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In this edition...
Finding a way is the theme this week. Clinuvel has found a way to have the European Medicines Agency (EMEA) grant orphan drug status to CUV-1647, a not insignificant achievement. Biosignal has found a way to raise funds to support its priority projects. Xceed's investee company PolyNovo, which while it has a very attractive technology, as demonstrated by its third major licensing deal (with Smith & Nephew), still has to find a way to raise funds to support feed stock manufacturing development. And Optiscan Imaging is still finding ways to improve sales of the flexible endomicroscope partnered with Hoya (Pentax).

The editors
Companies covered: BOS, CUV, OIL, XCD (PolyNovo)

	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)	-40%
Cumulative Gain	**96%**
Av Annual Gain (6 yrs)	**26.8%**

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Bioshares

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

Clinuvel Pharmaceuticals Successfully Changes Course With Regulators

Clinuvel Pharmaceuticals (CUV: 37.5 cents) successfully changed course as regulators in Europe (EMEA) granted orphan drug status to Clinuvel's drug candidate CUV1647. For a compound that had previously been promoted as a potential tanning agent, this marks a shift by regulators (in Europe) with the drug candidate now acknowledged as a potential therapeutic for the treatment or prevention of life threatening or debilitating chronic diseases.

CUV1647 is a peptide drug candidate with photo-protective properties. CUV1647 may prevent the damage caused from exposure to ultraviolet light. Exposure to the sun for the most part is not immediately harmful, however a small subset of the population risks immediate skin damage from sunlight exposure.

Clinuvel has been granted orphan drug status for two of the more rare such conditions; erythropoietic porphyria (EPP) and the even less common congenital erythropoietic porphyria (CEP). In Europe there are approximately 1000 people afflicted with EPP and around 100 with the CEP condition. People with these conditions can experience severe reactions to direct sunlight, including swelling and severe scarring.

Clinuvel likely to file for EPP approval in 2009

Clinuvel is likely to file its first indication for treatment of EPP next year pending positive Phase III results. Phase II studies have been successful and the company is currently conducting Phase III studies, which are expected to be completed by March next year. The drug could be approved for use in Europe by as early as the end of 2009.

With orphan drug status in Europe, the company receives a 10 year market exclusivity in Europe for that (and CEP) indication. In assessing Clinuvel's application, the EMEA brought in its own independent expert to assess Clinuvel's application and Clinuvel had brought in its EPP expert consultant as well. Not surprisingly, the two experts were no strangers to each other, highlighting the niche indication that is being pursued here. The positive Phase II results with CUV1647 for treating EPP, while not crucial, was submitted as part of its orphan drug application and was likely considered by the EMEA.

A niche application has its advantages and not so obvious difficulties. There are no effective therapies for EPP other than keeping out of the light or excessive and continuous use of sunscreens. The quality of life of sufferers from this condition can be severely affected. This dynamic makes it easier for companies developing such treatments to gain the attention of regulators, who understand the requirement to provide incentives for companies to develop therapies for such conditions.

Clinuvel's approach is to get the drug on the market initially for the treatment of EPP and then expand the claims for treatment to more prolific disorders such as polymorphic light eruption (PLE) and to prevent skin cancer formation in patients on immune suppression drugs (i.e. organ transplant recipients).

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Pricing quandary

It should be less difficult to get the drug approved for a more severe indication. However, the issue confronting the company is the selection of appropriate pricing for the drug. For a niche indication, a significant premium could be negotiated with health payors but for less severe and more common conditions, such a price premium would not be justified. Once a price has been negotiated it's difficult to reset. **Pharmaxis** has a similar quandary with Bronchitol for the treatment of the less severe but more common condition of bronchiectasis and the less common and more severe cystic fibrosis disorder.

US orphan drug status

The next challenge for Clinuvel is to gain orphan drug status for its programs in the US. Aside from the important market exclusivity offered (seven years in the US, 10 years in Europe), there are other financial incentives offered by regulators. The certification does not immediately offer an expedited review of new drug applications.

