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In this edition...
Pharmaxis gets a second chance to argue its case this week with European regulators, presenting to a scientific advisory group on why Bronchitol should be approved for the treatment of cystic fibrosis. We believe the company has a very good case.
Mesoblast has formed a key manufacturing alliance that will ensure the supply of its unique stem cell products in development. It's a major step for the company.
Axiron sales continue to make strong inroads into the US market for Eli Lilly and Acrux. Sunshine Heart has provided more colour around its pilot trial results. And we update progress at Medical Developments.

The Editors
Companies Covered: ACR, MSB, MVP, PXS, SHC

	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 - May '10)	49.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 now commenced	-27.0%
Cumulative Gain	**208%**
Av. annual gain (10 yrs)	**21.2%**

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Bioshares

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

Pharmaxis Argues Case For European Approval

Pharmaxis (PXS: 72.5 cents) will present to a Scientific Advisory Group (SAG) this Monday, to argue its case why it believes its drug candidate, Bronchitol, for the treatment of cystic fibrosis, should be approved. The company was unsuccessful in having its marketing application for Bronchitol approved in Europe in June this year and is appealing the decision.

Pharmaxis' original application was not reviewed by a scientific advisory group. The company is unaware of the composition of this team of cystic fibrosis and respiratory specialists. Attending the meeting on Pharmaxis' behalf will be its two medical officers, Brett Charlton and Howard Fox, and its COO Gary Phillips.

The Committee for Medicinal Products for Human Use (CHMP) will meet on 18 October to review the recommendations of the SAG and a decision on Pharmaxis' appeal should be made at the end of that week.

There are a number of possible outcomes for Pharmaxis. Its appeal may be unsuccessful. It could receive approval with no restrictions. The CHMP could restrict the product use to those age groups where a more beneficial result was achieved. Or it could be approved with a 'Continuation Rule', whereby there needs to be continued evidence of efficacy in patients using the drug to support continuation of use.

In *Bioshares* view, there appears to be clear evidence of efficacy and the drug candidate has shown to be safe. If has been tested in two global Phase III trials involving 600 people. The rejection of the company's marketing application in June was very surprising. On the data generated, our view is that this drug candidate should gain approval. Breaking the data down to efficacy across age groups appears inconsistent with the protocol in which new drug applications are assessed. However a restricted approval to certain age groups must now be considered a possibility given the CHMP's earlier findings.

Other programs
Pharmaxis has not let staff go as a result of its negative finding from the CHMP in June for Bronchitol. Some discretionary expenditures on early stage programs have been deferred, according to CEO Alan Robertson.

The second Phase III trial in bronchiectasis is nearing completion. This study, being conducted in 100 hospitals around the world, has passed 90% recruitment with almost 500 patients enrolled into the study. The patients are on Bronchitol for 12 months, so results should be available in early 2013, with the company potentially being in a position to file for approval in mid 2013.

There are around 600,000 people living with bronchiectasis, which is a condition charac-

Cont'd over

– PXS from page 1

terised by a general deterioration in lung function. Most people with CF end up with bronchiectasis. Of the people with bronchiectasis, about half (300,000) are classified as moderate-to-severe, and half of that group would be a realistic target market for Pharmaxis, of around 150,000 people.

This compares to around two thirds of the CF patient market, resulting in a target market of around 45,000 people. Similar to Chemgenex Pharmaceuticals, Pharmaxis has made its initial focus on an orphan drug status disease, with a speed to market strategy, then with the aim of expanding into larger markets. However like Chemgenex, Pharmaxis has also stumbled with its first approach.

Summary

In *Bioshares* view, it is very likely that Bronchitol will eventually get to market, both for the treatment of cystic fibrosis and also for the treatment of bronchiectasis. There are no safety concerns to preclude its use. The drug works spectacularly well in some patients, well in some patients, and less well in other patients says Robertson. Arguably this efficacy profile is the case for many drugs on the market. In *Bioshares* view, this drug should be made available to clinicians to have as a treatment option for their patients.

However the time it will take to bring Bronchitol to market, and the cost, both to the company and to investors, are unknown. No doubt these final regulatory stumbles provide fertile ground for larger potential suitors.

