Irrelevant 73(2)

Mr Hughes is also undertaking a consultancy for the Commonwealth Government in relation to a National Scale-Up Facility. Irrelevant 73(2)

Pages 2 through 15 redacted for the following reasons:
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s.73(2) Irrelevant

Irrelevant 73(2)

Recently the Federal Government Department of Industry, Tourism and Resources has let a tender for a project to evaluate the feasibility of a new mammalian cell-based biopharmaceutical operation. The tender will be performed by Zektingroup, a Melbourne-based consulting engineering firm. Allied with Zektingroup is Innovation Dynamics, who developed the first business case for a scale-up facility for the Queensland Government. Queensland's AIBN is also a party to the bid.

It would be very useful if the information collected during the Federal process could be combined with the conclusions in this report. If complementary capabilities from other states can be aligned with the Queensland strategy by way of network participation to assist in the crucial first stage, or by way of support for the larger facility, the chances of success will be increased.

Irrelevant 73(2)

Pages 17 through 76 redacted for the following reasons:
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s.73(2) Irrelevant

Irrelevant 73(2)

Since 2003, a number of reports were commissioned by the Queensland, Victorian and Federal Governments which all indicated a scale-up capability gap existed in Australia. Irrelevant 73(2)

Irrelevant 73(2)

Pages 78 through 86 redacted for the following reasons:
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s.73(2) Irrelevant

Irrelevant 73(2)

1.4 Related Commonwealth Government Initiative

The Commonwealth Government has also been progressing an initiative to establish a mammalian cell-based scale-up manufacturing facility in Australia. The federal industry group, Pharmaceuticals Industry Action Agenda (PIAA), identified an infrastructure and capability gap at the early pre-clinical and clinical trials phase for scale-up services (refer to 2.2 for more detail). In particular, the PIAA identified the need for a mammalian scale-up manufacturing facility in Australia.

In response, in October 2005, the Commonwealth Government's Department of Industry, Tourism and Resources requested a feasibility study for a new biopharmaceutical operation in Australia. The study was completed in December 2005. The Commonwealth Government has advised that it is seeking funds for such a facility through its current budget process.

Irrelevant 73(2)

Page 88 redacted for the following reason:

Irrelevant 73(2)

Irrelevant 73(2)

2.2 Market Gap in the Domestic Scale-Up Manufacturing Market

The unfilled demand described above indicates that the Australian biotechnology industry faces an infrastructure and capability gap for scale-up services at the early pre-clinical and clinical trials phase. Australia has a shortage of Good Laboratory Practice (GLP) and particularly Good Manufacturing Practice (cGMP) facilities and existing facilities are either running at capacity or do not have the technical capability to meet the demand. The lack of these facilities is impeding Australia's biotechnology industry from reaching its full potential.

The potential client base from Australia is fragmented and lacks the coordination to consolidate their needs into a single new commercial entity. Further, early stage biotechs developing drugs typically intend to outsource their process development and manufacturing needs. This reflects a desire to concentrate on areas of core competency, as well as the significant barriers to entry for biopharmaceutical manufacturing. Therefore these biotech companies have little or no aspiration to become CMOs. However, government support through BPA can provide this coordination and sectoral business development support.

In analysing the market gap, it is important to understand the barriers to entry into the CMO market. Firstly, the costs involved in establishing and operating a GMP scale-up capacity, even for a single product, are often prohibitive for small and early stage biotechnology companies. Further, the flow of locally originating projects is sporadic and unpredictable, making revenue and working capital requirements difficult to estimate. Also, the CMO market is relatively mature, and operates on a global basis, meaning that there are well-established competitors with reputations for service, longevity and reliability.

Long drug development lead times (8-12 years) and significant drug development costs ($500M - $1B) predispose Australian biotechs to partner with well established international CMO service providers who offer security throughout the product's early life cycle. Lack of an established reputation is therefore a major barrier to entry in its own right.

Due to these significant barriers to entry for a new CMO, Government support and assistance is required, particularly for a CMO of the size, capability and scale envisaged in the BPA initiative. Additionally, against this backdrop of high barriers to entry, there has been a lack of major

incentives for international pharmas and CMOs to establish a CMO facility in Australia. For example Australia has not been able to match the financial and tax incentives of other biotech focused countries such as Singapore, Scotland, Ireland and some States in the United States.

