ISSN 1443-850X

In this edition...
Some investors have maintained a scepticism towards biotech stocks but they can be a little more justified in maintaining a healthy optimism, now that Acrux and Mesoblast have cemented significant licenses with big pharmaceutical partners. And that healthy optimism has been fed further by a recent spate of drug approvals. We introduce readers to Helicon Group's pending acquisition of Leading Edge Instruments, a company that is developing a nasal airway management product and a fascinating vibrating needle technology. CSL recently held its annual R&D Day and we include extensive coverage of updates on several biotech products and also of life-cycle improvement to several currently approved products.
The Editors
Companies Covered: HCG, IPD, CSL R&D Day

	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 - Current)	23.1%
Cumulative Gain	**257%**
Av Annual Gain (9 yrs)	**18.5%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$350 (Inc.GST)
Edition Number 390 (17 December 2010)
ISSN 1443-850X

Bioshares

17 December 2010
Edition 390

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

Biotech Delivers in 2010... Momentum Set To Continue Into 2011

Well what a year it's been for Australian biotech! Following on from 2009, when biotech stocks in Australia doubled as recorded by the **Bioshares Index**, it was a patchy start to 2010. However the year is ending with multiple drug approvals and the biggest biotech licensing deal this country has ever seen. Finally the Australian sector is trading not on blue sky potential – which has rarely offered any generous premiums – but now on delivering significant commercial outcomes. And the momentum looks set to continue in 2011.

The year began with investors being forgiven for thinking the biotech bull run of 2009 – which followed seven consecutive quarters of negative returns in 2007 and 2008 – was too good to last.

A number of setbacks occurred in the first half of 2010. These included the discontinuation of **Avexa**'s ATC HIV program, delays at the FDA with **Chemgenex**'s oncology drug candidate Omapro, some ambiguity with Pharmaxis' second Phase III cystic fibrosis result, and a strong correction in Biota Holdings' share price after abatement of the global pandemic flu threat. The sector looked like it was going to not deliver, similar to a patch in 2004 when five Phase II program were discontinued or suffered setbacks.

However, the strength of this sector was, arguably for the first time, proven as these setbacks showed to be more minor stumbles in the final stages of product development rather than irreversible events.

Acrux set the new direction for the year, when it showed that a US$50 million upfront biotech deal could in fact be achieved by an Australian biotech for the very first time. In March Acrux signed a US$335 million deal with **Eli Lilly** for global rights to its testosterone gel, Axiron. This product has now been approved (in November), which triggered a US$87 million payment to the company. Investors are now keenly awaiting a 60 cent a share dividend, with the product due for launch in early 2011.

Multiple Drug Approvals

A number of new drug approvals have occurred or are due to occur towards the end of 2010 and in early 2011. This represents a truly unique period for Australian biotech sector.

Publication Dates over Christmas and through January 2011
No Bioshares Edition for Friday December 25
Bioshares 391 - Week of January 3, 2011
Bioshares 392 - 14 January 2011 (emailed January 17, 2011)
Bioshares 393 - 28 January 2011 (emailed January 31, 2011)

Biota Holdings was first away, with Japanese approval for its long acting flu drug, Inavir, through its partner **Daiichi Sankyo**. Acrux then followed in November with approval of Axiron by the FDA. Australia's drug advisory body has recommended **Pharmaxis**' Bronchitol for approval with a decision expected in early 2011. European approval for Bronchitol is also expected shortly.

Psvida Corporation is expecting to hear back from the FDA by 31 December this year on approval of its Iluvien drug candidate. Iluvien is a corticosteroid delivered to the back of the eye in a tiny intravitreal implant that lasts for up to three years. It will be used to treat diabetic macular edema. Psivida will receive a US$25 million milestone payment from its partner **Alimera Sciences** on approval and will receive 20% of net profits from sales of the drug.

Alchemia is also waiting on the FDA for approval of its generic fondaparinux drug. It's been a long wait for Alchemia and its shareholders, with the drug having been filed for approval 21 months ago. Our expectation is that approval should be received in the next two weeks.

