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In this edition...
We look at the next IPO for the sector, Impedimed, a medical device company that measures swelling in the limbs using an impedance measurement technique. Tissue Therapies is a stock well worth considering with a major clinical trial hurdle approaching.

And in a two-part feature, we look at ways drug developers and investors are seeking to minimise technical risk in pharmaceutical development and with some success in Australia recently.

The editors
Companies covered: TIS, Impedimed
IPO preview

	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 (from 4 May '07)	-6.6%
Cumulative Gain	**205%**
Av Annual Gain (6 yrs)	**26.8%**

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9671 3633
Email: info@bioshares.com.au
David Blake
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz
Ph: (03) 9671 3222
Email: pachacz@bioshares.com.au

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Bioshares

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

Reducing Technical and Investment Risk in Biotech

The last eighteen months have on balance been a successful period for Australian biotechs as judged by success in Phase II clinical studies. In fact results have been disproportionally positive to what could historically be expected, with about an 85% success rate in the clinic (see edition #228). Investors have become more welcoming towards biotech stocks that exhibit a perceived lower technical risk. In a two part feature in *Bioshares*, we will look at this trend in Australia which is reflective of a global biotech trend where both investors and drug developers are looking at ways of reducing technical risk to achieve a higher rate of commercial success and counter the poor success rate in bringing new chemical entities to market.

The characteristic of 'low' technical risk

The current pack of leading biotech stocks largely shares the characteristic of 'low' technical risk, although it should be emphasised that we are referring to low technical risk in a relative sense. Why technical risk has been diminished is because generally, proof-of-concept has been established in prior clinical studies or prior use in humans. Other factors such as the choice of indication within a disease area, selection of the route of delivery and the degree of understanding of the mechanism of action have also lowered the technical challenges for many of these programs. Another facet of the lower relative risk of these therapeutic product programs is that the target markets are smaller (not 'blockbuster drugs') and targeted at specialist clinicians where the distribution channels are narrower and the pivotal clinical trials smaller, allowing the companies also to potentially take the drugs all the way through to market.

A leading example is **Peplin**. Its compound, PEP005 for the treatment of skin cancers, is derived from a garden weed which had been used as a folk medicine for many years for treatment of sunspots. Pilot study results were first announced in 2000, where in a 40 patient study the drug candidate achieved an 88% complete response in treating non-melanoma skin cancers (BCC and SCC) in an interim finding. That the drug was delivered topically also increased probability of success in later trials. The company is now moving the compound into Phase III trials.

Pharmaxis established early efficacy in pilot trials well before the company listed in 2003. The company then completed a positive 49 patient study in 2005 in patients with cystic fibrosis and has most recently generated positive results in a Phase III study in 362 patients with bronchiectasis (degeneration of the lung). And added appeal to Pharmaxis is that the mechanism of action of its compound, Bronchitol, is more straightforward, relying only on the physical process of osmosis rather than any chemical of biological reactions.

ChemeGenex Pharmaceuticals obtained its lead drug, Ceflatonin, through its US acquisition of **Chemgenex Therapeutics Inc** in 2004. Ceflatonin had been widely tested through the **National Cancer Institute** in the USA and was shown to have a good effect in treating

Cont'd over

chromic myeloid leukemia. However, the program was shut down when Gleevec came along and began delivering outstanding results for CML patients. It was not until Gleevec resistance began to emerge that the drug was resurrected. The drug has now been administered to over 500 patients and delivered the expected positive results in December last year. The company is hopeful of submitting the drug for approval next year.

Avexa has delivered very clear results from its Phase II HIV trial reducing viral load to undetectable levels in 80% of patients. It is now moving the compound through to a Phase III program. The compound was in-licensed from **Shire Pharmaceuticals** in January 2005 after that compound delivered very strong results in a Phase IIa trial in 63 patients affected by the wild-type (non-mutated) virus. The success rate of HIV drugs in getting through the clinical has been very high, with over 20 HIV drugs on the market. And with all drugs that have previously been through Phase III studies being successful, the probability of this drug getting through the final stage of development should also be high.

Over the last fifteen months **Clinuvel Pharmaceuticals** has delivered positive results in three separate clinical studies in patients with various UV-related skin disorders. The development of this drug, CUV1647, goes back over 15 years, having successfully increased the level of melanin levels in several human pilot trials. It is argued that an increased level of melanin in the skin reduces an individual's likelihood of skin cancer lesion formation. Clinuvel is now progressing the compound through two Phase III trials for two distinct skin disorder applications with more expected to follow, including prevention of skin cancer formation in immunosuppressed patients having undergone organ transplant. The drug candidate has been administered to over 200 people to date.