Irrelevant 73(2)

Pages 91 through 112 redacted for the following reasons:
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s.73(2) Irrelevant

Irrelevant 73(2)

Commonwealth Government and International Investment

Mr Brian Anker, Deputy Director-General, Innovation and Smart State Policy, has now communicated further details of this Queensland initiative to Mr Craig Pennifold, Head of the Innovation Unit within the Commonwealth Department of Industry, Tourism and Resources. Mr Pennifold had previously advised that he was pursuing Commonwealth funding between $5M and $10M. This decision is based upon the preliminary recommendations of a feasibility study commissioned by the Commonwealth Department of Industry, Tourism and Resources.

Irrelevant 73(2)

Irrelevant 73(2)

Mr Hughes has prepared a comprehensive Business Case on the Queensland Scale-Up Manufacturing Facility for DSDTI (refer MN=70799 at **Attachment 1**). Mr Hughes has also completed a consultancy for the Commonwealth Government in relation to a National Mammalian Scale-Up Facility.

Irrelevant 73(2)

Business Case Analysis for an Australian Mammalian Cell Biopharmaceutical Facility

January 2006

Note: some sections of this report have been deleted to protect Commercial-in-Confidence material

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1.0 Executive Summary

The survey conducted as part of this study provides the most recent and comprehensive review of research and clinical development involving therapeutic applications of mammalian cell-derived molecules in Australia. Most compounds are at the discovery or preclinical stage of development, with 49 of the 59 mammalian cell products identified falling in this category.

The status of biotherapeutics manufacturing in Australia has been reviewed in order to determine the capability of the local industry to accommodate the potential demand indicated in the survey data. In broad terms, biotherapeutics are either produced in-house or outsourced to Contract Manufacturing Organisations (CMOs). There is an increasing trend toward outsourcing of scale-up and commercial production to CMOs, and this trend is forecast to grow in future.

In Australia there is currently no CMO able to offer mammalian cell stirred-tank fermentation services under Good Manufacturing Practices (GMPs) that are compliant with the requirements for sterile injectable drugs in their finished form. There are, however, a number of local CMOs offering biotherapeutics development capabilities which can offer at least partial solutions to the future needs of the industry. This report also investigates those capabilities.

The international biotherapeutics manufacturing industry has been examined in some detail to provide the context for a strategic development plan to address the current capability gap in Australia. The latest international survey data indicates that the biotherapeutics industry has been growing at 15-20% per annum, and that this growth will continue. The report focuses in particular on the international CMO sector in order to identify key success factors which should be incorporated into the business strategy for development of enhanced local capability.

Whilst CMOs have proliferated over the past two decades and now constitute a major industry in their own right, there are relatively few worldwide (about 20) who are dedicated to scale-up production of biotherapeutics. This indicates a possible niche-marketing opportunity for an Australian initiative. This report seeks to define this opportunity in more detail. Options for a "greenfield" plant, and for extension to capability of existing operators have been developed.

Reference to overseas examples of similarly sized biotherapeutics scale-up facilities suggests that a greenfield development will not occur without significant government support. 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 CMO's operational reputation and existing client base. The favoured business model evident from overseas is for the facility to be funded from public sources (or from a mix of public/private funds), with the CMO having an operating lease or similar arrangement.

The process of attracting a suitable CMO-alliance partner for the operation of a new facility represents a challenging undertaking. An attractive and tightly structured proposal must be developed, and then promoted and supported in coordinated

fashion to best leverage the capability of governmental and industry interest groups. Further, it needs to be recognised that the probability of an Australian proposal falling on fertile ground within the strategic planning cycle of the major CMOs is likely to be low. The "courtship" process may therefore take some time in its execution.

The report provides an operating financial model for a new facility. In assessing potential revenues, discussions with local industry have established the costs of access to overseas CMOs. These specialised services typically cost $1.5 - 2.0M for preclinical process development and for generation of early clinical batches, and up to $5 -10M for full technology transfer at Phase 3 and transition to commercial production. These valuations have been applied to the current and forecast number of biotherapeutic molecules in development in order to create a turnover projection for a new facility.

The future revenues from the current pipeline of Australian mammalian cell-derived products are, alone, marginal in terms of being able to sustain the operation of a greenfield facility, the capital cost of which has been estimated to be close to $40M. Hence the business model for such a facility needs to contemplate catering to other modes of product expression, such as microbial and viral cultures. International marketing of the new facility is suggested as a way of reducing risk associated with limitations of the local market. Additionally, an alliance with a big-pharma company (by way of supply contracts) and/or with an established CMO (as operator) is regarded as pivotal to the commercial success of such a scenario. Preliminary contacts along these lines have been initiated as part of this study, but require a separate, dedicated effort to move such overtures to fruition.