Pending Product Registrations and Approvals for 2011

This week **Mayne Pharma** (formerly Halcygen Pharmaceuticals) submitted its drug candidate, SUBACAP, for approval with European regulators. The drug is a super generic version of the poorly soluble antifungal drug, itraconazole. Mayne Pharma's drug has a significantly better absorption profile to all existing itraconazole drugs on the market. The global market is worth an estimated $600 million a year. Mayne Pharma is anticipating a decision by the end of 2011 and for the product to be launched in 2012.

QRxPharma is expecting to release final Phase III results for its MoxDuo IR drug candidate in early 2011 with a marketing submission expected to be filed with the FDA in the first half of 2011.

Bionomics is anticipating major results from its two clinical programs in oncology and anti-anxiety treatment in the first half of 2011. Approval of the first animal health product from **Acrux/Eli Lilly** is expected in the US in early 2011. **Universal Biosensors'** new glucose monitoring product is expected to receive wider European approval in 2011 and then also US approval through its partner **Lifescan (J&J)**.

Starpharma's lead product, a microbicide to be included with Durex condoms marketed by **SSL (Reckitt Benckiser)**, is due to reach the market in coming months, which should start to generate a significant royalty stream for Starpharma. **Clinuvel Pharmaceuticals** should complete the Phase III studies and file its drug Scenesse with European regulators in the third quarter of 2011 for the severe sun intolerance disorder, EPP.

Stunning Deal by Mesoblast

And Mesoblast stunned the market earlier this month, eclipsing Acrux's deal earlier in 2010, with a massive biotech deal with **Cephalon**. Under the terms of the deal, Cephalon will invest US$350 million in Mesoblast (US$130 million upfront) with a total potential deal value worth US$2.05 billion, for access to Mesoblast's unique stem cell technology.

Merry Christmas from the Bioshares team

Bioshares would like to wish all subscribers a very enjoyable festive season and successful year in 2011. It is a unique period for Australian biotech that we are now moving through and we very much look forward to continuing to provide you with investment research advice into 2011 and beyond.

Bioshares

Impedimed Finds Continued Support From Investors

Impedimed (IPD: 80 cents) earlier this month completed a $10 million capital raising through a private placement and has also announced a share purchase plan that will allow smaller shareholders to participate in the capital raisings, which will all be conducted at 70 cents a share. The SPP will be underwritten by **Wilson HTM** and **RBS Morgans** to a maximum $4.27 million.

The Impedimed technology is now accepted as the new gold standard in assisting in the detection of preclinical lymphedema, following a recent *Journal of Lymphedema* found no opposing views as to why the technology should not be considered such.

At the company's AGM last month, chairman Mel Bridges said that the Impedimed technology detects the early start of lymphedema four months before clinical symptoms appear, allowing prevention of this condition before it reaches an irreversible form. Lymphedema is a common side effect from cancer resection, where lymph tissue is disrupted.

The first market application is in breast cancer, specifically lymphedema in the arms, where the potential market is estimated in excess of $150 million a year by the company. The second target market is in pelvic cancer, where lymphedema in the legs is common. This potential market is estimated by the company as being worth in excess of $400 million a year. These markets are based on current pricing.

The company has completed a health economics model with IMS Health which shows that even at a reimbursement rate of $600 for each of the company's L-Dex tests, this would equate to an annual savings of $2 billion a year after five years if the test was used on all patients in the US who had undergone breast cancer surgery.

The **Stanford University School of Medicine** recently announced that it would run a BIS (Bioimpedance Specotrosocpy - the Impedimed technology) registry with the aim of gaining CMS reimbursement in the US.

The company currently has 106 of its devices in place with around 140 surgeons with access to the device. The initial aim for the company is to have around 800-1000 surgeons, who make up 45% of the market, to adopt the Impedimed system. For that to occur, the company will need to get private insurance coverage in the US which is a long process. The company has now extended its target to the end of the first quarter of 2011 to gain 20 million covered

– Cont'd on page 8

Helicon Seeks To Acquire Leading Edge Instruments

Helicon (HCG: 3.6 cents) shareholders are about to vote on the acquisition of two very interesting technologies. Helicon has previously been seeking to commercialise pharmaceuticals into the Chinese market. If the acquisition proceeds, Helicon will move its focus onto commercialising the assets of **Leading Edge Instruments** (LEI).

