Pharmaceutical and Biomed Smart Working Hub

Southern Highlands NSW

"Keeping our innovation local"

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September 2014

Keeping our innovation local

Pharmaceutical and Biomed Smart Working Hub

Southern Highlands NSW

"At this moment, in a laboratory or research centre, one of the 92,000 researchers in this country is on the cusp of a breakthrough. If leveraged in the right way, that research could solve an industry problem, create new jobs and ultimately help business prosper." NSWBC Autumn 2014

Concept:

- **That new medicines and healthcare innovations designed in Australia are successfully made and marketed globally from Australia**

Executive Summary

It is proposed that a Pharmaceutical and Biomed Smart Working Hub be established in the Southern Highlands.

Traditional manufacturing in Australia is dying. We cannot compete with manufacturing in countries where labour and on costs are far cheaper and high volumes are required. So, to remain competitive as a nation, there is a compelling reason to develop industries where we can provide the brain power to get started, and where economically viable, to also continue the end-to-end manufacturing of the product.

Pharma Biotech is an ideal industry for Australia and the Southern Highlands is perfectly situated to host a Pharmaceutical and Biomed Smart Working Hub to further develop this industry.

This proposal provides a compelling case to take the next steps in developing such a Hub.

The proposal outlines:

- Challenges facing Australian industry and the three reasons – economy, people, innovation – and how these can be addressed in the Highlands with the development of a Pharmaceutical and Biomed Smart Working Hub

- How similar Pharmaceutical and Biomed Smart Working Hubs have been developed successfully overseas and what the issues are for Australia and the Highlands

- Proposes a methodology for both undertaking a full Development Risk Assessment and producing a Concept Design for the development of a Pharmaceutical and Biomed Smart Working Hub in the Southern Highlands

1. The current challenges that need to be addressed; "the Economy", "the People", "our Innovation"

1.1 The Economy

Traditional manufacturing in Australia is dying; a classic case is the recent demise of the car industry. If Australia is to remain competitive then we must turn our attention, skills and resources to "smart manufacturing" – where brain power is the key attribute rather than brawn. Historically, Australia has been a world leader in innovation in many fields (e.g. telecommunications, agricultural sciences, building technologies), and particularly in medicine, for example Cochlear (ear cochlear implants), vaccines (human papilloma virus vaccine, avian vaccines).

We cannot compete with manufacturing in countries where labour and on costs are far cheaper and high volumes are required. So, to remain competitive as a nation, there is a compelling reason to develop industries where we can provide the brain power to get started, and where economically viable, to also continue the end-to-end manufacturing of the product.

Pharmaceutical and biotech medicine development and production are the ideal vehicles to achieve this economic aim.

1.2 The People

From a people perspective, in the developed world there is a world-wide aging of the population. This is particular pertinent to Australia with its high standard of living where residents are now expected to live well into their late 80s and many into their 90s. Australia will therefore need an increasing supply of medicines to cater for this aging population. We should provide these locally made – not imported (and in some cases generically manufactured with dubious raw materials, formulations and problematic manufacturing processes).

1.3 Our Innovation

As the New South Wales Business Chamber quoted (Autumn 2014) there are some 92,000 researchers currently working in Australia on the cusp of a breakthrough. The outcome of many of these "breakthrough" discoveries will be lost to Australian manufacturing as the idea or patent is often snapped up early by an overseas pharmaceutical company. We need to have facilities in Australia where many of these researchers can work hand in hand with people, organisations, and governments from 'end to end' right along the production process.

Let's keep Australian innovation in Australia.

There is no logical reason why we should sell-off our innovation. The patents, intellectual property and value must be retained in Australia and the benefits go to Australian business.

We can do this successfully, reliably and cost effectively; all the elements are here as much as they are in any other country, and in fact, more so. In particular the Southern Highlands is well situated and placed to be a hub for such development.

1.4 What part can Ramsay Health Care play?

As Ramsay Health Care is committed to being a leading provider of health care services through delivering high quality outcomes for patients and ensuring long term profitability, supporting and sponsoring the development of a Pharmaceutical and Biomed Smart Working Hub in the Southern Highlands (the Hub) would be an ideal way to further progress and achieve these aims.

It's evident that Ramsay Health Care is an extremely successful organisation both in providing excellent health care services (in Australia and internationally) and in terms of profitability. We understand that the organisation now has a need to re-invest some of its resources in areas of health care that will make a real difference to its patients and potential patients. Applying some of these resources to the development of a Pharmaceutical and Biomed Smart Working Hub in the Southern Highlands would fill this need.

The remainder of this proposal shows how this can be achieved.

2. What's the current situation with Pharmaceuticals and Biomed in Australia? Do we have overseas experience to draw on?

Internationally, Contract Manufacturing Organisations (CMOs) are becoming more numerous. CMOs whilst perhaps originally having their own products, are organisations that now focus more on manufacturing products for other companies. A classic example in the electronics industry is Foxcom (Taiwan) who manufacture Blackberry, Ipad, Iphone, Kindle, Playstation, Xbox One and Wii U – a stunningly successful organisation. (See Appendix A for further Examples of Biotech Hubs)

For healthcare and medicines there are CMOs such as Lonza Switzerland; Baxter's Cook laboratories in the USA for ethical pharmaceutical product development, and in Australia there is LIPA Industries for herbal supplements and food supplements.

The Southern Highlands Hub would ultimately work in a similar manner to a CMO, where products are researched, developed and produced for both the local and international markets. (See Appendix B for the full Rationale for Developing a Bio-Tech Hub)

2.1 For Efficient and Profitable Production, Effective Plant Design is Key

For example in Australia, Contract Pharmaceutical Services Australia Pty Ltd have developed a $17.5 million multi-use, purpose built facility at Eden Park, North Ryde.

The facility comprises 2,800 square metres of production space, 600 square metres of office space and car parking accommodation for 270 cars over two basement levels. The facility also has a further 4,800 square metres of additional space for another tenant.

There are now a number of such hubs being developed around the world from which we can draw experience to develop a world class facility in the Highlands. Our key differentiating feature would be the end-to-end research, design, development, production and marketing of various products as opposed to many others (e.g. Contract Pharmaceutical Services Australia Pty Ltd) who only take already developed products to market.