Based on an assumption of $30M (2005$) revenue being ultimately attained in a greenfield facility developed in two stages, a positive NPV and IRR of 19% have been determined. The staging assumptions for facility construction and market penetration are relatively conservative.

Beyond the direct operations of the plant, major benefits also potentially accrue from the local replacement of currently imported CMO services, and from attracting foreign income. The economic spillovers of such a facility have been considered, and the benefits in terms of an expanded skill base and integrated value chain for drug development should be considerable.

A less ambitious strategy would be to focus on improving the capability of existing Australian manufacturers, both in terms of the range of technical solutions offered, and in terms of the quantum of business development effort. However, this option would offer less to the economy both in terms of direct benefits and non-financial spillover effects.

In summary, if Australia is to best leverage its investment in biopharma R&D infrastructure and to reap the benefits of the sustained growth in discovery research and clinical development, a scale-up facility which offers a comprehensive range of manufacturing services is needed. Such a facility should be internationally marketed to spread the risk associated with uneven and unpredictable flow from local lead-compound development activity. Ideally, supply contracts with a major international pharma player and the participation of a well-known CMO should also underpin the proposal.

2.0 Methodology

This Report has been prepared in response to the Request For Tender (RFT) "Requirement for Mammalian Cell Facility", reference number ITRINNOVRFT280705, issued by the Department of Industry, Tourism and Resources (DITR).

The Study was carried out by:

- Joe Gangi - Project Manager, zektin*group*
- David Hughes - Project Team Leader, zektin*group*
- Kelvin Hopper - Innovation Dynamics
- Lyndal Thorburn - Innovation Dynamics
- Miranda Bailey - Innovation Dynamics
- Maha Nasser - SeerPharma
- Peter Gray – Australian Institute of Bioengineering and Nanotechnology

In Conjunction With:

- Bio-Manufacturing Working Group of the Pharmaceuticals Industry Action Agenda
- DITR

The report has generally been structured according to the detailed requirements laid out in the RFT. Where appropriate, some responses to the requirements have been integrated with related items. For instance, the response to the economic evaluation requirement has been integrated into the discussion regarding the impact of the capability gap on Australia's competitiveness and the financial evaluation of the options for filling the gap.

A selection of Australian biotechnology companies were interviewed to establish the current and future demand in Australian for mammalian cell expression technology. In addition, companies were also asked to provide the location of current and future manufacturing with the aim of gaining an understanding of the number of companies taking their manufacturing requirements offshore. Details of the survey and participants are given in the Appendices.

Also contacted were a range of research institutions to ascertain the level of activity with mammalian cell-based projects, both from the aspect of fundamental research, as well as from their perspective as Contract Research Organisations (CROs). The "CRO" terminology is also sometimes taken to encompass Clinical Research Organisations. Again a range of companies operating in this sector were contacted. It was useful in this context to have SeerPharma as a partner contributing to this report, since SeerPharma provides contract regulatory affairs management and other related services, which form an important part of clinical research activity. Further, SeerPharma operates internationally, with a particular focus on the South East Asian area.

Contact was also made with a number of local and international Contract Manufacturing Organisations (note that CMOs also commonly offer CRO services). These preliminary contacts had limited success in eliciting responses, given the relatively short duration of the study period. This was particularly the case with international CMOs.

The information arising from interviews and discussions with researchers, biotherapeutics developers, suppliers to the biopharma industry, CROs, CMOs, large pharmaceutical companies, and clinical trials and clinical research providers have been combined throughout the report with data gathered from internet research, and published materials to provide a comprehensive and current overview of the environment within which a new scale-up facility for production of biotherapeutics would operate.

3.0 Gap Analysis

3.1 Preamble - Background to Mammalian Cell-Based Products and Processes

Mammalian cell expression systems may be used in the manufacture of several types of products with therapeutic activity or having diagnostic utility. These are:

- Recombinant proteins
- Recombinant vaccines
- Peptides (usually large peptides that are not satisfactorily manufactured synthetically)
- Monoclonal antibodies – usually whole antibodies used either as therapeutic products or in diagnostics. These are not satisfactorily manufactured in other expression systems due to the folding required and their multichain structure.
- Whole cells (will include mammalian cell vaccines, stem cell expansion, ex vivo treatment and other cell applications and types)
- Other products of mammalian cells such as DNA, carbohydrates and lipids etc.

The major product groups currently in development in Australia are recombinant therapeutic proteins, vaccines and monoclonal antibodies. This analysis focuses on proteins (therapeutics, vaccines and monoclonal antibodies) and peptides but also considers other products that may be derived from mammalian cells in culture. In the future, cell-based therapies will increase in use, but their manufacture is likely to be limited to local, patient-sourced material and in low amounts. There will also be a large increase in the use of adult stem cells and treatments based on more generalised cell types.