Clinuvel is in the process of preparing an IND which will allow it to launch trials with its drug candidate in the US. The EPP Phase III trial underway in Europe involves between 50 - 70 patients. A Phase III PLE trial is underway in Australia and Europe and will involved around 150 patients. The EPP trial is likely to be the first Phase III to be completed. Phase II studies showed that CUV1647 delivered a statistically significant improvement for patients with EPP, albeit in only five patients.

Summary

Clinuvel is capitalised at $113 million with $57 million in cash at the end of calender 2007. Its current burn rate is around $1 million per month, although this is likely to increase as further trials, particularly in the US, are commenced, including larger trials in the prevention of skin cancers in around 200 people on immune suppression drug treatment.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Orphan drug status received for drugs in development by Australian biotechs

Company	Date received	Drug candidate	Region	Indication
Pharmaxis	February 2005	Bronchitol	USA	Bronchiectasis
Pharmaxis	November 2005	Bronchitol	Europe	Cystic fibrosis
Chemgenex Pharmaceuticals	March 2006	Omacetaxine	USA	CML
Progen Pharmaceuticals	September 2007	PI-88	Europe	Primary liver cancer
Clinuvel Pharmaceuticals	March 2008	CUV-1467	Europe	EPP, CEP

Biosignal and Polynovo: Multiple Application Technologies Provide Many Shots At Goal

The case for multiple-application technology companies

Multiple-application technology companies are defined as those companies that are developing a technology that can be converted into more than one product in more than one field of use, and even in other fields of use in other industries.

MAT companies are different to platform technology companies, which are developing technologies that have the potential to be used by many other firms in the discovery and development of other technologies and products. A platform technology company is oriented to developing technologies used by other businesses, but not to the manufacture of products used by buyers at the end of the value chain.

With markets experiencing intense downward pressure and the window for biotech financings so shut that one could argue its been bricked in, companies that have been built on the back of multiple-application technology technologies are suddenly beginning to look attractive. This is because they can partition their technology and IP and can out-license, sell or spin-out selected applications of the technology into new companies and into the hands of new owners. The upside? Some cash in the hand to keep the 'parent' company viable until market conditions and share prices improve and increased management focus and cash to spend on priority programs.

Investors often find MAT companies unappealing because they are 'too complicated' and tend to lack focus. These points are fair criticism: MAT companies are 'complicated' and focus is an undeniably huge challenge.

And when they do cut deals, the upfront and milestone payments for MAT companies tend to be small, and the royalty terms can also be lower, although royalty terms usually and simply reflect the development status of the technology. If a technology has been developed into a product for which safety and efficacy data is well advanced or the product has achieved registration and commenced sales, albeit in a small market setting, then royalty terms can tend to be higher.

However, MAT companies can survive despite experiencing development failures, unlike single product companies that will live of die by the success or failure of a single program.

Australian MAT companies loosely defined include Starpharma Holdings (dendrimer chemistry applied to drug research, RNAi

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– PolyNovo, Biosignal cont'd from page 2

transfection, drug delivery and drug transport, industrial applications), Alchemia (carbohydrate drug development and drug research), Stem Cell Sciences (stem cell products and know how), Phylogica (peptide libraries), Tissue Therapies (biologic derived products), BioLayer (design and assembly of coatings for immunoassays and bioseparations), PolyNovo and Biosignal. The last two companies have made recently made further progress in commercialising their respective technologies and are discussed below.

PolyNovo

PolyNovo has cemented a third licensing deal covering aspects of the company's NovoSorb technology. Xceed Capital (XCD: 9.3 cents) holds a 64% stake in PolyNovo, with the remainder held by the **CSIRO**. Xceed had flagged in 2007 an IPO for PolyNovo, however market conditions have meant this has been put on hold.

A global exclusive license was recently awarded by PolyNovo to medical devices firm **Smith & Nephew** for the rights to develop products in the fields of bone void filler and fracture fixation. PolyNovo has previously inked deals with **Biomet**, covering the application of the Novosorb technology for cranial, facial and cartilage repair, and with **Medtronic**, covering the use of the technology in the prevention and treatment of cardiac and vascular disease, in particular the development of stents.

The NovoSorb polymer technology is the culmination of a research program that has resulted in biodegradable polymers that can be configured or manipulated to express different structural and mechanical properties, depending on the use required.

