

In this edition...

A surge in volume sales in the US for Sirtex Medical's liver cancer product Sir-Spheres may see the company deliver a record volume sales result for FY2012, despite weakness continuing in Europe. Sirtex is a standout stock and well suited to the patient long term investor.

Calzada, through its subsidiary company Polynovo's joint venture with an Adelaide burns surgeon, is finally entering the all important clinical proof of concept stage for its wound and burn treatment products. By the end of the year clinical data should be available to confirm the efficacy of the PolyNovo's polymer technology for treating burns and other wounds.

A clinical trial slowdown for its partnered product, Urocidin, has caused Bioniche to tighten its cash spend and obtain debt finance.

The Editors

Companies Covered: BNC, CZD, SRX

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May '11)	45.4%
Year 11 now commenced	-20.0%
Cumulative Gain	236%
Av. annual gain (10 yrs)	21.4%

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

David Blake
Ph: (03) 9326 5382
Email: blake@bioshares.com.au

Mark Pachacz
Ph: (03) 9348 9317
Email: pachacz@bioshares.com.au

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Bioshares

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

Extract from *Bioshares* –

Big Year for Calzada Ahead with Two Clinical Trials Underway

Calzada (CZD: 5.7 cents), through its subsidiary **Polynovo Biomaterials**, has commenced its second clinical trial this year with its biodegradable wound healing technology. It should be a significant year for the company with the company's products now being investigated in the clinical setting after many years of development. Results from the two trials are expected by year's end.

The Polynovo technology, called NovoSorb, uses a biodegradable form of polyurethane. It has many potential medical applications, including use as a bone void filler, fracture fixation and even as a drug delivery vehicle. The leading application is for use in the treatment of burns and other skin wounds.

The skin wound application is being commercialised through a joint venture with Adelaide-based burns and plastic surgeon, John Greenwood. Polynovo (Calzada) owns 80% of the joint venture, called **NovoSkin Pty Ltd**. Greenwood is particularly important to this program, providing the clinical guidance and expertise for commercialising these products.

For both clinical trials underway, Greenwood is the principal investigator, although will not be the surgeon performing the treatments. Both trials are being conducted at the **Royal Adelaide Hospital**, where Greenwood is the Director of the Adult Burns unit.

There are two commercial phases of the wound application. The first is to deliver a better alternative to Integra (**Integra Life Sciences**), the current gold standard in treating full thickness wounds. This first stage of treatment involves sealing the exposed full thickness wound with a 'temporising' matrix. The aim is to immediately seal the wound and then to allow the split skin graft (taken from another part of the body) to be applied to complete treatment of the wound.

There are three reasons to properly seal the wound. The first is to prevent infection in the wound. The second is to prevent water evaporation from the site. And the third is to prevent contraction of the wound area. From an evolutionary perspective, the body naturally seeks to close the wound. If the wound is not sealed, the body contracts to achieve closure, which is the main visual distortion of the skin synonymous with burn wounds. This distortion is devastating on the face. From a functional perspective, rapid wound closure is particularly important around joints, where the body bends to achieve closure, thereby limiting joint movement when the wound has healed.

Preclinical Trial Result

A preclinical study was completed and published recently comparing Integra with Novosorb BTM. The study involved treatment of wounds in six pigs and was conducted by Greenwood and his team. Three of the key parameters that were measured were infec-

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tion levels, the degree of contraction of the wound, and the level of scarring.

On all three measures, Novosorb BTM clearly outperformed Integra. With Novosorb BTM, there were no incidents of infection. With Integra, five of the six wounds became infected. A point to note was that a particular dressing was used on all wounds and this type of dressing is not generally used in the clinic with Integra. This could have contributed to the high infection rates with Integra.

The high infection rates with Integra may also have contributed to the increased contraction seen with Integra. With the sealed Novosorb BTM there was only a 23% contraction in the wound area, compared to a 55% contraction with Integra. The more contraction, the more cosmetic distortion of the skin.

With respect to scarring, with Novosorb BTM the scarring was very thin, between 0.16mm-1.0mm thick. Integra treated wounds left a thick scarring level, in some cases being up to 8.0mm.

On the downside with Novosorb BTM, in some of the wounds (in the tail), the wound sites had become disrupted, requiring repair and reattachment. There were also some issues with bonding the sealant to the BTM scaffold which the study report indicated the group was working on improving.

First Human Clinical Study – Vacuum Assisted Closure

The first clinical study with NovoSorb started in February this year. This trial will investigate the Novosorb polyurethane foam for use in a particular wound treatment, called vacuum assisted closure of pressure sores to deliver topical negative pressure.

This treatment method received FDA approval in 1995. It uses a vacuum pump over the pressure sore to remove wound fluid and waste material from the wound. The problem with this therapy is that in a small number of cases, the dressing material remains attached to the wound, causing bleeding or requiring surgery to remove the dressings. Between 2007 – 2011, the FDA received reports of 12 deaths and 174 injuries from the therapy and has issued a warning about the complications associated with this treatment.

