ISSN 1443-850X

In this edition...
As regulators and investors struggle to work through confusion in global equity markets, Bioshares continues to provide fundamental analysis on emerging biotech and pharmaceutical businesses. The focus of this edition is Pharmaxis which is approaching a transformational point in its evolution. A key market for Pharmaxis' Bronchitol product is the cystic fibrosis market. Pharmaxis is pushing ahead very steadily but very surely in its attempt to complete the necessary trials to get Bronchitol for CF to market in the US.

Defying the odds and impossibly tough market conditions, life science tool kit company Fluorotechnics is seeking an IPO, with confidence appearing to stem from a strong order book.

Companies covered: PXS, IPO Profile Fluorotechnics

	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 - current)	-12.9%
Cumulative Gain	**81%**
Av Annual Gain (7 yrs)	**17.8%**

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

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Individual Subscriptions (48 issues/year)
$320 (Inc.GST)
Edition Number 281 (19 September 2008)
ISSN 1443-850X

Bioshares

19 September 2008
Edition 281

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

Major Clinical Endpoint Approaching for Pharmaxis

Pharmaxis is approaching a pivotal point in the development of its key asset Bronchitol. Bronchitol is an inhaled powder for the treatment of Cystic Fibrosis (CF) and bronchiectasis (degeneration of the lung).

Bronchitol is currently undergoing two Phase III trials for CF with a final Phase III trial in bronchiectasis due to begin shortly. The first CF trial, for European (and Australian) approval, has completed recruitment and results are expected in early 2009. The second CF trial, required for US approval, began recruitment this month. The next six-to-nine months herald a critical period in the transformation of Pharmaxis from a drug development company to a pharmaceutical business.

US Cystic Fibrosis Program

Arguably the key market for Pharmaxis is cystic fibrosis treatment in the US. This is an established and concentrated market, with an existing CF drug, Pulmozyme from Genentech, currently generating sales tracking at US$250 million a year in the US and growing at 15% (sales outside of the US in fragmented markets are approaching US$200 million a year). (Earlier commentary on the CF market oppportunity can be found in *Bioshares* 143 and *Bioshares* 220).

It has taken Pharmaxis longer than expected to form its game plan for the US, where it expects to build a direct sales force for the 130 or so CF clinics in the US to 33,000 people in the country with CF. However, this more cautious and diligent approach will help build certainty of getting this drug established in that market.

For the US, Pharmaxis has achieved Orphan Drug Status (in July 2005) from the FDA, the program has been awarded Fast-Track status (in November 2006) with the FDA and received a Special Protocol Assessment status (in June 2008) from the FDA.

Special Protocol Assessment (SPA)

The SPA with the FDA serves as important protective measure, whereby the outcomes to be measured in the pivotal trial are agreed to by the regulator. So lonfg as the endpoints are met, then a drug should get approved. The agreed trial design will include a 26 week efficacy program, then a further 26 week safety program. This trial started earlier this month and results from the efficacy side should be ready by the end of 2009. The safety side of the trial should be completed by mid-2010. This program is receiving considerable non-financial support from the the US Cystic Fibrosis Foundation.

This trial will be double blinded against a placebo in about 300 patients, who are either on or off treatment, including Pulmozyme, and will continue their existing treatment throughout the trial. The endpoints will be as follows:

Primary endpoints

- Frequency of exacerbations
- Improvement in quality of life

Secondary endpoints

- Antibiotic use
- Sputum volume
- Exercise tolerance and lung function

Orphan Drug Status

The Orphan Drug Status will give the company a seven year market exclusivity in the US.

Fast-track Status

The Fast-track status allows the company to file its new drug application with the FDA in parts, which reduces the time taken for approval. For instance the company may file its CMC (Chemistry, Manufacturing and Controls) package, then data on efficacy (which should submitted by the end of 2009), and finally the safety data which should be in by mid-2010. A response from the FDA could be received at best by late 2010.

European Approval

The European program is running about 12 months ahead of the US. The company also has Orphan Drug status in Europe, which gives it 10 years market exclusivity for Bronchitol for CF if it gets to market, and has agreed on the trial design with the European regulatory agency.

The Phase III trial for European approval of Bronchitol of CF completed recruitment last month, in 325 patients. Similar to the US trial, patients will continue their existing treatment during the trial, including Pulmozyme. The primary endpoint is improvement in lung function (FEV1). It includes a 26 week efficacy assessment followed by a 26 week open safety assessment. The trial design was formed in consultation with the European regulator. Pharmaxis expects to submit the drug for approval in mid 2009 (with the extended safety data to be submitted later that year), and may be on the market as early as mid 2010.

