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In this edition...
Universal Biosensors has signed a manufacturing supply agreement with Siemens, covering one named and two un-named products. This brings welcome diversity into UBI's revenue streams. Another piece of good news for UBI investors is that it appears that J&J's investment arm has left the register with the stock being taken up by two funds. Stock overhangs can depress stock prices to the point that incorrect price signals end up damaging a company's prospects.
Bionomics has acquired a small, private US firm, Eclipse Therapeutics, which has expertise and assets in the cancer stem cell space. While a diversification, the acquisition will increase funding risks for Bionomics. Reva Biomedical's progress with the latest version of its bioresorbable stent will be worth tracking over coming months.
Companies Covered: BNO, RVA, UBI

	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)	-13.2%
Cumulative Gain	**200%**
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.

Universal Biosensors Enters Supply Agreement with Siemens

Universal Biosensors Inc (UBI: $0.80) has signed a manufacturing supply agreement with **Siemens Healthcare Diagnostics** which covers the manufacture of three different tests being developed for point-of-care coagulation measurements in the blood.

UBI expects the first of these products to reach the market in 2013. The collaboration with Siemens was formed one year ago. The first product will be a PT/INR test which is used to calibrate the correct warfarin dosage. The test will go up against **Roche**'s CoaguChek, which is the clear market leader. The other two tests being developed by UBI have not been disclosed. The terms of the supply agreement have not been provided, however UBI will be reimbursed US$1.7 million to develop an additional reader for one of the coagulation tests.

The signing of a supply agreement between the two companies confirms Siemens' commitment to the tests being developed by UBI and that will be sold by Siemens. UBI has probably learnt from its collaboration with **Johnson & Johnson**, which should result in a better commercial outcome for UBI. UBI is contributing to more of the development costs as well, looking to gain more of the profit outcome.

J&J Investment Arm Exits UBI

Johnson and Johnson markets and sells globally the OneTouch Verio glucose diagnostic product for UBI. UBI manufactures the test strips and receives around one cent for each strip that is sold, whether that strip is made by UBI in Melbourne or by J&J at its plant in Scotland. Johnson & Johnson Development Corporation held 15 million shares, or 9.4% of the company at the end of last year.

Bioshares understands J&J has recently exited the stock, although no change of substantial shareholding has been filed to date by J&J. The stock has been placed with local fund Australian Ethical and New Zealand fund Fisher Funds Management. Australian Ethical now owns just under 8.4 million shares, or 5.33% of the company. Fisher Funds Management now owns just under 10 million shares, or 6.25% of the company. Most of the stock was exchanged at 60 cents a share.

We understand J&J had been planning to exit its investment for some time, and the weakness in the share price has likely been due to this perceived overhang of the stock. With the stock now placed with investment funds, the price weakness in this stock should change.

It's unclear why J&J has exited the stock, but presumably the proceeds will be used for the development of other earlier stage assets.

UBI is capitalised at $127 million.

Bioshares recommendation: **Speculative Buy Class A**

Reva Medical – Following the Path of Abbott Lab's ABSORB Stent

San Diego-based Reva Medical (RVA:$0.635) was founded in 1998 and listed on the ASX in 2010 raising $85 million. The company is commercializing the REZOLVE bio-resorbable coronary stent. This product and similar rival products are more accurately termed scaffolds because they are not permanent devices.

Stents have been, until the development bio-resorbable designs, thin metal tubes which are positioned using an angioplasty procedure into arteries leading to the heart where plaque has built up and caused blockages and inflammation.

Developers of bio-resorbable stents include of **Abbott Laboratories**, **Biotronik**, **Elixir**, **Arterius** and Reva Medical.

Stenting evolved as coronary heart disease intervention because it alleviated the need to perform heart bypass surgery. Stenting does not cure heart disease, instead it alleviates symptoms of the disease.

