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In this edition...

There are two trends for Acrux watchers to follow. One is the sales growth rate for testosterone replacement products in the mens health market, with growth in the US market for the twelve months ending March 31 close to 30%. The other trend that should become clearer in the next half year is of the growth rate for Axiron prescriptions as opposed to royalty payment trends.

An attempt is being made to push the IPO window further ajar, this time with Cortical Dynamics seeking funding to advance its Brain Anaethesia Response product. The algorithm-based technology may overcome the problem of alertness that can occur when some patients undergo surgery.

The Editors

Companies Covered: ACR, CUV, PVA, IPO profile - Cortical Dynamics

	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 - May'11)	45.4%
Year 11 now commenced	-12.6%
Cumulative Gain	**268%**
Av Annual Gain (10 yrs)	**21.2%**

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Bioshares

24 June 2011
Edition 413

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

Acrux – Growth in Testosterone Product Sales Indicate Strong Potential for Axiron

Sales of testosterone products have started to take off. In the 12 months to the end of March 2011, sales in the US increased by 27.8% to US$1.3 billion, according to one of the players in this space, **Auxilium**. That equates to a dollar increase in sales of US$288 million in that period, the largest ever seen. Of that figure, gels made up US$1.15 billion of sales, or 86%, accounting for most of that increase.

As the sales increase, the market is seeing a number of new entrants into the space, including **Eli Lilly**, which is marketing the product developed by Acrux (ACR: $3.35), called Axiron. The rapidly expanding market is now seeing a race by pharmaceutical companies to form entrenched positions in this market, which has been, and continues to be held largely by **Abbott** with its Androgel product.

New Testosterone Products

Axiron is the first of these recent new product approvals in the testosterone gel/solution space. Its product was approved by the FDA in November last year and was launched at the end of March this year. In April this year Abbott gained approval of a stronger dose of its testosterone gel, called Androgel 1.62%, that only requires half of the original volume.

In May this year, **Endo Pharmaceuticals** received approval for its testosterone gel product, Fortesta.

Product Differentiation

It would appear that Axiron retains product advantages over its competitors. Other products still need to be applied to larger areas of the body – Axiron is applied under the arms; Testim (from Auxilium) and Androgel 1.62% are applied to the shoulders and upper arms; and Fortesta is applied to the insides of the thighs. Axiron would appear to have the least chance of passing the drug on to others, such as children or women, which is a big risk with these products, and only Axiron is applied with an applicator rather than spreading the gel or solution with the hand or finger.

– Cont'd over

Axiron is also the only solution product rather than a gel, and our assumption is that it has a faster drying time. On a volume basis, only Eli Lilly indicates the volume of each of its 30mg metered doses, equating to 1.5 ml, and in fact this is listed just below the product logo.

Axiron sales ramp up

Eli Lilly has started its marketing campaign on specialists in the US. That is now expanding with the introduction of two sales forces that will market the product to general practitioners. That marketing team is expected to be in full force by the end of July this year. From there Eli Lilly will likely move to a direct to patient media marketing campaign.

Eli Lilly has a very large sales force that it is using to market and sell Axiron, no doubt using its very large, established men's health sales force the sells the Cialis product that competes with Pfizer's Viagra.

Royalties

At the end of August, Acrux will receive its first royalty cheque from Eli Lilly. CEO Richard Treagus said that the company anticipates having discussions with Eli Lilly on what it can reveal to the market. There are two different measures that will emerge and these will take a while to merge. The first is ex-factory sales, and this is what the royalty is based on. However this includes stocking orders and will be impacted by initial promotional discounts and samples, so will not be a true reflection of demand. The more meaningful measure in the short term will be prescriptions and prescriptions growth.

Speed to market

In this escalating market, Treagus said for Eli Lilly it is about speed to market. Eli Lilly is doing many things in parallel, with product registrations in a number of countries, including in Europe. Treagus said that there is no doubt Eli Lilly will try and grow this market outside of the US (using its established men's health sales and marketing teams).

Competition

There are a number of competing products to Axiron as would be expected in this escalating market.

Testim 1% gel

Testim is a testosterone gel made by Auxilium. It was approved by the FDA in 2002. Sales in the last year have flattened out (4% increase) tracking at US$184 million based on the March 2011 quarter sales.

The gel is applied once daily, however it needs to be applied by the hand on the shoulders and upper arms. It takes a few minutes to dry.

Testim comes in 5g dosages, of which either one or two can be taken. Of the testosterone in the product, 10% is absorbed across the skin. The starting dose is one 5g tube (equating to 50mg of testosterone).

