CSL also have a relatively large number of compounds in R&D, some of which could spillover to a new facility once its credentials were well-established. Furthermore, some demand already exists for stem cell expansion, and fill-and-finish capability for cell-based therapies, and this will definitely increase and provide potential revenues on the lower end of the CMO earning scale.

To develop a business model, an estimate of the revenues which can be attributed to this demand is needed. A number of approaches can be used to generate revenue forecasts. These include:

"Lost business" model

In section 4.2, an attempt was made to quantify the value of mammalian cell-based clinical development work known to have recently gone to overseas CMOs. The value of lost business is taken to represent the theoretical revenue available to a facility, had it been in place.

A very rough method of estimation indicated these contracts would be worth at least $18M per year.[1] If [redacted] work could have been catered-to instead of forcing the in-house development path, this figure would rise to $22-28M. Assuming a facility with capability to embrace larger-scale bacterial fermentation, and [redacted] future needs could thus be accommodated, the valuation of "lost business" would rise to circa $27-35M.

This must be regarded as an underestimate, given that not all companies are included, and the valuation model neglects the growth in early stage activity which has yet to manifest as commercial contracts.

"Current valuation" model

An alternate method of valuing potential revenues is to apply the typical clinical cost per project (given in Table 4) to the actual number of projects currently in clinical development (Table 3). This method thus derives a "snapshot" of the value currently invested in clinical development.

The table below illustrates this theoretical cost associated with the projects currently underway in Australia and as surveyed by Innovation Dynamics as part of this report. Note that this valuation is conservative because it neglects GMP work associated with stem cells and autologous therapies. Additionally, not all companies responded to the survey.

[1] (refer 4.2 and explanatory footnote page 33)

Table 6 Nominal valuation of CMO-serviced clinical demand for mammalian cell based-products

Project Type	Cost/project ($M)(Table 4)	No. of projects (Table 3)	Total Value ($M)
Preclinical/process development	1.5	19	28.5
Phase 1	2.0	2	4
Phase 2	1.5+	3	4.5+
Phase 3	5.0+	1	5+
TOTAL		25	42+

Whilst there is clearly a significant value associated with clinical projects in aggregate, it is important to realise that it typically takes about 2 years to move from preclinical to clinical, and about 6 years to move through the clinical trial process [10]. Hence to translate the total value in table 6 into a forecast annual revenue for a scale-up facility, one needs to divide by these factors. A theoretical figure of at least $16M/yr is arrived at using these assumptions (ie $28.5M/2 + $13.5M/6).

"Future pipeline" model

If the typical industry percentages for transition from one phase of development to another[24][25] (see also section 3.3.2 "Future Pipeline") are applied to the 19 compounds in preclinical development, a prediction can be made of the value of future clinical development projects if they were all out-sourced. From the 19 products at the preclinical stage now, 14-17 compounds would pass through to Phase 1, 7-14 through Phase 2, and 6-13 drugs would be predicted to enter phase 3.

By assigning the cost/project values from Table 4 to these predicted future pipeline numbers, potential revenues of $26-35M/yr would result (using the same timing and project costing assumptions given in the example above). This valuation is higher than the preceding "current valuation" model, where the relatively low number of drugs currently in late stage trials affects the calculation.

Based on the three models considered, potential annual revenues attributable to Australian-origin, mammalian-cell products may be in the range $16-35M. Up to double this amount may be forecast if other types of expression are included within the capabilities of the facility (based upon feedback from Progen that the number of enquiries regarding microbial expression exceed those for mammalian cell).

Considering all these issues, on balance, a revenue target for a new facility of ***$30M*** is felt to be reasonable and conservative, particularly with an assumption that a significant proportion of revenue be sourced from outside of Australia, as discussed in the following section.

5.2.2 Regional and Global Demand

- Forecasting of revenues arising from Australian drug-developers remains risky, given the likelihood of unpredictable timing of projects entering clinical development, uncertain capture-percentage of potential market, alternate commitments via alliances, and impact of unknown product mix (number of, and value of, different types of projects).
- This observation lines up with the recommendations arising from various previous reports [10][11][12] which all indicated that overseas marketing of capability would be needed for financial viability to be assured.
- The Australian case should not necessarily be seen to rest upon local self-sustainability alone. Indeed this comprises a very narrow view of the world, given the clear evidence of sustained global and regional growth (as outlined in section 3 above). For example, the commitments made by Singapore, Malaysia and Dubai[15] to development of their biopharmaceutical industries were made notwithstanding the very low numbers of local discovery firms and drug developers [11].
- Rather, in those cases, a strategic business opportunity was perceived, and investment made accordingly. Whilst this approach is not without risk, experience in Singapore reveals that if appropriately supported, appealing to foreign demand will eventually bear fruit. Singapore's A-Bio Pharma facility came on line in late 2002 with a 200 litre mammalian cell reactor, and anecdotal reports were that it took some time to attract clients. Recently, however, deals with GSK Bio and Novo Nordisk have been announced and these agreements have resulted in recent commitment to expansion, comprising a US$5.5M extension - including a new 500 litre bioreactor. Leveraging this success at the scale-up level, a major deal was recently struck between Bio*One Capital and Lonza to build a full scale CMO plant in Singapore[14]. This facility will ultimately comprise 4 mammalian trains with capacity from 1,000 to 20,000 litres.
- In comparison with Australia, where ready access to a well-developed database of companies active in therapeutics development was available for further interviews, the current study was somewhat limited in terms of ability to survey Asia Pacific's regional demand for a scale-up facility. However, feedback from local CMO/CROs was taken to be a reasonable surrogate for a more comprehensive market research effort [redacted] were contacted in this regard, and all indicated that there are, as yet, very few expressions of interest being received from discovery companies in SE Asia. This may reflect the fact that the large new biomedical precincts in Taiwan and Singapore have not yet had enough time to bring fundamental work to the stage of commercial development.
- With a focused and dedicated business development effort, there is no reason to suppose that an Australian facility could not leverage Australia's pre-eminent position regionally to tap into the biotech efforts being promoted in SE Asia, NZ and elsewhere. Feedback from Australian CMOs and others indicates that regional biotherapeutics developers remain primarily at the discovery and preclinical stages of development. For this reason it is difficult to quantify the potential represented in the region. A detailed survey of the type undertaken in Australia for this report would be a logical extension of the study.
- The desirability of an alliance with a big pharma or big CMO has also been noted on several occasions, since such an alliance would remove some of the

uncertainty regarding demand, by way of locking-in commitment to capacity, or by increasing the attractiveness of the new facility as a supplier to other customers.