Over the next three weeks, this will be a high volatility stock. Pharmaxis is capitalized at $166 million. It had $44 million in cash at the end of June.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Mesoblast Strikes Global Manufacturing Alliance With Lonza

Mesoblast (MSB: $8.09) has signed a strategic manufacturing alliance with Lonza Group. Lonza is arguably the leading biologics manufacturer in the world, having built up its business from third party contract manufacturing deals for antibody drugs, including Genentech's Avastin. It's a key alliance for Mesoblast, with manufacturing a crucial aspect to the company's success.

Mesoblast has had a five year commercial relationship with Cambrex (which specialized in the contract manufacture of cell therapy products) which was acquired by Lonza in 2007. It manufactures Mesoblast's allogeneic stem cell products for its clinical studies. Initially, material for Mesoblast's Phase III cardiovascular study will be made at Lonza's new cell therapy products facility in Singapore. It is expected this facility will have the capacity to manufacture product for the cardiovascular therapy for the first 18 months after product launch.

This new facility will also supply material for multiple Phase III product applications. It will be primarily used to make material for Mesoblast, with no other company's allogeneic product to be manufactured there, but some autologous products for other companies can be produced there.

Mesoblast also appears intent on ensuring each application is served by a distinct stem cell therapy product, which will allow the company to better control the distribution of its therapies which it may sell either directly or through different licensors.

Striking a quality manufacturing alliance is of major significance to Mesoblast. As part of the agreement, Lonza will also manufacture a purpose-built facility once directed by Mesoblast. Capital expenditure costs will be high, expected to be around $150 million for this purpose-built facility, and this will be funded by Lonza.

Timing for construction of purpose-built facility

The timing to go ahead with this facility will be tricky. Whilst Lonza will pay for construction, Mesoblast will agree to purchase an agreed amount of material. It is expected this facility will take two years to build and gain regulatory certification.

Construction of this facility is expected to begin before product approval is received, before the completion of the first Phase III cardiovascular trial. Mesoblast will pay Lonza for the doses produced and will receive a transfer price from Teva based on net sales of product. There are fixed orders for up to the first year and then guidelines for subsequent years. However these terms are generally matched with future orders from Cephalon (Teva) to minimize this risk to Mesoblast.

Under the terms of the alliance, Mesoblast has the right to buy back the manufacturing facility two years after the facility receives regulatory approval. This facility is expected to supply material for the third year of product sales of the cardiovascular therapy.

The quality of product, including the consistency and reproducibility of stem cell products, will be a key parameter for the companies, and one that regulators such as the FDA, will be monitoring closely.

One of the strength's of Lonza is its reputation and experience. It has shown its ability to get multiple IND applications through the FDA in the minimum period of 30 days according to Mesoblast CEO Silviu Itescu. Mesoblast will also gain access to Lonza's cell manufacturing technologies.

This agreement is a major step for Mesoblast to become a vertically integrated pharmaceutical company. The terms of the alliance would suggest that Lonza is placing a large bet on the Mesoblast becoming the leading commercial stem cell product provider.

Mesoblast is capitalized at $2.27 billion.

Bioshares recommendation: **Speculative Hold Class A**

Acrux – Axiron Strong Product Entry Continues

Eli Lilly's Axiron product, licensed from Acrux (ACR: $3.20), is continuing its very strong entry into the US testosterone market. The transdermal testosterone market in the US is valued at $1.2 billion year. Axiron now has achieved a 7.5% market share in the first six months from launch.

Its US market share has grown 1.4% in the last five weeks. If that penetration rate continues, Axiron will gain a 22% market share in 12 months time (18 months after launch). That corresponds to sales at the current market size, of US$264 million. Currently Axiron is tracking at sales of US$90 million per annum (assuming no discounting is applied). In 2010, the lead testosterone gel, Androgel, generated sales in the US of around US$900 million.

In the first year of sales, pharmaceutical companies introduce loyalty cards to provide discounts to patients while the pharmaceutical company secures coverage from patients' health insurers.

Acrux receives royalties from Axiron sales on a sliding scale. Our estimate is that peak royalties of just over 20% are payable. Acrux has indicated that it estimates it will receive $8 million from Axiron rights in the current financial year, and this should increase to $40 million in FY2013, which includes the payments of some milestones. Acrux CEO Richard Treagus does not expect the maximum royalty rate to be achieved in FY2013.