2.2 From our research, the one contributing factor necessary for success of any Hub is to have one dedicated product line already committed and supported by a commercial sponsor

It's evident, that to start entirely from scratch with a group of scientists working through R&D to develop products in such a Hub has limited success. However, where there is one potential product that has the backing of a sponsor, this tends to act like "seed money" and a model for other products to be developed in the same facility. It also provides immediate purpose to the Hub. (See Appendix C for a list of Potential Clients/Partner Companies)

3. A Proposed Solution to some of the Economic, People and Innovation challenges facing us in Australia and how Ramsay Health Care can assist

It is proposed that a Pharmaceutical and Biomed Smart Working Hub be established in the Southern Highlands.

3.1 Design Proposal:

The aim is to develop robust manufacturing of different materials for clinical trials and early stage commercial use (and ultimately in some cases, full-scale production). This would involve defining the scope of technologies based on 10 examples with a mix of fixed (stainless steel) and flexible systems. The facility (Hub) must therefore have the capability for end to end manufacture from active substances (starting materials) to formulated product which is packaged and tested (tablets, vials, devices).

Such a facility must be designed to:

a. be a Hub for early stage production and proof of concept
b. provide training and development of technologists, engineers and manufacturing sciences
c. provide security, capability and flexibility for multiple 'products'
d. be built to Australian and international standards enabling global reach of products

The Hub must be designed to be flexible and scale-able multi-product with minimum capital investment, reduced utilities (compared to standard facilities) and increased speed for product pipeline compared to traditional facilities.

A modular system with a capacity to run 6 to 10 product processes simultaneously would be ideal. Such a system would be built with a hybrid of fixed (hardwired technology) and flexible (single-use technology). (See Appendix D for Logistics and Design Requirements)

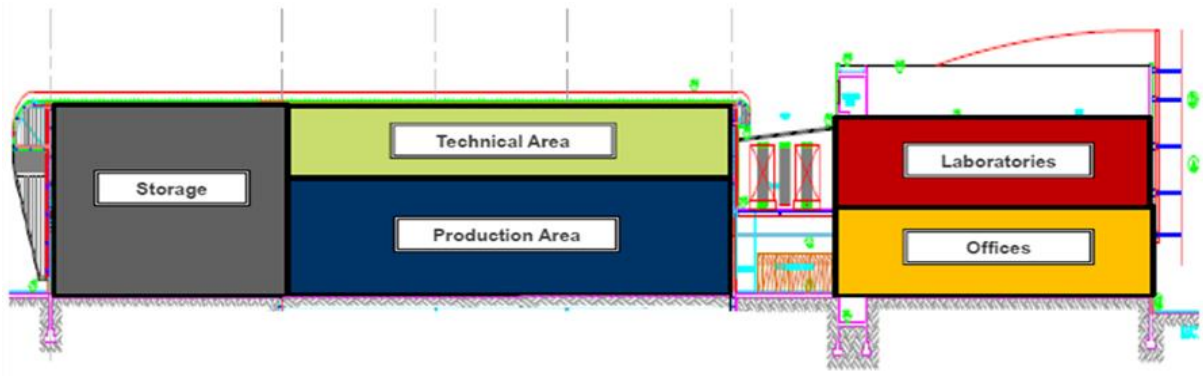
3.2 The objectives of such a Hub are to:

- Provide an incubator for Australian scientists, innovators and researchers
- Provide a confidential setting to bring innovative ideas to the early manufacturing stages
- Develop a forum for experts to propose pathways to design and realise innovations
- Provide a place where process design facilities are available and process modelling is possible
- Gather technical expertise and technology in one place for small scale and proof of concept development

- Provide technology, equipment and resources for the research and manufacturing development of products
- Provide researchers, manufacturers, financiers and marketers with access to international best practices
- Provide access to experts for patent protection, risk assessment and regulatory pathways
- Engender clinical operations support (design, set-up, management of clinical trials)
- Promote access to the best marketing conceptual expertise
- Provide a place where investors and manufacturers can see what the product does and assess its potential

3.3 What will the Pharmaceutical and Biomed Smart Working Hub look like?

The Hub will be a specifically designed series of buildings to enable researchers, marketers, businesses, investors and potential manufacturers to come together in one place to bring innovative ideas to the initial stages of manufacture. In the past, the manufacture of many Australian inventions and innovations has been lost overseas because of the lack of an ability and or willingness to take the idea through to market.



3.4 The ultimate outcomes from the Hub will be:

- The manufacture of innovative medicinal and healthcare products in Australia from end-to-end, and/or
- Once developed, the design and licensing of the high-end manufacturing process of these new products

3.5 Why the Southern Highlands?

The Wingecarribee Shire Council is keen to attract "Smart Manufacturing" to the region. Steps will be taken to ensure the smooth planning, development approvals and appropriate resource support should Ramsay Health Care decide to progress with the development of the Pharmaceutical and Biomed Smart Working Hub.

From a logistical perspective, the Southern Highlands:

- Is easily accessible to both Sydney and Canberra; located on an intercity train line; has dedicated rail freight access to Illawarra Harbour; connected by the Hume Highway and 75 minutes to Mascot Airport (and even closer to the new Badgerys's Creek airport)
- Has many of the "Brains Trust" (innovators, researchers, technologists and business people) already living here
- Is where ethical business practices are the norm
- Has the internationally recognised Garvan Institute already established in Moss Vale
- Has at least one existing property (with some appropriate buildings) and other potential sites ready and waiting to be developed
- Has a very supportive business community that encourages new and innovative developments in the region
- Has a lifestyle and ambiance that creates an alluring locale that encourages new settlers to live and work