As part of the current project, contact was made or attempted with Lonza, Diosynth and Cambrex to ascertain the interest level on an early, in-principle basis. At the time of this report, no such interest has been confirmed, but the lines of communication remain open. [redacted] Eden Bioscience, the operator of the UK's National Biomanufacturing Centre indicated that they were prevented under the terms of their operating agreement from engaging in any competitive interest. The smaller CMO, Cobra Biomanufacturing (53) indicated that they saw the best prospects for growing their UK business into Canada and USA rather than the Asia Pacific.

With regard to attempting to attract the interest of a foreign CMO or big pharma the following are relevant:

- An approach from a consultant (as in the current project) will not necessarily elicit a serious consideration, as the courtship phase for major projects usually involves a high-level delegation comprising industry and government representation.
- There is a "chicken and egg" issue involved, given that a potential partner expects to see a comprehensive proposal, yet the development of a "bankable" Australian proposal requires the backing of a major partner. This situation suggests some time will be required for iterative development of a proposition based upon an in-principle interest from both parties.
- The probability of an Australian proposal falling on fertile ground within the strategic planning cycle of the major CMOs or big pharma is not high. Most companies should already be looking out 2-5 years in their planning, and it will require an element of luck for the Australian proposal to be complementary with existing strategies of potential partners, or for the proposal to come to the table at the same time as long term strategy is under review within a potential partner. Cognizant of these issues, the importance of attracting a strategic CMO alliance partner should be central to any Australian development initiative.

5.2.3 Ability to Capture Potential Customers and Secure Revenues

- As outlined in section 3.4, Australia's CMO's represent a fragmented picture to the potential market. No Australian CMO has hitherto made its primary mission to develop the Australian and regional markets, or provided a focused and dedicated business development resource toward such an endeavour. With a professional and well-funded campaign, a new Australian scale-up facility could be expected to more effectively harness the overseas catchment for start-ups in the biotherapeutics arena.
- Effective marketing is critical in order to provide early-stage potential customers with a visible and attractive alternative for clinical development. Without this, start-ups may adopt a wide array of partnering deals which can effectively lock-out independent CMO's from a share of the pipeline

development. Australia is well-positioned to offer a one-stop shop solution to clinical development needs upstream and downstream of the CMO work in isolation (see also section 3.6.1).

5.2.4 Demand Influence Upon Timing of a Decision on Facility

The growth in discovery and development efforts locally will inevitably create an increased demand for suitable CMO facilities. This is only a matter of time, and can be predicted with a high degree of confidence. However, because of the extended duration associated with design, construction and validation of any new facility (at least 2 years for a greenfield option), the risk to the Australian economy is that there will be a serious misalignment of need vs. availability. Clearly local companies will have no alternative to go offshore if local CMO capability has not come on-line in anticipation of the likely future demand.

5.2.5 Demand for CMO services: Influence on Type of Facility

Scale of operation

The forecast local demand arises primarily from early stage companies seeking services for preclinical and early clinical development (section 3.3.4 a). This suggests that any new facility should cater to smaller-scale opportunities in terms of reactor volume and mass of product produced. Indications from potential facility users such as Ludwig and CSL are that a scale-up facility aiming to supply clinical trial quantities of monoclonals should be equipped with fermentation capacity of at least several hundred litres. Indeed, CSL's planned in-house facility will cater exactly to this range (up to 500 litres). However, it should be stressed that there is no particular reactor size that represents a threshold or absolute crossover point from small to pilot or large scale. In the range 400 – 1000 litres working volume, the capital cost and operating issues are relatively insensitive to volume.

Furthermore, every project has its own issues affecting time and motion and therefore capacity and scale). Some cells grow faster than others, and the productivity of a system is dependent on a host of factors. Also, some processes have many more unit operations than others and take much longer. These demand-side issues make it difficult to predict the number of projects, and the rate of project throughput, that can be accommodated.

Types of expression

Whilst the focus of this report is upon the mammalian-cell based route to product expression, there are other products which can be made in the same types of facilities using other host/vector systems. The commercial risk could therefore be offset by planning a facility catering to other expression systems such as microbial and viral. [redacted]

Capability gaps beyond mammalian cell

The ideal design for a new facility would also include technologies to address gaps in capability beyond that relating to mammalian cell culture. The ability to perform aseptic filling and freeze drying and packaging are prominent in this regard. [redacted]

Infrastructure adequacy

Resourcing and infrastructure upstream and downstream of a scale-up facility appears adequate to support an expansion in capability. Even an ambitious greenfield development would only require perhaps 50 people. There is a reasonable pool of GMP-trained technical people in Australia, many with skills gained from employment with CSL or big pharma chemical drug companies with a presence in Australia (Glaxo, Sigma, Mayne etc). Additionally, the number of managers with overseas big pharma and big CMO experience is increasing, as expatriates and immigrants are attracted to Australia's benign climate and high quality life-style. Furthermore, there are now tertiary courses delivering GMP training, most notably the postgraduate course offered by Swinburne College which incorporates teaching input from a range of industry professionals.

The historically high rates of employment in Australlia are currently placing pressures on many sectors in terms of availability of labour. However, given the size of the local pool of suitably trained people, the lead-time to bring a new facility on line, the fact that tertiary institutes are increasing the throughput of GMP literate biological science graduates, and the ability of a unique and high-profile facility of the type proposed to attract staff both locally and from overseas, it is not anticipated that the scale-up facility would cause a major perturbation to the local labour market.

Increasing regulatory impost

GMP requirements also influence the type of facility needed. The trend in international regulatory standards is toward higher standards of GMP earlier in the clinical development process. For instance, until recently it was acceptable to produce Phase 1 materials under Good Laboratory Practice (GLP). Now, however, European authorities in particular, are mandating GMP even at Phase 1. This means that early stage customers need sophisticated facilities which should be capable of producing up to Phase 3 and commercial material. Therefore, even in a scale-up facility, for certain products types -- principally those with high potency and needing smaller quantities of the active compound -- the facility may be capable of accommodating commercial manufacturing projects. It is important to realise that there is no hard-and-fast demarcation between the type or size of equipment or facility required to produce Phase 1 and 2 vs Phase 3/commercial production.

