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In this edition...
This week our focus is on the biotechs that are reducing risk by re-working or improving established drugs through the application of novel drug delivery technologies or re-formulation or unique manufacturing strategies.

Such strategies can pay off significantly and with eight companies working in the 'super generics' area, it is clear that the approach is not a flash in the pan. One product developed through this strategy, Acrux's Evamist, is on the verge of achieving its first sales in the US.

The editors
Companies covered: ACR, ACL, BTA, CUV, HGN, BNE, IMU, PSD, POH, GIA,QRX

	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)	-9.3%
Cumulative Gain	**197%**
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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Bioshares

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

Bypassing the Technical Risk – Super Generics

Last week we discussed the above average success rates for a number of recent Phase II studies completed by Australian listed drug development firms, where technical risk has been diminished through the adoption of a number of development strategies.

Another way to reduce technical risk is through the repositioning of pharmaceutical compounds (see *Bioshares* 204). This approach continues to generate interest from smaller and medium sized biotech companies, where new indications are being investigated for existing or failed drug candidates. And technical risk can be managed further through the application of drug delivery, manufacturing and reformulation technologies to existing drugs. Often drugs that are managed in this way have lost patent protection and have become open to generic competition.

The term 'super generics' applies to drugs where the original approved product is off-patent, but where improved versions with new forms of patent protection have been developed. Such 'super generics' and technology-enabled generics have also gained popularity in Australia over the last few years. There are now at least eight listed biotechs that can be broadly grouped as 'super generic' technology plays in Australia.

An important driver of the growth in 'super generic' companies is that drug development costs and time to market of new chemical entities has escalated in recent years.

Acrux (Capitalisation $208 million)

The most advanced super generic play in Australia is **Acrux** (ACR: $1.34). Acrux applies its proprietary drug delivery technology to the delivery of primarily existing generic pharmaceuticals across the skin through a spray-on applicator.

The company's leading product, Evamist, is a transdermally delivered hormone replacement therapy for treatment of side effects such as hot flushes associated with menopause. The product was recently approved by the FDA (through a New Drug Application or NDA) and will be released in the US and sold by **KV Pharmaceutical**. Acrux will receive a double-digit royalty from sales. KV Pharmaceutical estimates sales will peak at US$125 million in the US although our expectations are that this figure will be well exceeded. KV Pharmaceutical purchased US rights to this compound from **Vivus Inc** (Acrux's previous development partner) for US$150 million with further payments due if Evamist sales pass US$200 million.

Acrux has a series of compounds in clinical and preclinical development. The most prominent to is a transdermal version of male testosterone, which will be moving into Phase III clinical studies, where only pharmacokinetic data (blood absorption levels) should be required. The compound will be filed through a New Drug Application (NDA) approval process.

Cont'd over

Acrux will seek to complete the Phase III studies independently, retaining further value in the asset.

Evamist FDA approval route: **New Drug Application (NDA)**
Efficacy and safety data delivered

Male Testosterone approval route: **New Drug Application (NDA)**
Bioequivalence and safety data required

Alchemia (Capitalisation $117 million)

Alchemia (ACL: $0.74) is commercialising a 'technology enabled' generic of the **GlaxoSmithKline** drug Arixtra, or fondaparinux. Alchemia has developed a significantly simplified and lower cost method of manufacturing fondaparinux using its proprietary carbohydrate synthesis technology. Alchemia's partner **Dr Reddy's** will look to register fondaparinux in the US in coming months (the exact time is not specified) with a view of bringing fondaparinux to the US market by early 2009. It will be the only generic version of Arixtra in the US. Current sales of Arixtra in the US are tracking at around US$120 million a year and should exceed US$200 million in early 2009 by our estimates.

Alchemia will receive at a minimum a 50% profit share from sales after manufacturing costs. At these levels, our estimates are that Alchemia would receive around US$22 million a year.

Fondaparinux FDA Approval Route: **Abbreviated New Drug Application (ANDA)**
No efficacy or bioequivalence data required

QRx Pharma (Capitalisation $111 million)

QRxPharma (QRX: $1.48) is developing a combination product (Q8003IR) of two existing opioid-based drugs, morphine and oxycodone. Opioid use has very strong side effects, which excluding physical and psychological dependence and sedation, include severe constipation. The company has shown that by using these drugs in a particular combination, it can reduce morphine usage by 34% - 40% while maintaining the same level of pain control.

QRxPharma raised $50 million through its IPO recently and is looking to begin two 660 patient Phase III studies with its combined opioid therapy to demonstrate the improved nature of its drug therapy. The company is considering building its own sales force in the USA to sell its product once approved.