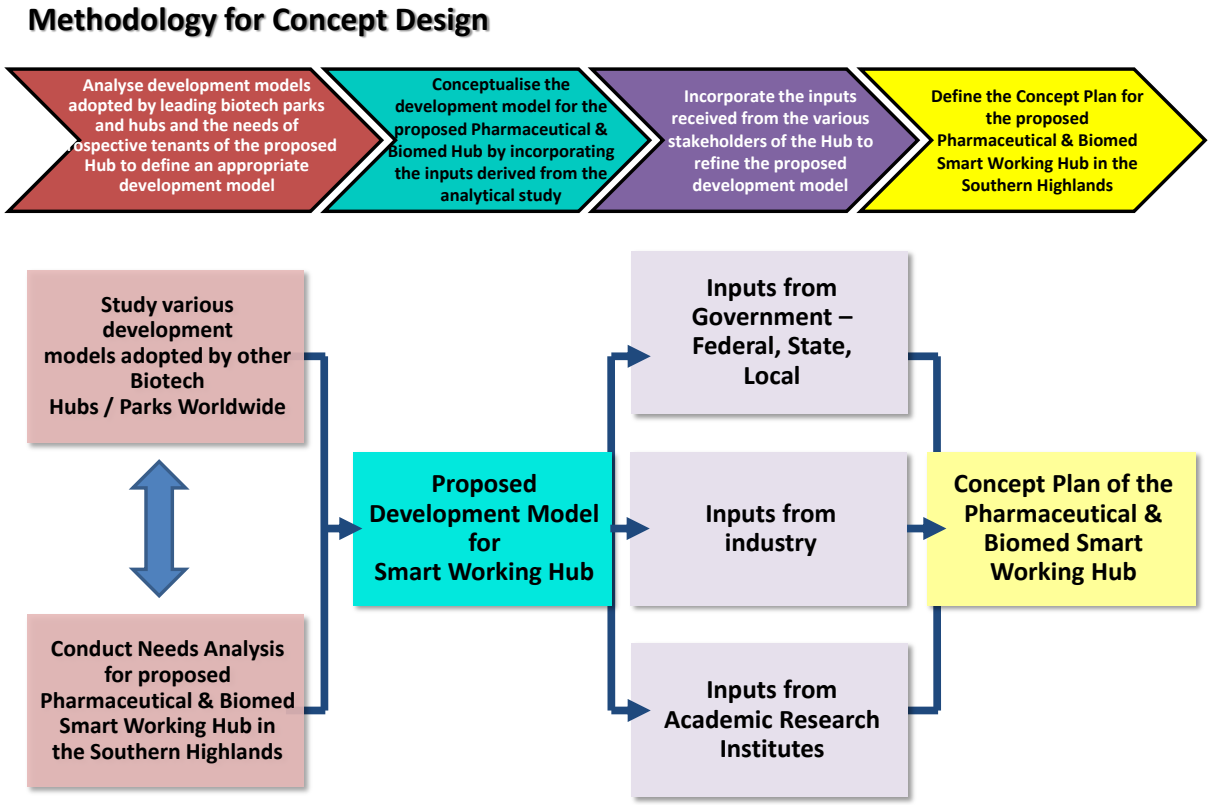
4. How will the Hub be developed?

Once interest in progressing such a Hub is obtained, the next step would be to draw up a consortium of interested parties and other key stakeholders who would need to be influenced and ultimately committed to the Hub.

Such a consortium could be led by Ramsay Health Care Pty Limited and may include:

- Specially selected scientists
- Architects
- Engineers
- Economists
- Business Development Specialists

The consortium may be guided by the following Concept Design Methodology:



(See Appendix E for a larger version of this Methodology Outline)

Note: As mentioned earlier, it is essential to have one product concept ready (at proof of concept stage) to be developed through the process. So an essential task of the consortium will be to source such a product. (Appendix B provides a list of Possible Clients/Partners)

5. The Investment

The solution to address economic, people and innovation challenges that is recommended in this proposal is that Ramsay Health Care provide an initial estimate of say $M18 to set up the facility (perhaps as a mix of money and land). This figure includes land, building and equipment. Ongoing running costs could well be approximately $M40 pa. These figures are based on the development of similar facilities both here and internationally and would obviously need to be fully scoped as part of the initial research for the Hub.

It is projected that the Hub will become profitable within five years of operation. From experience overseas, the eventual profits from the investment rise exponentially year on year once the initial capital has been repaid.

The point of this proposal to Ramsay Health Care Pty Limited, is to gauge interest and the level of support for the development of such a Hub in the Highlands. It is recognised that a full cost/benefit analysis will need to be carried out and detailed business, financial and development plans produced before the project can proceed.

However, at this early stage, a guide to the investment and time lines may be gained from some international experiences.

For example, the successful Penang Biotech Park in Malaysia which concentrates on providing services to bio pharma and pharmaceutical companies by supporting the development of biologic drugs through pre-clinical, phase 1 and phase 2. It plays host to two new biotech companies. The two companies are part of a $32m investment made by Springhill Bioventures from which two facilities have been constructed.

- These two new plants started full-scale operations in 2008 following outfitting and validation; construction of the buildings was completed in October 2006. The facilities are managed by Alpha Biologics (set up in 2003 with the aid of the Penang Development Corporation and Malaysian Industrial Development Authority), based in Malaysia and the UK, main investors; SpringHill BioVentures, Asiaprise Biotech and Pequot; and Progenix.
- Both of the plants provide training for graduates in the biotech field. However Alpha Biologics concentrates on the production of pre-commercial scale pre-clinical trial drugs (completed in June 2007 and now employs around 25 staff) and Progenix specialises in preclinical R&D work (completed in March 2007).
- The construction of the buildings was completed in October 2006 and the cleanroom installation for Alpha Biologics began in November 2006. The plant was commissioned in April 2010. The multi-product Alpha facility operates stirred tank reaction vessels, ranging from 10l to 500l, and also uses perfusion technology - this results in a 20 times increase in productivity per reaction vessel.
- In November 2006 Alpha Biologics announced further investment of $3m from US-based Pequot Capital Management for the construction of the new 5,000m² facility in the Penang Biotech Park. The facility cost a total of $18m to construct and outfit.

6. The Next Steps

Once Ramsay Healthcare supports this concept in principal, the next step would be to commission a full Risk Assessment (including a Needs Analysis), e.g. conducted by one of the major consultancies specialising in such proposals.

