

In this edition...

This week we focus on three well positioned companies that biotech investors can do well to monitor. Arana, an antibody drug developer, is proving more and more it is a well positioned company in one of the the hottest areas in the world of drug development. Biota, has, we argue developed a sustainable model for drug development and, despite its litigation blow-up with GSK, has a viable future. Cellestis is a profitable company that looks to be set for a year of strong growth in sales and profits, thanks to non-cyclical, recession proof demand for TB testing and the publication of 230 scientific papers.

Companies covered: AAH, BTA, CST

	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 - current)	-39.0%
Cumulative Gain	26%
Av Annual Gain (7 yrs)	17.8%

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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* –

Biota Holdings – A Sustainable Business Established

Investors in Biota Holdings (BTA: 37.5 cents) have experienced a disappointing year following the capitulation by the company's board of litigation initiated against **GlaxoSmithKline** for failure to properly market the influenza drug Relenza.

Biota ended up settling with GSK, for a payment from the pharmaceutical giant of \$20 million, with \$7.5 million of that having been paid out, presumably to its lawyers in the first quarter of this financial year. The result was disappointing, given the company had previously received but rejected a settlement offer from GSK in 2006, valued by the Biota in the order of \$80 million. There were two previous offers, also rejected, of \$11 million at the commencement of the litigation and one in 2005 for \$25 million.

On the positive side, Biota has now become a sustainable true biotech business. The company is generating sufficient revenue from Relenza royalties and from product development collaboration that should see the company run now a near cash flow neutral business.

The company aims to create value through drug discovery and development but mitigates risk through a portfolio of development programs that are partnered early with collaborators.

At the end of the first quarter of this financial year, the company had an estimated \$70 million in cash assets following the final litigation receipts and expenses. We estimate the company has a further \$80 million in revenue from Relenza royalties to flow over the next five years, with its patent expiring on 26 July 2013 in the US according to a Wilson HTM report, which includes a 633 day patent extension.

The company now has five main assets, those being Relenza and four drug development programs. These are a long acting neuraminidase inhibitor (LANI) program which is partnered with **Daiichi Sankyo**, Japan's third largest pharmaceutical firm, and is ready to move into Phase III clinical testing as a once a week flu drug; a Phase I RSV (respiratory syncytial virus) program which has been partnered with **MedImmune** (now part of **AstraZeneca**); a preclinical hepatitis C program that has been partnered with **Boehringer Ingelheim**; and a Phase IIa human rhinovirus (common cold) program which the company is seeking to partner.

Relenza Royalties

The seasonal flu drug market is now almost entirely dominated by the competing drug Tamiflu, sold by **Roche**. It is now a US\$600 million a year market. GSK is focusing its efforts on selling Relenza into the government stockpiling market. This market is made up of governments completing, increasing, and replenishing of stockpiles, which have a five year shelf life.

Cont'd over

Biota cont'd

Biota estimates the replenishment market is worth around US\$1 billion a year, with Relenza gaining between 15%-20% of that market. As of March this year, the US stockpile had reached 50 million courses of flu drugs from a target of 81 million courses. These stockpile levels are arguably still very low and would provide protection to a small percentage of the population over an extended period.

LANI Program

Biota's LANI program, which could be described as a next generation longer lasting version of Relenza, is progressing well. The LANI program involves the development of a prodrug of a Relenza active compound (zanamavir) that is taken into the lungs and converted over time into the active neuraminidase inhibitor, which allows the drug to be effective over a longer period (at least one week). The lead compound is called CS-8958.

A Phase II study was conducted by Daiichi Sankyo in several hundred patients who naturally acquired a flu infection. The study compared a once only dose of CS-8958 against Tamiflu taken twice a day over five days. It found the two treatments to be statistically indistinguishable. In the laboratory, the drug candidate was found to be effective against influenza A and B and against the pandemic strain, H5N1.

Last week Biota and Daiichi Sankyo announced that the Phase III study will start in Asia (Japan, Taiwan, Hong Kong and Korea) in the current flu season. Daiichi Sankyo will conduct the trial and will also run a Phase II/III trial with CS-8958 in Japan in children less than nine years old. Daiichi Sankyo will pay for the Asian trials and Biota will be entitled to a royalty from sales.

For areas outside of Asia, it is likely that a development partner will be secured to run the Phase III study/studies, and market the drug. Depending on the size of the Asian trials and the results, it's possible only one or two small western supplementary trials may be required to get the drug approved. Biota has US\$2.5 million available in NIH funding to run Phase I studies with the compound in western studies.

Depending on the severity of the current Asian flu season, if sufficient numbers of patients who have contracted the virus are enrolled, then the company may be in a position to file for approval in Asia in 2009 if the results are positive. Once again, the control arm will be Tamiflu taken twice daily for five days.

The LANI program has the potential to become a valuable asset for Biota and Daiichi Sankyo. Daiichi Sankyo has the rights to the drug in Asia, from which Biota will receive a royalty, and both companies will equally share the rights outside of those Asian markets. The seasonal Japanese flu market alone is worth US\$100 million a year with Tamiflu having secured most of that market. Tamiflu has shown to have side effects in adolescents and a once-a-week version would be very competitive against Tamiflu if shown to be as effective.

