ISSN 1443-850X

In this edition...
The conventional approach to sales in the pharma game has been to make drugs that serve large markets. But that wisdom has been challenged as more and more companies seek to develop drugs for small patient groups, otherwise known as the orphan drug (OD) category. Driven by special incentives, this sector now boasts 27drugs that each garner more than US$1 billion in sales. Five Australian companies have adopted the OD strategy.
We also profile healthcare safety products company Medivac and comment on activities at Avexa.
The Editors
Companies Covered: ANP, AVX, CUV, CXS, MDV, MSB, PXS

	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 - May '09)	-7.3%
Year 9 (May '09 - May '10)	49.2%
Year 10 (May '10 - Current)	-3.4%
Cumulative Gain	**200%**
Av Annual Gain (9 yrs)	**18.5%**

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

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Individual Subscriptions (48 issues/year)
$350 (Inc.GST)
Edition Number 365 (25 June 2010)
ISSN 1443-850X

Bioshares

25 June 2010
Edition 365

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

Orphan Drugs – The New Way To Build Blockbuster Products

Investors can be forgiven for thinking orphan drugs, that by definition treat niche medical indications, deliver small returns for drug developers. However, very lucrative businesses have been built around orphan drug indications, a point not lost on major pharmaceutical groups such as **Novartis** and **Pfizer**, the latter which earlier this month formed an orphan drug division, called the Rare Diseases Research Unit.

The Most Successful Orphan Drug Business

The most successful biotech company that has built its business around orphan drug products is **Genzyme**. The company was formed in 1981 to develop drugs to treat patients with enzyme deficiencies which mostly fall into the orphan drug status. Its first orphan drug Ceredase was approved for the treatment of Gaucher disease. This drug went on to become a blockbuster which was replaced with a second generation product called Cerezyme.

Today the company is capitalised at US$14.3 billion, and still has the same CEO as it did 27 years ago, Henri Termeer, who is also Chairman and President of the company. (No prize for who runs the show at Genzyme). In 2008, Genzyme generated sales of US$2.15 billion from its four orphan drug products (Cerezyme, Myozyme, Fabrazyme and Aldurazyme), which made up 47% of the company's sales. The largest selling orphan drug product was Cerezyme, which generated sales of US$1.2 billion. (In the last six months sales of Cerezyme have fallen 70% due to manufacturing issues raised by the FDA).

Cerezyme sells for around US$200,000 for a year of treatment. The orphan drug diseases that Genzyme sells into are all chronic diseases, ensuring long lasting sales for its products.

Orphan Drug Incentives

To encourage drug developers to tackle diseases that affect minority groups of patients, the FDA and EMA (European drug regulator) offer incentives to drug developers. The FDA waives regulatory filing fees, offers tax credits on clinical trial expenses, and offers assistance with clinical trial design. The largest incentive is that of a seven year market exclusivity in the US, and from the EMA, a 12 year market exclusivity in Europe. In the US, an orphan drug is classified as a disease that affects less than one in 5,000 people, and in Europe less than one in 2,000 people.

According to an article in *Genetic Engineering News* in December last year, prior to the Orphan Drug Act being introduced in 1983, less than 10 drugs were approved for orphan diseases in the 10 years prior. In the next 26 years, 339 orphan drugs have been approved by the FDA. In that article, Timothy Cote, director at the FDA's Office of Orphan Products Development indicated that the FDA expects to continue and expand of one the US government's most successful grants programs (for orphan drugs) and will likely in-

– Cont'd over

crease the number of drug candidates receiving orphan drug designation.

Expanding Indications for Orphan Drugs

One of the strategies of many orphan drug developers is to expand the indications of their orphan drug, either into other orphan drugs or into non-orphan drug uses. Cancer drug Rituxan was first approved for a type of non-Hodgkin lymphoma as an orphan drug. It has since been approved for non-orphan drug indications including chronic lymphocytic leukemia, in the process becoming a blockbuster drug generating sales of US$5.2 billion last year.

Remicade was first approved for the treatment of pediatric Crohn's Disease and has since become a multibillion dollar product when its use was expanded for the treatment of rheumatoid arthritis. It's sales last year were US$6.5 billion.