FDA Approval Route: **505(b)(2)**
Efficacy data required

Halcygen Pharmaceuticals (Cap'n $33 million)

Halcygen Pharmaceuticals (HGN: $0.43) listed recently (at 50 cents a share). It is developing two 'super generics' that it has accessed from **Mayne Pharma** (now **Hospira**). The first is an improved version of the generic antifungal agent, itraconazole, called SUBA-itraconazole. Its version has improved bioavailability that should allow the drug to be given at half the dose while achieving the same therapeutic blood levels. Itraconazole produces side effects in about 10% of patients and a reduced dosage form would very likely reduce the unwanted side effects. Halcygen believes its version may also have the added benefit of patients not requiring food to be taken with the drug, particularly high fat foods that assist absorption of the drug.

Halcygen has a key meeting with the FDA approaching, with the outcome to stipulate the type and size of trials required to get the drug to market. The company is anticipating that only pharmacokinetic studies will be required, which it is hopeful of starting in coming months.

The company's second drug in development is an improved reformulation of the antibiotic minocycline which Halcygen similarly is seeking to reduce side effects with an improved absorption profile.

SUBA-Itraconazole FDA Approval Route: **505(b)(2)**
Bioequivalence data preferred, to be confirmed with FDA

FDA registration route - NDA, ANDA, 505(b)(2)

Although Acrux has developed a version of an existing drug (estradiol for hormone replacement therapy (HRT)), because the compound included penetration enhancers, it was approved through a **New Drug Application** (NDA)route. Full clinical trials to show efficacy as well as safety were required.

Alchemia is developing a standard generic replica of fondaparinux and as such, it will be assessed under an **Abbreviated New Drug Application** (ANDA). This is a considerably easier path to market because preclinical and clinical safety and efficacy data is not required to be generated. For oral drugs it is only required to demonstrate the drug is bioequivalent to the innovator drug (Arixtra) i.e. the time taken for the drug to reach the bloodstream. But given this drug is an injectable, bioequivalence should not be required, with Alchemia needing only to show the drug has the same chemical composition.

Where changes are made to existing drugs, the company may refer to studies reported in literature on safety and efficacy of the generic drug the company is modifying without necessarily needing to repeat those studies. If this is the case, the drug is filed with the FDA through a **505(b)(2)** application. It is still considered a new drug application. Changes to existing drugs applicable to this route include:

· Dosage
· Strength (moving to a higher or lower strength)
· Route of administration
· Combination product

Halcygen Pharmaceuticals is hopeful that its variation of the generic drug itraconazole will be assessed through this route.

Cont'd over

Giaconda (Capitalisation $33 million)

In a similar approach to QRxPharma, **Giaconda** (GIA: $0.42) is developing combinations of existing drugs but to treat gastro-intestinal disorders. Giaconda has filed patents on these combinations. The combination use of pharmaceutical compounds been used in the HIV area very successfully by the major groups such as **Gilead Sciences** and **GlaxoSmithKline,** although the combination approach in the HIV area seeks to reduce the number of tablets taken daily rather than offering any efficacy advantages.

Giaconda has five products in development. Its lead product, Myoconda, is a combination of three existing antibiotics for the treatment of Crohn's disease. The company's theory is that Crohn's disease is caused by a bacterial infection. This program is moving into a Phase III trial which is expected to take one year to complete. The company this week partnered with Prague Clinical Services to conduct the study across Europe and the company is anticipating submitting the drug for regulatory approval in Europe in the second half of 2009. The company expects it will conduct a second Phase III trial in the USA, after completion of the European Phase III.

The company's second program is the use of two existing pharmaceuticals, ursodeoxycholic acid and bezafibrate for the treatment of Hepatitis C in patients who have failed to respond to standard treatment. The program is current in a Phase IIa trial with results expected early next year.

FDA approval route: **New Drug Application (NDA), 505(b)(2)**
Efficacy data to be produced

pSiVida (Capitalisation $85 million)

pSiVida's (PSD: $0.12) lead compound, Medidur, is currently in a Phase III study for the treatment of diabetic macular odema. Medidur is a depot injection of a corticosteroid fluocinolone acetonide that is injected into the eye and may last for up to three years. The 900 patient Phase III trial should be fully recruited next month. However trial subjects will need to monitored for two years. The program is partnered with **Alimera Sciences**, which is managing the trial.