Such an assessment would be guided by Concept Design Methodology mentioned previously. The consultants would be briefed to develop an initial Concept Plan for the Hub. Logical research steps will include:

1. Study various development models adopted by other Biotech Hubs / Parks worldwide
2. Conduct a Needs Analysis for proposed Pharmaceutical & Biomed Smart Working Hub in the Southern Highlands
3. Conceptualise the Development Model for the Hub
4. Obtain expressions of interest from potential stakeholders – Federal, State, Local Government; Industry and Academic Institutions
5. Define the Concept Plan for the Hub (to also include, staffing, management, ownership and so on)
6. Finally, complete a full cost/benefit analysis of the development of the Hub

Dependent on the positive outcome of the Risk Assessment, a brief would be developed for the purchase/acquisition of land, construction of buildings, staffing and so on.

Appendix A:
Examples of Recently Developed Biotech Parks

MALAYSIA - Penang Biotech Park

As mentioned the body of this proposal, Penang Biotech Park is situated in the Bukit Minyak region of Malaysia in Penang (north-western coast of Peninsular Malaysia) and is playing host to two new biotech companies. The two companies are part of a $32m investment made by Springhill Bioventures from which two facilities have been constructed.

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Alpha Biologics also develops stable cell lines and Master and Manufacturing Working Cell Banks prior to the start of cGMP manufacture. There is also a cell line storage services provided so that repeat manufacture of drugs can occur with little delay. Both upstream process development and downstream process (purification) development at the Penang facility.

Finances

In November 2006 Alpha Biologics announced further investment of $3m from US-based Pequot Capital Management for the construction of the new 5,000m² facility in the Penang Biotech Park. The facility cost a total of $18m to construct and outfit.

Alpha Biologics was set up in 2003 with the aid of the Penang Development Corporation (PDC) and Malaysian Industrial Development Authority (MIDA). The company will concentrate on providing services to biopharma and pharmaceutical companies by supporting the development of biologic drugs through pre-clinical, phase 1 and phase 2 trials.

"Alpha Biologics in mammalian cell expressed peptide and antibody drugs."

The company specialises in mammalian cell expressed peptide and antibody drugs and the facilities used in full compliance with US Food and Drug Administation and European Medicines Agency requirements.

BRAZIL - Fiocruz Instituto de Tecnologia em Imunobiologicos (Fiocruz)

Fiocruz Instituto de Tecnologia em Imunobiologicos, also known as Instituto Bio-Manguinhos, is a Brazilian Government Institute near Rio de Janeiro, that is completing what will become the largest manufacturing centre for vaccines in Latin America. This was a major construction project with the addition of a total of 15,000 m2 (161,483 ft2) in area added to their existing facilities.

At a total cost of about U.S. $70 million, it will have the capability to process a total of 180 million doses per year of vaccines against yellow fever, smallpox, tuberculosis, typhoid fever, and measles. This list will be extended within the next two years to include DPT (diptheria, pertussus, and tetanus) and a vaccine for meningitis AC.

The project began in 1991 and they expect to be shipping product by 1998. Fiocruz has occupied their present site since the beginning of the century when the original building, known as the Castle, was built on a hill overlooking the site by Fiocruz founder, Oswaldo Cruz. The Castle, which was constructed from materials brought from France, is an elegant building designed and furnished in a style which would be impossible to replicate in our contemporary era. Today it serves as an Administration building and is the logo and symbol for Fiocruz.

Although Fiocruz has been producing vaccines since they first developed a vaccine for yellow fever, their new facility with its two new lyophilization units, each capable of delivering 45 million doses a week, will allow them to expand their operation from a purely domestic market to worldwide distribution of their products.

Quality has been a major consideration in building this facility since Bio-Manguinhos will have to comply with international standards in order to export their products to other countries. With a goal of constructing the new facililty to a standard that would meet FDA specifications in the United States, Bio-Manguinhos Director Joao Quental partnered with design engineer Fernando Avila of COBRAPI and engineering contractor, Celso Carvalho, of Termo Engenharia Ltda. (tel-termo).

State-of-the-art equipment, such as multieffect stills and clean steam generators, was purchased in Europe and three new cleanrooms have been constructed. Some of the more critical piping systems have been constructed from electropolished 316L stainless steel and installed with automatic orbital welding. Orbital welding is the preferred method of joining stainless steel tubing for biopharmaceutical applications in the United States because the smoothness of the orbital weld compared to manual welds makes it easier to maintain the cleanliness and sterility of the piping systems which is critical to the successful production of pharmaceutical products.

AUSTRALIA

- Melbourne, (Digital Harbour at Docklands)
- Macquarie Park, Sydney, NSW (including the Research Park - Macquarie University) Western Australia
- Bentley Technology Park, adjacent to Curtin University of Technology

Research in Australia

Australia is home to numerous world class medical research organisations, including the Garvan Institute, Institute for Molecular BioScience, Menzies Research Institute, John Curtin School of Medical Research, Walter and Eliza Hall Institute of Medical Research (WEHI), Australian Institute of Bioengineering and nanotechnology, Brain Insititute, Diamentina Institute, The Lowy Research Centre, Victor Chang Cardiac Research Institute, Baker Medical Research Institute, The Burnett Centre and South Australian Research & Development Institute. *(reference: Aus Biotech homepage)*

South Australia

The establishment of BioSA in 2001 by the State Government. BioSA was tasked with fostering the growth of the South Australian bioscience industry. Since then, the number of bioscience companies in South Australia has doubled, with 100 bioscience companies now operating, sustaining more than 1,700 full time equivalent jobs, and generating about $280 million in revenue per year.

This has been achieved by providing world-class infrastructure, high-level business advice and expertise, financial assistance, marketing and communication services to support the growth of our thriving bioscience industry.

BioSA also actively promotes and accelerates the commercialisation of R&D in South Australia. Companies producing leading edge technology in areas including pharmaceutical manufacturing (Mayne Pharma, Hospira and BTG), agricultural biotechnology (Australian Centre for Plant Functional Genomics), wine research (Australian Wine Research Institute), medical device development (Ellex Medical) and reproductive health (Repromed), all represent South Australia's success in commercialising technology on the world stage.

South Australia boasts a number of innovation clusters, including the Thebarton Technology Precinct, which is home to one of the largest clusters of medical bioscience clusters in Australia.