Flexibility in technical services

Wide variety in the technologies employed for the development of early stage client processes can be expected. This, in turn, imposes a requirement for flexibility and range of equipment to be provided by the facility. Early stage projects will involve much cell-line work, process development, and process optimisation as part of the contract. This will happen partly on the bench and in small scale equipment. For these reasons, general laboratory areas, QC, and specialist microbiological laboratories will be required in addition to the GMP production labs. The actual uptime in the main fermenter may be only a small part of the project plan. For phase 3 work, trial batches and multiple runs of the production equipment for process validation are more typical.

6 Options for Addressing Biomanufacturing Capability Gap

The options outlined below include a range of possibilities spanning low-entry cost and high-entry cost alternatives. In the former category is an option which attempts to leverage and further develop existing CMO capability. At the other end of the spectrum, a new, stand-alone facility is described. The possibility of combining these approaches is also discussed.

Any further development of Australia's national biomanufacturing capability should be seen in context of the National Collaborative Research Infrastructure Strategy (NCRIS). NCRIS seeks to integrate the development of national capability, and given the central importance of a major biotherapeutic scale-up facility in providing a route to commercialisation for Australian R&D, there is an obvious opportunity to link the two initiatives.

6.1 Option A Enhanced Capability of Local Biotherapeutics Manufacturer(s)/CMO(s)

6.1.1 General outline

The capabilities of existing CMOs and biotech manufacturers within Australia have been reviewed in the preceding discussion (section 3.3.3).

[redacted]

[redacted]

Option A (i)
Enhanced Capability of Local CMOs

Financial

Revenues would depend upon the participants in such a scheme, and the extent of incremental business attainable with synergist development and appropriate addition of new capabilities to the existing facilities.

Perusal of the publicly available annual reports for Progen and Bresagen (the two most prominent CMOs in Australia) indicates annual turnover of $1-2M each for CMO work in 2004/05 and 2003/04. [redacted]

Because this option is at such a preliminary stage, it is not possible to attempt to develop financial models or consider funding strategies.

A detailed evaluation of the individual needs and perceived limitations and aspirations of the candidates for an alliance is required, and comprises an obvious and logical extension of the work undertaken for this report.

Swot Analysis of Option A (i)

Strengths

- Provides vehicle to strengthen local CMO base.
- Builds on existing customer base and market knowledge.
- Provides options for start-ups to generate phase 1 and 2 materials.

Weaknesses

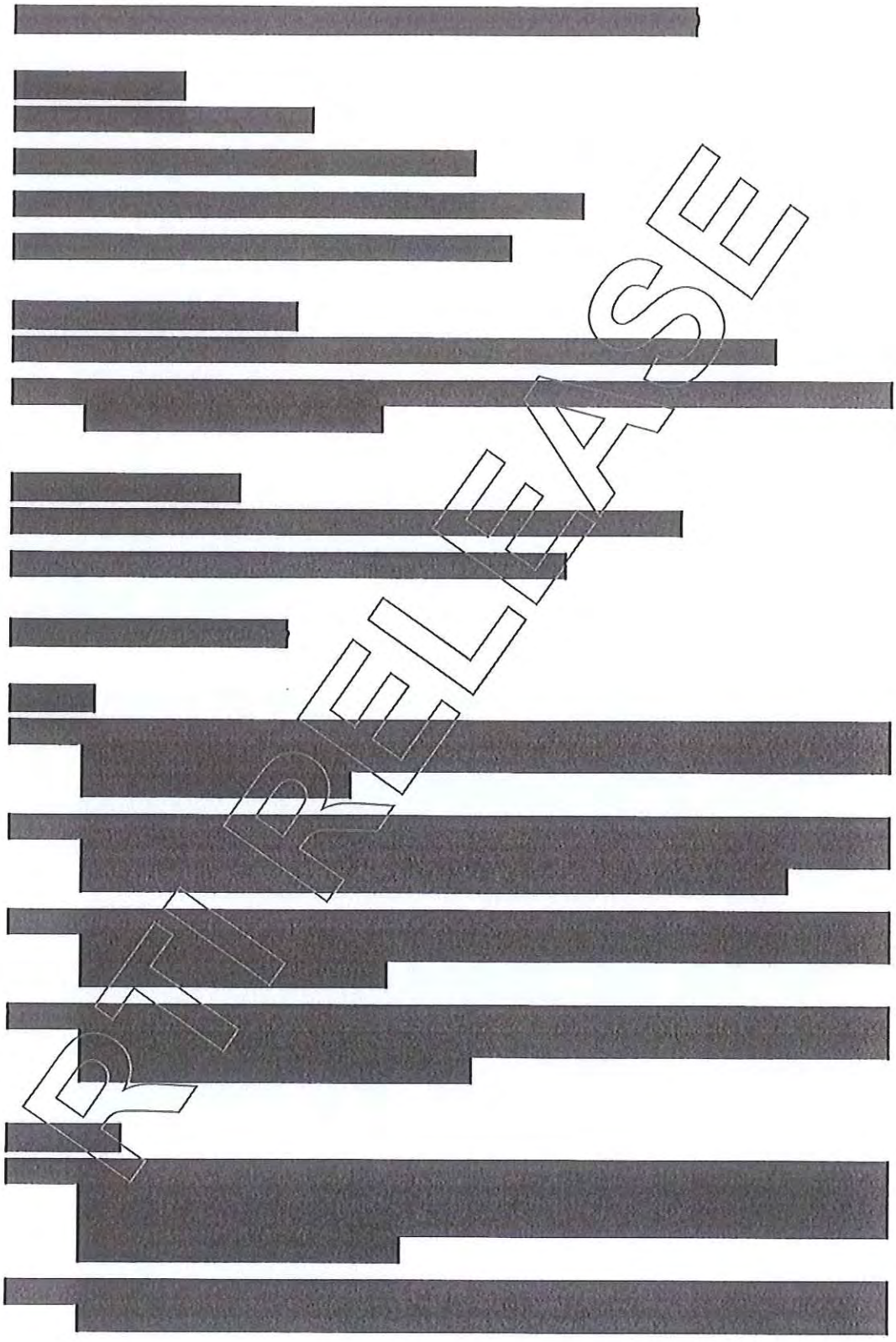
- Revenue growth prospects will be limited by infrastructure constraints (availability of land for expansion etc.).
- Without an integrated and over-arching client cultivation and maintenance and business development function, synergy would be difficult to attain in practice.
- Local CMOs have limited credibility/visibility in the international pharma market.