Advantages over Pulmozyme

There is an established market for CF drugs, with a number of inhaled antibiotics for the CF market and one drug on the market that aids mucous clearance (by reducing the elasticity of the mucous), Pulmozyme. We estimate this drug is currently generating sales between US$400 - 450 million a year. In the US, this drug is used by 35% - 40% of CF sufferers.

Bronchitol also aids mucous clearance, however by other mechanisms (through osmosis, by rehydrating the airways). Bronchitol, which is inhaled through a small portable device, has an advantage over Pulmozyme, which is a solution inhaled through a nebulizer. Its ease of use may make it more appealing to users.

Bronchitol Phase II results in CF

In a study reported in April this year and conducted by independent investigators, Bronchitol achieved the same improvement in lung function (7%) as Pulmozyme in a trial in 20 children. (Surprisingly, the trial showed only a 2% improvement lung function when both of the drugs were used although was likely an anomaly skewed by the small trial numbers.)

In a separate Phase II trial reported in 2005 (in 39 CF sufferers), Bronchitol similarly improved lung function by 7% as measured by FEV1 levels after only two weeks of treatment. In absolute terms, this equates to about 120 mls increase in air exhaled per patient.

Generic barriers to Bronchitol

One of the likely hidden benefits of Bronchitol is that it may not be straightforward to introduce generic competitor drugs when the core patents and market exclusivities expire (around 2020 with patent extensions). Bronchitol is not absorbed into the blood stream. A chemical equivalence test would not apply, as it has more to do with the physical properties of the drug. Competitors are likely to be required to conduct their own head-to-head clinical studies to show similar efficacy. There is also likely to be further patent protection over the delivery device to extend the product's patent life.

Bronchiectasis

Pharmaxis has successfully completed one Phase III trial with Bronchitol in patients with bronchiectasis. It reported the results in August last year. In a 363 patient trial, Bronchitol produced a statistically significant improvement in (a) quality of life and (b) mucous clearance. In August this year the company completed a 12 month safety study with Bronchitol.

The company expects to file the drug for regulatory approval in Australia this year. An additional Phase III trial will need to be conducted for US and European approval. This trial will start this year, in 300 patients, and the company expects to file the drug for approval for bronchiectasis in Europe and the US in 2010. This forthcoming Phase III trial will measure (a) changes in frequency of exacerbations (a worsening of symptoms requiring a change in treatment) and (b) changes in quality of life.

The company has received Orphan Drug status in the US but not Europe. For a more thorough assessment of the bronchiectasis application, see *Bioshares* 230.

Valuation

Using a probability adjusted discounted cash flow model, *Bioshares* values Pharmaxis at **$2.90** a share. We expect sales for CF will build reasonably quickly, reaching $300 million in FY2015 (3-4 years from market launch). For bronchiectasis, we expect the take-up will be slower, with no established market (no drugs on the market) for this condition. By 2015, we estimate sales for bronchiectasis will reach US$70 million, and increase to US$220 million by 2020. This is a conservative estimate because there is no established bronchiectasis market. There will also be a trade off, between the higher pricing that the CF market will accept, to the larger population but lower price that could be achieved for bronchiectasis. (This valuation excludes the value of Aridol and other early stage programs.)

We applied a discount rate of 15%, and we estimate that Bronchitol has an 85% probability of reaching the market for CF and bronchiectasis. The valuation could increase significantly as the product reaches the market and uncertainly over gaining market share falls away, reducing the discount factor.

Summary

Pharmaxis is building a pharmaceutical business in a measured, by-the-book approach that to date is largely on track. It is a slow process but the company has ensured it has used all available regulatory mechanisms to reduce risk and maximize the commercial benefit of its core asset, Bronchitol, for mucociliary clearance and sputum induction in the respiratory system.

A major technical risk is approaching at the end of the first quarter in 2009, when results from the first Phase III (325 patients) cystic fibrosis trial are delivered. That a positive Phase III study was completed in 363 patients with bronchiectasis and that 150 people continue to use the product under special access schemes suggest a positive result should be delivered. The main question is how clear the outcome will be.

We expect that new clinical programs will start next year, PXS25 for lung fibrosis and PXS4159 for asthma.

The company is well funded with $112 million in cash at mid-year, which will reduce to $60-65 million by the end of this financial year (FY2009). By that point its new manufacturing facility should be built and a large part of the costs of its Phase III programs will have been paid.