We expect that these Axiron revenue targets will be easily met. The above sales estimates of Axiron assume no growth in the US testosterone market, which has grown from US$450 million in 2005 to US$1.3 billion in 2010. Eli Lilly Chief Marketing Officer Rob Brown said he hasn't seen many markets that look like this testosterone market in a long time. Brown said he still sees growth in the US market but not at the 19% experienced over the last five years.

Our expectation is that in two years time, Axiron royalty rates should hit their peak of just over 20%, and some sizeable milestone payments will start to be reached. Acrux is still due to receive up to US$195 million in milestone payments, which the company says are achievable milestones.

Acrux's price weakness recently has been due to some short selling in the stock, coinciding with the entry of the stock into the ASX200 Index. The company remains very confident on the commercial potential of Axiron.

A major pending milestone are patent decisions in major regions around Axiron, potentially extending protection out to 2026.

Bioshares recommendation: **Accumulate**

Bioshares

Sunshine Heart – Update

Bioshares this week met with the Sunshine Heart (SHC: 4.7 cents) team, including the CEO, Dave Rosa, the inventor, Will Peters, and the co-lead Principal Investor to the 20 patient pilot trial, cardiologist Dr William Abraham, as the company conducted a roadshow to discuss trial results. More light was shed on the results from the pilot study recently completed, following the Ohio State University Medical Center press release from Dr Abraham.

Some of the key aspects to this program that remained unclear were: whether the trial protocol for future trials would need to be altered following the death of one of the patients in this pilot study, which occurred when the device was remove following an infection; what is the acceptable risk profile for the Sunshine Heart C-Pulse system; and how effective was the C-Pulse system, given that full details will not be reported now until early November.

Correct Trial Protocol?

Of the 20 patients in the trial, there was one patient death. This occurred when an ongoing infection required surgical removal of the device. Inventor Will Peters said that trial protocol clearly states that if a major infection occurs in the chest cavity, the device should be removed early. In this case, the device was removed 137 days after infection and correct antibiotic treatment was not followed. The risk is if the infection persists, significant damage and weakening of the surrounding area occurs.

Acceptable Risk Profile of C-Pulse

The Ventricular Assist Devices, which are used to treat the more ill Class IV heart failure patients, have a higher accepted risk profile. There is a 9.1% annual risk of stroke alone. Dr Abraham believes for Class III patients for whom the C-Pulse device is directed, that an acceptable risk of a major complication would be between 3%-7%, but certainly not 20%. With the one major complication (death) in the pilot trial, even through it was not directly linked to the device, such a risk might be tolerated.

To be clear, this death did not occur due to device failure, and it did not occur because of any weakening of the aorta caused by the device. The risk of an infection in the chest infection following open chest surgery always exists.

In the planned pivotal trial, the aim will be to encourage most implants to occur with a minimally invasive procedure. If that does not occur, then there will be very rigorous site monitoring.

Drive-line infections are likely to continue, but this is expected to be reduced with the introduction of a 'C-Patch' system to better secure the drive-line which protrudes through the skin.

Efficacy of the Device

Dr Abraham believes that in treating heart failure with a new therapy, there are four categories of outcomes: progressors (those who get worse), non-progressors, responders, and super-responders. Gen-

Cont'd over

– SHC cont'd

erally around 10% are super-responders (with treatments such as beta blockers), and this was the case with the C-Pulse, with two patients responding very well.

One patient moved from a Class IV patient classification to a Class I heart failure patient classification after 11 months, and a second patient improved from a Class III to a Class I category at six months.

Of note, the patient who died did not want the device removed because he was getting such relief from the C-Pulse system. His ejection fraction had improved, his heart size had decreased (positive) and the patient was doing well aside from the infection.

Summary

There is a very large market application for the C-Pulse system. Dr Abraham, who has been involved with the C-Pulse device since 2003, believes the C-Pulse device has the potential to become the next standard of care for heart failure.

Dr Abraham believes there is sufficient evidence of efficacy and safety to warrant progression of this program to a pivotal study. That study will take two years and two months to enroll with a 12 month follow-up period. The trial is expected to start in early 2012.

Although the full trial results have not been released, *Bioshares* is more comfortable with the interim results that have been released which shows a positive risk-benefit profile for this device.

Sunshine Heart is capitalized at $56 million.

