ISSN 1443-850X

**In this edition...**
Pharmaxis is an impressive company that goes about its business very seriously. While some might think it leads a charmed life, our view is that the company does not take anything for granted; every inch of progress is hard fought. 2008 is shaping up to be another very big year for one of the standard-setters in the Australian biotech sector.

Elsewhere we profile ASDM, a Sydney device manufacturer, which is set to make a compliance listing this week. We note Bionomics' recent FDA acceptance of its IND application and place this event in an historical context.

**The editors**
**Companies covered: BNO, PXS**
**IPO profile-ASDM**

| | 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) | -12.0% |
| **Cumulative Gain** | **188%** |
| **Av Annual Gain (6 yrs)** | **26.8%** |

*Bioshares* is published by Blake Industry & Market Analysis Pty Ltd. The company also provides market and company analysis of the Australian pharmaceutical and biotech industries for local and international funds management institutions, venture capital funds and other related industry groups. For further details contact David Blake (see details below).

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Individual Subscriptions (48 issues/year)
**$320** (Inc.GST)
Edition Number 243 (30 November 2007)
ISSN 1443-850X



# Bioshares

**30 November 2007**
**Edition 243**

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

## IPO Profile

## Advanced Surgical Design and Manufacture

Advanced Surgical Design and Manufacture (ASDM) is set to list next Wednesday on the ASX raising $1.9 million at 60 cents a share through what is largely a compliance listing. As the name suggests, the company has developed a suite of medical implants and devices, such as knee replacement prostheses. To some degree, the company can be compared with **Portland Orthopaedic**, which listed on the ASX in 2005, although there are some differences, in particular access to a vascular repair device that recently achieved widespread media attention.

### History

The genesis of the company occurred in the early 1990s when the key inventor behind this company, CEO Greg Roger, designed a novel knee replacement prosthesis in conjunction with surgeon Mervyn Cross. The device was licensed to a Swiss medical device group which sold the device until it was acquired and the rights returned to Greg Roger in 1999. In 2001, ASDM began making and selling the knee prosthesis in Australia and has since added over 20 surgical implants to its product range, the majority of which have been invented by Greg Roger.

Greg Roger has a formal background in medicine, having working as an assistant surgeon, and a Master of Engineering, which makes him ideally positioned to bridge the needs and the capabilities of the two disciplines.

### Financials

In the last financial year the company broke even (loss of $64,000) with sales of $5.8 million. Sales are expected to increase to $7.2 million in FY2008, largely due to a price increase negotiated with the Australian Government for one of its products and the company expects to make a small profit ($172,000).

The purpose of listing the company is to provide shareholders, including founders, liquidity in their stock, which explains the small amount of funds being raised.

**Orthopedic Company Comparison**

| Company | Sales FY2007 | Loss FY2007 | Capitalisation |
|---|---|---|---|
| ASDM | $5.8M | $64,000 | $21M* |
| Portland Orthopaedics | $5.7M | $5.7M | $29M |

**At 60 cent listing price*

### Business Model

Where ASDM differs to **Portland Orthopaedics** is that its primary market at present is in Australia, generating 85% of sales, where Portland sells mainly into the US through a combination of distributors and more recently has added its own staff. ASDM has its

*Cont'd over*

own sales force in Australia, and uses a combination of distributors and sales agents in Europe and the US. Last year the company formed a manufacturing and supply agreement for five years with one of the largest medical device groups, **Stryker**, for its Active Uni-Knee product. Other products ASDM sells include cranial-facial plates, surgical screws, clavical pins and a range of knee replacements.

### Upside in ASDM

ASDM continues to develop and improve existing products, and in-license new products to add to its suite of medical device implants. New products in development include hip and knee instrument sets, and a polishing technology licensed from St Petersburg Institute in Russia. Of most interest to investors might be the vascular peripheral access device (PAD), which may deliver a major advance in prevention of limb amputation.

This technology was licensed from the inventing company, AllVascular Pty Ltd for a period of 15 years and provides ASDM with a manufacturing arrangement, whereby ASDM will receive 25% of sales for manufacturing the device, should it successfully make it to market.