Novartis' Gleevec is an example of an orphan drug for which its use was expanded into other orphan drug indications. The drug was first approved for the treatment of Chronic Myeloid Leukemia and this drug has now been granted orphan drug indication and approval for five other orphan cancer disease indications.

The success of Teva's orphan MS drug Copaxone helped transform that company from a generics business into a fully integrated global pharmaceutical business which today is capitalised at US$46 billion. Copaxone was launched in 1997 in the US under orphan drug exclusivity protection. The patents on Copaxone had long since expired and it was only the orphan drug protection that allowed that drug to get to market. In 1996 Teva had sales of US$954million. Today those sales have shot up to over US$14 billion with Copaxone still contributing US$2.5 billion in annual revenue for Teva.

Market Size

Orphan drugs were estimated by BCC Research to generate sales of US$85 billion in 2009 with about 65% of those sales coming from biologic drugs. Of these, 58 drugs generated sales in excess of US$200 million and 27 were considered blockbuster products (sales greater than US$1 billion), up from 19 only three years earlier.

Big Pharma Moves into Orphan Drugs

Novartis, which developed Gleevec, has been an early mover in the orphan drug class area, with three other drugs in its portfolio launched as orphan drugs. These drugs, Gleevec, Zometa, Sandostatin and Exjade are expected to generate sales of US$8 billion this year with Gleevec contributing US$5 billion! Not exactly niche market sales.

As mentioned above, Pfizer just this month announced the formation of an orphan drug diseases research unit. This follows on from its in-licensing of a Phase III compound that may compete with Genzyme's Cerezyme in Gaucher Disease.

In February this year GlaxoSmithKline also announced the formation of a special research unit to develop drugs for rare (orphan) diseases. GSK stated that whilst there are over 5,500 rare diseases, only 10% are currently being treated, presenting a significant unmet clinical need. This follows on from two strategic collaborations formed in 2009 with companies developed orphan disease products. One was with **Prosensa**, which is developing therapeutics for sub-populations of patients with Duchenne Muscular Dystrophy.

'Niche' Orphan Drug Sales or Drugs Launched as Orphan Drugs

Drug	Company	Indication	Sales in 2009 ($US billion)
Remicade	Centocor (J&J)	Pediatric Crohn's disease, now rheumatoid arthritis	$6.50
Rituxan	Genetech/Biogen	Non-Hodgkin's lymphoma and now leukemia and rheumatoid	$5.20
Gleevec	Novartis	CML	$4.00
Copaxone	Teva	Multiple Sclerosis	$2.50
Avonex (Interferon beta-1a)	Biogen	Multiple sclerosis	$2.30
Zometa	Novartis	Bone cancer	$1.30
Topamax	J&J	Lennox-Gastaut Syndrome in children	$1.15
Sandostatin	Novartis	Acromegaly	$1.10
Cerezyme	Genzyme	Gaucher disease	$0.80
Fabryzyme	Genzyme	Fabry disease	$0.43
Pulmozyme	Genentech	Cystic Fibrosis	$0.36
Myozyme	Genzyme	Pompe disease	$0.32

The second is with **JCR Pharmaceuticals**, which is developing orphan drug therapeutics for the treatment of Hunter syndrome, Fabry disease and Gaucher disease. It looks like big pharma is aggressively honing in on some of Genzyme's orphan drug franchises.

Australian Biotechs Getting it Right with the Orphan Drug Approach

Australian biotechs have been quick to seize on the benefits offered from developing orphan disease drug candidates. At lease five listed companies have orphan drug development programs. And like many of the successes seen to date, all five Australian companies have strategic plans to expand indications from the lead orphan drug disease being tackled.

Pharmaxis

Pharmaxis has filed Bronchitol for the treatment of cystic fibrosis with European regulators. It has completed its first Phase III study successfully in the treatment of patients with bronchiectasis which is a non-orphan indication. Its second Phase III trial is underway and has recruited over 100 patients. It has also completed a pilot study in patients with chronic pulmonary obstructive disease.

Chemgenex Pharmaceuticals

Chemgenex Pharmaceuticals has filed its lead compound Omapro for the treatment patients with CML with the T315I mutation. The company is looking to expand into other orphan indications in CML, for patients who have failed two tyrosine kinase inhibitor

drugs, and for use further up-line in combination with Gleevec. The company is also looking to apply the drug for treatment of two other orphan drug diseases, acute myeloid leukemia and myeloplastic syndrome.