Bone void filler

A bone void filler is likely to be developed as a two part injectable system. The filler would be injected as a foam that would form into a solid. This solid is similar to cancellous bone or light porous bone. As the bone grows, it increasingly incorporates itself in the material, which is also biodegrading at the same time.

The bone void filler product is expected to move into the clinic fairly rapidly as the less onerous 510(k) pathway is a realistic US regulatory pathway option. Unlike the stent partnership with Medtronic, for which human clinical trials will be necessary to establish safety at a very high level, the safety issues for bone void filler are less stringent.

Augmentation fixation

Smith & Nephew has also selected to evaluate and potentially develop Novosorb as a material that can augment fixation, that is when plates or pins need to be attached to bone. S&N is likely to use the Novosorb technology to complement one of its own technologies that more effectively deal with the problem of stress shields, which occur when artificial implants shield the bone from stress. There is a range of normal stress conditions that support normal bone function. But if too much shielding occurs, the bone can lose its proper functioning and be broken down by the body.

Deal terms

Specific deal terms were not disclosed, with an up-front payment made, certain milestone payments to follow and with the royalty rate indicated to be in the high single digit range.

Comments

With the signing of a third major partner, PolyNovo has again confirmed at a commercial level that its technology has multiple application possibilities. It has also confirmed that big medical device companies see a great deal of potential for the NovoSorb technology. Although the Novosorb products have yet to be tested in humans, in any proper safety studies, the fact that three of the worlds largest medical device companies have signed separate deals over the technology is a very, very positive investment signal.

What has not been outlicensed by PolyNovo are applications of the NovoSorb technology in the fields of spine, soft tissue, biologics delivery and anti-surgical adhesion. In addition to the agreements with the three large medical device companies, PolyNovo has a joint venture (NovoSkin) in place with Dr John Greenwood of Royal Adelaide Hospital aiming to develop skin regeneration products.

Challenge

While PolyNovo now has an impressive line-up of partnerships underway, it now needs to address its own commitments to these programs, insofar as it needs to expand and build a commercial feed stock manufacturing facility. The mooted IPO, now on hold, was in effect designed to supply capital for this stage of development. However, the company will be seeking funding through a mezzanine finance round.

CEO departure

Xceed Capital announced the departure of CEO David Kenley on Friday to conserve cash within its investee businesses (the other being chemistry products company **Boron Molecular**). Xceed Capital is capitalised at $9.3 million and retained $4.4 million cash at the end of last year.

Bioshares recommendation: XCD – **Speculative Buy Class B**

Biosignal

Biosignal (BOS: 13.5 cents) has been researching and developing the application of a class of chemical compounds called furanones since it was founded in 1999 (the company listed in 2004). These compounds are capable of inhibiting bacterial signalling and consequently inhibit bacterial colonisation behaviour known also as the formation of bio-films.

Furanones do not kill bacteria but stop them from establishing colonies or bio-films. Since Biosignal's class of compounds are not biocidal, they offer the advantage of avoiding resistance mechanisms that micro-organisms often establish through mutation when confronted with direct chemical attacks. Bacterial drug resistance is a very significant and very costly global healthcare problem.

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– Biosignal from previous page

Biosignal has had over the years a number of R&D collaborations in play, including two with companies that market contact lenses. The contact lens programs have suffered setbacks, with the company citing failure with the technology that attaches the furanones to contact lenses as the source of degradation in performance in human trials of the extended wear contact lenses. The programs will require further resources to solve the attachment chemistry problems and it is possible that this aspect of Biosignal's business will be restructured into another vehicle in 2008.

In 2007, the company began examining alternative strategies to leverage its portfolio of development opportunities. This week the company announced it will spin out two companies to commercialise (a) wound and hospital hygiene applications and (b) to commercialise applications in the oil and gas (anti-corrosives), water treatment and industrial infrastructure areas. All current arrangements that Biosignal has with other parties will be assigned to the new entities The spin-out companies *do not* have rights to domestic and personal care applications, agricultural and acquaculture, or medical and animal health applications.