BreathAssist

The first technology is called BreathAssist. This will be a direct competitor to the **GlaxoSmithKline** product called Breathe Right. Breathe Right is a very good product that opens the airways in the nose. The product is a rigid adhesive strip that is placed over the nose, springing back to open the nasal airway. It is a disposable product that costs around $1 per strip.

The product was developed by **CNS Inc**, which GSK bought for $566 million in 2006. Approximately 82% of that purchase price could be attributed to the Breathe Right product, based on proportionate sales, which gives an acquisition value of the Breathe Right product of $464 million. At the time of sale, Breathe Right was generating global sales of $85 million a year and last year GSK generated sales of $144 million from Breathe Right.

The BreathAssist product that Helicon is considering acquiring is being commercialised by Rod Tomlinson who founded drug delivery company **Soltec Research** that was sold to **FH Faulding** in 1996. Listed biotech OBJ previously had an option to acquire the BreathAssist technology products.

The technology consists of two bridged plastic inserts that are placed inside the nasal cavities. These disposable devices have shown in a clinical trial in Melbourne to increase airflow by 36%. Tomlinson believes the device delivers considerably better airflow improvement than the competing nasal trip product on the market.

Patents over the technology have been granted in the US (with 15 years patent life remaining) and in China and Japan (17 years patent life remaining).

The potential for the technology is not only to improve nasal breathing, but can potentially also be incorporated with pharmaceuticals as a nasal drug delivery device. The device can also be used as a filter for sufferers of hay fever.

Further product development is required of the device to improve the comfort of the device and that is expected to occur over the next six months. The company is then looking to commence discussions with potential licencees of the technology in the second half of 2011.

Vibrovein

The second technology has been developed by sclerotherapist and sports vascular medicine physician Dr John Marx. The technology is a vibrating needle system that allows almost pain free delivery and removal of needles. Marx runs a clinic in South Yarra, Melbourne, where varicose and spider veins are treated. The technology will not increase the cost of needles as it's a system that slips over existing needles and can fit to all needles. This is a very important distinction as the oligopoly that controls the global needle industry is controlled by six companies and entry into this space has shown to be incredibly difficult.

The Vibrovein system consists of a micro mechanical motor that is attached simply to the barrel of any modern hypodermic syringe. The motor delivers a smaller lateral vibration to the needle, the frequency of which can be controlled by the operator.

Advantages of the Vibrovein Device

Varicose veins and the larger spider veins are removed through multiple injections of a sclerosing solution that seals that vein of blood flow. A sclerotherapist for 20 years, for the last four years Marx has been using his vibrating needle system with patients. "The difference is massive not tiny," says Marx.

Not only does the technology dramatically reduce the pain experienced by patients, but it allows Marx to target veins that he did not even try hitting before. Patients who had the procedure previously with a standard needle are 'blown away' says Marx, when he uses his vibrating needle technology. Marx believes the modern needle is a frustratingly poor instrument that inflicts pain, causes bruising and delivers results that are ordinary at best. The Vibrovein device results in limited or no bruising according to Marx.

Time benefits

Another advantage is that using a vibrating needle can cut down on time, by five to 10 minutes on a varicose vein procedure that normally takes around 30 minutes per leg.

Marx says there are many precedents that have pointed him in the direction of applying vibration to improve penetration. Mosquitoes are the perfect example in nature which use vibration to efficiently and painlessly penetrate human skin (in fact it is only the female mosquitoes that draw blood from humans and the sting occurs when the mosquito's proboscis is withdrawn and as a result of the allergic reaction). The humming bird, the butterfly and the bee also use vibration to extract their foods.

Accuracy

Accuracy is also another benefit. The mosquito has almost a 100% hit rate in finding the vein. Standard needles require pressure to be paced against the skin which compresses the vein causing tissue distortion and resulting in over penetration. This means often the vein can be missed and further injection attempts may be required. This is a particularly frequent problem in traumatized patients, presumably where blood pressure may be low. Marx says this means that now 100% of veins can be targeted, where using a standard needle only 40% of veins can be accessed.