Calzada believes its Novosorb material has better biocompatibility than current products on the market. Presumably, an advantage of the product should also be that if some of the polymer does remain in the wound, then it will eventually dissolve in the skin, within three to six months. The consumables market in this area is worth over US\$400 million a year.

This trial will recruit 20 patients, 10 in the active arm using the Calzada product and 10 in the control using a commercially available product. The trial is designed to show that the Calzada product is not inferior to an existing product.

For Calzada, the trial will also provide early information on biocompatibility of its polymer. And commercially, it's a faster way to get its first product to market, potentially within the next two

years. At the start of this month, four patients had been recruited into the trial.

Second Trial – Free Flap Procedure

The second trial at the Royal Adelaide Hospital started this month. It will enrol 10 patients who are scheduled to undergo a 'free flap' procedure, where a full section of the tissue is removed, often from the forearm, to be used to rebuild another part of the body that has been removed due to injury or illness. Free flaps can be rolled up to make a section of the oesophagus or repair a section of the mouth. This controlled trial will be easier to coordinate than an emergency burns wound.

The NovoSorb biodegradable temporising matrix (BTM) that will be evaluated will include a sealing membrane on the top layer which will be removed just prior to a skin graft being placed as a final treatment of the wound.

This is a key trial for Calzada. What the company will be looking at is how easily the sealing membrane can be removed from the NovoSorb BTM, and how much the wound contracts.

From this trial, the company will be looking at the rate and quality of the integration of the product into the skin. A bad result from this trial would be significant contraction of the wound, or a negative reaction from the polymer material from patients.

Third Trial

The company is also looking to conduct a third trial, in 10-20 patients with burn wounds, towards the end of this year. This could also be followed with treatment of larger burn wounds.

Stages of Commercialisation

The first stage of the skin replacement product is to commercialise the Novosorb BTM product, which acts as a skin scaffold for full degree burns or wounds. A split skin graft would be used in the weeks following application of the Novosorb BTM.

A longer term project is the development of a composite skin product that could be used alone or with the Novosorb BTM skin scaffold. This would replace the use of skin grafting. It would take a small sample of skin, culturing (growing) that skin sample and sealing it into the BTM polymer scaffold. This would thereby provide a dermis and epidermis for full thickness wounds.

At the earliest, the company could have two of its products on the market within two years.

Competition

The leading product on the market is called the Integra Dermal Regeneration Matrix, made by Integra Life Sciences Corporation. Estimated sales of the product are around \$100 million a year. This product has its limitations. These include its high cost. It is a three dimensional wet sponge made from bovine collagen fibres and shark cartilage. It also needs to be stored refrigerated.

By comparison, the NovoSorb BTM is produced as a foam and

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being a polymer, its cost of manufacture is substantially lower. This also makes the product lighter, with less material to be dissolved by the body. The product is not heat sensitive, so does not need refrigeration. This makes the product suitable for use by the military and also in second and third world countries.

The high cost of Integra limits its applications to more essential burns wounds. The incidence of infection with Integra is also an issue. The product is also very delicate, like a fibrous wet sponge and the product can be destroyed if the patient rolls over and lies on their wound.

Integra includes a dermal scaffold together with a silicon epidermis to seal the wound. Calzada's NovoSorb BTM is similar, including a dermal scaffold with a sealant layer. Other products on the market include Alloderm, which does not seal the wound, and Matriderm, which is a high cost product that also does not seal the wound.

With all of these products, a split skin graft is still required. However closing the wound whilst the patient is being stabilised and before the skin graft can be applied reduces the occurrence of infection. Both Integra and Novosorb BTM are absorbed by the body over time.

Commercialisation Model

The commercialisation plan for the NovoSorb products is based on Calzada partnering the products after completion of clinical studies, but retaining manufacturing.

AOD9604 Asset

Calzada also has the peptide AOD9604 which had previously been trialed as a treatment for obesity. It has licensed the application of its use to Phosphagenics as a cosmetic for the reduction of cellulite. It is continuing to investigate low cost options as to how any potential value could still be unlocked from this compound.

Summary

After 12 years of technology development, Calzada now has two products in clinical evaluation. Results from both of those studies are due by year's end, setting up some major milestones, with results from the second clinical trial to be more significant. With the clinical stewardship of burns and plastic surgeon, John Greenwood, commercialisation of the lead application of the technology is being well guided.

Through John Greenwood, Calzada can move products rapidly through the clinical proof of concept stage. The company can also move to clinical proof of concept at little cost. The first trial is expected to cost the company \$150,000, and the second trial only \$50,000.

Calzada is capitalised at \$20 million. At the end of last year the company had cash (and short term investments) of \$5.6 million. The company has a low spend rate of around \$2.1 million a year.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

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

Sell

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