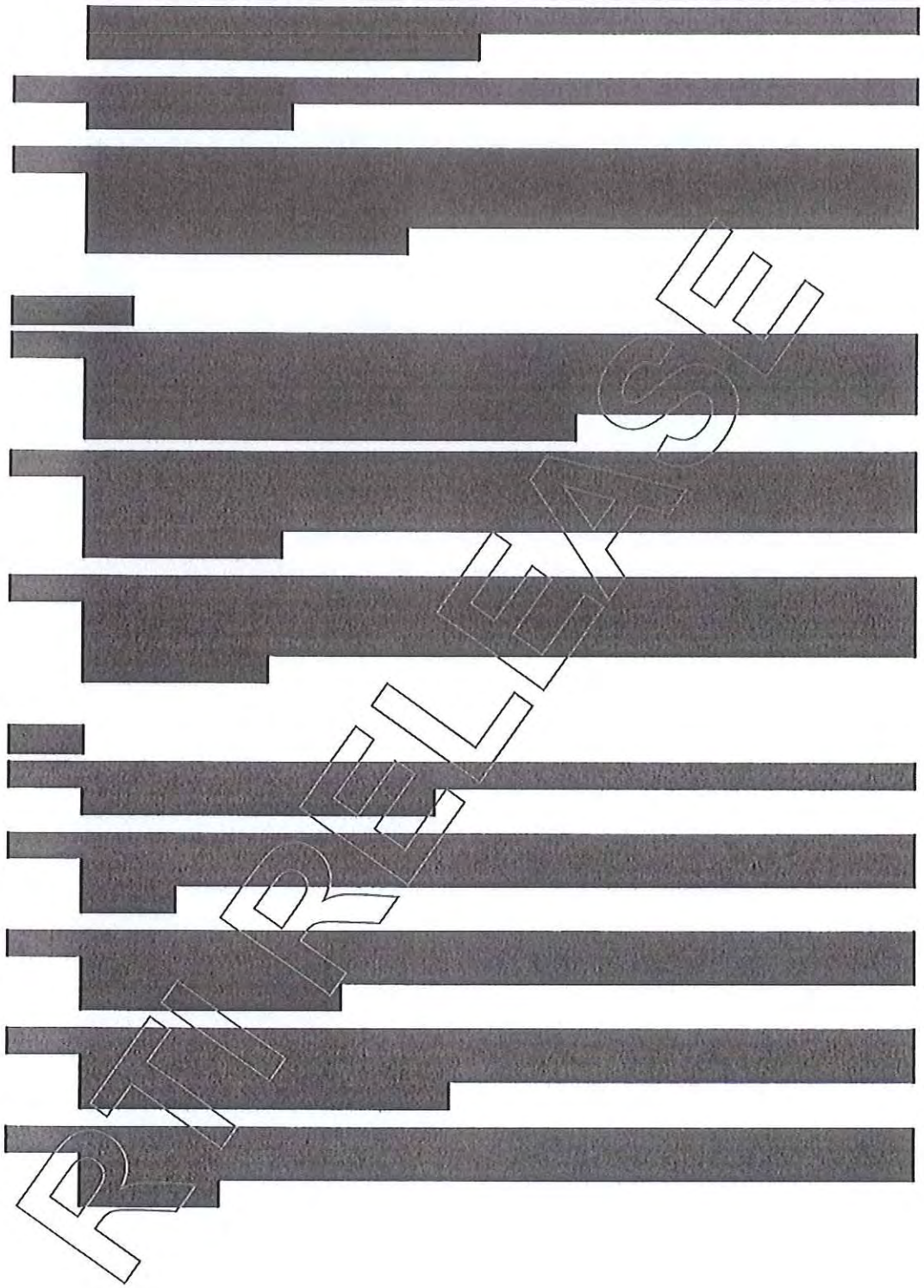
Opportunities

- Ability to leverage other capabilities in the drug development pipeline by promoting one-stop shop solutions to clinical development.
- Could provide a stepping-stone strategy toward the development of a larger scale greenfield facility.
- Linkage with NCRIS initiatives.

Threats

- Most local CMOs are currently loss-making and could fail despite support envisaged under this option.





6.2 Option B

Greenfield Production Facility

The most elegant and comprehensive solution to the need for a biotherapeutic scale-up facility is to design and construct a new state-of-the-art facility fully dedicated to contract manufacturing, and unconstrained by existing site or infrastructure limitations. Such a development on a new site is termed a "greenfield" project.

The Australian CMO scene is characterised by fragmentation of technical capability, both in terms of size of equipment, GMP compliance, and number of expression solutions available. Furthermore, there is often fragmentation of focus, given that contract manufacturing work often takes second priority to in-house development and production objectives. A greenfield facility avoids such fragmentation, and offers the perception of having the "critical mass" necessary to attract international as well as local clients.

It is envisaged that a new facility would work in liaison with complementary service providers to provide an integrated "one-stop-shop" option to early-stage developers. This feature provides an additional point of distinction vs. existing smaller CMOs. Whilst some competitive tensions may arise between a new facility and existing CMO providers, the opportunities provided by alliances, mergers etc offer the prospects of "win-win" outcomes, and the opportunities are seen to outweigh any downside arguments based on competition.

An illustrative scale-up facility is outlined below, including a general description of the facilities and a discussion of the factors influencing the design. Detailed capital expenditure item lists, floorplan explanation, and factors affecting location are given in the appendices. The design represents a further development of a previous study for an Australian mammalian cell facility (8).

6.2.1 Design Philosophy

Scale of Operations and Technical Capability

- Complementary with capabilities of existing Australian CMOs

  The sizes of fermenters and related plant have been selected to complement rather than compete with existing CMO companies. This leaves open a strategy for staged development involving an existing CMO as part of the way forward.

  In particular the mammalian cell capacity indicated at 500 - 1,000 litres is larger than present in Queensland at Agenix or Q-Gen. The plan could see existing CRO/CMO's specialising in servicing the needs of small-scale/early-stage clients, particularly during the transition period whilst the new larger facility is being built.