Sample Collection

A further advantage of the Vibrovein device is that smaller gauge needles can be used to take large blood samples in the pathology industry.

– Cont'd over

Needle Life
An additional advantage of using a vibrating needle is that the needle needs to be replaced much less frequently in varicose vein removal procedures. After about 20 injections a standard needle needs to be replaced because it becomes blunt. Marx says the vibrating needle, which also gets blunt but much more slowly, needs to be used 13.5 times before its performance resembles that of a new standard needle.

Commercial Precedents
Vibration can make any surface almost frictionless. There are commercial precedents of products that use vibration to deliver improved devices. These include the vibrating toothbrush, the vibrating razor, and vibrating rollers which allows significantly better penetration of the paint into the pores in the surface. (In fact Marx believes that razor companies have pulled back on the marketing of their vibrating razors because the blades last so much longer, reducing blade sales.)

Improves two key aspects
There are two limiting factors for needles. The first is penetration resistance, which Marx's vibrating needle reduces by 25%. The second is stiction, which is the tissue drag on the needle as it is being pulled out, and that is reduced by 70%.

Intellectual Property
Marx has filed intellectual property around two aspects of the technology. The first is the lateral vibration of the needle rather than traditional axial vibration down the shaft of the needle which is similar to a tattooing system.

The second IP is around the vortex created in the vein as a result of this lateral vibration. This improves the delivery and perfusion of the sclerosing agent into the veins, with the vibration decreasing the viscosity of the agent.

(This vortex created by lateral vibration is now being used to create clean energy in rivers – the vortex behind the pylons creates a vibration effect that can deliver energy, and in fact it is this phenomenon that oil rig platforms must account for in design to counter vibration effects).

Competition
Vibraject in the US markets a vibrating needle product used in dental anaesthesia, although this system is very expensive selling for around $340. The system relies on a different system where nerve ending function is disrupted by vibration. Another dental vibrating needle product is marketed by **Vibringe** that is used in root canal cleaning. Vibrating needles are also used in cataract surgery.

Affordable technology
The motors that Marx uses come from mobile phone technology. Five years ago these motors cost $100. The price has now reduced to a few cents, allowing a very accessible product to be commercialised.

Other uses
The vibrating needle is used by Marx to also treat what's called sports pressure syndrome to remove excessive veins on athletes. In fact there is a growing trend now by athletes to use compression garments on muscles because the more you can compress a muscle the better its function is.

However, sclerotherapy is just a small application area. The use of vibrating needles could be used in many areas, including blood donation and blood sampling by pathology groups. The Vibrovein device may also be used by self-injecting consumers, such as those taking regular insulin injections. The vibrating technology can also be applied to other medical instruments, according to Marx, such as scalpels.

Challenges
The big challenge for Helicon, should it acquire the technologies, is to access the diverse distribution channels to sell its products and create a market for its products. The company will seek to license out the technologies once the prototypes have been completed next year. This will be a key risk for the company, which will only have around $1.8 million at its disposal. The company believes will require between $300,000 - $500,000 to complete the prototype development of the Vibrovein product.

Together with the BreathAssist product, $1.2 million is slated for product development.

Acquisition Price
Helicon currently has 249 million shares on issue, giving it a market capitalization of $9 million. Under the terms of the deal Helicon will acquire an 81% interest in LEI by issuing 248 million shares and will have a market value of $18 million at the current share price.

The remaining 19% stake in LEI can be acquired by Helicon at any time up to April 2012 by issuing 252 million LEI shares. Or alternatively, LEI shareholders can sell their remaining 19% of LEI for 252 million LEI shares, however only if certain licensing and marketing performances must be achieved within 18 months.

Bioshares recommendation: **Under review post shareholder vote**
(Helicon shareholders will vote for the proposed acquisition of LEI on 23 December, 2010.)