Fortesta 2% gel

Endo Pharmaceuticals received approval for its testosterone gel, Fortesta, in May this year. It is applied once daily to the inner thigh, spread on the thigh using a finger. The product takes a few minutes to dry.

The Foretesta starting dose is 40mg of testosterone (equating to 2g of gel), and this can be decreased to 10mg or increased to 70mg.

Axiron 2% solution

Under the Axiron logo on promotional material is the fact the Axiron is 1.5ml per 30mg. Obviously Eli Lilly is promoting this as one of the key features. The patient generally starts with 60mg (two doses of the pump equating to 3ml) and this can be eventually decreased to 30mg or increased to 90mg or 120mg of testosterone as required.

Androgel 1.62% gel

In April this year Abbott released a stronger dose of its testosterone gel product, called Androgel 1.62%, up from 1% in the previous product. The company says the new product is delivered using half of the volume that the first product requires.

The product is applied to the shoulders and upper arms. Its starting dose is two pumps, which equates to 2.5g of product.

Summary

Acrux has not disclosed royalty rates, but we estimate it stands to receive around a 20% royalty from sales, plus there is up to another US$195 million in sales based milestone payments.

Axiron could generate sales of around $500 million at a minimum in our estimates, and that is largely factored into the share price. However if the growth in testosterone replacement market continues to escalate and can be expanded outside of the US, then $800 million - $1 billion sales of Axiron are certainly not factored into the share price.We also believe there still remains a strong possibility that Eli Lilly will seek to acquire the company.

Acrux is capitalised at $557 million.

Bioshares recommendation: **Speculative Buy Class A** (upgraded)

Bioshares

IPO Profile – Cortical Dynamics

Cortical Dynamics was founded in 2004 to commercialise a brain function monitor technology, termed Brain Anaethesia Response (BAR) in its first product form.

The value proposition for the BAR system is that the objective monitoring of hypnotic states improves anaesthetic and surgical outcomes including reducing recovery times and reducing costs of anaesthetic drugs. The BAR system, it is proposed, is more sensitive in detecting the effects of a number of drugs, which means that over-dosing and under-dosing can be better managed.

Cortical is seeking to raise up $2 million through the issue of 10 million shares at 20 cents, with the offer also including 10 million free attaching options. The 20 cent options are exercisable from after July 26, 2011 and expire on June 30, 2012

The offer is underwritten by **Grandbridge Securities Pty Ltd**, an entity controlled by the listed investment vehicle **Grandbridge Ltd** (GBL). Grandbridge Ltd is an entity in which company chairman David Breeze holds a 35.5% stake. The underwriter stands to receive 5 million underwriter options which have the same terms as the offer options. David Breeze currently has interests in 9.9 million Cortical Dynamics shares.

The number of pre-IPO shares is 103 million. On completion of the offer, the company expects to holds funds of $1.6 million. Cortical Dynamics' indicative capitalisation is $22.6 million.

Research from Swinburne Uni

The technology is based on research conducted at the **Swinburne University of Technology** led by Associate Professor David Liley. In 2005 Biopharmica (now BPH Energy) invested in Cortical and took over management control of the company. Approximately $1 million has been invested to date in the Cortical technology. Cortical Dynamics is based in Perth.

Two of the company's current objectives are to validate the BAR system and develop market ready products that can be integrated with leading patient monitoring systems and gain regulatory approvals in key markets.

Product and Technology

Cortical Dynamics has developed a brain function monitor and index for quantifying depth of anaesthesia while patients undergo surgery. The benefit of the monitor and index is to reduce the awareness of the surgical procedure being conducted (intra-operative awareness). The current depth of anaesthesia monitors include the Bispectral Index (sold by Covidien), the Narcotrend Index, the State Entropy and Response Entropy Indices and A-line ARX Index. The Bispectral Index is considered to be the industry standard.

The BIS and other approaches are inadequate in assessing the hypnotic effect of short-acting opioids and nitrous oxide. The limitation of the BIS and other approaches is because (it is theorized) that they ignore information contained in the amplitude of EEG signals.

Cortical Dynamics combines amplitude information using mathematical techniques with frequency information describing the cortical state.

Based on Alpha Wave Theory

The theory supporting the Cortical technology is based on the observation that the brain emits alpha rhythms, which arise possibly for several reasons, including the pacing of cortical neurons, interactions between excitatory and inhibitory cortical neuronal populations, and wave generation stemming from long range cortico-cortical connectivity (see the company's patent PCT/AU2004/000045).

The rhythms can be measured used electrical sensing apparatus more commonly known as EEG sensors.

Studies Conducted To Date

Cortical Dynamics has completed several studies, evaluating the technology to detect the effects of remifentanil, nitrous oxide, remifentanil and noxious stimuli and the sedative alprazolam.