  The bacterial fermentation capability at 1,000 litres also represents a scale of operations unmatched in Australia for CMO-based production of biological therapeutics under conditions meeting international human codes of GMP. This scale is justified by the forecast needs of [redacted]

- Provide services which target other gaps in Australian infrastructure

  Currently there is no aseptic freeze drying facility in Australian available on a contract basis to perform fill and finish to meet human therapeutics cGMPs'. Such capability therefore forms part of this proposal. However, given that two CMO aseptic liquid-filling GMP facilities are planned ([redacted]), and one larger GMP freeze-drying facility ([redacted]), the option of *not* including fill and finish capability in the capex plan is also described.

Size of facility and configuration

The design proposed (see Appendix 2 for floor plan and outline of design) assumes a greenfield location, as this permits the ideal layout in terms of inbound and outbound logistics. A new site also enables the ideal arrangements to be built into the design insofar as movement of personnel and materials within the facility are concerned . The latter feature is an essential element of GMP compliance.

However, should a compelling case be made for a "brownfield" refurbishment, or extension to an existing facility, it may be possible to adapt the ideal design features to the alternate situation without losing the essential features required.

Compliance with codes – GMP, ISO, OGTR

This proposal is predicated upon delivering a world-class scale-up facility able to compete in the international CMO market. As such, the facility must comply with the most stringent quality systems, including US FDA cGMPs and relevant design codes. Additionally, the fact that human therapeutics are increasingly made by methods involving recombinant organisms means that compliance with OGTR guidelines is also assumed.

Expansion and staging

The proposed building provides a large floor area capable of housing at least 4 independent GMP manufacturing suites. These can be installed in staged fashion dependent upon funding and demand. The recommended way forward would be to fit out the first two suites with equipment dedicated to bacterial and mammalian fermentation (ie. one suite each) This reflects known demand from [redacted] for microbial GMP facility. The remaining suites would be completed in planned sequence in response to confirmation of demand, ideally confirmed during the facility design period.

6.2.2 Revenue Assumptions

Based on continued growth in domestically-derived drug development activity and aggressive overseas marketing, a revenue target equivalent to a current value of $30M is assumed (refer also 5.2.1). The local market potential may already be of this magnitude, particularly if microbially-derived drugs are included. The facility plan should

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* Mayne Pharma has large scale capability which is occasionally available, but availability is limited because of focus on in-house production; see also 3.7.1.

in any event target a significant proportion of its business offshore to spread risk and cover for a gradual penetration of the local market.

A typical operating scenario is given below to illustrate the project mix and number of projects required to attain the $30M forecast sales when the facility is at full capacity. Note the emphasis on early stage projects as the primary source of revenue (the average contract value per project was taken as the midpoint of the ranges quoted by industry, with the exception of phase 3, where the bottom end valuation was taken).

The sensitivity of revenues to different start-up strategies and to project mix is examined in the following section 6.2.5.

Table 7 Operating Scenario – Projects and revenues

Project type	$M/project	Projects / GMP suite 1	2	3	4	Developmental Lab Projects 1	2	TOTAL $M
small preclinical/clinical	0.3			1		2	2	1.5
major process development	1.5	1	1					3
preclinical/phase 1	2.0	2	2	2	2			16
phase 2	1.5	1	1	1	1			6
phase 3	5.0				1			5
		4	4	4	4	2	2	31.5

Note that the assumptions regarding facility revenues in Table 7 are relatively conservative. If a best case approach is taken, with more bullish assumptions regarding the number and value of Phase3/commercial production batches, and with greater throughput of process development projects, a revenue of $62M is forecast (refer also Sensitivity Analysis 6.2.5 below and associated Appendix 5).

6.2.3 Operating Cost Assumptions

The following assumptions have been used in the financial model given in Table 7 below):

Cost of goods
- 50% of sales years 2-3
- 40% of sales years 4-11

Overheads
- 40% of sales years 2- 3
- 30% of sales years 4-5
- 25% of sales year 6 – second wing on-line

Industry experience and feedback has been used in the derivation of these figures. Feedback from local industry indicates gross margin targets for biological products are commonly in the 60-70% range. Suggested typical margins for CMOs may be somewhat lower at 50-60%. A high proportion of the operating costs of GMP facilities must be

regarded as fixed costs, since the staff and systems must be maintained regardless of the project throughput. The variable costs associated with actual production will essentially be limited to raw materials and some utilities.

Given that the products and product mix to be made are as yet unknown, it is not possible to work up costs of production using yield and recovery data and estimates for direct input costs. The assumptions may however be fine- tuned by further research into similar operating companies.

6.2.4 Capital Cost Assumptions

A facility incorporating 4 GMP suites and support laboratories capable of performing process development contracts has been proposed. A substantial facility of this type with the ability to flexibly accommodate several production and development projects simultaneously is suggested to spread the overhead costs associated with the building and operating infrastructure.

The table below provides an indicative cost for the proposed facility. A detailed breakdown is provided in Appendix 3. The equipment items comprising the fill-and-finish capability have been highlighted in the Appendix as an optional module, given there is an outsourcing possibility via Radpharm. In the event of out-sourcing, the effect on capex will be approximately $3M.

Table 8 - Capital Cost Estimate For New Scale-Up Facility

ITEM	Total Facility Costs - AUD	Stage 1 Facility Costs -- AUD [ONE WING ONLY]
Buildings and Services	20,640,755	15,969,634
Equipment	13,160,384	9,564,753
Land	2,500,000	2,500,000
Total ex GST	**36,301,139**	**28,034,338**

Whilst the costing has been built-up in an objective fashion, many assumptions have been made regarding the suitability of the layout and the types of equipment. Estimates should be considered to have an accuracy of no better than ±25% until process and design are locked down.

Previous reports have given indications as to the likely capital costs for greenfield developments in Australia [redacted]

By way of international comparison, a similar sized new facility (4,100m^2), the National Biomanufacturing Centre (NBC) in the UK is reported to have cost £34M. That facility comprises 3 GMP production suites and targets an early stage clientele similar to the proposed modus operandi for this option. It is due to commence operations in 2006 [17]. The valuation of the NBC is considerably in excess of that in Table 8, and the local comparisons canvassed in 5.4 (above). This may reflect particular design features, equipment capability, land value, and peculiarities of the funding structure.