Bioshares

CSL R&D Day Report

The annual CSL R&D Day was held on December 7, 2010. The purpose of the day is to update the investment community on the status of CSL's portfolio of assets in development. The event was led by CSL's Director of Research, Dr Andrew Cuthbertson, who provided a general overview of the portfolio, the immunoglobulin program and an update on IP and licensed programs. Dr Russell Basser discussed several speciality products, Dr Simon Green discussed recombinant coagulation products and Dr Andrew Nash reviewed the antibody drug development programs.

In FY2010, CSL expended $317 million on R&D compared to $312 million in the previous year and $225 million in FY2009. (We estimate that approximately 45% of R&D spending in FY2010 was for new product development.)

Specialty Products – Berinert, Beriplex and Fibrinogen

Dr Russell Basser discussed CSL's specialty products development program.

Berinert

Berinert was developed to treat a condition known as hereditary angioedema (HAE). This condition exists because sufferers lack the protein known as the C1-esterase inhibitor, which controls the leaking of blood vessels. Angioedema is a term that refers to the swelling of blood vessels.

With angioedema, patients can experience swelling and painful rashes. The condition can be life threatening if the throat swells which can mean urgent treatment is required. These episodes of swelling can occur without warning but are also caused by factors such as stress, infection and menstruation.

Berinert, which is a concentrate of the C1-esterase inhibitor protein, is a very effective treatment for HAE.

Berinert was developed initially for use in Germany and Central Europe. CSL is now aiming get Berinert approved in additional territories. Berinert received an Orphan Drug Designation in the US in 2009. However, the treatment is administered by IV in emergency departments.

CSL intends to develop a high-concentration, low-volume preparation that could enable Berinert to be administered subcutaneously instead of by IV, which could improve patient convenience. CSL is also believes that a prophylactic option should be available to patients, although a prophylaxis program is dependent on the development of a subcutaneous product.

The company would like to bring the prophylaxis indication to market when the ODD designation of a competitor product expires in 2015.

CSL believes that Berinert has potential beyond its replacement use in an inherited disorder. Berinert may have applications where inflammation occurs because C1-esterase sits high in the 'complement cascade' within the inflammatory response. A possible application includes the management of solid organ transplant.

Acquired Bleeding Disorders

CSL markets and develops products to treat inherited and acquired bleeding disorders. The acquired bleeding disorders occur where there is lack of coagulation factors caused by infection, surgery, trauma or medication which expose the patient to a high risk of bleeding.

Current treatment options include the use donated blood products, such as platelets, fresh frozen plasma and cryoprecipitate and crude preparations of coagulation factors. Alternatives include the highly processed concentrates which exist in the CSL portfolio.

However, a number of problems exist with donated blood products. They can cause sensitivity reactions, especially when a blood transfusion takes place. They often require large volumes and can take time to administer. Storage is a challenge (e.g. FFP is, as the name suggests, frozen) and donated blood products also have a limited life span.

In this context CSL is conducting a program to develop Beriplex for the reversal of coagulation where anti-coagulants in the class of Vitamin K antagonists (e.g. warfarin) have been prescribed.

Warfarin is commonly used in patients at a risk of clotting, such as deep vein thrombosis, or with heart valve replacement patients. The issue is that sometimes these patients can get too much blood thinning, due to infection or other illness. And spontaneous bleeding demands immediate reversal where it is threatening. Reversal of warfarin treatment is needed if trauma-initiated or urgent surgery is required.

Beriplex provides the Vitamin K dependent coagulation factors (FII, FVII, FIX, FX) that warfarin inhibits. In other words it is a very specific antidote.

Beriplex has been on the market for more than ten years of in Europe. A next goal for CSL is to expand Beriplex use to the US, in (a) people on warfarin therapy who are experiencing 'over-coagulation and (b) patients who require urgent surgery who require reversal of anti-coagulation therapy.

To this end, CSL has conducted two large randomised clinical trials. The bleeding study has been completed and the data is currently being analysed. CSL plans to submit a BLA in H2 2011.

The surgical trial is more complex and is two-thirds the way through recruitment.

Fibrinogen concentrate

Fibrinogen concentrate is a product that is approved in Europe for a very rare congenital deficiency and is approved in Central Europe for acquired bleeding disorders.

An interest for CSL lies in developing Fibrinogen concentrate to be used in aortic surgery, a major operation that requires cardiopulmonary bypass, so there is no blood involved.