Due to the cost of mammalian cell culture, its use is generally restricted to production of high value products where the advantages of the mammalian expression system, for example, particular protein structures and folding or post-translational modification, are required Bacterial or yeast fermentation are alternatives for the production of some protein products and chemical synthesis is a preferred alternative for the production of small peptide products. In the future other novel routes for protein expression are likely, including in transgenic plants (such as tobacco) and animals (for example protein expression in milk). Such approaches will also be used for production of lower cost, bulk material, whereas closed, eukaryotic or prokaryotic culture systems will be more likely used for biopharmaceutical and highly regulated and high value items.

3.2 Global Capability Review

This section of the report firstly gives, by way of setting the scene, a high-level overview of the state of the biotherapeutic industry. The report then examines in more detail some of the driving forces behind the demand for biotherapeutics manufacturing, and the emergence of an outsourced manufacturing sector specialising in that area. A more comprehensive analysis of driving forces has been included in the appendices (Appendix1), with salient drivers highlighted below.

The manufacturer's perspective is then reviewed in a discussion of factors affecting the supply-side of the equation. Again a high level introduction is followed by a summary of the key drivers.

The mammalian cell culture-based subset of the global biomanufacturing industry is then reviewed along the same lines as outlined above for the broader biotherapeutics arena.

A previous report by Innovation Dynamics(9) compared Australia's preclinical and scale-up situation with that of Canada and Germany, two of the pre-eminent biotech centres after the USA. That information has been revised and summarised as part of the current investigation in order to illustrate the potential demand arising from key countries.

3.2.1 Biotherapeutic Manufacturing

a. Biotherapeutic Drug Industry growth - Overview

The biotech drug market is one of the fastest growing sectors globally. This growth is evident in a wide range of indicators, and provides a very positive overall context for investment in the biotherapeutic drug pipeline.

Global biotech revenues have increased about 20% per year over the last decade(1). During 2004 revenues grew 17% to US$54.6B (2). This followed 15% growth in global biotech drug sales worldwide in 2003 (3).

Further, the global biotech industry raised 15% more capital in 2004 vs 2003 (to US$21.2B), R&D spending rose by 12% (to US$20.9b) and employee count went up by 5% to 184,000 worldwide . There were 365 products in phase 3 clinical trials in December 2004, up on 290 in the prior year, with 55 New Drug Applications submitted to the FDA in early 2005 (2).

Biotech companies in the Asia-Pacific region increased revenues by 36% during 2004, fuelled in part by increased sector focus from regional governments. The R&D spend in the local region rose 17% to US$253M in the same period, and headcount increased from 9,810 to 13,410(2).

b. *Biotherapeutics Global Demand - Overview*

Growth in commercial opportunity for scale-up and production is reflected in the number of companies which are active in discovering and developing biological drug products. Frost and Sullivan(1) indicated that there were some 4,400 biotech companies worldwide in 2003, and about 370 biotherapeutics in clinical trials by 2004. More than 600 biopharmaceuticals were known to be in advanced development (5).

There has also been a distinct movement in strategy toward biopharmaceuticals by some of the largest drug companies in the world, whose traditional product base comprised small molecules made using synthetic chemical methods. Many big pharma companies have made an entry into biotech via major acquisitions(7). Pfizer took over Pharmacia in 2003, Wyeth purchased Genetics Institute, and Abbott took a biotech presence via acquisition of Knoll Pharmaceutical (2001). Roche had made the move to biotech products earlier, adding hugely to its already-significant existing capability by buying Boehringer Mannheim (1998) and taking a majority stake in Chugai.