The Cambrex Baltimore facility, comprising 5,000m^2 and leased from government instrumentality Mbio, cost some US$21M in the mid 1990's.

NEW SCALE-UP FACILITY FINANCIAL MODEL TABLE 9 CASHFLOW STATEMENT

Year			2006 0	2007 1	2008 2	2009 3	2010 4	2011 5	2012 6	2013 7	2014 8	2015 9	2016 10	2017 11
Net Revenue	Phase 1		0	0	5,788	12,155	19,144	20,101	21,107	22,162	23,270	24,433	25,655	26,938
	Phase 2					0	0	13,401	21,107	22,162	23,270	24,433	25,655	26,938
	TOTAL		0	0	5,788	12,155	19,144	33,502	42,213	44,324	46,540	48,867	51,310	53,876
Cost of Goods Sold		0.4 0.5	0	0	2,894	6,078	7,658	13,401	16,885	17,729	18,616	19,547	20,524	21,550
Gross Profit			0	0	2,894	6,078	11,487	20,101	25,328	26,594	27,924	29,320	30,786	32,325
Overheads		0.4	0	0	2,315	4,862	5,743	10,051	10,553	11,081	11,635	12,217	12,828	13,469
% of sales		0.3 0.25												
EBITDA			0	0	579	1,216	5,743	10,051	14,775	15,513	16,289	17,103	17,959	18,856
		%sales			0.10	0.10	0.30	0.30	0.35	0.35	0.35	0.35	0.35	0.35
CAPEX	Phase1	28,034	12,000	16,538	1,197									
Phase2 - second wing fit out		36,301					10,551							
CASH MOVEMENT			-12,000	-16,538	-618	1,216	-4,807	10,051	14,775	15,513	16,289	17,103	17,959	18,856
CUMULATIVE CASH MOVEMENT			-12,000	-28,538	-29,156	-27,940	-32,748	-22,697	-7,922	7,591	23,880	40,983	58,942	77,798
INFLATION		5%		Notes	assumes $30M sales in 2005$ for 100% operation, year 6 (Stage2)									
NPV		7,098			assumes $5M sales in 2005$ in year1 of operation (2008) at 50% capacity (Stage1)									
COST OF CAPITAL		15%			assumes $10M sales in 2005$ in year 2 of operation at 50% capacity (Stage 1)									
IRR		19%			assumes year 1 of second wing achieves $10M sales in 2005$									

6.2.5 Sensitivity analysis and scenario modeling

6.2.5.1 Impact of timing of start-up and staging of capacity

Several scenarios representing variants on the "base case" given in Table 9 are summarised in the following table. These scenarios examine the adverse impact of lower-than-forecast revenues and deferral of stage 2 of construction. The project remains viable even if key assumptions regarding commencement of revenues and construction of the second suite are pushed out by one year. Conversely, if the facility were built in one stage and revenues for stage 2 brought forward by a year, the NPV for the project becomes significantly more attractive.

Table 10 Sensitivity Analysis : Effect of timing and staging of facility

Variable	NPV
Base case NPV (see spreadsheet Table 8)	$7,098
Don't construct Stage 2 at all and get 50% value of incoming projects	-$7,078
Delay start of all revenues 1 year, delay Stage II construction 1 year	$327
Bring forward Stage 2 construction and revenue by 1 year	$19,649

6.2.5.2 Impact of project revenues and project mix

If the assumed revenues are built in a "best case" fashion rather than the conservative model outlined in Table 7, the project's financial performance improves markedly. This "best case" scenario assumes higher project valuations for conducting phase 2 and phase 3/commercial projects, as well as a project mix comprising a larger contribution from late stage clinical development work. Under this scenario, the annual facility revenue at full capacity rises from $30M in the "base case" to $62M. The IRR is 34% and NPV $49,176 under these circumstances. The cashflow statement and revenue build details are given in Appendix 5.

6.2.5.3 Impact of government grants

Application of public funds to reduce the upfront capital cost to the facility improves the attractiveness of the facility to investors. Whilst the base case (Table 9) indicates the project is viable, the project does not break even in cashflow terms until year 7. Such a payback period will be unattractive to many investors. Further, the calculated IRR at 19% will fall below the rate required by many venture capital providers (often seeking 25-30% returns to compensate for the risk exposure).

Examination of the assumption base for the base case indicates a relatively high level of risk, including the uncertainty of timing and of valuation of individual clinical projects. Furthermore, viability will also be critically dependent upon the effectiveness of the marketing and business development strategies in capturing a high proportion of potential projects

arising from the domestic industry. These uncertainties flow-on to lack of predictability of revenue streams.

The effect of a government grant of a nominal $10M is illustrated in Appendix 5, Tables 3,4 and 5. Assuming the grant is applied to capital expenditure in Year 0 of the "base case" project (ie. $30M revenue at full capacity), the cash breakeven is brought forward by two years to year 5. The IRR improves to 27%, at which point the project should be attractive to a wider range of potential investors.

The sensitivity of the financial model to government assistance was also examined in a low revenue situation. This case is of interest, since the risk factors to the project are most likely to result in revenues below the "basecase". Tables 3 and 4 (Appendix 5) illustrate the effect of the same $10M grant upon the cashflow forecast when revenues are $16M.

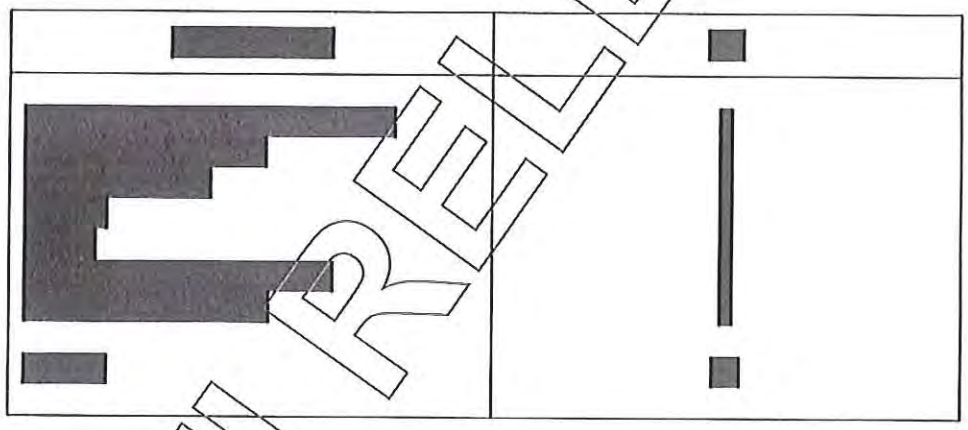
Without the government grant, the project returns a negative NPV, breaks even in year 9, and the actual rate of return of 7% falls well below the 15% assumed cost of capital (Table 4). With application of the grant, the project still returns a negative NPV, but the breakeven occurs in year 8, and the actual rate of return at 13% now approaches the assumed cost of capital