Clinuvel Pharmaceuticals

Clinuvel Pharmaceuticals' compound Scenesse has been granted orphan drug status for the treatment of Erythropoietic Protoporphyria (EPP). Its second indication is for the treatment of a second sun intolerance condition, called Polymorphous Light Eruption (PLE). The third potential application is for the treatment of transplant recipient patients to prevent skin cancers in this immuno-compromised group. This is a much larger market and is not an orphan drug class. However it's another example (as is Pharmaxis's move into bronchiectasis) to secure approval through the orphan drug class route and then expand into larger markets. The fourth application, which has been put on hold for the moment to focus on the lead applications, is for the treatment of a second orphan drug indication, Solar Urticaria.

Australian Orphan Drug Developers

Company	Compound	Lead Indication	2nd indication	3rd indication	4th indication	5th indication
Pharmaxis	Bronchitol	Cystic fibrosis	Bronchiectasis	COPD		
Chemgenex Pharmaceuticals	Omapro	CML - T315I mutation	CMI - 2 TKI failures	CML - combination	AML	Myelodysplastic syndrome
Clinuvel Pharmaceuticals	Scenesse	EPP	PLE	Skin cancer in transplant patients	Solar Urticaria	
Mesoblast	MPCs	Bone marrow transplant				
Antisense Therapeutics	ATL1103	Acromegaly	Diabetic retinopathy			

Mesoblast

Mesoblast has been granted orphan drug status for the use of its adult stem cells in expanding cells in bone marrow transplantation. The company has many other indications for its adult stem cell therapies, however it's expected that these will be distinct products.

Antisense Therapeutics

Antisense Therapeutics is looking to move its compound ATL1103 into clinical studies for the treatment of Acromegaly, an orphan drug indication which results in excessive production of growth hormone leading to enlarged internal organs, face, hands and feet. It affects a similar number of people as cystic fibrosis, estimated at between 40,000 - 70,000 in the US and Europe.

The lead product in this market is Sandostatin (Octreotide) from Novartis (see previous page) and in 2009 it generated sales of US$1.1 billion. The drug however is only effective in normalizing IGF-1 levels in 60%-65% of patients. Remaining patients can be treated with Pfizer's Somavert (Trovert) which generated sales of US$168 million in 2008. However this drug has side effects and needs to be administered by injected (subcutaneous) daily and needs to be reconstituted.

ATL1103 is an antisense inhibitor to the growth hormone receptor. Antisense has successfully completed animal studies in mice and primates, showing that circulating IGF-1 levels can be suppressed using the company's antisense drug candidate. This program has a number of attractive features. Firstly the biomarker, circulating IGF-1 in the bloodstream, can be readily measured and is in fact one of the primary endpoints. Secondly, antisense drugs are known to accumulate in the liver. That the growth hormone acts on the liver to produce excessive IGF-1 gives ATL1103 a good chance of working.

ATL1103 may also have application in treating Diabetic Retinopathy by blocking the effect of excessive growth hormone and IGF-1 on the eye.

Genzyme Leads

Genzyme now has three main Phase III programs underway. One is in multiple sclerosis, repositioning its monoclonal antibody drug Alemtuzumab to treat not just chronic lymphyocytic leukemia, but for the treatment of multiple sclerosis, with two Phase III trials having been completed.

The company has two Phase III trials underway with an oral drug candidate for Gaucher disease. It has also in-licensed an antisense compound from **Isis Pharmaceuticals**, Mipomersen, which is in Phase III studies for the treatment of hypercholesterolemia. The deal was signed in 2008 with Genzyme paying US$325 million upfront for access to the compound. And hypercholesterolemia is also an orphan drug disease.

Can Australia Build its Own Genzyme?

One of the local sector traits emerging is that Australian companies are showing that drug development of orphan drug products, from the bench through to market, is achievable and within sight for at least three local companies. The lower patient numbers required in clinical trials for orphan diseases and accessible narrow distribution channels to patients makes this drug class an achievable pursuit for Australian companies. (See table of Australian orphan drug candidates in development). Other appeals of orphan drug markets include the lack of competition, high prices and lower marketing costs.