Two US-based companies

The two spin-out companies will be US entities in which Biosignal will have no equity. However, Biosignal's rights will include 50% share of revenues and a 50% share of the proceeds of sale for the industrial applications company. For the wound-care company, the right will be to a 50% share of revenues, where minimums are agreed to and a 50% share of the proceeds of sale of the company.

The US entrepreneur who is establishing the companies, Paul Hawken, will pay Biosignal an up-front licensing fees of US$1 million for the oil and gas and industrial rights and US$0.5 million for the wound and hygiene rights.

The deals at the time of announcement were in draft form and are expected to be finalised by mid-April.

Comments

If Biosignal successfully outlicences its furanone technology to two new US based entities, it will immediately have improved its cash position at a time when share market funding opportunities are extremely difficult.

Are they good deals?

Yet the key questions are whether these deals are the right deals and whether they are good deals. The arrangements have neither an equity component or a royalty component, and in that way stand outside of typical licensing conventions. They also have no control over or say in the new entities. By these measures they are not the optimal deals.

However, it would appear that Biosignal has no funding obligations towards the two entities and this is a plus in current market conditions. From a risk point of view the company will have completely de-risked two programs for which it had no funds to progress, and it has created *some* chance of generating plenty of upside.

What happens if the US spin-outs do generate significant revenues but the owners are reluctant to forward Biosignal's entitlements in a timely manner, or siphon revenues to other vehicles? This is a potential risk and legal action might be required if the licensing agreement is not constructed with sufficient mechanisms to support Biosignal's entitlements.

One argument for arranging the deal on a no-equity/no-royalty/revenue share basis is that the proposed entities will appear as fully owned US companies, unencumbered by royalty obligations. With this particular ownership and asset structure, it may mean that the companies can more easily facilitate sub-licensing arrangements. And location and formation of the companies in the US will enable the recruitment of personnel of the calibre needed to grow and drive the businesses. Tapping appropriate human resources is a much more difficult task for Australian based companies.

Strategy

Biosignal's objective is to position itself as an IP holding company and as a developer of higher value applications of its furanone technology, which includes human therapeutic applications, for example, potentially developing a therapeutic product to treat cystic fibrosis.

The company intends to engage in further out-licensing and structuring in areas including contact lenses and medical devices, and in seed protection, green house and cut flowers applications to be out-licensed in the near-to-medium term.

Summary

Biosignal has experienced several technology failures since it was founded almost ten years ago. However, the company has a rich chemistry base that is permitting it to stay alive in today's very difficult market conditions. On a long term basis, Biosignal continues to be an attractive investment proposition.

Biosignal is capitalised at $14.3 million, and held $1.9 million in cash as of December 31, 2007.

Bioshares recommendation: **Speculative Buy Class B**

Optiscan Imaging's Market Challenges

Optiscan Imaging (OIL: 18.5 cents) has received a setback in recent months with its lead product, the confocal endomicroscope, called the ISC1000, and being sold by **Pentax** (acquired recently by **Hoya** in Japan). Late last year Pentax notified Optiscan that demand for the Optiscan components of this device would be scaled back and there was, and remains, some uncertainty as to the commitment of its Japanese marketing partner to the product.

Pentax/Hoya merger a distraction

The merger between Pentax and Hoya completed last year proved to be a sizeable distraction for Pentax with Optiscan continuing to seek a more comprehensive or clearer commitment from its marketing partner.

The ISC100 allows specialists to image tissue at a cellular level in real time inside the body. To gain a greater penetration of the device into the market, the companies need to continue to educate users and conduct multi-centre studies where an understanding of the reproducibility of the benefits of product use can be gained. Efficacy of the device in detecting intestinal diseases such as Barrett's oesophagus and early cancer in ulcerative colitis, without the need for biopsy, have been stunning in single centre studies.

Other impediments to the technology uptake is the lack of reimbursement for these specific procedures, where arguably a larger reimbursement figure would be appropriate if the procedure obviates or reduces the need for biopsy assessment by pathologists.

Multi-centre studies in four centres in Europe and in around 300 patients are due to start shortly in these gastro-intestinal disorders. There are at least a further 10 GI disorders this device could be applied to, such as detection of microscopic colitis, which is one of the treatable causes of irritable bowel syndrome.