Lessons from drug failures - Clear biomarkers crucial

Considering drug candidates that have failed recently in the Phase II setting, a common element that emerges is the lack of positive pilot study data in people. Metabolic Pharmaceuticals stopped two programs this year, both after Phase II trials, and it can be acknowledged were difficult therapeutic areas. The first was in an obesity treatment trial in 536 patients which followed on from an earlier Phase II failure. Because the endpoint of weight loss anticipated was so small (a target of 2% per month), and the multiple factors that can contribute to weight changes, early pilot data on clinical efficacy was not possible. Similarly with the company's more recent Phase II neuropathic pain trial, it was not possible to establish efficacy in a smaller pilot clinical study. The assessment marker in pain is a very subjective measure and blinded, larger trials are required to gain meaningful data.

Summary

It goes without saying that drug development is a technically very challenging pursuit. Crucial to its success is the structure of a testing regime that needs to be objective with the ability to clearly test medical hypotheses. Without the presence of an objective marker or diagnostic that can be directly linked to the disease, or even better, a direct target of the disease, then the syntax for assessing clinical success or failure becomes less clear. This helps explain why cognitive degenerative diseases such as Alzheimer's disease, where the measure of success is the difficult to assess parameter of cognitive change, have yielded very few effective therapeutics. Accurate biomarkers also allow early insights into a drug's efficacy to be gained which helps reduce development risk going forward.

A reduction in sputum levels or improvements in lung function, a drop in plasma HIV levels, a clearance of skin lesions or an increase in melanin levels can all be easily measured for early indications of drug efficacy.

These factors become clearer with hindsight although are valuable tools for assessing risk/return parameters in future biotech investment opportunities. With another wave of Phase II results in Australia approaching - Biodiem in diabetic macular odema (November), Prana Biotech in Alzheimer's disease (December) and Antisense Therapeutics in multiple sclerosis (in early 2008) - these points are worth considering.

Next week, in Part II of this feature on how investors are reducing the risk in their biotech investment portfolios, we will look at the growing interest in 'Super Generics' in Australia, where reformulations and improvements to generic drugs seeks to avoid the risk inherent in new chemical entity drug development altogether.

Next Week: ***Bypassing the Technical Risk - Super Generics***

Bioshares

Tissue Therapies – Major Clinical Milestones Approaching

Tissue Therapies (TIS: 48.5 cents) is approaching a pivotal point in the commercialisation of its wound healing treatment, VitroGro. Major studies will be started and completed by year's end, according to the company. VitroGro is a synthetic version of naturally occurring proteins and growth factors that seeks to promote cell growth and migration. The trials will involve around 240 patients with three types of wounds: diabetic ulcers, venous ulcers and pressure ulcers.

The trials are expected to take about one month to complete and results should be available a month later. These trials will be conducted in Canada with the company expected to receive the go ahead to proceed in the very near future. Tissue Therapies has adopted a clever and sensible approach to bring its wound healing product to market. The company is focusing on the Canadian market initially, where the completion of the clinical trials can be facilitated quickly and where the Canadian Health authority has agreed to assess the treatment as a topical biologic, meaning it receives a more straightforward regulatory approval process similar to a medical device.

Cont'd on page 5

IPO Profile – Impedimed

Impedimed is a Brisbane-based medical devices company that has developed a suite of devices that measure lymphoedema and body hydration using bioimpedance technology. Bioimpedance analysis involves the application of a very small electric current to the body. Sensors are used to measure resistance that is created by tissues and fluids. The technology is attractive from a diagnostic perspective because it is non-invasive but also is potentially more convenient and more cost effective than X-rays and MRI scans.

Lymphoedema occurs as a result of build-up of lymphatic fluid, due to natural degeneration of the lymph nodes, from the surgical removal of the lymph nodes or where the lymph nodes have been damaged as a result of radiation therapy. A major driver for lymphoedema detection stems from the numbers and growth in survivors from breast cancer, particularly in the USA, where it is estimated that 2.4 million people have been treated for breast cancer.

Lymphoedema is often characterised by extensive swelling, typically in the arm. The condition, when detected early enough, can be treated with the application of pressure bandages. However, if left undetected, a chronic debilitating condition can develop.

The Market Opportunity

The lymphoedema and body hydration diagnosis markets are poorly served. Current diagnostic methods include measurement of limbs by measurung the cicumference of the limb or by emersing the limb in water and measuring water displacment, DEXA (a form of X-ray) or magnetic resonance imaging. These approaches vary from being cheap and unreliable or lacking specificity, to being more reliable but expensive and limited by location in specialised hospital settings.

History

Impedimed was founded in 1999 by Lucille and Mel Bridges (the company chairman), based on research conducted at the **Queensland University of Technology** and the **University of Queensland**. The researchers first involved with developing the bioimpedance technology were Dr Leigh Ward (UQ) and Drs Bruce Cornish and Brian Thomas (QUT). Approximately $20 million has been invested in Impedimed to date.