More than $70m has been invested on new facilities in the precinct, including the BioSA Business Incubator and four purpose built buildings that are now home to Bionomics, Hospira Adelaide and TGR BioSciences. The 12 hectare precinct has proven to be hugely successful, and now hosts 90 small to medium bioscience and advanced technology companies, including many that started their business from IP originating in the State's research bodies.

The BioSA incubator located in the heart of the Thebarton Technology Precinct, is Australia's first dedicated bioscience incubator. The A$12 million incubator was fully funded by the South Australian Government to facilitate the commercialisation of research and development in South Australia. This purpose-built, state-of-the-art building provides modular office and laboratory space to accommodate early stage bioscience companies.

The 3700m^2 incubator is a thriving high-tech hub, currently home to a diverse mix of early stage bioscience companies operating in sectors such as medical devices, diagnostics and environmental biotechnology.

Queensland

BioPharmaceuticals Australia.

Through its commercial partnership with Patheon Biologics (formerly known as DSM Biologics), BPA aims to deliver tailored contract manufacturing solutions to Australian and international biotherapeutic drug developers. BPA's new, world-class cGMP manufacturing facility offically opened in October 2013.

In an Australian-first, the Brisbane based facility is designed to manufacture biologic drugs for preclinical and clinical trials as well as for market. BPA, supported by the Queensland Government, has significantly enhanced Australia's ability to produce biopharmaceuticals and to take discoveries from bench to clinic. BPA's vision is to bring Australia to the forefront of biopharmaceutical development, scale-up and production by providing quality facilities and expertise in conjunction with our commercial operating partner Patheon Biologics.

BPA's $65 million facility, operated by Patheon Biologics (formerly known as DSM Biologics), is now open for business in Brisbane. BPA now seeks to leverage this investment by supporting and growing the number of mammalian cell based biopharmaceutical drug candidates progressing through the manufacturing stage into clinical trials and eventual commercial supply.

BPA has established the BDF as a pilot program to support access to the new BPA facility, with specific focus given to Australian research and not-for-profit organisations. A BDF grant will allow financially constrained entities with biodrug prospects to accelerate their commercial translation by co-funding access to pivotal development services.

Victoria

CSL: Leading-edge science at the core of $250 million expansion to drive long-term growth in promising bleeding disorders portfolio

• CSL Behring to commercialize therapies produced in part at the facility, pending required approvals

• Opening taking place in advance of World Federation of Hemophilia 2014 Congress in Melbourne, Australia

CSL Limited (ASX:CSL), parent company of CSL Behring which is based in King of Prussia, PA, today opened the CSL Behring Biotechnology Manufacturing Facility in Melbourne, Australia. The new facility, located adjacent to the site's manufacturing plant for plasma products, is the centerpiece of CSL's $250 million expansion at its Broadmeadows site and will play an increasingly important role in the company's global operations, particularly in the late-stage development of new types of hemophilia products. It is one of the largest and most advanced facilities of its kind in the world and will produce novel recombinant therapies on a large scale for international clinical trials.

"This world-class facility is key to the ongoing success of our global R&D strategy and reflects our commitment to providing better treatment options for people who are managing certain bleeding disorders and other life-threatening conditions," said CSL Chief Executive Officer, Paul Perreault.

The company's recombinant factor development programs, which comprise the AFFINITY trial and the PROLONG trial for the study of therapies to treat hemophilia A and B, respectively, are central to its long-term growth plans. Several candidates in these trials are showing promise, including rVIII-SingleChain, rIX-FP, and rVIIa-FP.

NSW

Australia Contract Pharmaceutical Services Australia Pty Ltd have developed a $17.5 million multi-use, purpose built facility at Eden Park, North Ryde. The facility comprises 2,800 square meters of production space, 600 square meters of office space and car parking accommodation for 270 cars over two basement levels. The facility also has a further 4,800 square meters of additional space for another tenant

As described in the body of this proposal, Architectus has designed a $17.5 million multi-use, purpose built facility for Contract Pharmaceutical Services Australia Pty Ltd at Eden Park, North Ryde.

The facility comprises 2,800 square metres of production space, 600 square metres of office space and car parking accommodation for 270 cars over two basement levels. The facility also has a further 4,800 square metres of additional space for another tenant.

Drug Product Manufacture (sterile products):

The design scaled up a lab process into a full production process that takes place on two floors. The sterile filling area, which utilizes a washer, in-line sterilization tunnel, time pressure filler, freeze dryer, and capper, was modified to improve airflow and maintain sterility. A new air balance was provided for the production and compounding areas.

The scope of work included integrating a new Product Delivery System (PDS), which had to maintain a temperature control of 2C to 8C, with water and steam plus clean steam (CIP, SIP, and WFI); the creation of a new weighing and kiting area; and build of several clean rooms:

- A Class 100,000 to a Class 10,000
- A Class 10,000 to a Class 100
- An aseptic Class 100 area

Appendix B: Rationale for Multiproduct Manufacturing Facilities

This Appendix outlines the rationale for developing a Pharmaceutical and Biomed Smart Working Hub and identifies some of the challenges that need to be addressed.

1. Flexibility is the Key Driver whilst maintaining contamination controls and compliance to regulations.

Many Contract Manufacturing Organisations (CMOs) across Europe are spreading their investment risk by building multiproduct manufacturing facilities. Such plants face issues that mono-production ones don't, including the risk of cross contamination from the product mix in manufacture or left after change-over and cleaning processes, not to mention the constant addition of new customers and biotherapies to manufacture, diverse customer compliance expectations, and strict contractual commitments.

So why are so many CMOs choosing this route?

Being a multiproduct site gives one the advantage of flexibility, as it's never known with biotherapies which products will make it to market. This makes running a mono-product plant risky. By running a multi-use plant, you are dividing the fixed costs of manufacturing, including the large outlay of paying employees among many different products, so it runs competitively. There is no idle capacity when marketing forecasts for manufacturing specific biotherapies are not met.

Sandoz is among the largest players in recombinant microbial manufacturing and an emerging force in mammalian cell culture. One of the most valuable lessons they have learned is how to run bio-manufacturing facilities effectively.