The remifentanil study was published in the August 2010 edition of the journal *Anethesiology*. The study showed that the BAR index was able to clearly differentiate the effects that remifentanil and propofol have on brain activity in human studies.

IP and Patents

Cortical Dynamics has five patent families that cover its technology. The titles of these patents or patent applications are "Method of monitoring brain function", "Brain Function Monitoring and Display System", "EEG analysis system" and "Neurodiagnostic monitoring and display system". These four patents are at the national stage of examination, with the first patent "Method of monitoring brain function" having been granted in Australia and New Zealand. A fifth patent "Composite Brain Function Monitoring and Display System" is in the provisional stage.

Clinical Development Plan

Cortical Dynamics has two clinical trials planned. The first, scheduled to be completed this year, is a 20 patients validation trial of the BAR system. In 2012, the company plans to conduct a 45 patient BAR sensitivity trial

Observations

Lack of experienced life science investors

In its current form, and from our study of the prospectus, there appear to be no experienced life science investors on the register involved with Cortical. Specialist life science investors can at times be an indicator of investment merit, with their experience aiding the structuring, funding and organisation of start-up firms.

Lack of commercialisation skills on the board and in management

We do not discern personnel on the board or in management with medical device development experience gained from working with medical product firms. The onus on the company to access experienced personnel, either directly or on a consultancy basis, is critical to achieving commercial success.

– Cont'd over

Convertible Note issue
Cortical Dynamics entered into a Convertible Note funding agreement with BPH Energy on the 19th of November 2010 for a term of one year, for a maximum amount of $500,000, of which the company has drawn down $50,000.

Dominant Technology
Our observation and one discussed in the prospectus is that the technology is a competitor to a dominant and entrenched technology (the BIS system). It is not unusual for emerging yet superior medical technologies to take many years to displace or disrupt incumbent technologies and for key opinion leaders to endorse new approaches.

A key challenge for the company will be to establish a scientific advisory board in addition to communicating the benefits of its technology to key opinion leaders in the world of anaesthesiology.

Other Risks

The company has identified several important risks for the company, its technology and products.

- The first is that computational hardware may not evolve at a sufficient rate to support advances in the algorithms that underlie the DAM of the BAR monitoring system;
- EEG recording electrodes require gels, which impede the recording quality of the EEG sensor;
- EEG systems compete with MRI and CT scanning technologies, however, EEG systems are spatially more convenient and cheaper that MRI and CT facilities.

Summary

Cortical Dynamics represents a very interesting investment opportunity in the area of anaethesiology support, which is something of a rarity for Australian biotech investors to consider.

The primary attraction of the company is that it is addresses a limitation with existing approaches, in which currently available depth of anaethesiology indices do not detect the effects of a number of hypnotic drugs.

A second attraction is that the technology can be extended into other product areas including brain analgesia response, early-warning of degenerative disease and managing pain response and tranquilliser monitoring of trauma patients in intensive care units. It may also have applications in drug discovery and evaluation and even in the area of software and gaming or Brain Computer Interface market.

The company has set out a number of important development steps ahead, including conducting more clinical studies and gaining product approvals and seeking a marketing partner. These tasks are not trivial and may test the company in its current form. A logical evolution of the company would include the expansion staff numbers to include experienced commercialization personnel.

Investors can access a copy of the prospectus at www.corticaldynamics.com.au .

The opening date of the offer is June 10, 2011.
The closing date of the offer is 22 July, 2011.
The expected date of listing of the shares on the ASX is 29 July, 2011.

Bioshares

pSivida Amends Pfizer Deal to Set Up Second Core Program

pSivida has amended its 2007 R&D deal with **Pfizer** using pSivida's drug delivery technologies to deliver sustained release of pharmaceuticals to treat eye diseases.

pSivida had been receiving US$0.5 million quarterly payments from Pfizer to conduct preclinical studies with ophthalmic drugs. To date pSivida had received $7 million as well as Pfizer having invested in pSivida to take a 10% stake.

The revised agreement centres around moving one program into Phase I/II clinical studies in delivering a drug called latanoprost (a prostaglandin analogue) to treat patients with ocular hypertension and glaucoma.

Under the revised arrangement, pSivida will receive a US$2.3 million payment to fund the study. After the Phase II study, Pfizer will have an option to develop and commercialise the product. It will need to pay an upfront fee to pSivida of US$20 million to move the program into Phase III studies. pSivida will also be entitled to a double-digit royalty from sales, and milestone payments of up to US$146.5 million.