Drug Eluting Stents

An evolution in stent usage occurred with the advent of drug-eluting stents (DES). This is a class of stent which has typically been coated with a controlled release polymer formulation that contains drugs that can manage or control inflammation. One widely used compound is sirolimus, which has both anti-inflammatory and immune-suppressive actions. Sirolimus is now off - patent and is incorporated in Reva Medical's REZOLVE stent.

In 2006 concerns were raised about the long term safety of drug eluting stents, regarding the frequency of 'late stent thrombosis' (blood clots), occurring one year after implantation.

However, results from the 8,700 patient PROTECT study which reported this year, showed rates at the three year mark post implant of 1.79% for Cypher sirolimus DES (**Johnson & Johnson**) and 1.42% for the Endeavour zotarolimus DES (**Medtronic**).

Several earlier studies which initiated concerns had reported rates of 3-4%. Interestingly, the blood clot rate for the Endeavour stent at 12 months was 0.3% compared to 1.1% for the Cypher stent. The Cypher stent is no longer marketed by J&J, which has exited the stent business. The PROTECT trial re-established the safety of drug eluting stents.

The global stent market is defined by estimated 3.2 million procedures worth US$5.9 billion in stent sales.

The design progression to resorbable stents is based on the thesis that as a stent slowly decays (is resorbed) over time, with its dissolution restoring the natural movement of the artery. Its dissolution may also reduce the rates at which blood clots occur compared to the rates associated with the use of rigid and permanent metal stents.

Recent research from Dr Ian Meredith at the **Monash Medical Centre** suggests that permanent stents can disturb the flow properties of blood (endothelial shear stress) potentially biasing blood vessels to stimulate plaque formation, inflammation and calcification. An objective of resorbable stent technology then is to restore blood flow to an undisturbed state.

Evolution of Reva's REZOLVE Stent

The mechanical and chemical design of Reva's resorbable stent has evolved over the years. Its 2007 design was based on the use of a polyethyleneglycol (PEG) backbone.

The company then switched to a polyactide backbone in 2009 for its REZOLVE design and then in 2012 embarked on a next generation design using desaminotyrosine polycarbonate for the chemical back bone of the REZOLVE 2 version.

Each generation of design has included an iodine compound to support the optical recognition of the stent through either X-ray or other imaging technology. Abbott's Absorb stent is not as visible to imaging technologies, relying on gold dots to mark the ends of the stent.

The REZOLVE 2 product also differs from earlier versions by being thinner, by not being encased in a sheath and offering increased radial strength.

A ratchet design feature of REZOLVE stents mean they can be custom-fitted to a patient's anatomy, in other words tailored to suit the specific size of the portion of artery targeted for implantation.

The REZOLVE stent is also designed through the 'tuning' of the polymer backbone to remain strong for three months, and then to decay gradually over several years.

Interim Results

Interim results of the 50 patient RESTORE pilot trial from 26 patients showed no major adverse coronary events to have occurred to date. Most patients have passed the acute phase, four month mark and one patient is in excess of eight months. The primary endpoint of the trial is freedom from target lesion revascularization at six months.

It also showed that the sheathed delivery system could not be used to deliver the stent to small and 'tortuous' arteries.

Trial Start Time Delay

The commencement of the 50 patient RESTORE pilot trial exceeded the original target date by six months. The trial was originally scheduled to commence in 2011 Q2, but did not commence until 2011 Q4.

The company cited the application of very narrow entry criteria as a factor that slowed down recruitment. Another trial site related issue was access to intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA), modalities required to study the *in situ* effect of the REZOLVE stent.

Cont'd over

Abbott's Absorb Stent

Abbott's polyactide-based Absorb stent was approved for sale in Europe in January 2011, but Abbott is only now looking to launch the product in Europe.

The Absorb stent was evaluated in the two stage ABSORB study. After five years implantation in 30 patients, there were no reports of cardiac deaths, blood clots or revascularization. At two years, for a second cohort of 44 patients, no blood clots and a major coronary adverse event rate of 6.8% was reported.