6.2.6 Funding and Corporate Structure

The cost associated with the proposed facility represents a major undertaking, and options for funding will require a separate dedicated investigation. Funds are likely to be drawn from a number of sources. For indicative purposes only, a funding option to meet capex and working capital needs is given in Table 10. The table is illustrative only [redacted] Financing of the second stage fit out could be treated as a separate exercise if necessary.

Key tasks for implementation of a funding package include alignment of government initiatives and the need to lock-in commercial partners. Commercial interests may be represented as investors in the facility itself, as long-term clients, as manufacturing partners offering related services, or as facility operators. Because of the range of possibilities for involvement of local manufacturing partners, and reflecting the aspiration to have the participation of an international CMO, it is important that a flexible corporate structure be developed for progression of the project. These issues are addressed in more detail in section 7.2 "Action Plan".

[redacted]



[redacted]

6.2.7 Swot Analysis of Option

Strengths

- Proposed scale and range of operations will provide a point of difference with any other Australian CMOs, and equal any similarly focused operation globally.
- The marketability of the facility is enhanced by drug development capabilities upstream and downstream of the facility itself; particularly the process development strength in universities and institutes, and integrated clinical support available.
- There are strong indications that local biotherapeutic drug developers could underpin the revenue stream. In particular, [redacted] and [redacted] have indicated a preference for a competitive local facility for their mammalian cell production needs. [redacted] could offer supply contracts for Pi88 protein derived from microbial processing.
- [redacted] is a candidate as a facility operator, as they are not averse to spinning out their existing CMO operations.

Weaknesses

- The slow development times and attrition rate for local drug discoveries may create cashflow disruptions for such an expensive facility. Working capital requirements would increase significantly.
- Lack of locked-in supply contracts weakens the case for fundraising.
- Lack of a big CMO as facility operator weakens the attractiveness of the facility in terms of reputation for consistency and reliability.

Opportunities

- Contacts with big pharma and big CMO's thus far have been very preliminary in nature. Also time and resources have not permitted a thorough canvassing of all the major players. The opportunity for a significant alliance to support the facility therefore remains open. Similarly, serious discussions regarding supply contracts or preferred supplier arrangements have not yet been pursued with local firms.

Threats

- Local firms comprising potential customers for a new facility may have, or may develop, alternate preferred deals through existing or future commercial relationships.
- Competition from CMO's specialising in scale-up. Regionally, A.Bio in Singapore is a threat, whilst further afield, UK's National Biomanufacturing Centre is targeting the same niche market.

6.3 Option C
Staged development – Option A+B

There is the possibility of adopting a staged development option. During the first stage, the capability of an existing CMO would be enhanced in order to provide a short-medium term boost to ability to service local demand , whilst a comprehensive longer term solution (stage 2) is validated, designed, constructed and commissioned.

A variant on this theme would be to create a stage 1 alliance group comprising more than one existing CMO, each focusing on areas of particular complementary expertise. A formal alliance between CMOs with complementary capability, and with funding to support business development and new facilities, could create a synergistic effect. A new umbrella company with an over-arching business development and coordination function would be needed to align the independent interests.

According to this option, the first stage is a transitional one, during which market knowledge and business development savvy could accumulate whilst plans for larger facilities were being implemented. The existing CMO(s) in collaboration could be assimilated into the new larger enterprise, or continue as autonomous complementary units specialising in servicing particular segments of the market.

A business model based upon synergistic development of existing CMOs cannot be determined other than on a conceptual basis at this point in time. This reflects the fact that participation has not been canvassed with the potential partners, and the perceived limitations and blockers to expansion of the individual enterprises have not been assessed. Therefore the needs in terms of capital, technology and other forms of industry support cannot be determined, nor can meaningful estimates of future revenues or earnings be undertaken. Such endeavour may form a logical extension of the work conducted for this report.

7 Recommended Option and Action Plan

7.1 Greenfield scale-up facility

The most visionary option and the one which constitutes the ideal or best case for national long-term wealth creation is the Greenfield Model (OptionB). A facility of this type would position Australia as a global player in the niche CMO segment catering to scale-up clinical development. It would also showcase Australia's broader biotechnology and biomedical expertise by its linkages with and promotion of Australian upstream and downstream capabilities in drug development.

Reference to overseas examples of similarly sized biotherapeutics scale-up facilities (NBC, Mbio, A-bio), suggests that a greenfield development by a new entrant to the CMO space will not occur without significant and visible government facilitation, even with a big CMO partner involved. The potential for low initial utilisation of a new facility, combined with high ongoing overheads represents a downside risk for early years of operation. An alliance with an established international CMO potentially reduces this risk by virtue of leveraging the CMOs operational reputation and existing client base. The favoured business model evident from overseas experience is for the facility to be funded largely from public sources, with the CMO having an operating lease or similar arrangement.

This business model does not preclude a mix of public and private funding for the construction of the facility; indeed such a mix should be pursued as one of the recommendations of this report. Such an effort will, however, entail brokering discussions to establish the interest levels of a range of different organisations, and further tightening of the business case to increase the attractiveness to investors.

A stand-alone international-class CMO facility of the type outlined in this report should cater for a range of routes to expression, with complementary process development and process optimisation services able to deliver-up robust and production-ready technologies. A range of capabilities significantly expands the potential client base, and spreads risk associated with one technology or one client.

The ability to perform aseptic fill-and-finish including lyophilisation will be necessary to meet market need. This capability forms part of the capex budget for the Greenfield Model, but a possible alternate route would be to outsource these activities [redacted]

The greenfield option prospectively provides for future demand currently building-up locally in the discovery and early clinical development areas. The survey performed for this report indicates that at least 59 compounds produced using mammalian cells are in development. Whilst these comprise a range of product types and different production requirements, it is certain that Australian drug developers will increasingly be seeking a facility of the type described. In the course of the current survey, 12 organisations indicated they had sought or are currently seeking biotherapeutics development quotations from foreign CMOs, and of these 8 related to mammalian cell applications.