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One problem that can occur is that coagulation factors get absorbed on to the tubing of the bypass machine, leaving the patient deficient in necessary coagulation factors. On occasion, patients can experience ongoing bleeding.

Although patients are treated with donated blood products, CSL is exploring the use of highly concentrated, fast acting, low volume product to reduce the use of donated blood products.

The concept came to the attention of CSL through the work of Dr Neils Rahe-Meyer at the **Hanover Medical Centre**, who developed an approach to use fibrinogen to reduce blood loss. After studying fascinating data from a retrospective trial, CSL determined a prospective randomised placebo controlled pilot trial at Hanover Medical Centre would be needed to test whether the data was sold enough to warrant making a major investment decision.

Importantly, Dr Rahe-Meyer developed a number of standards for surgery, measurement of blood loss, and ways of administering fibrinogen, which assisted in yielding meaningful data from the pilot trial. Also devised was a method to weigh the sponges used to mop up blood.

Dr Rahe-Meyer also determined a way to identify patients with a particular stage of bleeding. Trivial bleeding was excluded as was major bleeding. Rahe-Meyer determined how identify a middle zone of microvasculature bleeding, occurring because blood was not clotting properly.

The data is from the pilot trial is currently being analysed. However, headline prospective data mirrors retrospective data, which is that there was a 70% reduction in the amount of blood products used by each patient. A more compelling finding was that 100% of patients receiving saline needed donated blood products, whereas half of the patients who received fibrinogen concentrate did not require donated blood products at all. "These are fascinating data" said Basser.

CSL will commence a multi-centre trial in Europe in the next twelve months to confirm the findings of the pilot study.

Recombinant Coagulation Factors – Extending Half Life

Dr Simon Green reviewed CSL's program to extend the half life of several recombinant coagulation factors.

The purpose of developing coagulation factors with a greater half life is to decrease the frequency of injections, e.g. from one every second day to one injection per week. This can improve compliance but it could also create an opportunity to move from acute treatment to prophylaxis.

CSL has chosen albumin as the core half-life extension technology. Albumin has a very long half life, around 20 days. CSL has achieved proof-of-principle data to show it can extend the half life of recombinant (r) FVIIa-FP and rFIX-FP [FP- Fusion Protein].

CSL has used genetic engineering to combine albumin and selected coagulation factors, creating proteins with a half life that resembles the half life of albumin rather than of the coagulation factors.

The two proteins are held together by activation peptides. The fusion protein circulates in an non-active form. At a site of coagulation, the protein is cleaved in two courtesy of the activation petide and the FIX then functions normally.

rFIX-FP

CSL has shown that at two different doses in monkeys (50 mg/kg and 100 mg/kg), rFIX-FP circulates for seven days at the lower dose and even longer with the higher dose, and within the desired window for patients with hemophilia B, who are currently dosed every second day.

CSL began dosing ain Phase 1 clinical study in October. It expects results will be available in 12 months from now. Pivotal Phase III trials would follow, and take 5-6 years to complete.

rFVIIa-FP

rFVIIa-FP is being developed to treat patients with haemophilia A and haemophilia B who have developed inhibitors to blood clotting factors such as rFVIIa.

Novoseven (**Novo Nordisk**) is effective for treating haemophilia A and haemophilia B but it has a very short half life of about 4 hrs and is rapidly cleared. In contrast, rFVIIa, the fusion protein has a half-life greater than 24 hours (at 9 mg/kg, in a rat model).

CSL has evaluated rFVIIa-FP in mice, rabbits and rats and dogs and it has demonstrated efficacy in mice, showing that rFXIIa-FP was able to dramatically reduce blood loss in a tail clip model.

This program is trailing the rFIX-FP program by twelve months. CSL has now developed a pilot scale manufacturing process and will commence formal toxicology studies early in 2011. A Phase I trial may start towards the end of 2011 or early 2012.

Some Comments on Manufacturing

Simon Green contributed an update on CSL's new biotech manufacturing facility that is being constructed at Broadmeadows and developments at Marburg, Germany.