The PAD system uses a catheter system that blocks the vein supplying the limb, allowing the lower limb to be pressurized at three times normal pressure in a process lasting several days. When the vein is depressurized, the theory is that vascular cells are stimulated, with genes up-regulated to rebuild the blood vessels that have near collapsed and threatening limb amputation.

Several patients have now been treated with the device with clinical trials expected to be completed by mid next year in 20 patients. It is potentially a revolutionary way to treat vascular damage. About 330,000 people in the western world have limbs amputated each year and the technology has the potential to be used in regenerating other blood vessels.

### Summary

ASDM will have a market capitalisation of $21 million upon listing. The company has built a modest but solid medical device business based on harnessing a strong inventive capability. The process of listing the company on the ASX may help improve the company's performance moving forward. A successful listing may provide the opportunity to accelerate the company's business plan. And access to the potentially very lucrative vascular PAD system provides the potential for good upside with this stock.

The offer to this IPO has closed with the expected listing date Wednesday 5 December at 12.30pm. The stock will trade under the code AMT.

**Bioshares**

## *Pharmaxis – Commercialisation On Track*

Australia's leading biotech company, Pharmaxis (PXS: $4.13), is steadily moving its products to market. The next 12 months should see its first product Aridol, an asthma diagnostic test, gain a solid footing in the European market, and its second product, Bronchitol, for the treatment of cystic fibrosis and bronchiectasis, complete final testing over the next 18 months through the completion of Phase III studies.

### Aridol: Reimbursement challenge in Europe

Aridol was approved by the European regulatory authority in June this year through the European Mutual Recognition Procedure. From there, it needs to receive marketing authorization to sell the drugs throughout Europe, which is more of an administrative process. To date the company has received marketing authorization in Denmark, Ireland and the Netherlands, with the test currently being sold in Australia (directly) and Sweden (through a distributor). Over the next year it's expected that full marketing approval will be received throughout Europe, where the test will be sold mainly through distributors.

From there, the challenge for the company is to have its test reimbursed by health insurers throughout Europe. In the third quarter of this year, the company generated sales on only $47,000, although we anticipate this figure should start to show strong growth over the coming 12 months.

***Sizable asthma test market in Europe***

The market for asthma tests is larger and more established in Europe than in Australia, estimated at over three million tests a year. At an estimated sale price of 45 Euro per test, it represents an annual market in Europe of $110 million after distributor costs.

Germany is likely to be a major target for Pharmaxis, where 750,000 asthma diagnostic tests are conducted annually and are reimbursed by one main health insurer. In Korea, which has the highest rate of asthma in Asia, around 700,000 asthma tests are conducted each year, using a methacholine challenge test. This liquid causes mild asthma symptoms, similar to the Aridol test. Arguably Aridol arguably offers a cleaner approach over methacholine, which has some safety concerns, specifically in women who are pregnant or the possibility of having just become pregnant. Pharmaxis has filed for regulatory approval in Korea and has appointed a distributor in that country.

In the US, approximately two million asthma tests are conducted each year using methacholine. Pharmaxis plans to file an NDA (new drug application) in the first quarter of next year, with the aim of gaining regulatory approval by the end of 2008 and launching the test in early 2009.

To gain widespread acceptance in the US, the company is working

*Cont'd over*

on an education process to convey the benefits of its alternative test. The company is working with biotech and pharmaceutical companies (for example, **AstraZeneca**) developing new asthma medications, to have its test used in clinical trials and to have the test associated with the use of emerging therapeutics for asthma.

In the US, Pharmaxis' aim is to build its own sales force, where a team of around 25 sales representatives could reach the bulk of respiratory physicians in that country. The establishment of an Aridol sales force in the US will position the company well for the subsequent launch of its key product, Bronchitol.

### Bronchitol: Special Protocol Assessment (SPA)

Pharmaxis recently passed a significant hurdle, having negotiated with the FDA a Special Protocol Assessment (SPA) for the forthcoming Phase III trial in the US in patients with cystic fibrosis. Pharmaxis is currently conducting its first Phase III trial in cystic fibrosis in 250 people in Australia, New Zealand and Europe, with the trial approaching 50% enrolment.

Completion of the European trial, expected by the end of next year should allow the company to file for approval in Europe in early 2009.