Positive Phase III CF data in early 2009 will help launch this company into an international pharmaceutical business. We expect demand for this stock in the lead up to those results will accelerate and the stock remains a core biotech holding.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Correction – Starpharma Holdings

Please note a correction to last week's article on Starpharma Holdings. In relation to Starpharma's lead product, Vivagel, which is being commercialised for a number of uses, including a microbicide coating for condoms, previously only *spermicides* (e.g.Nonoxinol-9) have been used in this market (in around 30% - 40% of condoms). Starpharma's product is likely to be the first microbicide used with condoms, giving it added protection against the spread of sexually transmitted diseases. Nonoxinol-9 has in fact been shown to increase the risk of viral infection.

IPO Profile – Fluorotechnics

Fluorotechnics is a Sydney-based life sciences services company that sells fluorescent stains and labels to scientists who study proteins especially in the purpose of real time analysis. Fluorotechnics is a revenue generating company that sells proteomics consumables both directly and through distributors.

Fluorotechnics is seeking to raise $10 million, issuing 10 million shares at $1.00. The indicative capitalisation at the offer price is $26 million.

The company intends to apply the funds raised to expand production capacity, expand its sales team and purchase **GelCo**, a small US-based company that manufactures and sell proteomics equipment (e.g. gels) that complements Fluorotechnics' existing products.

History

Fluorotechnics was founded in 2001 and commenced trading in July 2002. The company was founded by the CEO Duncan Veal and the company chairman Rick Taylor, and its origins can be traced to fluorescence research conducted at Sydney's Macquarie University. Other board members include former CEO of Coles Myer John Fletcher, David Weber (US based), a former Americas Region President for **GE-Healthcare,** and Peter Bergquist, a former Deputy Vice Chancellor at Macquarie University.

Growth through acquisition has also been a part of the Fluorotechnics strategy, with the company buying the German ETC Elektrophorese-Technik GmbH in 2007 for its proteomics consumables and is looking to build on that purchase with of GelCo and its line of proteomics consumables.

Fluorescence – staining and labelling

In years gone by, researchers have used colour staining (e.g. methlyene blue or eosin) or radioactive labels to quantify and study the structure and interactions of proteins in cells and tissue. Radioactive labelling has the obvious limitation of radioactivity which places stringent demands on handling and disposal. Other heavy metal based dyes or labeling agents have been developed but must be disposed of with great care.

Fluorescent stains and labels may be obtained from fluorophores, which are unique molecules that absorb light at one particular wavelength and emit it again at another wavelength. There are 595 fluorophores entered in the fluorophores.org database.

Fluorotechnics has developed a number products based on a fluorophore, epicocconone, produced by the fungus *Epicoccum nigrum.* The company has isolated more than 50 from that species of fungus. It has developed a suite of thirteen products, and has identified more than 20 that could be developed.

The company argues that the competitive points of difference for its epicocconone-based products are that they fluoresce on finding a protein in a single process, offer superior measurement accuracy, offer higher sensitivity, increased dynamic range and can be multiplexed (i.e. can be used for multiple simultaneous measurements). Furthermore, they do not interfere or alter with target proteins, they are water soluble and their disposal (waste) profile is more environmentally friendly.

The Toolkit World

There is a large number of companies that service the needs of drug discovery firms, hospital and university-based researchers and scientists within biotech and pharmaceutical firms. These companies sell pipettes, centrifuges, fridges, glassware, plastics, weighing machines, labeling machines, chemical reagents and cell culture media, software, mass spectrometry machines and many other instruments and products. This is the toolkit world.

And similar to the therapeutic product focused world of biotech and pharma, the sector comprises many small specialist providers and innovators and a few larger sales and distribution companies. Typically, the large companies grow through acquisition, buying up innovative smaller companies as and when they begin to show strong sales growth.

Sales approach and competition

The company has sales staff located in the US, the UK and Germany but also sells through third parties. For example, the company sell its LavaCell product through **Active Motif**, which sells the 200 µg (1 mg/ml) LavaCell product for US$220. Fluorescence kits range in price from US$150 to US$400. **Sigma-Aldric**h and GE -Healthcare also distribute Fluorotechnics' products.

There are more than twenty companies that market fluorescence products led by **Invitrogen,** Sigma Aldrich**, Becton Dickinson, beckman Coulter, Perkin-Elmer,** GE-Healthcare, Active Motif, **Novus Biologicals**, **AnaSpec**, **Calbiochem**, **CaliperLife Sciences**, **Covalysys**, **Stem Cell Technologies**, **Princeton Separations**, **Thermo Scientific Pierce Protein Research Products**, **Assay Metrics**, **Kamiya Biomedical Company** and **LI-COR Biosciences** to name a few. Invitrogen sells the Alexa Fluor range of fluorophore products; GE-Healthcare markets the CyDye Fluors range; CaliperLife Sciences, the XenoFluor range and AnaSpec, the Anatag range.