Abbott has now also commenced a 500 patient randomized trial to compare its Absorb stent to its own Xience drug eluting stent.

Abbott's US trials are still in the design phase.

Reva's CE Mark Objective

Reva Medical plans to submit data from two studies in support of a CE Mark application. Further enrolments of 24 patients in its RESTORE pilot study will evaluate the REZOLVE 2 version of its stent. Enrolment in this second arm of trial will commence in 2012 Q4.

The company will initiate a pivotal trial, termed RESTORE II, in 2013 Q1. This trial will recruit 125 patients from up to 30 sites in Brazil, Germany, Poland, Australia and New Zealand.

The study will involve clinical assessment at one, three and six months, angiographs at nine months and annual follow-ups at 12 though to 60 months. Endpoints will include major coronary adverse events at 12 months and measures of Late Lumen Loss (the change in the diameter of the blood vessel) at nine months.

Reva Medical is aiming to receive a CE Mark in 2014.

Risks

The leading risk pertaining to an investment in Reva Medical relates to the company's ability to manage its clinical programs. The company's pilot trial was originally planned to commence in 2011 Q2 with an interim review conducted in 2011 Q4. This was to be followed by the commencement of its CE Mark (pivotal) study in 2012 Q1.

As stated above, this study is not expected to begin until 2013 Q1. The competition risk for Reva Medical is not trivial with at least two companies, Abbott Laboratories and Biotronik, competing in the resorbable stent arena with substantial capital resources and market access.

Competitor risk is compounded in respect of Abbott Laboratories; if that company experiences regulatory, clinical, market, or technical difficulties or pricing hurdles, such problems could precipitate a negative knock-on effect to Reva Medical

Reva's stent is a product that must be studied from a safety point of view over the long term e.g. five years. Although product approval can be obtained with data at 12 months, the risk is that adverse events in the long term could jeopardise the product's chance of commercial success.

It is unlikely that Reva Medical will have the capital resources to support registration studies for the US market. This is because the likely requirement of the FDA for clinical studies by stent device sponsors is to enrol many thousands of patients in order to 'uncover' or 'reveal' anticipated very low rates of adverse events. The clinical program devised by Abbott for US registration will be an important determinant of potential future value for Reva Medical.

The implication of funding requirements for the US studies is that the discount that would impose on the company's valuation in the eyes of potential acquirers. Realistically, any current valuation of the company can only be based on product registrations obtained around the world based on the receipt of a CE Mark, with a US product value tending towards low figures at this stage, primarily stemming from Abbott's slower commercialisation progress in the US and the current lack of clarity regarding the FDA's expectations of patient numbers required for pivotal trials.

Summary

Reva Medical's position as a follower behind Abbott's Absorb stent has several merits, with that company's pioneering of clinical studies, registration strategies and price setting to benefit Reva's commercialisation of its REZOLVE 2 stent, especially where trial designs are pioneered by Abbott. A small field of competitors also favours Reva Medical.

Reva Medical has strong and experienced management. However, the company has been slowed in its path towards European registrations because of limitations with its product design, although those limitations appear to have now been addressed.

The timing of entry into an investment in Reva Medical will be influenced by progress the company makes with its existing RESTORE trial, the commencement of its RESTORE II trial and evidence of recruitment in the RESTORE II trial being on track.

Reva Medical is capitalised at $210 million. At June 30, 2012, the company held cash resources of US$50 million.

Bioshares recommendation: **Speculative Hold Class B (Wait)**

Bioshares

Bionomics Makes Early Stage Oncology Acquisition

Bionomics (BNO: $0.375) has made a $10 million acquisition of an early stage US oncology company, **Eclipse Therapeutic**s. Eclipse is working in the area of cancer stem cells, which has become an area of strong interest in the cancer drug discovery and development area.