The company also as a product called Retisert on the market for the treatment of posterior uveitis, an inflammatory disorder in the back of the eye. It uses the same active compound as Medidur and lasts for up to two and half years. It has been licensed to **Bausch & Lomb**. Sales of the product have been modest due to the implant procedure which requires an overnight stay in hospital following surgical placement of the device. The Medidur implant procedure is considerably more straightforward taking only several minutes, and it's expected the release profile of the drug over 30 months will be more consistent than Retisert.

FDA approval route: **New Drug Application (NDA), 505(b)(2) likely**
Efficacy data sought

Phosphagenics (Capitalisation $160 million)

Phosphagenics (POH: $0.265) is also developing a penetration enhancer to be applied to the transdermal drug delivery of generic drugs. The company has found that phosphorylating drugs – adding a phosphate group to the active drug – improves the bioavailability of the pharmaceutical and allows transdermal delivery of some drugs that can only be delivered in an injectable

Cont'd over

form. The technology also allows potential improvements in absorption of existing oral and transdermal drugs and products. The company's lead program was a transdermal delivery of morphine which is at the Phase II stage of development. This program has recently been re-prioritised to make way for an oxycodone transdermal program which will be moving into Phase I studies.

The company is also developing a transdermal insulin patch using its penetration enhancement technology. This program generated positive Phase Ib results in 45 volunteers. A phase II trial in 60 patients with Type I and Type II diabetes is expected to begin this month.

FDA approval route: **New Drug Application (NDA)**
Efficacy and safety data to be produced

Bone Medical (Capitalisation $30 million)

Bone Medical (BNE: $0.35) has in-licensed a drug delivery technology from **Axcess Ltd** in the UK and is applying this technology to make well known generic compounds orally deliverable. Its lead program is an oral version of the salmon form of the calcitonin peptide, called Capsitonin. Salmon calcitonin has been used for over 30 years for the treatment of osteoporiosis. It is currently delivered either by injection or through a nasal spray, although the latter has not appealed to many users.

The Axcess technology is based on the use of bile salts that are recognised as very effective penetration enhancers in the intestine together with additives that allow the bile salts to maintain solubility in the acidic environment of the stomach (bile salts are normally insoluble in an acidic solution although soluble at around a pH of 7.5).

The company is looking to move the Capsitonin program into a final 400 patient bioequivalence trial to show that its oral version delivers the same quantity of the active drug into the blood stream as a nasal spray product. Bone Medical's second program is the development of an oral version of a synthetic parathyroid hormone peptide (Perthoxal) used in aiding bone formation. The Perthoxal program has just received ethics approval to begin a Phase I/IIa clinical study.

FDA approval route: **505(b)(2)**
Efficacy data sought

Conclusion

The modification of generic pharmaceuticals has become a recognised biotech business activity in Australia. Either through a novel delivery mechanism, as illustrated by the respective technologies of Acrux, pSiVida and Phosphagenics, or through novel combinations designed to improve efficacy as QRxPharma and Giaconda are looking to achieve, or as technology-enabled generics that allow cheaper manufacture of existing drugs, such as Alchemia's fondaparinux or through improved formulations such as Halcygen's SUBA-itraconazole, a set of Australian biotech companies are seeking to largely eliminate the very high technology risk that is associated with new chemical entities.

Development risk is also reduced because commercialisation timeframes are often significantly shortened. With Acrux's Evamist marked as the first of these products ready to begin selling in coming months, the 'super generics' strategy is set to gain increased investor attention.

Bioshares Model Portfolio (21 September 2007)

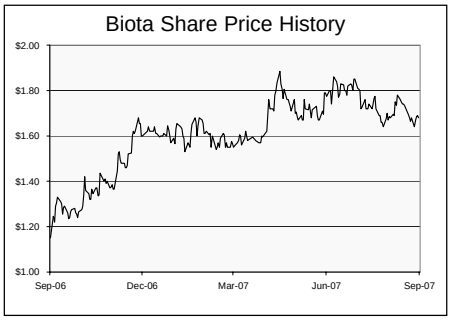
Company	Price (current)	Price added to portfolio
Acrux	$1.34	$0.83
Alchemia	$0.74	$0.67
Biota Holdings	$1.68	$1.55
Circadian Technologies	$1.18	$1.45
Clinuvel Pharmaceuticals	$0.50	$0.66
Cytopia	$0.58	$0.46
Chemgenex Pharma.	$0.97	$0.38
Optiscan Imaging	$0.39	$0.35
Peplin	$0.82	$0.83
Peptech	$1.22	$1.31
Pharmaxis	$3.99	$3.15
Phylogica	$0.31	$0.42
Probiotec	$1.13	$1.12
Progen Pharmaceuticals	$3.38	$3.52
Sirtex Medical	$3.86	$3.90
Starpharma Holdings	$0.37	$0.37
Sunshine Heart	$0.18	$0.19
Tissue Therapies	$0.50	$0.58
Universal Biosensors	$1.21	$1.23