With Australia's focus on the orphan drug class of diseases, considerable expertise has been developed in negotiating the regulatory pathways and building entry into niche markets. And food for thought, what a powerful global biotech business in Australia could be delivered from the merger of three of these orphan drug companies, Pharmaxis, Clinuvel Pharmaceuticals and Antisense Therapeutics.

The author of the BCC report on orphan drugs, Syamala Ariyanchira, wrote in his *Genetic Engineering News* article that: "Pharmacogenomics is forcing a paradigm shift in patient care. An inevitable impact will be shrinking patient populations as this approach may eventually lead to a scenario where the majority of

MediVac – Will the Metamizer Mark II Save the Business?

Medivac (MDV: 0.8 cents) is a company that provides safety solutions to the healthcare industry. It has two main product lines, the first being the Metamizer on-site hospital waste disposal system, and the second being the SunnyWipes range of personal hygiene products.

The company has had a chequered history since it listed in 2004, and as is typical of many biotech and healthcare companies, continues to evolve its product offerings and business model.

The company was distracted by an investment in the Diakine business which it made in 2007 and is now looking to divest. Diakine was brought to Medivac by Paul Ralph, previously known for his association with Avastra in its first iteration when it was developing a bio-weld technology. Diakine had developed a technology that could detect trace elements in blood or other body fluids. The Federal Court ruled that Medivac could recover a $110,000 payment from Paul Ralph, a ruling that was successfully defended by Medivac after appeal by Paul Ralph.

Metamizer

The Metamizer is a 5m x 2m x 3m high automated system that requires a room with at least 56 square metres of area. Hospital waste, exclusive of major body parts, pharmaceuticals and cytotoxics, is tip-loaded in from a bin and is subject to high pressure steam in a pressure vessel, converting all material into a sterilised, granular waste. The system reduces landfill waste by 80%.

The system reduces handling and also reduces community risk from the transport of hazardous materials through suburban areas.

Despite the attractive environmental features of the Medivac unit, sales of Metamizer waste disposal system have been disappointing with only 10 units installed to date, in part because the product is a high capital cost. Three units have been sold in Japan and one in Russia.

The first generation product has not been able to compete with waste removal companies which offer a more competive solution to large capital city hospitals. Also, the system has not met the volume requirements of many of these hospitals.

The company is now developing a larger, stronger, second generation unit that can take both 120 litre and 240 litre bins, processing 32, 240 litre bins in an eight hour shift. The new system also has a round chamber, eliminating corners in which refuse can be remain. The new system is also designed for transport with a standard shipping container.

The company expects to begin fulfilling orders for the new system in the second half of 2010.

SunnyWipes

Medivac's second product line is a range of hand sanitising gels and surface wipes. The key features of these products are that they are made from natural ingredients and include a moisturising ingredient. The TGA recently granted Sunnywipes approval as an antimicrobial hand gel, however, it is still waiting on gaining a virucidal claim for the gel and an anti-microbial claim for the wipes.

These products are being targeted at the health professionals market, where Medivac believes demand exists for more skin friendly hygiene product exists. [In 2009, the company entered the general consumer market through an agreement with Kimberly-Clark to sell two gel products under the Kleenex brand - see http://www2.kleenex.com/au/range/kleenexhandsanitiser/.]

However, Medivac's main challenge is that is a very small player offering only a partially differentiated product with an essentially unknown brand. The task of winning sales in the healthcare professional market is in our opinion, immense.

Shareholders

A major shareholder of Medivac is non-executive director Steven Copulos (through several vehicles), with a 38% stake. Copulos also held a 28 % stake in Healthlinx (as of August 2009).

Key Risk

Medivac is in a weak financial position, holding $0.8 million at the end of the March quarter. We expect a capital sourcing event to take place in the near future.

Summary

Medivac has an opportunity to provide a more environmentally favourable solution to the management of hospital waste. Its challenge has been to provide economies of scale, which it is aiming to do with its second generation system. That said, the company has demonstrated that it can manufacture and export a product.

We suggest that investors monitor the company, and look for growth in sales from the second generation version of the Metamizer as an indicator of its future prospects. Medivac is capitalised at $9 million

Bioshares recommendation: **Speculative Hold Class C**

Bioshares

– Orphan Drugs cont'd

blockbuster drugs are suitable only for a small group of patients." Perhaps it is this paradigm shift that is shifting the efforts of big pharma. Orphan drugs have become the new way to build blockbuster products.