Revenue forecasts

Fluorotechnics has indicated it has a strong order pipeline going forward. Unusually for a life sciences firm, the company has published projected revenues for the company for the 2010 financial year, projecting $18 million in sales as achievable, with $3 million emanating from the GelCo business and $15 million from the Fluorotechnics and ETC side of the business. These projections assume the acquisition of GelCo occurs.

Intellectual Property

Fluorotechnics possesses five families of patents, two of which encompass the epicocconone fluorophore technology. The core patent has a priority date from April 2000, with the second from March 2003. Although both patents have yet to be granted in the US (an outstanding risk), the epicocconone patents can be considered as having a reasonable protected life to run (~2020).

Comments

Fluorotechnics is a manufacturer of research products, which are sold in markets that have a very low regulatory threshold. Relative to diagnostic, medical device and drug development firms, the product development risk associated with the company is therefore very low.

The most obvious investment risk with Fluorotechnics is that it must compete with products sold by at least twenty firms. While its products may have attractive points of difference, the company does not possess the marketing reach of some its rivals and may not have the market power to set premium prices it might theorectically be able to command. A secondary consideration related to its diminutive market position is its ability to supply and service customers scattered around the globe.

Product uptake and acceptance can often be improved by the publishing of studies with emerging technologies in relevant scientific publications and ease of substitution of products in the researchers workspace. Fluorotechnics has had fifteen scientific papers published and produced twenty-six conference abstracts that support its products. And it would appear its products are also easily substituted in the workplace for rival products.

The profitability of life science tool kit companies is subject to the scale and flow of government supplied research funding as well investment by pharma and biotech firms in protein research. Declines in public research funding could impact negatively on the Fluorotechnics business.

There is potential for Fluorotechnics to develop a business with strong margins. Life science industry leader Invitrogen generated gross margins of approximately 70% in 2006 and 2007 in its BioDiscovery business, a division which sells a large range of research tools.

Summary

Investors can reasonably contemplate an exit from an investment in a company such as Flurotechnics through acquisition by a large life sciences firm. If a company such as Fluorotechnics was generating very strong sales growth it would not be inconceivable to see an acquisition made on a multiple of between three and five times sales (or higher). The acquisition of **Molecular Probes** by Invitrogen was made on a sales multiple of 5.8 X in 2003.

There is some limited experience of Australian toolkit companies being acquired, with the take-over of **Axon Instruments** by **Molecular Devices** in 2004 and the sale of **Corbett Life Science** (privately held) to **Qiagen** this year.

Investors are required to read the prospectus before subscribing to this offer, a copy of which can be obtained at http://www.fluorotechnics.com

Offer opens: 10 September
Offer closes: 10 October

Bioshares

Bioshares Model Portfolio (19 September 2008)

Company	Price (current)	Price added to portfolio	Date added
Impedimed	$0.72	$0.70	Aug-08
Antisense Therapeutics	$0.05	$0.07	Aug-08
Mesoblast	$1.18	$1.25	Aug-08
Avexa	$0.20	$0.32	Jun-08
Cellestis	$2.00	$2.27	April 2008
IDT	$2.07	$1.90	March 2008
Circadian Technologies	$0.85	$1.03	February 2008
Patrys	$0.27	$0.50	December 2007
NeuroDiscovery	$0.09	$0.16	December 2007
Bionomics	$0.35	$0.42	December 2007
Cogstate	$0.15	$0.13	November 2007
Sirtex Medical	$2.25	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.26	$0.66	September 2007
Starpharma Holdings	$0.29	$0.37	August 2007
Pharmaxis	$2.03	$3.15	August 2007
Universal Biosensors	$0.78	$1.23	June 2007
Biota Holdings	$0.71	$1.55	March 2007
Probiotec	$1.35	$1.12	February 2007
Peplin Inc	$0.41	$0.83	January 2007
Arana Therapeutics	$0.98	$1.31	October 2006
Chemgenex Pharma.	$0.79	$0.38	June 2006
Cytopia	$0.17	$0.46	June 2005
Optiscan Imaging	$0.18	$0.35	March 2005
Acrux	$0.99	$0.83	November 2004
Alchemia	$0.25	$0.67	May 2004

Portfolio Changes – 19 Sept 2008

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, Pharmaxis, NeuroDiscovery, Biotech Capital, Cytopia,Arana Therapeutics, Starpharma Holdings, Cogstate, Xceed Biotechnology, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcygen Pharmaceuticals, Peplin, BioMD, Impedimed, QRxPharma, Patrys, Labtech Systems, Hexima, Proteome Systems

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48 issues per year (electronic distribution): **$320**

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