For pSivida it gives the company a second core program after Iluvien, which the FDA is currently assessing for approval. Psivida has also regained considerable intellectual property from the first deal with Pfizer which frees up pSivida to look at other applications for the Durasert implant technology.

FDA decision expected in November

The FDA is reassessing Alimera Sciences/pSivida's new drug application for Iluvien, which is a corticosteroid implant for the treatment of diabetic macular edema. A decision is expected in November. Upon approval, pSivida will receive a US$25 payment from its partner Alimera Sciences and is eligible to receive a 20% profit share from sales of the product. We believe the product has a strong chance of gaining approval.

pSivida is capitalised US$89 million and held funds of US$24 million at the end of March.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Bioshares Model Portfolio (24 June 2011)

Company	Price (current)	Price added to portfolio	Date added
Acrux	$3.37	$3.37	June 2011
Psivida	$3.67	$3.95	May 2011
Bioniche	$0.96	$1.35	March 2011
Somnomed	$1.30	$0.94	January 2011
Phylogica	$0.069	$0.053	September 2010
Sunshine Heart	$0.055	$0.036	June 2010
Biota Holdings	$0.94	$1.09	May 2010
Tissue Therapies	$0.60	$0.21	January 2010
Atcor Medical	$0.14	$0.10	October 2008
Impedimed	$0.55	$0.70	August 2008
Patrys	$0.09	$0.50	December 2007
Bionomics	$0.56	$0.42	December 2007
Cogstate	$0.17	$0.13	November 2007
Sirtex Medical	$5.00	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.70	$6.60	September 2007
Starpharma Holdings	$1.28	$0.37	August 2007
Pharmaxis	$0.94	$3.15	August 2007
Universal Biosensors	$0.95	$1.23	June 2007
Alchemia	$0.58	$0.67	May 2004

Portfolio Changes – 24 June 2011

IN:
With sales of transdermal testosterone products in the US escalating, now worth US$1.3 billion a year, and given Acrux's product advantages, we have returned Acrux to the portfolio at $3.37.

OUT:
No changes.

Clinuvel Generates First Million Dollars of Sales

Clinuvel Pharmaceuticals (CUV $1.685) has generated its first million dollars of sales from its product in Italy. The company last year was allowed to sell its drug, Scenesse, into Italy for the treatment of a sun intolerance condition called EPP. The company is reimbursed for the product at around Euro 32,000 for a year's treatment.

Scenesse increases the melanin density of the skin, giving it a darker appearance, protecting the skin of those people who have severe reactions from direct sunlight exposure.

There are not many people with this condition – about 200 in Italy and it is estimated 4,000 in Europe. To date the product has been sold for use in 40 patients in Italy. At current pricing, that translates to an immediate market of $20 million in Europe alone, however that market should grow as awareness and comfort with the safety of the product grows.

In Europe there are about 20 specialists in the area of EPP and the company has already worked with around 90% of them. What Clinuvel has done well is build awareness and demand for its product from patients and doctors, even before the drug has gained widespread approval. This narrow distribution channel and awareness potentially allows Clinuvel to sell the product directly once approved in other parts of Europe.

Before that happens, the company needs to see the results form to remaining pivotal studies in EPP, one in the US and one in Europe. If all goes well, the company will file the drug for approval by the end of this year. The program is under an Orphan Drug Designation and approval could be received as early as mid 2012.

Clarifications and Corrections: QRx Pharma
In last week's article on QRxPharma, we incorrectly stated the p-value where MoxDuo IR was shown to have a statistically significant improvement against oxycodone in a trial measuring respiratory impairment. The p-value should have read "p<0.02" not "p<0.2".

In referring to "12mg/8mg" MoxDuo, the correct dosage component is 12 mg of morphine (not oxycodone) and 8mg of oxycodone (not morphine). The equivalent analgesic opioid dose in the other two arms should have read 24mg of morphine and 16mg of oxycodone.

Not mentioned in the article is that patients were required to take anti-vomiting drugs, which was not required in earlier studies and which can make it very difficult to accurately assess nausea and vomiting in patients.

The next core application for the product is in the treatment of vitiligo, which is a skin discoloration. That market is substantially greater, estimated at $400 million a year, compared to around $50 million for EPP. Vitiligo trials have started in the US (with up to 60 people) and are due to start in a similar number patients in Europe. The company's core management team is now located in Switzerland where between 12-15 staff are based.

Clinuvel has dedicated management, is in the final stages of clinical development, and already has its product approved for use in one market (Italy), which is generating sales of $1 million a year. Clinuvel is capitalised at $51 million and held funds of $20 million at the end of March.

Bioshares recommendation: **Speculative Hold Class A**

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. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

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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