### US CF trial to begin in 2008

In the US, a 250 person trial involving adults and children with cystic fibrosis is expected to begin early in the new year. The protocols agreed to with the FDA include the primary measure of improved lung function, as measured by an improvement in FEV1 levels, which is a surrogate for improving life. The trial will run for 26 weeks. Together with the results from the European trial, Pharmaxis should be in a position to file for approval in the US for cystic fibrosis in 2010.

Pharmaxis successfully completed its European trial of Bronchitol for the treatment of bronchiectasis, achieving a statistically significant improvement in mucous clearance in a trial that involved 362 patients. The company is currently finalising the Phase III trial design with the FDA for the US trial, where the endpoint is likely to be a reduction in antibiotic use.

### Meeting with regulators in early 2008

Pharmaxis will meet with European and Australian regulators in early 2008 to discuss regulatory approval of Bronchitol for the treatment of bronchiectasis. The unknowns at this stage are the claims that Pharmaxis will seek for its drug in Europe and Australia. The options are either to register it as a drug that improves mucous clearance, or we assume to wait for the completion of the US trial and aim for higher claims with the drug i.e. reduction of antibiotic use and thereby improvement in quality of life and extension of life.

### The issue of claims

The issue is an important one as greater claims will allow a higher level of reimbursement to be negotiated with insurers. If the company opts for the latter, it could be in a position to file Bronchitol for approval for the treatment of cystic fibrosis and bronchiectasis at around the same time in Europe.

An estimated sale price of Bronchitol is approximately $6000 a year. This low price, compared to other pharmaceuticals that can cost in excess of $30,000 a year, has some advantages for Pharmaxis as it will be affordable to many with or without reimbursement. Given the positive feedback from trial users of the drug in clinical trials to date suggests that many patients afflicted by these illnesses may readily seek the treatment when available.

### Manufacturing capabilities

The current manufacturing facility at Pharmaxis allows sufficient quantities of the drug to be produced to treat 900 patients annually. A new facility is being built to supply sufficient quantities of Bronchitol to treat 40,000 patients a year (equates to a potential revenue of $240 million) and this capacity can be doubled through the addition of an additional spray dryer at the new facility. This facility is due to come online in early 2009.

### Summary

With the first product, Aridol, now on the market, and with the first Phase III trial of Bronchitol successfully completed, a large amount of the development risk has been removed although there are technical hurdles that still need to be passed. The commercial potential of Aridol will start to become better known over the next year and may positively surprise the market, although a measured but sustained uptake should be expected.

The clear health benefits to sufferers of respiratory illnesses, such as bronchiectasis, have been shown and our expectation (and that of the market) is that this drug will be a very successful product. In 2006, **Genentech**'s Pulmozyme, for the treatment of cystic fibrosis through assisting mucous clearance, generated sales approaching US$300 million. *However*, this drug failed to show a benefit in treatment of patients with bronchiectasis.

While there may be some setbacks on the commercialisation path moving forward (although there have been few to date), Pharmaxis is an appealing investment for a number of reasons; the business is well managed, the key product Bronchitol has shown to offer clear health benefits to treat unmet clinical needs, the company controls the manufacturing and will control the distribution into the US, and an affordable expected price for the drug should see rapid penetration once approved.

*Bioshares* recommendation: **Speculative Hold Class A** (look for price weakness to add to portfolio)



**Corrections and clarification:**

In last week's edition (Bioshares 242) we omitted our recommendation for Arana Therapeutics: '*Bioshares* recommendation: **Speculative Buy Class A**'

And in our discussion on sales of the three marketed anti-TNF drugs we did not include sales by marketing partners, Wyeth, Schering Plough and Tanabe. An adjusted total for 2006 is US$10.8 billion and for 9 months - 2007, US$9.7 billion.

# *IND Covering Bionomics' BNC105 Accepted by FDA*

Bionomics (BNO: 38 cents) announced recently that an Investigational New Drug (IND) application covering its anti-cancer compound had been accepted by the US FDA. (For a summary on INDs filed by Australian and NZ biotechs, please turn to the next page.)