Bioshares recommendations
Pharmaxis: **Speculative Buy Class A**
Clinuvel Pharmaceuticals: **Speculative Buy Class A**
Antisense Therapeutics: **Speculative Hold Class C**
Mesoblast: **Speculative Hold Class A**
Chemgenex Pharmaceuticals: **Speculative Hold Class B**

Bioshares

Bioshares Model Portfolio (25 June 2010)

Company	Price (current)	Price added to portfolio	Date added
Sunshine Heart	$0.034	$0.036	June 2010
Biota Holdings	$1.06	$1.09	May 2010
Tissue Therapies	$0.19	$0.21	January 2010
QRxPharma	$1.15	$0.25	December 2008
Hexima	$0.23	$0.60	October 2008
Atcor Medical	$0.13	$0.10	October 2008
CathRx	$0.25	$0.70	October 2008
Impedimed	$0.58	$0.70	August 2008
Mesoblast	$1.90	$1.25	August 2008
Circadian Technologies	$0.56	$1.03	February 2008
Patrys	$0.11	$0.50	December 2007
Bionomics	$0.26	$0.42	December 2007
Cogstate	$0.25	$0.13	November 2007
Sirtex Medical	$4.96	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.24	$0.66	September 2007
Starpharma Holdings	$0.55	$0.37	August 2007
Pharmaxis	$2.27	$3.15	August 2007
Universal Biosensors	$1.63	$1.23	June 2007
Probiotec	$1.35	$1.12	February 2007
Acrux	$1.83	$0.83	November 2004
Alchemia	$0.51	$0.67	May 2004

Portfolio Changes – 25 June 2010

IN:
No changes.

OUT:
No changes.

Avexa – Comment

An EGM has been requisitioned for July 6 by a group of shareholders seeking to take control of the board and recommence the development of apricatabine (ATC).

This attempt to continue development of ATC, under a proposed new management, seems flawed for one key reason.

The patents that cover ATC will expire in Europe in 2011 and 2015 and in the US in 2012.

The Phase III trial of ATC, involving 970 subjects, was scheduled to complete by July 2011, according to Avexa's filing on clinicaltrials.gov . As such, it is likely that any passage through regulatory agencies in the US and in Europe would be completed well after the patent expiration dates.

In our view, the most likely reason no partners have been found for ATC is that any prospective partner would have come to the view that the drug would be coming to market with insufficient patent protection.

Even allowing for the possibility of gaining marketing exclusivity of up to 5 years, it is unlikely that this extra time, if indeed fully granted, would generate the returns needed to cover a potential partner's costs for the marketing of the drug and not forgetting the standard industry royalty they would have to pay Avexa, in the order of 20-25%. The potential market position of ATC is made more difficult by the emergence of Gilead's hugely successful three-in-one drug combination Atripla (combining tenofovir, emtricitabine and efavirenz) and its newer four-in-one drug (tenofovir, emtricitabine, elvitegravir and GS9350), which is still in the pipeline. Medicines such as these have the potential to improve patient compliance and decrease the rate at which mutations arise.

Another signal of commercial stress in HIV drug markets can been seen with GlaxoSmithKline and Pfizer merging their HIV drug units into a joint venture (on a roughly 85/15 split). This is remarkable considering GSK was a pioneer in the HIV drug business. While GSK has been a leader, drugs coming off patent and a failure to generate new HIV drugs caused it find a solution with Pfizer, which has a better pipeline, but only one drug on the market. The message this JV delivers is that the competition coming from companies such as Gilead, is very intense. Gilead has a greater than 30% share of the HIV market.

In light of what we believe is the commercial reality facing ATC, continued development of ATC is not warranted.

The current board may or may not be the best board for Avexa in the long term. However, any board existing or proposed should at the minimum set forward a transparent and credible plan for the management and application of funds that Avexa holds as its main asset, which is estimated by the board to be $23 million as of June 30, 2010.

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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: Pharmaxis, Starpharma Holdings, Cogstate, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Halcygen Pharmaceuticals, Impedimed, QRxPharma, Patrys, LBT Innovations, Hexima, Tyrian Diagnostics, Mesoblast, Atcor Medical, CathRx, BioMd, Tissue Therapies, Viralytics

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