2. Plant Design Is key

Staff in multiproduct CMOs agree that the risk of cross contamination is the biggest problem they face. According to companies that construct biomanufacturing facilities, such as NNE (www.nne.dk) and Pharmadule (www.pharmadule.com), before even starting work in a multiproduct facility, the design of the building has to be right.

Ulf Danielsson, V.P Sales and Marketing for Pharmadule, says, "We have constructed facilities of 100200 m^2 up to 15,000/20,000 m^2 for many biotech and pharma companies around the world, so we are experienced at what is needed for these buildings to meet regulatory requirements. With each client, we design and construct a customized building that meets their operational and product needs. However, we do use some basic principles that apply to most projects; for example, the room classifications need to be in accordance with the regulatory requirements."

"Also there is often a need to have uni-directional material and personnel flows to prevent contamination, as well as interlocked doors in airlocks between cleanrooms. This prevents staff from opening both doors and exposing the cleanroom directly to an adjacent room or corridor. For biotech projects, the required biosafety level needs to be taken into consideration, and the air

pressure between rooms needs to be designed properly to contain the active substances. In most designs, we also include windows in doors and walls so that staff can see inside the airlocks and suites to check who is in and what they are doing before they enter." He continued.

Derek Ellison, Ph.D., Business Development Director of U.K.-based Eden Biodesign (www.edenbiodesign.com), a CMO that manufactures therapies from microbial and mammalian cells, as well as live virus for Phase I and Phase II studies, agrees with Danielsson. "Because we recently built our facilities, the design was led by the technical team that will work in the suites rather than the structural engineers, says Dr. Ellison."

"To do this, we took ten candidate biomanufacturing processes and used those to map out how we would use and clean the workspace, the material we would use, and waste flows we would generate each time. We then used all this information to provide input into how each suite should look. This is where we have a great advantage, as we haven't had to adapt an existing building or had legacy equipment to try and fit into the process. We have been able to drive the design so our facilities match today's stringent quality regulations. We have knock-out panels in each suite so that we can easily move large equipment in and out to maintain future flexibility" adds Dr. Ellison.

3. Preventing Product Cross Contamination

To prevent contamination from other products, most CMOs, especially the larger European ones, such as Girindus (www.girindus.com), Miltenyi Biotec (www.miltenyibiotec.com), Lonza (www.lonza.com), and Sandoz, use, where practical, closed systems that rely on automating as much of the process as possible and using fixed piping to prevent contamination from getting into the joints between systems and pipes.

Additionally, during a GMP campaign, CMOs that have a number of different production suites available only have one biotherapeutic at a time in each dedicated area.

At Medipolis, a microbial fermentation CMO in Finland that manufactures products mainly for Phase I and II trials, only one product will be in the 930-L fermenter area until this part of the production is finished.

However, since not all of the processes can be automated, the staff plays a key role in making sure products are kept apart (segregated). One important way to prevent contamination is to ensure staff turnover is low within the facility and that there is continuous GMP-training program in place. "The quality of your processes relies on your people being experienced in what they are doing" comments Dr. Nachtmann.

"Many companies also restrict the flow of personnel in and out of each area to prevent potential contamination from the different therapies in production. In our facilities we have a central corridor and an external corridor that runs around the suites", Dr. Ellison says, "so that you cannot go from one to another without going out via the external corridor and then back through the change area into the central corridor again."

4. Other Challenges

Other challenges that face multiproduct facilities are the constant addition of new clients and therapies, along with the diverse compliance expectations and contractual commitments they bring. Many CMOs do not see these additions as large an obstacle to their business as preventing cross-contamination because being able to scale up manufacturing and purify a range of different biological molecules according to strict timelines and regulations is their core expertise. Many CMOs can also often modify their standard manufacturing processes to fit their clients needs whereas any cleaning procedures that CMOs use may have to be customized for the product.

Being a successful CMO is all about good communication. “We put in place quality agreements and project-management teams internally and in the client company at the beginning of work so that both parties have to take responsibility for time lines and costs. This way we can all manage our expectations of how the project is progressing”, says Dr. Henninger.

“Another issue that multiproduct manufacturers face, which is not often touched upon, is confidentiality. In this type of environment it is critical that you protect the identity of your clients’ biotherapy, and we do this by giving products codes so that only those working on the project are aware of what they are manufacturing. We also do not have external visitors to the plant when a therapeutic is at a crucial stage of production”, says Dr. Henninger.

5. Making the Facility Financially Viable

“The market for bio-manufacturing is still growing in Europe because bio-techs are maturing here, and the mid-sized bio-techs are now looking for manufacturing facilities. The big pharmas don’t want to block their plants with small-scale production runs for smaller campaigns so CMOs are able to fill that gap very well in Europe”, says Dr. Brammer.

‘If you build and run a multiproduct facility, then there is much less chance of wasting time and money as there are several cases in the biotech and pharma industry where we have constructed single-use sites only to see them sit idle because the product did not become as successful, or worse, did not obtain regulatory approval. By running a multiproduct plant you are less likely to be left with this type of white elephant, and with our modular buildings, the smaller ones could even be shipped to a different location to meet a capacity crunch elsewhere”, says Danielsson.

Recent history of the pharma industry shows that facilities originally set up to manufacture one product need major reconstruction work for multiproduct manufacturing. It saves a lot of money and reduces risk to set up your plant as a multiproduct unit to begin with.

“Being fast and flexible are the best ways to become a successful CMO in Europe, and despite the challenges working in a multiproduct facility present, you have no choice but to run this type of manufacturing to achieve that in today’s market”, agrees Dr. Nachtmann.

