of interest, a comment from ATCC in the announcement was that the Bluechiip technology "has the potential to enhance future offerings by ATCC". This could perhaps include continuous temperature monitoring of individual samples.

ATCC is a mid-tier storage company. The largest group in this area is **Fisher BioServices**, which holds over 170 million biological samples.

In January, ATCC and equipment supplier **Corning** evaluated the Bluechiip identification technology system. Schwarz said the group subjected the technology to a variety of conditions and situations, including radiation, ultra low temperature environments, physical damage and placement in a centrifuge, testing all of the claims of the Bluechiip technology. Schwarz said his company's technology ticked all of the boxes. Official results will be presented in an industry publication.

Schwarz said in the US there are over 100 large potential users, including pharmaceutical companies, contract research organisations, and specialty storage businesses such as ATCC. At the moment, 90% of Bluechiip's focus on the US, although it is talking to groups in the UK and continental Europe. Other groups that should be interested in this technology include pathology labs and IVF clinics.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

– Benitec cont'd

Hepatitis B (target: HBV polymerase gene, delivery: adeno-associated virus)

Benitec is working with **Biomics Biopharma** in China to deliver an RNAi therapy for hepatitis B infection. A triple cassette (delivering three shRNAs) is expected to go into preclinical studies in the second half of this year. The aim is to knock down the hepatitis polymerase gene. The researchers in China have already shown that almost 100% of the therapy can get to the liver from an intravenous injection.

Clinical studies in China are not scheduled to start before 2015.

Oculopharyngeal Muscular Dystrophy (Target: PABPN1 gene, vector: lentivirus & AAV)

Benitec's fourth in-house program is to develop a therapy for a particular form of a genetic disorder, called Oculopharyngeal Muscular Dystrophy (OPMD). This is often a fatal disorder with people having severe problems swallowing.

Benitec is working with researchers in the UK (at the **University of London**) and in France (at the **Institut de Myologie**). Using a gene therapy approach, the company will seek to silence the expression of the PABPN1 gene. Some success in *in vitro* has been achieved, with a 65% knock down of the target gene using lentiviral and adeno-associated virus vectors

The company is looking to start preclinical studies this year, with clinical studies scheduled to commence in 2014/15 at the earliest.

Summary

Benitec is commercialising a sophisticated technology, using DNA constructs that are (mostly) inserted into cells using a benign virus to program those cells to deliver a continued RNA interference to block the production of specific proteins.

There are regulatory challenges for companies which use viruses to deliver therapeutics. Perhaps more importantly safety will be a high priority given the irreversible and long-acting effect of these potential therapies.

Benitec is capitalised at $17 million. It had $3.9 million at the end of March.

Benitec is a high risk investment suitable for investors with a longer term investment timeframe.

Bioshares recommendation: **Speculative Buy Class C**

Bioshares

Bioshares Model Portfolio (22 June 2012)

Company	Price (current)	Price added to portfolio	Date added
Nanosonics	$0.500	$0.495	June 2011
Osprey Medical	$0.38	$0.40	April 2012
QRxPharma	$1.65	$1.66	October 2011
Mayne Pharma Group	$0.380	$0.435	September 2011
Somnomed	$0.84	$0.94	January 2011
Phylogica	$0.044	$0.053	September 2010
Biota Holdings	$0.73	$1.09	May 2010
Tissue Therapies	$0.54	$0.21	January 2010
Atcor Medical	$0.07	$0.10	October 2008
Bionomics	$0.29	$0.42	December 2007
Cogstate	$0.250	$0.13	November 2007
Sirtex Medical	$6.00	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.60	$6.60	September 2007
Pharmaxis	$1.01	$3.15	August 2007
Universal Biosensors	$0.57	$1.23	June 2007
Alchemia	$0.470	$0.67	May 2004

Portfolio Changes – 22 June 2012

IN:
No changes

OUT:
No changes

Patrys Secures Funding for Phase I/II for Multiple Myeloma Trial

Human antibody company Patrys (2.2 cents) has secured by way of a placement $2 million and it will also conduct a share purchase plan to raise up to $0.9 million. The funds will be used to pay for the company's planned Phase I/IIa trial of PAT-SM6 in multiple myeloma patients, prepare PAT-LM1 for a clinical trial and support out-licensing activities for PAT-SC1.

This latest funding round brings the total of funds raised by Patrys since it listed in July 2007 to $42 million (excluding $3 million in cash obtained from issuing shares to acquire the outstanding shares of Acceptys). The company's IPO raised $25.9 million. Subsequent raisings included a $5 million rights issue in June 2009, a $4.3 million placement and SPP in November/December 2010 and a $3.4 million placement in December 2011. The balance of funds raised to date was sourced from convertible note financings.

Patrys graduated to a classification as a clinical stage development company in October 2010 when it commenced a Phase I melanoma trial of PAT-SM6, but more than three years after it listed in 2007. Ethics approval for the trial was obtained in August.

The nine patient Phase I melanoma trial was completed in February 2012. The trial showed the drug was safe and that cell death was detected in two post treatment biopsies and that the drug was active at low doses.

Phase I/IIa Trial Multiple Myeloma Trial

The Phase I/IIa multiple myeloma trial will be an open-label study that will enroll 12 relapsed patients who have become resistant to treatment by other drugs. The primary endpoint will safety and tolerability and secondary endpoints with include pharmacokinetics, immunogenicity and progression free survival.

Commentary

Patrys has progressively become a higher risk investment opportunity in the past few years for several reasons. The company has suffered because of a fall-off in interest by investors in early stage drug discovery and development companies. Investors' attitudes have been shaped by the ongoing flux and volatility in international capital markets.

However, Patrys has also been at fault because it has been slow to get to a key stage in clinical development of medicines, the Phase II trial, in which clinical benefit can begin to be explored and the technology can be proven. The company's original prospectus plan listed as an objective the completion of Phase I/IIa trials for two antibody candidates by October 2009. The company did not initiate its Phase I melanoma trial until October 2010. Problems with a third party manufacturer also slowed down Patrys' development program.

Patrys has now bought itself some time to see it through the completion of a Phase I/IIa trial. Should the trial be successful, then the company's prospects may improve. It is possible that PAT-SC1 could be out-licensed (in Japan) in the next twelve months, which might see Patrys receive a modest upfront license payment.

However, the fact that Patrys has not filed any Investigational New Drug Applications with the FDA is a sign that the company has not been confident (with funding being a contributing factor) that it can undertake the more expensive and demanding phases of clinical development in a key pharmaceutical market.

Investors are more likely to better served by waiting until the company completes its Phase I/IIa multiple myeloma trial before investing in Patrys, given the company's execution record to date.

Patrys is capitalised at $10 million.

Bioshares recommendation: **Sell**

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, Circadian Technologies, Biota Holdings, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phosphagenics, Immuron, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Genetic Technologies, Calzada, Bioniche