CSL currently uses a small scale facility for manufacturing clinical trial material at its Parkville site. This is a 500 litre facility sufficient for the manufacture of material for pre-clinical studies, toxicology testing and for Phase I programs. For Phase III studies and early commercial launch CSL has engaged a contract manufacturing organization (CMO) until the Broadmeadows facility comes on line. Site works began last month.

The Broadmeadows facility is designed to be highly flexible and to accommodate a range of fermentation techniques and biotech manufacturing strategies, with the goal of delivering fast turnaround times and decreased costs. The facility is expected to manufacture all of CSL's recombinant products.

– Cont'd over

Green said that CSL is also moving recombinant intermediates from contract manufacturing organizations into its Marbug facility for the large scale purification and formulation of recombinant proteins. This renovated facility opened in November 2010, and exploits extensive knowledge at the Marburg site concerning plasma coagulation factors.

Early-stage Antibody Projects

Dr Andrew Nash provided an update on two of CSL's antibody projects, CSL362 and CSL324.

CSL362

CSL362 began its life as CSL360, which was unsuccessful in a clinical study in patients with relapsed or refactory acute myeloid leukemia (AML). However, the study demonstrated that that IL-3 receptor (CD123) was a suitable target but only the antibody could be improved through re-engineering.

CSL 362 is a fully humanised antibody, which should reduce immunogenicity. More importantly, CSL362 has enhanced tumour killing properties. It is designed to more effectively interact with receptors on cells that will kill tumour cells (e.g. recruited NK cells and macrophages)

Acute myeloid leukemia

Acute myeloid leukemia is typically an adult leukemia which is fatal if untreated. Treatment with idarubicin or cytarabine induces a response in 50% to 75% of patients but relapses occur. There has been little improvement in survival in the last 30 years. Overall survival had improved to 21% by 2008, but at the age of 65, survival is less than 5%.

AML is thought to derive from mutations to hemopoietic stem cells (HSC) or later stage progenitor cells, to give rise to leukemic stem cells. These cells do not 'turn over' very often, which is why relapses occur. The leukemic stem cell population produces a class of cells called (leukemic) blast cells.

Both the HSC and the blast cells both express CD123. This is the target of CSL 362. CD123 is termed a differentially expressed target because it expressed on very few normal cells.

Some normal cells that express CD123 are basophils and PDCs. They are rare cells that express high levels of CD123. Significantly, it appears they do not perform a role that has a negative consequences if they are deleted through the treatment of an antibody such as CSL362.

The advantage they give is to provide a clear biomarker population to show if CSL362 is working, because the depletion of the basophils and plasmacytoid dendritic cells (PDCs) can be easily measured.

CSL has shown that when CSL362 is administered to monkeys, six hours after administration the basophils and PDCs disappear. CSL has also shown that in model populations of tumour cells, CSL362 eliminates primary AML cells. It has shown the same result in samples taken from AML patients.

In terms of future clinical studies CSL intends to apply CSL362 to treat patients in remission or at earlier stages of relapse, the goal being to kill the residual disease.

CSL is planning a Phase I/II trial to assess safety, pharmacokinetics and immunogenicity, with efficacy a secondary endpoint. The next milestone for the program will be to complete toxicology in 2011 and enter the clinic in 2012.

Another possible application

It is not unusual for antibodies targeting cytokine receptors to provide opportunities in more than one disease. CSL 362 effectively targets PDCs and basophils. PDCs are thought to be pivotal to the progression of lupus, which is characterized as an interferon signature disease. It is well understood that the major source of interferon are PDCs. They are one of the major cell populations underlying the initiation and development of lupus. Basophils have been implicated in lupus as well. CSL is hopeful that in addition to targeting AML, it may also be to address autoimmune diseases as well.

CSL324

CSL324 is an antibody that binds to GSCF receptor, indirectly controlling neutrophil production and transport.

Neutrophils are very common white circulating blood cells. They are the key effector cells of the innate immune system. The front line defence against a bacterial infection will involve a neutrophil response. However, too many neutrophils accumulating in the wrong spot at the wrong time can contribute to acute and chronic inflammation. They play a major role as mediators of acute and chronic inflammation and hence form a target for disease management.