Source: ***Genetic Engineering and Biotechnology News:*** **Mar 15, 2006 (Vol. 26, No. 6)**

Appendix C:
Potential Partners / Clients -
Companies in Australia involved in Medical Biotech Products

Company	Location	Business Type
Antisense Therapeutics	Toorak, Victoria, Australia	Antisense drugs
Audeo Oncology (Alchemia)	Brisbane, Qld., Australia	Oncology Compounds
Avexa	Richmond, Australia	Drug Discovery
Baxter	Toongabbie, Australia	Medication Delivery
Benitec Biopharma	Sydney, Australia	ddRNAi
Bionomics	Thebarton, Australia	Small Molecules
Biota Holdings	Notting Hill, Australia	Anti-Infectives
Biota Pharmaceuticals	Notting Hill, Victoria, Australia	Biologics
Genetic Technologies Group	Fitzroy, Australia	Genetic Testing
GI Dynamics	Baulkham Hills, Australia	Device to prevent digestion and promote weight loss
Implicit Bioscience	Woolloongabba, QLD, Australia	Acquisitions and development
iNova Pharmaceuticals (Valeant)	Thornleigh, Australia	Small Molecules
Invitrogen (Life Technologies)	Newcastle, Australia	Molecular Biology & Biotech Lab Products
Mesoblast	Melbourne, Australia	Regenerative Medicine
Mimotopes	Clayton, Victoria, Australia	Peptides
Novogen	Macquarie Park, Australia	Isoflavonoids
Novozymes	Thebarton, SA, Australia	Enzymes, Biologics
Pfizer	Bentley, Australia	
Pfizer	W. Ryde, Australia	
Pharmasynth	Darra, Queensland, Australia	
Pharmaxis	Frenchs Forest, Australia	Small Molecules, Diagnostics
Phosphagenics	Melbourne, Australia	Product Improvements
PolyActiva	Melbourne, Australia	drug-polymer conjugate technology, implants
Prana Biotechnology	Parkville, Australia	Biological Metals
Progen Pharmaceuticals	Darra, Queensland, Australia	Anti-angiogenesis & Anti-metastatic Oncology Small Molecules
Servier	Melbourne, Australia	Small Molecules
Spinifex Pharmaceuticals	S. Yarra, Australia	Small Molecules
Sypharma	Victoria, Australia	Contract Small Molecule Manufacturing
Teva	Macquarie Park, Australia	Antibody Therapeutics
Teva	Parkville, Australia	Antibody Therapeutics
Universal Biosensors	Rowville, Australia	Molecular Diagnostics & Medical Devices
Viralytics	Pymble, Australia	Oncolytic Viruses

Appendix D:
The logistics and design requirements for a Pharmaceutical and Biomed Smart Working Hub in the Southern Highlands

This Appendix:

- Provides a general overview to Hubs in Australia
- Describes the benefits of developing such Hubs
- Outlines what the design proposal should include
- Identifies the need for an Operational Plan
- Describes the proposed Infrastructure required for the Hub

1. Hubs in Asia Pacific:

In the Asia-Pacific region, Australia is one of the leading players in biotech related activities:

- Sydney is home to leading international Pharmaceutical companies (primarily focussed imported product distribution and clinical trials of new products) , research organisations and five research parks.
- New South Wales has four research parks supported by major universities. The Australian Technological Park (ATP) is operating as an incubator with a strong focus on biotechnology, fostering the growth of start-up companies for all manner of concepts not only medicines. Other Parks include the Macquarie University Research Park and the Riverside Corporate Park. (research from CONCEPT PLAN – SAVLI BIOTECH PARK- March 2006).

2. Benefits of Biotech Hubs / Parks:

Access to specialised infrastructure at competitive cost, largely benefits the bio-entrepreneurs in NSW. So, a biotech Hub with Business Incubator offering multiple occupancy, would essentially promote the growth and acceleration of start-up or early stage companies.

A Biotech Hub would also assist in optimising the capital expenditure that may be incurred for buying expensive equipment by promoting sharing of resources within the tenants. Further, players with excess capacity can utilise their resources by letting out their equipment/facility during lean periods

3. Design Proposal:

The aim is to develop robust manufacturing of different materials for clinical trials and early stage commercial use:

- To define the scope of technologies based on 10 examples with a mix of fixed (stainless steel) and flexible systems.
- To have the capability for end to end manufacture from active substances (starting materials) to formulated product which is packaged and tested (tablets, vials, devices).

Such a facility must be designed to meet all the key objectives:

e. To be a hub for early stage production and proof of concept
f. To provide training and development of technologists, engineers and manufacturing sciences
g. To provide security, capability and flexibility for multiple 'products'
h. To be built to Australian and international standards enabling global reach of products

The Hub must be designed to be flexible and scale-able multi-product with minimum capital investment, reduced utilities (compared to standard facilities) and increased speed for product pipeline compared to traditional facilities.

A modular system with a capacity to run 6 to 10 product simultaneously would be ideal. Such a system would be built with a hybrid of fixed (hardwired technology) and flexible (disposable technology).

4. Operational Plan:

An Operational Plan must be developed that outlines:

- How the Hub will be managed on a day-to-day basis
- Roles of the respective partners
- Financial responsibilities and appropriate role accountabilities

5. Proposed Infrastructure:

The Hub will be entirely developed and operated by a private partner, for instance Ramsay Health Care, and would be spread across an area of about 130.00m²

Infrastructure will include:

1. Amenity and Administrative Block
2. Common Instruments and Equipment Facility
3. Built-to-Suit-Suites
4. Laboratories
5. Services Block
6. Utility Services

5.1 Amenity and Administrative Block

This block would cater to the managerial, administrative and organisational needs of the Hub. Moreover, it would act as a centre for business support and other recreational facilities at the Hub.

Some of the key facilities that are proposed in this block include:

- ***Auditorium:*** The amenity centre would house a 100-seat auditorium that would provide an ideal location for conducting seminars and trade shows. The auditorium would have all the modern equipment such as high-tech amplification systems, super quality projection screens, slide projectors, audio and video recording facilities etc.
- ***Audio-Visual Room:*** The Audio-visual room would cater to the tele-conferencing and video conferencing needs of the tenants and would be equipped with current telecommunications and audio visual tools.

- ***Modular Meeting Rooms:*** These would provide a conducive environment for executive meetings or presentations. These meeting rooms would also be available to the tenants of the Hub on a first come first served basis.
- ***Business Facilitation Centre:*** The centre would cater to the business services' needs such as photocopying, faxing, typing, printing, etc. of the tenants.
- ***Food Court:*** A multi cuisine restaurant would be set up, which would be operated by a private party.