Stock holding advantage

If CS-8958 is shown to be as effective as the current flu drugs Relenza and Tamiflu, there would be considerable advantages

gained from stockpiling a drug that only needs to be taken once a week versus twice daily, both from a storage perspective but also from compliance and distribution of the drug during any possible pandemic.

One possibility for the companies would be to partner the drug for seasonal use but maintain rights to sell the drug for government stockpiling. There is an extremely narrow distribution path for stockpiling that could be managed by even a small company and out-source manufacturing similar to the major pharmaceutical companies. Biota has indicated that its role as a biotech company is not to be involved with later stage drug development or sale and distribution.

RSV Program

Another of the very attractive assets that Biota is developing is its respiratory syncytial virus (RSV) infection therapeutic. Biota's scientists first started work on this program in 1998/1999, when there was no blockbuster market for this viral infection. In 1998 MedImmune released its drug Synagis, a monoclonal antibody used as a prophylactic for RSV infection in at risk infants. In 1999, that drug achieved sales of US\$352 million. (Synagis replaced MedImmune's Respigam, a polyclonal antibody drug approved in the US in 1996).

Sales of Synagis have increased steadily over the last decade. Synagis remains the main drug for RSV and last year generated sales of US\$1.15 billion. Ribavirin is used for treatment of RSV in high risk cases. It is a dangerous drug to handle, being an aerosol that is teratogenicity, or its ability to cause birth defects in pregnant women.

The commercial success of Synagis has encouraged several groups to become active in the RSV space. Biota, because of its interest in flu virus research and because RSV infection is often mistaken for influenza infection, has been early into RSV research and development. With MedImmune, it is now placed as one of only two other companies with major clinical programs underway in RSV (according to an earlier Wilson HTM report), the others being **Alnylam** with an RNAi approach, and **Novartis/Arrow Therapeutics**. Both Novartis/Arrow Therapeutics and Biota/MedImmune are developing fusion protein inhibitors, the same target as Synagis. AstraZeneca/MedImmune has also developed the antibody motavizumab (MEDI-524), for which it has filed a NDA with the FDA and a marketing authorization application is expected to be filed with the EMEA in 2009 H1.

Biota's program is progressing particularly well. The drug candidate has shown excellent potency and looks to be very competitive against other drugs in development. AstraZeneca/MedImmune appears to be very committed to the collaboration. Biota had received US\$8 million in upfront and milestone payments between December 2005 and July 2007, then in August this year, AstraZeneca paid an additional US\$3.5 million to expand the license deals to parts of Asia not previously covered in the agreement. This brings the total to US\$11.5 million received to date from AstraZeneca/MedImmune, of which US\$8.5 approximately covers Biota's initial investment in the program.

Biota cont'd

The Phase I trial is being conducted by Biota. It's expected the program will move into Phase II studies in late 2009. At some point during Phase II development, AstraZeneca will take control of the program. Biota continues to work on second and third tier back-up compounds that will be used as either a follow-on drug should the first drug be successful, or as a back-up should the lead fall over. This is a strategy adopted by many drug developers.

Another appealing aspect of the program is that there is an extremely strong patent position around the program, with patents going out to 2024 with back-up compounds out to 2028.

Even though both Synagis and Biota's compound hit the same target, it is expected the Biota/AstraZeneca drug candidate will be used as a therapeutic. Synagis does not work well as a therapeutic for which the reasons are not well understood. It is used as a prophylactic treatment.

There is a very large market for children who are not eligible for Synagis. There is a high RSV disease burden in the elderly and untreated RSV infection is almost fatal in organ transplant recipients because of their immuno-compromised position from transplant rejection therapy. **AstraZeneca, Novartis, Johnson & Johnson, Bristol Myers-Squibb, Merck** and **GSK** all have RSV programs underway suggesting this is a major market opportunity for drug developers that remains poorly served.

Hepatitis C Program

The Hepatitis C program was licensed/partnered with Boehringer Ingelheim in November 2006. Biota received a US\$3 million technology access fee. The program is still in preclinical development. Boehringer Ingelheim is funding development costs.

Rhinovirus Program

The human rhinovirus program has moved into Phase IIa studies. The company will seek to complete the current study before finding a partner to finish development. The Phase IIa study will test the drug as a prophylactic in 200 health volunteers challenged with the virus.

Summary

The focus on Biota's failed litigation against GSK and the continuing Relenza stream has resulted in the progress of Biota's other development programs progressing somewhat unnoticed. The LANI and RSV programs will be well worth monitoring over the next 18 months and have the potential to become valuable assets. The RSV program alone has already paid for itself with US\$11.5 million received from AstraZeneca/MedImmune.

The biotech model is proving successful with Biota. Over the next five years, the company would like to double the number of programs it is working on, partnering early with partners funding much of the clinical development costs.

Biota has an estimated \$70 million in cash. It is capitalised at \$66 million with up to \$80 million in further royalties and four main programs, three of which are in clinical stages of development and three of which have been partnered or are in co-development. At current prices, Biota Holdings is yet another of a number of very appealing investment options available as a result of the turbulent market conditions.

Bioshares recommendation: **Speculative Buy Class A**

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.

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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