The lead compound, BNC105, is a vascular disrupting agent (VDA) which is designed to destroy the rapidly created vascular network in solid cancers. Australia is developing somewhat of an expertise in this area, with Cytopia set to move its VDA into Phase II trials this year.

The event is significant for Bionomics because it prefaces the establishment of the company as a clinical-phase development firm. BNC105 came from Bionomics' acquisition of Iliad Chemicals in 2005. The drug is an analogue of Combrestatin-A4 being developed by Oxigene in the UK which has been redesigned to improve the safety profile and efficacy of the compound. The drug candidate will be delivered by a bolus injection.

The FDA has agreed to a clinical trial protocol with Bionomics which will include some elements of adaptive design into the trial. Bionomics will start the Phase I study in an accelerated single patient format to assess the safety and maximum tolerable dose. What is clever about the study design is that if any efficacy is seen in a patient with a particular type of cancer, then subsequent patients enrolled may being ones afflicted with a similar cancer category, such as melanoma for instance.

It is planned that the trial will be fully enrolled by the end of 2008 and results due by the first quarter of 2009. It will be an open label trial so some interim information may emerge during the trial.

Aside from the primary endpoints of safety, maximum tolerable dose and pharmacokinetics, the company will also receive visual information from CT scans and DCE-MRI, with patients required to have imaginable tumours to be eligible for the trial. There will also be several biomarker tests to give further information on tumour behaviour.

The company's second program, BNC210 for the treatment of anxiety, is on track to move into the clinic one year after the company's lead oncology program.

*Bioshares* recommendation: **Speculative Buy Class A**



| Company | Price (current) | Price added to portfolio | Date added |
|---|---|---|---|
| Cogstate | 0.135 | 0.13 | November 2007 |
| Ventracor | $0.70 | $0.625 | October 2007 |
| Sirtex Medical | $5.00 | $3.90 | October 2007 |
| Clinuvel Pharmaceuticals | $0.41 | $0.66 | September 2007 |
| Progen Pharmaceuticals | $2.66 | $3.52 | September 2007 |
| Starpharma Holdings | $0.40 | $0.37 | August 2007 |
| Pharmaxis | $4.13 | $3.15 | August 2007 |
| Universal Biosensors | $1.44 | $1.23 | June 2007 |
| Biota Holdings | $1.28 | $1.55 | March 2007 |
| Tissue Therapies | $0.41 | $0.58 | February 2007 |
| Probiotec | $1.46 | $1.12 | February 2007 |
| Phylogica | $0.21 | $0.42 | January 2007 |
| Peplin Inc | $0.78 | $0.83 | January 2007 |
| Arana Therapeutics | $1.15 | $1.31 | October 2006 |
| Sunshine Heart | $0.15 | $0.19 | September 2006 |
| Chemgenex Pharma. | $1.07 | $0.38 | June 2006 |
| Cytopia | $0.55 | $0.46 | June 2005 |
| Optiscan Imaging | $0.29 | $0.35 | March 2005 |
| Acrux | $1.40 | $0.83 | November 2004 |
| Alchemia | $0.67 | $0.67 | May 2004 |

## *Portfolio Changes – 30 Nov 2007*

**IN:**

No changes.

**OUT:**

No changes.

# *US FDA IND Filings by Australian and New Zealand Biotechs*

Investigational New Drug (IND) applications are applications made by either companies (company sponsored) or physicians (physician sponsored ) in support of clinical trials within the USA. Technically speaking an IND is a means by which a company obtains an exemption from the FDA so that it may ship an unapproved drug across the USA. In practise, an IND enables companies to undertake clinical trials within the US, the results of which may then be used in support of a marketing application with the FDA. It is not an exclusive route, with other routes such as Special Protocol Assessment, and Orphan Drug designation also open to drug developers. Furthermore, the FDA does not stipulate that drug developers seeking US marketing approval must file INDs and/or run US-based clinical trials. The FDA will consider foreign data so long as the data generated and the conduct of the clinical trials and calibre of the clinical investigators meet appropriate standards.

Since Progen Pharmaceutical's IND authorisation of PI-88 in June 1999, there have been in our estimate at least 26 accepted IND submissions sponsored by 16 public and private Australian and New Zealand companies, with Bionomics the most recent. As many as another six were received by other companies but are now under the authority of Australian listed companies, and at least three are in the pipeline.