These facilities would be established and managed by the site owner.

5.2 Common Instruments and Equipment Facility

Within the Hub a "Common Instruments and Equipment Facility" will act as a multi-user resource.

For example, the Bio-Incubator would have a provision for a Pilot Plant facility, which can be utilised by tenants on a per day rental basis. The business model of this facility is primarily structured to provide fermentation and bio-processing facilities. The proposed Pilot Plant facility would be designed to meet the operational requirement of various processes. These processes can be categorised as fermentation, primary downstream processing, and secondary downstream processing.

The common instruments and equipment facility will assist in providing online and offline analytical support for the development and analytical activities undertaken by the tenants. The tenants would be charged based on the usage. The per day charge-out rates would be determined on the basis of cost incurred for each laboratory.

5.3 Built to Suit Suites

Outsourcing of manufacturing for research purposes is subject to higher risk of intellectual property violation. Hence, availability of processes and expertise must be carefully segregated.

The Hub will comprise "Built-to-Suit-Suites". These will be developed to include:

- Water supply
- Effluent drainage & Sewage Treatment Facility
- Gas pipelines for all types of gases connected to their respective
- Chambers
- Acid-proof drainage and vent piping system connected to a neutralisation system
- High bandwidth fibre optic connectivity for voice and data transfer
- Internet access
- Uninterrupted power supply
- Well laid out roads
- Green belts
- Storm water drains
- Street lighting
- Underground electricity lines

- Underground telecommunication lines
- Fire Hydrant points

5.4 Laboratories

The laboratories should be built to accommodate:

a. The Serology and PCR Suite Laboratory
(characterise cell lines, activity testing, potency testing)
b. Cell culture laboratory (develop and maintain Master and production culture collections)
c. Biochemistry laboratory (bioassay, biological activity testing)
d. Chemistry laboratory (Chomatography methods)
e. Wet Chemistry laboratory (testing starting materials bench chemistry methods):
f. Microbiology laboratory (bioburden in materials, air quality, water quality and sterility testing)

5.5 Services Block

The general facilities that would be made available in the Hub are:

- Work benching, modular drawer units and write-up bench
- Compressed air, vacuum, filtered water, soft water and DM water
- Gas pipelines for all types of gases connected to their respective chambers
- Acid-proof drainage and vent piping system connected to a neutralisation system
- Enclosures for fume cupboards & safety showers
- Laminar airflow hoods
- Effluent Drainage and Sewage system
- Uninterrupted Power supply with a provision of both raw power and back up through UPS/DG set
- Central air-conditioning
- Fire and smoke alarms, CO2 alarm and O2 depletion alarm
- Fire protection and detection system
- Safety shower
- Public address system in case of emergency
- Access control cards for entry
- High bandwidth fibre optic connectivity for voice and data transfer with Internet access
- 24/7 manned-security

5.5.1 An Indicative List of Equipment:

• NMR 300 • HPLC (several) • UV Spectrophotometer • IR Spectrophotometer • Polarimeter • Gel Documentation System

- PCR Machine
- ELISA Reader
- Electroblotter
- Fast Protein System
- Electroporator
- Ultrapure Water Facility
- Table top Centrifuge
- Sonicator
- Electrophoresis
- Vortex Mixer etc.

5.5.2 Fermentation Facilities:

Fermentation is a process in which an agent causes an organic substance to break down into simpler substances. It is the conversion of organic materials by organisms such as bacteria and yeasts. The proposed facilities would assist in carrying out fermentation process by two varied methods, which include:

(a) Mammalian Cell Culture

In the mammalian cell culture method the facility will have a variety of capabilities for airlift, classical and solid phase technologies. The cell culture process is continuous and not critical in nature.

(b) Microbial Culture

In the microbial culture method the facility each lab will have three fermentors with capacities of 2 litres, 20 litres, and 200 litres. The microbial process is done in batches and is critical in nature.

5.5.3 Downstream Processing Facility

The downstream processing is the next step after fermentation, which involves separation of cells from the media in which they are grown and protein isolation from the cells or media by combination of various techniques.

The proposed facility will have two downstream processing facilities; (a) Primary Downstream Processing Facility, and (b) Secondary Downstream Processing Facility.

(a) Primary Downstream Processing Facility

The primary downstream processing facility will provide the following services:

- Chromatography – various methodologies such as affinity, cationic and anionic exchange
- Membrane Separation and Trangential flow filtration
- Centrifuge
- Filtration – for virus and particulate removal

This facility will have different equipment for carrying out both cell culture and microbial operations.

(b) Secondary Downstream Processing Facility

The Secondary Downstream Processing Facility would provide the following services:

- Distillation
- Evaporation
- Precipitation
- Crystallisation

The secondary downstream processing facility would further house common infrastructure to carry out both cell culture and microbial operations.

5.6 Utility Services

In addition to the detailed list of services and infrastructure that have been discussed earlier, the proposed Biotech Hub would provide several other common utility services. An indicative list of such facilities are:

- ***Gas Supply***

Gas chambers for different types of gases would be connected to the wet labs through high safety gas pipelines. The gas supplies that would be housed in the Hub are Liquid Nitrogen Storage Chamber, Hydrogen Chamber, LPG Chamber and Helium Chamber etc.

- ***Dedicated Power Supply (limited backup)***

The Hub would provide a limited back-up facility to predefined critical systems from the power plant dedicated solely to serve the requirements of the Hub.

Main power supply would be from sustainable energy systems on site.

- ***Effluent Neutralization and Disposal Plant***

Effluent neutralisation and Disposal Plant would be used for the collection, treatment and disposal of effluents from the wet laboratories at the Hub. The plant would be dedicated to continuous neutralisation of spent acid from the various labs operating in the Hub. Effective management and control of the processes used for effluent treatment would help to achieve more effective compliance with legislation and ensure the Hub's public image as ecologically neutral.

- ***Sewage Treatment Plant***

Sewage pipes would be laid all through the Hub for the removal and disposal of chiefly non-harmful liquid wastes from the wet laboratories and of rainwater. These liquid wastes would be treated at the sewage plant for their future purposeful use.

Appendix E: Methodology for Concept Design