Eclipse's research started out at **Biogen Idec** in 2004. Biogen Idec invested around $15 million into this program. In 2010 Biogen Idec decided to move out of the oncology area. In March 2011, Eclipse was spun out, with a $2 million seed investment.

Eclipse has built expertise around assays for measuring cancer stem cell activity. This is the difficult aspect in working with cancer stem cells, working out when drug candidates have any impact on the stem cells. The impact a compound has on mature cancer cells can be more easily measured.

Eclipse is using humanised antibodies to target the stem cells. They will be used in combination with chemotherapy drugs. The company states that it has built up strong preclinical data with its candidates. The first drug candidate, ET101, is expected to go into manufacturing at the start of next year. The company will be using **Lonza** to make the drug. Toxicology work for ET101 is expected to start at the end of next year, and clinical trials are scheduled to begin in the second half of 2014. ET101 is targeting a known but undisclosed target.

The acquisition has also come with the appointment of the Eclipse CEO and Chairman, Jonathan Lim, to the board of Bionomics. A consequence of the acquisition is that Biogen Idec will own 6.5% of Bionomics.

Comments

For Bionomics to be involved in cancer stem cell drug discovery and development positions it at one of one of the new frontiers in cancer research. There is growing interest in targeting cancer stem cells, where a longer lasting treatment effect is potentially possible, that is, targeting the cells that give rise to cancer cells.

The deal also gives Bionomics more of a rounded approach to the treatment of cancer with at least two approaches, the other approach being the use of a vascular disrupting agent in BNC105.

On the downside, it increases the burn rate for Bionomics and brings forward the next time Bionomics will come back to the market to raise more funds. Bionomics expects to spend $4 million on the cancer stem cell program this financial year. Setting up the manufacturing process for antibody drugs is an expensive process, compared to other drug classes such as small molecule drugs.

Bionomics is expecting to receive a further $10 million in the next 12 months from its partner **Ironwood Pharmaceuticals** from the IW-2143 program in anxiety and depression. This cash flow will help fund the additional cost of the cancer stem cell programs.

The risk the company has is that it is over-extending itself at a time where access to capital can still be difficult, particularly for earlier stage assets. The cancer stem cell program is not expected to enter the clinic for about two years. Similar to Biota's investment in early stage assets, it increased that company's spend rate for little recognition in the company's share price.

Summary

Bionomics has recently broadened its management team with a Chief Medical Officer, Jose Iglesias, who will be based in the US. It has also added Jeremy Simpson as VP of Clinical Development, who is based in Australia. Eclipse co-founders Dr Peter Chu and Dr Chris Reyes will become US-based senior employees of Bionomics.

Bionomics has made a significant investment in new management and new projects recently. These moves are not without risks for the company, namely increased funding risk, and the risk of co-ordinating an expanded team into the US.

While there is much interest in the cancer stem cell area, the acquisition assets sit at the very early stage of the drug development timeline. Whether the acquisition is beneficial for Bionomics shareholders will take several years to determine.

Bionomics is capitalised at $138 million.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

Bioshares Model Portfolio (21 September 2012)

Company	Price (current)	Price added to portfolio	Date added
Nanosonics	$0.490	$0.495	June 2012
Osprey Medical	$0.33	$0.40	April 2012
QRxPharma	$0.69	$1.66	October 2011
Mayne Pharma Group	$0.410	$0.435	September 2011
Somnomed	$0.78	$0.94	January 2011
Phylogica	$0.027	$0.053	September 2010
Biota Holdings	$0.70	$1.09	May 2010
Tissue Therapies	$0.43	$0.21	January 2010
Bionomics	$0.38	$0.42	December 2007
Cogstate	$0.350	$0.13	November 2007
Sirtex Medical	$9.05	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.55	$6.60	September 2007
Pharmaxis	$1.10	$3.15	August 2007
Universal Biosensors	$0.80	$1.23	June 2007
Alchemia	$0.535	$0.67	May 2004

Portfolio Changes – 21 September 2012

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. 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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