The Offer

Impedimed is seeking to raise $8.7 million through the IPO from the issue of 12 million shares at 72 cents, which is underwritten by ABN Amro Morgans and Emerging Growth Capital. There is an allowance for over-subscriptions of 1.4 million shares, which is not underwritten. A free option (for two ordinary shares) will also be issued, for shares offered through the IPO.

At the conclusion of the offer Impedimed will also issue 11.4 million shares to redeem convertible notes issued when the underwriting agreement for the IPO was signed in September. This convertible note and redemption issue has resulted in the raising of $8.2 million and was essentially structured to allow the participation of VC group, **Starfish Ventures**. In total, Impedimed is raising a minimum of $17 million through the offer.

Application of Funds

Impedimed expects the funds it is raising through the IPO to be sufficient for 18 months of operations. Of the $16 million raised, $4 million has been allocated to sales and marketing, $2 million for contracted design and development, $1.4 million in staff salaries, $0.3 million for consulting R&D, $0.6 million for IP costs and travel costs, $0.7 million in clinical trial costs, $0.275 million in regulatory costs, and $3.3 million in general and administration costs.

Xitron acquisition

Impedimed is acquiring a US firm, **Xitron Technologies Inc** (San Diego), in conjunction with the IPO. Impedimed will pay an initial tranche of 2.1 million shares and another 3.1 million shares contingent on certain milestones being met. As part of the IPO application of funds, Impedimed will supply to Xitron $0.77 million towards debt repayment and working capital, and another $1.2 million to enable Xitron to amend a license agreement with **Fresenius Medical Care**. The payment will enable Xitron to regain exclusive world wide rights for Xitron's digital signal processing and hydra bioimpedance device technology exclusive of the areas of renal disease.

Impedimed's Products

Impedimed has developed four diagnostic devices based on bioimpedance technology. These are the first generation Imp XCA which is a single, low frequency device, the Imp SFB7, also a single channel device and the Imp SBF9, a multi-channel device. There is also the Imp DF50, a less expensive single channel product for determining general body composition.

The Imp DF50 and Imp SFB7 have received FDA 510(k) class II approval from the FDA for general body composition claims. In April 2007, ImpediMed received a 510(k) class II clearance for clinical assessment of lymphoedema in the arm for the Imp XCA.

Strategy and business model

Impedimed's business model is to expand and develop a business that manages the development, stocking and support services of diagnostic device products, with manufacturing out-sourced and distribution partnered out. The company has appointed **Lymphedema Products** and **Vodder** its US distributors and **EDN** as its European distributor of the Imp XCA product.

The company manufactures its products using the services of Australian firm **Startronics**. The company intends to acquire in conjunction with the IPO a US company, Xitron, for the purpose of establishing a US sales support and minor manufacturing facility, and to also enhance the company's IP position.

The company's strategy to build a profitable business includes a very strong focus on the US secondary lymphoedema market. It intends to support its business by conducting further clinical trials of its products.

Impedimed's strategy to protect its commercial prospects in the US and to create barriers to entry by achieving approvals for its

Cont'd over

devices through some of the more arduous regulatory approval routes at the FDA such as the 513(F)(2) denovo route and the Pre-market approval route. The 513(F)(2) is required where no other equivalent device is cleared for the indications sought.

The Imp XCA has been undergoing 513(F)(2) denovo process for the last two-and-a-half years. Impedimed intends to submit the Imp XCA and Imp SFB7 to the 513(F)(2) denovo process for lymphoedema diagnosis and risk assessment claims. For the Imp SFB7 the company will apply for claims for both arms and legs.

IP and patents

Impedimed has licensed the rights to several patents from the University of Queensland and Queensland University of Technology. The first licensed patent family covers the application of single frequency bioimpedance to the detection and measurement of tissue oedema. Patents have granted in Australia and the USA (US 6,760,617).

The second patent family covers multi frequency bioimpedance determination. With respect to an application made to the US PTO, a recent examination found examples of prior art. Impedimed has stated that it proposes to file arguments or amendments with the US PTO to show that distinctions can be made between the invention described and the cited documents.

Strengths

VCs on the register

Impedimed has been successful in attracting two venture capital investors including **Starfish Ventures** from Melbourne, which will hold a post-IPO voting stake of 30.6% and **Versant Ventures** from San Francisco (a 6.5% stake). Starfish Ventures is known for its investments in several Australian life science firms, including the listed **SirTex Medical**. Versant Ventures manages more than US$1 billion in committed funds and is currently managing investments in more than 70 companies. The presence of experienced life science investors is a welcome aspect of this IPO.