Portfolio Changes – 21 Sept. 2007

IN:
No changes

OUT:
No changes

Stock Updates



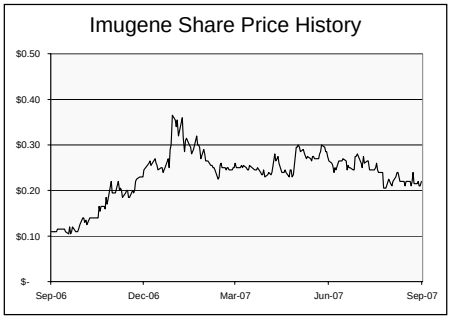
Biota (BTA: $1.68) Rival Neuraminidase Inhibitor Fails Trial

There are two neuraminidase inhibitor class of drugs approved for the treatment of influenza. They are Relenza, which is marketed by **GlaxoSmithKline**, and from which Biota receives a royalty, and Tamiflu, which is marketed by **Roche,** and from which **Gilead Sciences** receives a royalty. A third drug that has been in development for some years has been **BioCryst**'s peramivir. This drug failed a Phase III trial several years ago in an oral formulation and this week the same drug failed to meet endpoints in a Phase II trial, in which the drug was injected into muscle.

This set back for BioCryst is positive for Biota as it reinforces Relenza's market position and also reinforces the long acting neuraminidase inhibitor (LANI) compound (CS8958) being jointly developed with **Daiichi-Sankyo**. This compound has completed a Phase I study in Japan, and is undergoing a Phase I study in the UK. Biota also has backup LANI compounds (Flunet) that are being supported by a US government grant of US$8.5 million. Interestingly, BioCryst had received a US DHHS grant of US$102 million in January 2007 to develop peramivir.

Biota is capitalised at $308 million. Its cash reserves at June 30 totalled approximately $62 million.

Bioshares recommendation: **Buy**

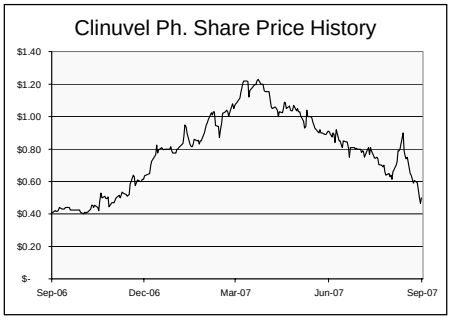


Imugene (IMU: $0.22) PRRS Outbreak in China and Viet Nam

Animal health company Imugene is developing a vaccine to treat Porcine Reproductive and Respiratory Syndrome (PRRS). The syndrome is caused by the arterivirus, which weakens the porcine immune system. Adult pigs can recover but secondary infections can kill piglets. The company commenced a three month trial of its vaccine at facilities in the USA in July. However, an outbreak of the disease this year in China is behind significant increases to the price of live pigs and the disease has now spread to Vietnam. The journal *Science* (24/8/07) reports that a more virulent strain may have emerged in China that is capable of killing sows as well as piglets. The economic loss of production animals in China suggests that Imugene's vaccine may have increased market relevance and potential.

Imugene is capitalised at $29 million, and held cash of $1 million at June 30, 2007.

Bioshares recommendation: **Speculative Buy Class A**



Clinuvel Pharm. (CUV: $0.50) Impact of Troubled Hedge Fund

Troubles at the AIM listed European hedge fund, **Absolute Capital Management Holdings,** seem to explain a pronounced weakness in Clinuvel Pharmaceutical's share price. The CIO of ACMH, Florian Homm, resigned suddenly on September 18, precipitating a slump in ACMH's share price slump and also causing a lock out on certain fund assets. ACMH and associated funds held a greater than 20% stake in Clinuvel, which may have been lessened of late. Clinuvel's share price slumped to 46.5 cents this week, down 48% from a recent high of 90 cents reached as recently as September 3. Clinuvel's CEO Philippe Wolgen has been quick to remind investors that activities of the company, including two Phase III trials, remain on track. The company will be actively seeking to supplant ACMH with other investors.

Clinuvel is capitalised at $151 million. The company is well funded with $60 million in cash at its disposal.

Bioshares recommendation: **Speculative Buy Class B**

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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