The Atlas of Endomicroscopy

The education process is underway for this new imaging technique, with a new book (104 pages) dedicated to Optiscan's device, called the *Atlas of Endomicroscopy*, now available for teaching hospitals and practitioners. Another three to four more Centres of Excellence are expected to be set up for the Hoya/Optiscan system. There are at least four training centers for the device, located in Italy, USA, Germany and the UK with a total of around 60 hospitals now using the system.

Previously in *Bioshares* we have estimated that there would need to be at least 500 installed sites around the world to reach a tipping point for commercial success of this product. This takes into account the ongoing revenue from ongoing probe sales to existing users, system upgrades and the then natural expansion when product use is written into the guidelines for various diagnostic procedures. The current installed base would suggest the company is about 12% of the way towards our target.

So the dilemma; how do the two companies accelerate the uptake of this system and will additional investment achieve the necessary returns for a large multinational such as Hoya? Or would it be better suited in the hands of a lower cost-base alternative company. More information from the companies should be forthcoming.

Rigid microscope systems – Zeiss collaboration

As the company resolves its way forward with the flexible endomicroscope system, there is plenty to keep the company busy with commercialization of a rigid endomicroscope system which has a variety of product line applications.

In July last year Optiscan signed a collaborative deal with **Carl Zeiss Group** in Germany to explore the development of portable rigid applications of the Optiscan microscope technology. Preclinical studies have been completed successfully under this collaboration delivery good results and the next step is for both companies to complete clinical studies using the technology. The collaboration is apparently progressing well and at a 'frenzied' pace. If the clinical studies show the device works well, it's believed Zeiss will expedite the product launch to market and potentially expand to a second application. Zeiss is a market leader and has the capacity to gain faster acceptance of the technology in specific markets.

Other rigid applications open to Optiscan

The Zeiss collaboration is for an estimated two distinct applications. Other applications available for Optiscan to explore include the *in vivo* detection and immediate treatment of endometriosis. This condition can be difficult to definitively exclude in certain lesions. The ability to conduct real time pathology on the tissue could be very helpful to the surgeon. Optiscan is enrolling 10 patients into an endometriosis study.

Other women's health applications include cervical cancer detection, with trials potentially beginning this year in the US. Ovarian cancer detection may be a major application. This may be dependent on better biomarkers for the disease being developed, however the use of an Optiscan system could be introduced with new procedures that might accompany the advancement of accurate biomarker systems.

Another potential use for the technology is in robotic surgery for prostate disease, not only to detect disease but to help the robot navigate through the nerves and muscle to access the prostate.

Summary

Optiscan is capitalised at $19 million with $4.5 million in cash at the end of last year. It has been a gruelling road to commercialisation of the Optiscan technology. Although significant achievements have been made, uncertainty still remains with this company. However, we suspect that when one application finds favour with users, it's likely that success will be enjoyed on a number of fronts with this unique technology.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (14 March 2008)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	0.95	1.025	February 2008
Patrys	$0.34	$0.50	December 2007
NeuroDiscovery	$0.15	$0.16	December 2007
Bionomics	$0.35	$0.42	December 2007
Cogstate	$0.12	$0.13	November 2007
Ventracor	$0.36	$0.625	October 2007
Sirtex Medical	$3.12	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.37	$0.66	September 2007
Starpharma Holdings	$0.34	$0.37	August 2007
Pharmaxis	$2.37	$3.15	August 2007
Universal Biosensors	$0.95	$1.23	June 2007
Biota Holdings	$1.27	$1.55	March 2007
Tissue Therapies	$0.16	$0.58	February 2007
Probiotec	$1.22	$1.12	February 2007
Phylogica	$0.12	$0.42	January 2007
Peplin Inc	$0.53	$0.83	January 2007
Arana Therapeutics	$0.90	$1.31	October 2006
Chemgenex Pharma.	$0.75	$0.38	June 2006
Cytopia	$0.37	$0.46	June 2005
Optiscan Imaging	$0.19	$0.35	March 2005
Acrux	$0.86	$0.83	November 2004
Alchemia	$0.38	$0.67	May 2004

Portfolio Changes – 14 Mar 2008

IN:

No changes

OUT:

No changes

Positions Vacant

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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