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In this edition...
Two companies that have failed to deliver on important milestones over the last 12 months are Progen Industries and Agenix. Both companies have been unable to deliver on licensing deals for their technologies within a set time. However both companies continue to progress their technologies and investment opportunities remain for investors.

We also conduct a very helpful Q&A interview with Dr Mark Treherne from Neurodiscovery on the area of neuropathic pain and he explains why his company has an edge in developing a potentially valuable therapeutic for this large unmet clinical need.

The editors

Companies covered: **AGX, NDL, PGL**

	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 (from 5 May '06)	-10.0%
Cumulative Gain	**150.0%**
Average Annual Gain	**22.2%**

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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.

Progen Industries and Agenix Strengthen Data Packages for Licensing

For investors, it's helpful when biotech companies provide forecasts for when important events such as licensing deals can be expected to be completed. However for biotech CEOs it can have dire consequences, as the former CEOs of Agenix and Progen Industries have discovered. Both companies failed to deliver on expected licensing deals and the reason in both cases was most likely the same – lack of clinical data available. In biotech, if you don't have the data you can't do the deal, at least the deal you want to do.

Agenix and Progen had both attempted to negotiate later stage licensing deals for their respective products when the data available at the time was more suitable to an earlier stage licensing arrangement. Had these companies surrendered to investor pressure to secure an agreement and signed lower value deals – and it's very likely such deals could have been available to both companies – they would have received a likely savage response from disappointed investors. And although both share prices have fallen, when a later stage licensing deal is negotiated, a strong revaluation of the companies will be appropriate.

Progen Update

Progen Industries is firming up its data package by expanding clinical programs with its lead oncology drug PI-88. A licensing agreement was expected last year for PI-88 although it appears the lack of data, in particular the lack of data comparing the drug with existing therapeutic treatments (control arms) looks to have delayed any potential deals being signed.

The company now has four ongoing Phase II trials underway that will contribute to its data package and a Phase III study in primary liver cancer is scheduled to commence midway through 2007.

Phase II lung cancer study – 100 patients
The lung cancer trial underway involves up to 100 patients. This trial started in February 2004. PI-88 is being tested in conjunction with and in comparison to Taxotere in patients with non-small cell lung cancer. This trial is almost completed and results are due to be released in the first quarter of 2007.

Phase II liver cancer study – 172 patients
In July 2004, Progen's partner Medigen Corporation initiated a Phase II study in patients with primary liver cancer. The trial is ongoing in 172 patients with results expected in the first quarter of 2007. Following discussions with the FDA, this trial will end in December, with results due to be released in the first quarter of 2007. A multicentre Phase III trial will begin in mid 2007 in as many as 1000 patients. There are no pharmaceutical control arms in these studies because none exist.

Phase II melanoma trial – Up to 118 patients
In May last year, Progen started a Phase II study in patients with metastatic melanoma, trialing PI-88 in combination with and in comparison to an existing chemotherapy agent, dacarbazine. The company will recruit up to 118 patients for the trial and PI-88 will be use as a first line treatment. It follows on from a successful Phase II study in 44 patients with melanoma that showed positive survival data when used as a stand alone therapy. Results from this trial could be expected in the second half of 2007.

Phase II prostate cancer study – up to 90 patients
In August last year, a physician-sponsored Phase II study of PI-88 in combination with and in comparison to an existing chemotherapy drug Taxotere was commenced. Data from this trial is expected in the second half of 2007.

Summary
When Progen was attempting to partner is lead oncology compound last year (and the year before), it had generated Phase II data in multiple myeloma as a standalone treatment and more recently in melanoma as a standalone treatment. However the lack of data, in particular comparisons with control arms, has very likely limited the company's ability to partner. Progen now has three Phase II studies underway in prostate cancer, melanoma and lung cancer which all include control arms. This data if positive, will significantly strengthen the company's position to license the technology. The fourth Phase II study underway, in primary liver cancer, is being tested as a standalone therapy because there are no standard treatment options for these patients after surgery.