Just as importantly, a scale-up facility offering a flexible and comprehensive range of technology-transfer services will encourage the capture of foreign-sourced projects and revenues. Australia should use its pre-eminent position in the region to leverage the attraction of the facility. With good IP protection, sophisticated regulatory environment, established clinical trials capability, skilled labour pool, and political and financial stability, Australia is well positioned to meet the needs of international clients, and hence represents an attractive destination for drug developers seeking a position in the Asian time zone.

With appropriate marketing and promotion, a greenfield scale-up biomanufacturing facility would make Australia the preferred regional supplier of clinical development services. Whilst there is, as yet, little evidence of emergent clinical-stage biotherapeutics from SE Asia, such demand is predictable, based on the major investments in biomedical research. ,Despite Singapore's impressive investments, that country still cannot boast the long history and depth of Australia's academic institutions nor the same critical mass in terms of research capability. These attributes augment the attractiveness of Australia as a regional destination for a scale-up facility and for clinical development in general.

The local unmet demand, today, for mammalian cell culture capacity for clinical trial material is marginal in terms of justification for a greenfield investment of the magnitude proposed. Potential revenues from Australian current mammalian cell-based projects could amount to a $16-35M per annum. By catering for a broader range of products and services (eg vaccines, peptides, contract fill and finish) and expressions systems (eg microbial, viral) this potential should extend to more than double that for mammalian expression alone (say $30-60M).

However, CMO competition and the likelihood of partnering deals which involve scale-up via other routes means that capturing this local potential in its entirety is unlikely. A more reasonable expectation might be to target (say) 70%* of potential revenue from Australia (ie. $40M per annum). Since revenues of $30M per annum will provide satisfactory commercial return for the proposed facility, the business case does not rely heavily on assumptions regarding attraction of international clients. However, given the uncertainty of the timing of locally originating projects and the uncertainty regarding ability capture these in practice, it would be prudent to plan for overseas project revenue to comprise a significant proportion (say 30%*) of total revenues.

* There is not an objective basis for determination of these percentages; rather they are tabled as reasonable business targets for a commercial operator to pursue.

7.2. Action Plan

Set up and fund a development entity

To provide focus and momentum to the scale-up facility project, a dedicated group will be needed. This group, or Development Entity (DE), should be commercially-focused and led by people with CMO industry experience. This should be funded by government for a period of 2-3 years, and the activities of the DE will address the matters outlined below. The DE could ultimately fold into the scale-up facility, or remain as an industry-support group after the scale-up facility is up and running.

Strategic plan for biotherapeutic scale up facility

A formal implementation plan should be the first task of the DE. This plan will scope the objectives of the organisation and establish a budget and timeline for attainment of the objectives. The primary objectives will be to establish a funding model for the new facility and to secure alliances with complementary service providers, future clients and with a major CMO or big pharma partner.

Alignment of government initiatives

Funding

Development of scale-up facilities to meet future and current unmet demand has been identified for attention by not only by the Federal government, but also by the Victorian, West Australian and Queensland governments. The Queensland Government has announced an allocation of $7M to progress scale-up development. The Victorian Government has indicated in-principle support for a well-structured, industry-led initiative. More recently the WA Government has expressed interest in a scale-up facility for expansion of specialist cell types such as those pioneered by Professor Fiona Wood. Beyond Australia, the NZ government has recognised a gap in their scale-up capability.

A key action item for the DE would therefore be to consolidate support from the various governments with a stated interest in enhanced scale-up capability.

NCRIS

Whilst NCRIS is aimed at building research infrastructure, it is important that the scale-up facility concept and model be integrated with any complementary NCRIS efforts towards development of bioproducts. The logic of this linkage is highlighted by the blurred demarcation between fee-for-service work conducted by academia and contract R&D which would be performed by the proposed CMO operation.

The Development Entity should progress this integration of the scale-up facility with any relevant emerging NCRIS strategies.

Project Management

The DE would control the design and building of any new scale-up facilities. Preliminary steps would include confirmation of the facility's functionality, and to translate this into a design brief. Capital cost estimates in this report have been quoted to an accuracy of no better than ±25%. Therefore it is recommended that a further study be conducted to more thoroughly analyse options, and to refresh pricing on key items of equipment.

Additionally, a detailed review of site options should be conducted by DE. The suggested approach would be to engage consulting engineers to perform the site evaluation, and to develop specifications for the facility and the equipment.

Lock-in strategic partners

Clients

- The capability of the new facility must be marketed vigorously to the potential client base, with a view to securing manufacturing contracts. Local targets should include those organisations identified in this report as having mammalian cell-based projects which are currently active

- Beyond the local scene, marketing plans should be drawn up to project the facility's capability into the Asia Pacific region. Such a plan should include detailed market research to quantify future regional demand.

- Bio 2006 would present a good forum for gaining international exposure for the facility.

- In order to properly support such an effort, a dedicated business development resource should form part of the DE human resources plan.

Manufacturing partners

Strategic linkages with a number of existing providers could avoid unnecessary duplication of resources. This report has identified potential partners including (aseptic fill and finish; especially lyophilisation), (small scale cell processing and expansion), and (microbial expression).

The Development Entity should engage these firms with a view to developing memoranda of understanding or other similar instruments to lock-in any win-win alliances. The philosophy should be to leverage existing capability where possible.

International partner

The pivotal importance of an alliance with a big CMO player to underwrite quality and operational credibility has been stressed on several occasions in this report. This interest could be via an equity position, or as the facility operating entity. A key target

for the DE should therefore to follow-up on the preliminary contacts made with overseas CMOs as part of this report.

Corporate structures and governance

Because of the range of possibilities for involvement of local manufacturing partners, and reflecting the desire for participation of an international CMO, it is important that a flexible corporate structure be developed for progression of the project. Advice should be sought by the DE as relationships develop.

The DE itself needs to be constituted in such a way that future options are not precluded for administrative/structural reasons. It is recommended that the DITR examine the options for corporate structure and governance in the first instance, given that public funding is suggested as the primary vehicle for commencing the project.