Bioshares recommendation: **Speculative Hold Class B**

Bioshares

Medical Developments International – Penthrox EU Trial Underway

Medical Developments International (MVP: $0.45) markets Penthrox, a fast-acting pain relief medication that is widely used by Australian emergency services. The company also markets a range of asthma devices and oxygen and resuscitation equipment.

Penthrox (methoxyflurane) is administered through inhalation, from a small green plastic device.

The company posted a strong result for FY2011, increasing profits by 98% to $1.7 million from sales of $10.205 million (up 23%). A focus on cost management resulted in a 16% improvement in the operating expenses-to-sales ratio of 16% (falling from 47.5% to 40%).

Medical Developments also announced a 3 cent final dividend, and re-instituted its dividend re-investment plan. Cash at June 30 was $3.5 million.

Clinical Trials

Although Medical Developments has been very successful in selling Penthrox into a select customer base in Australia and New Zealand and several other territories, it has not to generated sales in major medical markets due to a lack of appropriate clinical trial data to support regulatory submissions.

Several small studies on the use of Penthrox have been completed and some have been published. The most recent published study (Abdullah et al, Australian Dental Journal 2011) compared the use of Penthrox to nitrous oxide sedation in the treatment setting of third molar tooth extraction. The non-blinded, cross-over randomized study was small, involving only 20 patients, but over 40 treatment sessions. Third molar tooth extraction is noted for patients experiencing higher levels of anxiety. The study concluded that Penthrox produced comparable sedation to nitrous oxide. The study reported that sedation was significantly lighter after 15 minutes for Penthrox. Mean surgery time was 19 minutes with nitrous oxide and 20 minutes with Penthrox. However, on a patient-preferred basis, subjects preferred Penthrox. No major adverse events were reported.

A 300 patient study is underway at Royal Adelaide Hospital in patients undergoing colonoscopy procedures.

European Clinical Trial

To support its Penthrox registration objective in Europe, Medical Developments has commenced a Phase III study, entitled the STOP! study. The randomized, double blind, placebo controlled study will enrol 300 patients admitted to hospital emergency departments who have experienced a minor injury. Trauma patients aged 12 years and older will be eligible for recruitment.

The trial is being conducted at five sites in the UK, with the lead site at Nottingham University Hospitals.

The primary endpoint will be the difference in VAS pains scores at 20 minutes between Penthrox and placebo. One secondary endpoint will be time of request for rescue medication and quantity of equivalent opioid medication administered. Another secondary endpoint will be the time to pain relief.

The trial was first expected to be completed by the end of 2011 but with the start pushed back from April to August, results are now expected by January 2012 [see clinicaltrial.gov NCT01420159].

Cont'd over

Bioshares Model Portfolio (30 September 2011)

Company	Price (current)	Price added to portfolio	Date added
Mayne Pharma Group	$0.370	$0.435	September 2011
Genetic Technologies	$0.16	$0.18	August 2011
Acrux	$3.20	$3.37	June 2011
Psivida	$4.39	$3.95	May 2011
Bioniche	$0.70	$1.35	March 2011
Somnomed	$1.12	$0.94	January 2011
Phylogica	$0.057	$0.053	September 2010
Biota Holdings	$0.81	$1.09	May 2010
Tissue Therapies	$0.46	$0.21	January 2010
Atcor Medical	$0.07	$0.10	October 2008
Impedimed	$0.45	$0.70	August 2008
Bionomics	$0.48	$0.42	December 2007
Cogstate	$0.16	$0.13	November 2007
Sirtex Medical	$4.30	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.50	$6.60	September 2007
Pharmaxis	$0.73	$3.15	August 2007
Universal Biosensors	$0.93	$1.23	June 2007
Alchemia	$0.36	$0.67	May 2004

Portfolio Changes – 30 September 2011

IN:
No changes.

OUT:
No changes

– MVP cont'd

Summary

Medical Developments' commitment to investment in a European medical dossier for Penthrox is necessary if the company wishes to significantly leverage value from its Penthrox asset. Although the clinical program will be completed in a relatively short space of time, we expect the submission process to take longer. We anticipate a regulatory decision most likely to follow in late 2012 or early 2013. However, one commendable feature of the European clinical program is that it is being funded out of retained earnings.

Medical Developments is capitalised at $23 million.

Bioshares recommendation: **Buy**

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

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