"In biotech, if you don't have the data you can't do the deal, at least the deal you want to do"

In developing oncology drugs such as PI-88, it's shown to be crucial to conduct multiple trials in parallel to gain efficacy in one indication that can help bring that drug to market. If successful, incredibly large returns can be achieved for shareholders. The outstanding successful oncology drug Avastin, which is also an angiogenesis inhibitor similar to PI-88, previously failed a large Phase III study in breast cancer before its future was resurrected in a Phase III study in patients with metastatic colorectal cancer. Before these results were released in May 2003, Avastin had a capitalization of US$19 billion. The week following the Phase III colorectal cancer trial results, the company's capitalization jumped to US$28 billion. Today, Genentech is valued at a staggering US$84 billion.

With Progen moving this drug into a 1000 patient Phase III trial mid 2007, and with results from all four Phase II programs expected in 2007, it will be a major year of developments for the company. Progen is capitalised at $110 million with an estimated $11 million in cash.

Bioshares recommendation: **Speculative Buy Class A**

Agenix update
Agenix recently announced preliminary results from a Phase II trial in DVT (Agenix is developing an in vivo diagnostic imaging agent, called Thromboview, for the detection of blood clots in the body). In the trial, 39 patients with DVTs were imaged. Using the Thromboview product, an overall accuracy of 77% was achieved, which was the same as the result for the current standard procedure that uses compression ultrasound.

This was a disappointing result. Imaging using Thromboview is an invasive procedure that takes up to several hours to complete. In contrast, ultrasound is non-invasive and results can be achieved immediately. Although there are some cases where an ultrasound can not or should not be used, if the Thromboview test was to compete with ultrasound it would need to should significantly better accuracy.

However the most suitable market for Thromboview is not for imaging DVTs but rather pulmonary emboli (PEs). This is where the large unmet need exists. Detection of DVTs is largely covered by ultrasound although there remains a need for alternative imaging options in a small percentage of cases.

Imaging techniques currently available for PEs fall well short of the mark. They are either inaccurate, or as in the case of CT scans (CTPA), the high dose of radiation (equivalent to several hundred chest x-rays) poses health risks of its own and CTPA has also shown limits on sensitivity.

Agenix announced a positive result from the Phase Ib PE trial in March this year. This trial involved 14 patients with confirmed PEs and compared Thromboview with computed tomography pulmonary angiography (CTPA). This was primarily a safety study and requires a 90-day follow-up period before results can be revealed. Detailed results from these trials should be released in August/September and the company has labelled the results as highly encouraging.

Agenix plans to concentrate its partnering discussions around the PE diagnostic, where the clinical need is much higher, and also potentially where the product offers improved accuracy and safety against existing imaging modalities. Presumably, any licensing agreement will also include use for the detection of DVTs.

The company will prepare the product for registration trials via FDA regulation this year for the detection of PEs. At the end of last year when the company was seeking to partner, it had generated trial data with Thromboview in a 16 patient Phase Ib study in DVT. Interim data from the 39 patient Phase II DVT has now been received and 'highly encouraging' results in 14 patients with confirmed PE have been achieved. In total, safety data from 160 people has been generated, which will place the company in a stronger position to partner a later stage licensing deal. More efficacy data in PE would further support partnering opportunities although these are not planned at this stage prior to registration trials in 2007.

Agenix is continuing partnering discussions with the major imaging groups and other potential partners. A US-based consultant with strong experience in imaging technologies was appointed by the company late last year to assist in negotiations. The company has learnt from its previous experience and is now not setting a date

Cont'd over

for singing a licensing deal. However if Agenix plans to begin registration PE trials early next year with a partner, an agreement will need to be completed in 2006.

In other developments at Agenix, the company has been increasing its access to funding by selling non-core assets. The company's new CEO, Neil Leggett, has been very effective in managing sales of the company's animal health business and more recently property assets for the company at what appears to be very acceptable terms for Agenix. At the end of July this year, the company will have $10 million in cash with debt from a bank bill facility of $2 million.

The Agenix share price has fallen heavily since the beginning of this year. Reaching a high of 35 cents in February, the stock has fallen 54% because the company has failed to achieve set milestones. It's been a disappointing stock for investors. However the company's core technology in Thromboview remains potentially a very valuable asset for the company. Agenix is capitalised at $34 million.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares Model Portfolio (30 June 2006)