Filing of an IND (or similar protocol recognition process) signifies an investment re-rating event for a drug developer, because it confirms that the company has satisfied a major drug regulator, the US FDA, that its drug has completed sufficient and appropriate animal pharmacology and toxicology studies, has established the necessary manufacturing processes and quality controls, and has designed appropriate clinical trial protocols.



**Selected US FDA IND Applications - company sponsored - Australian & NZ companies**

| Company | Investigational Drug/Therapy | | Date Submit | Date Authorized |
|---|---|---|---|---|
| Progen Pharmaceuticals | PI-88 | Solid tumours | | Jun-99 |
| Genesis R&D (with Corixa) | PVAC | Psorisis | | 13/01/2000 |
| Novogen | Phenoxidiol (IV) | Ovarian cancer | 29/12/2000 | 29/01/2001 |
| Acrux | Estradiol MDTS | Symptoms of menopause | | 7/05/2001 |
| Acrux | Female Testosterone MDTS | Female androgen sufficiency | | 2/01/2003 |
| Novogen | Phenoxidiol - Oral | SCC | | 17-Jun-03 |
| Starpharma Holdings | Vivagel | HIV | 30/06/2003 | 31/07/2003 |
| Novogen | Phenoxidiol | Cancer- various | | Apr-04 |
| Xenome* | Xen2174 | Pain | 22/04/2004 | 23/06/2004 |
| Peplin | PEP005 | AK | 23/03/2004 | 29/06/2004 |
| Peplin | PEP005 | BCC | 23/03/2004 | 29/06/2004 |
| Peplin | PEP005 | SCC | 23/03/2004 | 29/06/2004 |
| Agenix | Thromboview | DVT/PE diagn. | 27/08/2004 | 18/10/2004 |
| Pharmaxis | Aridol | Lung function diagn. | 22/11/2004 | 23/12/2004 |
| Cytopia | CYT997 | Cancer- various | 10/03/2005 | 27/04/2005 |
| QRxPharma | Q80031IR | Pain | | Q1 2006 |
| Acrux | Male Testosterone MD-Lotion | Male androgen sufficiency | | 14/06/2006 |
| Starpharma Holdings | Vivagel | Herpes | | 19/07/2006 |
| Virax Holdings | VIR201 | HIV | 17/10/2006 | 17/11/2006 |
| Mesoblast | MPC (Stem Cells) | Spinal Fusion | 21/11/2006 | 18/12/2006 |
| Mesoblast (Angioblast) | MPC (Stem Cells) | Damaged Heart Muscle | 2/04/2007 | 2/05/2007 |
| Neuren Pharm | Glypromate | Cognitive impairment | 31/12/2006 | 31/01/2007 |
| Benitec | rHIV7-shI-TAR-CCR5RZ | HIV | 26/01/2007 | June 2007 est |
| Giaconda | Myconda | MAP in Crohn's Disease | | 24/04/2007 |
| Acrux | Fentanyl MDTS | Pain | | 29/06/2007 |
| Bionomics | BNC105 | Solid tumours | | 22/11/2007 |
| Avexa | SPD754/AVX754/ATC | HIV | | Date unknown |

***Likely but unconfirmed (legacy filings through merger with US firms)***

| | | | | |
|---|---|---|---|---|
| ChemGenex Pharmaceuticals | Ceflatonin | Cancer | | Date unknown |
| ChemGenex Pharmaceuticals | Quinamed | Cancer | | Date unknown |
| pSvida (legacy CDS) | Vitrasert | CMV | | Date unknown |
| pSvida (legacy CDS) | Retisert | Uveitis | | Date unknown |
| pSvida (legacy CDS) | Medidur | DME | | Date unknown |
| | | | | |

***Anticipated***

| | | | | |
|---|---|---|---|---|
| Hatchtech* | DeOvo | Head lice management | Late'07/early '08 | |
| Clinuvel | CUV1647 | Erythropoietic Protoporphyria | December 2007 | |
| Medical Therapies | Cuprindo | Distal Proctitis, Inflammation | 2008? | |

**private, unlisted company*

## 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***

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