Publications

The US **National Institutes of Health** recently completed a five year study on Impedimed's technology. Results from this study are expected to be published in various journals in 2008. Such publications are expected to considerably aid the promotion and market development of Impedimed's product in North America.

Strong team and CEO

Impedimed is led by Greg Brown bringing significant experience in the diagnostics industry to the firm. He has previously held senior positions with **Roche Molecular Systems** and **Digene Corporation**. Two other key appointments include that of Jack Butler, Vice President of Business Development North America and Sarah Edmonds, Vice President of Business Development Europe. Both Butler and Edmonds also worked previously at Digene Corporation and Butler spent thirteen years at Roche Diagnostic Systems.

Weaknesses

Patents

Impedimed's portfolio of 16 patent families includes only two granted patents in the jurisdictions of Australia and the USA. With many patents pending, including in the company's principle target market of the USA, then an identified risk sits over the Impedimed business.

Latent conservatism of practitioners

A general challenge for Impedimed is the latent bias of healthcare practitioners to continue to use an existing technology or practise despite the availability and affordability of new and superior approaches. Impedimed looks to have given this issue considerable thought and understands the financial drivers that are related to securing the adoption of its technology in its various product forms.

Distributors

Selling through third party distributors generates uncertainties for the company as the focus of the sales and marketing team can not guaranteed. Selection of the most suitable distributor is also a trial and error process.

Summary

Impedimed has assembled a strong team of experienced professionals to support and drive the sales of its products into the key North American market. It has articulated a clear understanding of the steps required to gain product acceptance and endorsement. The firm appears to have a comprehensive and solid grasp of the approval, coding, reimbursement and clinical data generation issues that must be addressed in order to achieve commercial success.

Details of the Offer

- Offer opens – 25 Sept 2007
- Closing date – 12 Oct 2007
- Expected date of quotation of securities – 24 Oct 2007
- Capitalisation on listing – $57 million

Investors are required to read the prospectus which can be downloaded from *http://www.impedimed.com.au*

Bioshares

– Tissue Therapies

An alternative strategy

Companies often make the US market the sole initial focus of their commercialisation activities. However, for smaller companies, an alternative strategy can be get the product on the market in one region, where product sales can gain traction, which in turn can generate share price appreciation that should allow capital to be accessed for supporting moves into larger markets.

The current strategy could see the product on the market in Canada early next year after Tissue Therapies forms a marketing and distribution alliance. The company may then be in a position to file its product for approval in Europe, Asia, Australia and New Zealand.

Tissue Therapies has been quietly making very solid progress on all levels. There is external commercial validation in a distribution agreement with **Invitrogen** for VitroGro for the research market and a collaborative agreement with **Novozymes** in the development of an advanced wound dressing product. (Don't be surprised in one of these companies makes a bid for Tissue Therapies, remembering that Novozymes acquired GroPep last year.) And the company has been devoting considerable time to improving and finalising its manufacturing processes for its VitroGro product.

Summary

Tissue Therapies is approaching a major development milestone with the start of its large wound healing trial for VitroGro. Based on preclinical results with VitroGro in accelerating healing and reducing scarring, it should have a very good chance of success in the upcoming trial. The company is capitalized at $15 million and is a very appealing speculative investment proposition. It has an estimated $2.5 million in cash.

Bioshares Recommendation: **Speculative Buy Class A**

Bioshares Model Portfolio (14 September 2007)

Company	Price (current)	Price added to portfolio
Acrux	$1.40	$0.83
Alchemia	$0.80	$0.67
Biota Holdings	$1.68	$1.55
Circadian Technologies	$1.20	$1.45
Clinuvel Pharmaceuticals	$0.61	$0.66
Cytopia	$0.60	$0.46
Chemgenex Pharma.	$1.00	$0.38
Optiscan Imaging	$0.39	$0.35
Peplin	$0.83	$0.83
Peptech	$1.28	$1.31
Pharmaxis	$4.00	$3.15
Phylogica	$0.31	$0.42
Probiotec	$1.19	$1.12
Progen Pharmaceuticals	$3.55	$3.52
Sirtex Medical	$3.91	$3.90
Starpharma Holdings	$0.37	$0.37
Sunshine Heart	$0.18	$0.19
Tissue Therapies	$0.49	$0.58
Universal Biosensors	$1.22	$1.23

Portfolio Changes – 14 September2007

IN:
No changes

OUT:
No changes

How Bioshares Rates Stocks

For the purpose of valuation, *Bioshares* divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, *Bioshares* grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Phylogica, Neuren Pharmaceuticals, Pharmaxis, NeuroDiscovery, Prima Biomed, Biotech Capital, Cygenics, Cytopia, Biodiem, Peptech, Starpharma Holdings, Cogstate, Xceed Biotechnology, Incitive, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Medical Therapies, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcygen Pharmaceuticals, Peplin, BioMD

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