Company	Price (current)	Price added to portfolio
Acrux	$0.73	$0.83
Agenix	$0.16	$0.22
Alchemia	$1.08	$0.67
Avexa	$0.23	$0.15
Biolayer	$0.20	$0.195
Bionomics	$0.18	$0.210
Biosignal	$0.17	$0.22
Cytopia	$0.81	$0.46
Chemgenex Pharma.	$0.42	$0.38
Evogenix	$0.56	$0.47
GroPep	$1.61	$1.43
Optiscan Imaging	$0.48	$0.35
Neuren Pharmaceuticals	$0.39	$0.70
Pharmaxis	$2.06	$1.90
Prima Biomed	$0.066	$0.09
Sirtex Medical	$2.32	$1.95

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Neuropathic Pain - Q&A with Dr Mark Treherne from NeuroDiscovery

Neurodiscovery listed on the ASX in July last year. It's a small biotech company with a wealth of experience in drug development, particularly in the area of neuropathic pain. The company has a subsidiary business based in the UK, Neurosolutions, which conducts electrophysiology work for biotech and major pharmaceutical companies.

We have invited the company's Executive Chairman, Dr Mark Treherne, to give readers a better understanding of neuropathic pain, the potential markets for its treatment, and to explain just what he believes gives Neurodiscovery an edge in the development of novel therapeutics for this important unmet clinical need. It's a valuable insight into the company Neurodiscovery and the area of neuropathic pain. Dr Treherne formerly led the Neurodgeneration research group of Pfizer in the UK and also founded Cambridge Drug Discovery.

Q. What makes neuropathic pain different from other types of pain, such as chronic or acute pain? Is it different enough to warrant a different drug development approach? What do we NOT KNOW about neuropathic pain? Are there sub-sets of neuropathic pain?

Neuropathic pain describes the intense discomfort that is caused by injury to the peripheral or central nervous system. This severe condition is often described by patients as "burning" or "shooting" in nature and can be continuous or paroxysmal (comes and goes). The highest unmet medical need is to treat chronic neuropathic pain that in many patients, once their nerves are damaged, can last the remainder of their life. It is estimated that up to 5% of the general population of the USA, Europe and Japan are affected by neuropathic conditions including, for example, diabetic neuropathic pain and post-herpatic neuralgia (which follows a viral infection). The incidence of the condition is increasing with an ever ageing population and recent forecasts predict a global market value for current neuropathic pain treatments of some US$4.1Bn by 2007.

Many factors are known to be the initial cause of neuropathic pain: diabetes, infection, trapped nerves, various cancers or just the general ageing process. However, the cause of some forms of the condition are unknown. Although there are many initial causes of neuropathic pain, these all lead to a common cellular pathology that subsequently results in damaged nerves constantly misfiring in a highly characteristic pattern. This abnormal pattern of nervous electrical activity can be accurately measured and understood by a specialist technique called "electrophysiology". Electrophysiology is NeuroDiscovery's real expertise and this allows you to identify which compounds can be selected for clinical development to treat neuropathic pain. One of the huge advantages of using this technique is that you can test whether the drug works almost straight away: does it return the electrical activity back to normal? Unlike other medical conditions, you don't have to look at complex varying patterns of disease progression, like tumour shrinkage, for example, over months (or even years) to see if your drug is working or not.

Q. What are the tradeoffs made in developing drugs for neuropathic pain?

Although you can test whether your drug works pretty quickly in the lab and the clinic, before you get registration of the drug for the treatment of chronic neuropathic pain, you would need to demonstrate that patients don't develop tolerance to the drug. For example, many of the existing drugs that are derived from morphine require the patent to keep taking more and more of the drug over time, which can lead to dependency and, eventually, addiction. However, drugs working by novel mechanisms, such as those currently being developed by NeuroDiscovery, should avoid these problems.

Q. What is deficient about many of the current neuropathic pain drugs?

Clearly there is the tolerance, dependency and addiction that is associated with the chronic use of the various forms of morphine that has just been discussed. Furthermore, the disease is predominantly treated at present with a variety of anticonvulsant, antidepressant and analgesic drugs but many patients fail to respond adequately to these agents. For example, these patients may not respond at all to many of the anticonvulsant drugs and other new mechanistic classes of drug have been withdrawn due to cardiovascular side effects. Consequently, neuropathic pain is still recognised as an area of highly significant unmet medical need.

Q. What are some of the challenges in running clinical trials for neuropathic pain drugs?

Demonstrating efficacy in the clinic during Phase 2 is relatively straightforward these days and the acute effects of a drug can be evaluated relatively quickly. Electrophysiology can be used a key surrogate marker in the clinic as well as the lab. The incidence and severity of the condition, as well as the unmet medical need means that patient recruitment is not really a problem.