There are a number of inflammatory diseases where excessive neutrophil production plays a role. The lung inflammatory diseases such as COPD, cystic fibrosis, acute respiratory distress syndrome, idiopathic pulmonary fibrosis are all mediated by neutrophils. Rheumatoid arthritis and vasculitis are also mediated by neutrophils.

The problem with targeting neutrophils is that they have a short half life, turning over in ten hours. An indirect target is granulyte colony stimulating factor (GCSF). The growth factor plays a role mediating the expression of neutrophils from bone marrow and in the transport of neutrophils from the blood stream to inflamed tissues. They also have a further role in activating the neutrophils and maintaining their life span.

CSL324 is a fully human antibody that exhibits a high affinity for its target, binding at 257 picomolars at the cell surface. CSL has demonstrated that CSL324 can inhibit GCSF induced neutropenia. In animals given pegylated GSCF (i.e an engineered long acting version of GCSF), CSL324 inhibited the pegylated GSCF from day 2 to day 3. When CSL324 is administered at the point when neutrophils are observed to peak, the neutrophils fall back to normal levels in 12 hours.

– Cont'd over

Bioshares Model Portfolio (17 Dec 2010)

Company	Price (current)	Price added to portfolio	Date added
Phylogica	$0.060	$0.053	September 2010
Sunshine Heart	$0.039	$0.036	June 2010
Biota Holdings	$0.97	$1.09	May 2010
Tissue Therapies	$0.48	$0.21	January 2010
QRxPharma	$1.365	$0.25	December 2008
Hexima	$0.37	$0.60	October 2008
Atcor Medical	$0.08	$0.10	October 2008
Impedimed	$0.80	$0.70	August 2008
Circadian Technologies	$0.58	$1.03	February 2008
Patrys	$0.095	$0.50	December 2007
Bionomics	$0.34	$0.42	December 2007
Cogstate	$0.25	$0.13	November 2007
Sirtex Medical	$6.04	$3.90	October 2007
Clinuvel Pharmaceuticals	$2.20	$6.60	September 2007
Starpharma Holdings	$0.88	$0.37	August 2007
Pharmaxis	$2.79	$3.15	August 2007
Universal Biosensors	$1.53	$1.23	June 2007
Acrux	$3.57	$0.83	November 2004
Alchemia	$0.64	$0.67	May 2004

Portfolio Changes – 17 December 2010

IN:
No changes.

OUT:
No changes.

– CSL cont'd

A concern with developing CSL324 is that it wipes out neutrophils. However, CSL324 appears to restores neutrophils to normal levels, suggesting that other factors contribute to maintaining baseline neutrophils.

CSL sees a number of opportunities for the clinical development of CSL324 and may conduct several parallel Phase II studies, to better understand some of the indications CSL324 could address. CSL will commence formal pre-clinical toxicology studies in 2012.

Expected Progress For The Next 12 Months

In the next twelve months, CSL expects to advance fibrinogen concentrate for aortic surgery and Berinert SC into Phase III trials, progress rHDL and rIX-FP into Phase II trials, move CSL362 and rVIIa-FP through toxicology studies and into Phase I trials and initiate pre-clinical studies for CSL324.

Bioshares

Correction and Clarification

In Bioshares 389 we incorrectly stated that IMM-124 E and and IMM 122-I increased insulin resistance, when in fact the opposite occurs. We apologise for this error.

In addition, the company has clarified that it plans to seek approval under a US NDA for IMM 124 E in order to sell a fully reimbursable pharmaceutical product.

– Impedimed cont'd

lives in the US (by insurers) and 50 million covered lives by the end of the third quarter in 2011. Impedimed already has Category III coverage that allows private insurers to reimburse tests that use the technology.

It is a difficult process to gain reimbursement in the US market. However once it is achieved, it places significant barriers to entry to rivals, particularly given Impedimed has a secured patent position around the BIS technology for lymphedema detection.

Bridges believes the company is on the cusp of significant breakthroughs and is poised for success. Impedimed is capitalised at $126 million (post SPP).

Bioshares recommendation: **Speculative Buy Class A**

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

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