However, safety is, as with all drugs, a prime concern. This is more of a concern with chronic pain drugs than it is in treating cancer, for example, where a much lower therapeutic ratio can be tolerated. It is well documented that many cancer patients will stop treatment due to severe adverse side effects even though this may well shorten their lives. It's worth noting that, in many cases, it's the inability to adequately control the pain relief in the latter stages of cancer that is one of the most unpleasant aspects of the disease. This concern over safety is why NeuroDiscovery has focused on drugs that have already undergone significant safety testing, for example, one the drugs in our pipeline has already completed Phase 3 trials for another indication.

Q. What are the toxicities that give most concern in developing pain drugs?

It's difficult to generalise but cardiovascular and central nervous system side effects must be fully investigated. This, yet again, is where electrophysiology can help to detect any potential side effects early on in the discovery process. As the heart and the brain depend on electrical activity to work properly, any abnormal effects on their electrophysiology allows for the early screening out of potentially toxic compounds. In fact, NeuroDiscovery is increasingly being asked to perform such a service for a number of multinational pharmaceutical companies.

Q. What was the 'last great pain drug' approved by the FDA?

I guess by "great" you mean "blockbuster". Neurontin, which has the generic name gabapentin and is now sold by Pfizer was the first new pain drug with a novel mechanism of action that had been approved for sometime. Gabapentin originally gained FDA approval as an anti-convulsant in 1993 but three years later it was becoming apparent that the drug was also useful for treating neuropathic pain. Even though only about half the people with neuropathic pain respond to the drug, annual global sales had still reached US$2.7 before the drug became a generic, in 2004.

The next major pain drug was Vioxx, Merck's infamous Cox-2 inhibitor. Merck withdrew the drug in 2004 due to cardiovascular side effects but, in the previous year, sales had grown to US$2.5bn, only four years after launch. The withdrawl of Vioxx had a major adverse effect on Merck's fortunes but opened up opportunities for small companies like NeuroDiscovery to develop safer pain drugs for this unmet medical need.

Q. What is the approach Neurodiscovery is taking to developing a therapeutic for neuropthic pain?

We only select products for development with a suitable safety profile to reduce the risk of early attrition of our pipeline in Phase I. The key differentiator of NDL is our use of our specialised electrophysiology techniques that allow us to work out the mechanism of action of our clinical development compounds on the nervous system to increase the probability of demonstrating early efficacy in the clinic. The third factor is that we select compounds that have a relatively fast onset of action that should enable us to demonstrate clinical efficacy in relatively short term clinical trails.

Q. What do you think gives you an advantage in this field?

The use of our highly specialised electrophysiology techniques enables us to make decisions quickly and then discard compounds that are unlikely to work. We can then focus our resources on the products that we really care about. We can use electrophysiology to look at very small (picoamp) currents that pass through individual ion channels through to

complex electrophysiological changes recorded from intact human nerve. This ability to move form recording the electrical activity of a single protein molecule and then relate that to changes in electrical activity in human tissues, allows us to understand how compounds can produce effective pain relief in man.

Q. What is it that excites you about your lead compound in preclinical development?

Although we have a complementary pipeline of compounds, we are particularly excited about NSL-101 and NSL-043.

NSL-101 is natural product preparation for topical use and is currently going through the ethics procedures in the UK, so that we can determine its efficacy in producing pain relief in a small human efficacy trail that we are planning to carry out this year. NSL-101 is the first of our products that we plan to commercialise.

NSL-043 is an orally bioavailable compound that we are developing with our Japanese partner Sosei for the treatment of neuropathic pain. The compound has already been into Phase III trials for another indication, so we are not currently anticipating that we should discover any serious problems in Phase I and we are currently on track for completing a CTA in the UK early next year. If NSL-043 demonstrates good efficacy in Phase II, it could have blockbuster potential.

Q. What experience does your team have in developing a therapeutic for neuropathic pain?

Quite a few of us came from Pfizer. I left there in 1997 but other key members of the NeuroSolutions team were originally at Warner Lambert that was subsequently acquired by Pfizer and they worked on the mechanism of action of gabapentin. So, between us we have many decades of experience in working on successful neurology related products that are out there on the market.

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

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