c. *Driving Forces - Demand Side*

- Biotechnology offers new solutions to diseases of aging and affluent societies. The Human Genome Project has opened the door to rational design of cures for previously intractable illnesses. This has led to the proliferation of biotech discovery companies.
- Rapid advances in screening technologies have accelerated the process of evaluating drug candidates; hence more drug candidates are being produced than ever before.
- Increasingly there is a movement toward biological drugs compared to the traditional dependence on small molecules (synthetic chemistry) (6). This driving force has seen all the big pharma companies move into biotech.
- Partnering is a major trend which has developed in the last 5 –10 years. Traditionally big pharma tended to rely on in-house resources from research right through to manufacturing. Increasingly it is the case that certain functions are outsourced in part or in full(2). Conversely, early stage discovery firms often had aspirations to conduct manufacturing in-house. Today a new paradigm has emerged, according to which discovery companies never plan to take on commercial development beyond proof of concept or early clinical trials. Such a business model inherently favours growth of Contract Manufacturing Organisations (CMOs).
- The cost of taking a drug from discovery to market is becoming increasingly costly; being variously mentioned at between US$500 million to over US$1 billion. The cost factor is a major driving force behind partnering and outsourcing of production. By outsourcing to a CMO, a drug developer avoids making major capital expenditure, and limits financial risk in the event that the product fails during clinical trials.
- Assuming availability of production slots, the time-to-market can be reduced by using a CMO, since there is no waiting period associated with design and construction of dedicated facilities. Time- to-market is a critical factor, since the period of patent coverage in the market can be

significantly reduced by the extended time taken for clinical trials and facility construction and validation.

- The cost of CMO services is perceived to be very high by prospective customers in the form of start-ups, who often have little appreciation of the complexity of the process development and clinical development issues.
- Regulatory agencies are imposing ever-increasing requirements for validation of efficacy, purity, safety and identity of drug compounds. This means customers will require cGMP compliance for all phases of clinical development, including phase1 (TGA has yet to adopt this requirement, but would be expected to pursue harmonisation).
- Monoclonal antibodies comprise a major compound class now emerging through clinical trials and these products are manufactured in mammalian cell culture. Seventeen monoclonal drugs have been approved for use, with sales expected to reach $9B by 2006 (22).
- Due to the heightened research effort over recent years, there has been a large increase in new technologies and drug modalities needing testing and clinical trials. Consequently, as well as demand for gross manufacturing capacity there is a need for highly efficient drug process development and optimisation to maximise yield. This requires scientific skills and problem solving and close co-operation with biotech companies and CMOs.

d. Biotherapeutics Global Supply - Overview

There are some hundreds of biotherapeutic manufacturers worldwide(1)(4), of which approximately 80 are cGMP-compliant contract manufacturers(5). Some manufacturers of biologics produce their own in-house products as well as offering contract services (e.g. Boehringer Ingelheim, DSM, Baxter).

The 2005 Bioplan survey(4) provides the most comprehensive and up-to-date situation analysis of global biotherapeutic manufacturing. There were 187 manufacturers in the survey, as well as 117 providers of services to the biopharma producers. Of the 187 manufacturing firms canvassed, 53% were involved in large-scale mammalian cell culture, 42% performed large-microbial fermentation for therapeutics, and 30% (n=56) described themselves as large-scale CMOs. Only 11% (n=21) producers were fully dedicated to scale-up production.

The specialist scale-up CMO segment is therefore relatively undeveloped, and represents an area of potential interest in terms of further investment. It is noteworthy, however, that large scale CMOs also offer scale-up capability, and often aim to provide a full range of services and the benefits of a one-stop shop approach.

Bioreactor capacity distribution amongst the major CMOs was reported in the 2005 Bioplan survey(4) as follows:

Table 1 Bioreactor Capacity Distribution -- CMOs (2004)

CMO	% CMO Capacity
Boehringer Ingelheim	41
Lonza	22
Abjenix	8
Diosynth	6
Other	23

This analysis of sector capacity differed somewhat from that reported by Frost and Sullivan (2003) (1), (see table 2 below). These differences may be attributable in part to new capacity coming on-line since the earlier report (refer altered ranking between Boehringer Ingelheim and Lonza), but there may also be some issues relating to the definitions of biopharmaceutical manufacturers. In particular, Fermpro and Biochemie have very large microbial capacity but are small players in the injectable biologics sector and may not have been included in the more recent report.

Table 2 Biopharmaceuticals Industry Analysis : Top 10 CMO's in Terms of Capacity (Global) 2003

Ranking	Company	Capacity (litres)
1	FermPro	500,000
2	Lonza	317,950
3	Boehringer-Ingelheim	186,300
4	Biochemie	66,000
5	BioInvent Production AB	60,000
6	Biosentrum AS	31,500
7	Alberta Research Council	30,000
8	Sandoz	26,000
9	Diosynth-Covance	13,000
10	DSM Biologics	7,500

Note: All figures are rounded. Source:Frost and Sullivan estimates (1)

In fermenter-volume terms, the top few CMOs control the lion's share of commercially available capacity (variously mentioned as being 65-90% of total CMO capacities held by the top 10 firms (1)).

Capacity utilisation has fallen somewhat since the last BioPlan survey in 2003. This has been attributed to significant new capacity coming on line in the last year. An additional influence is the progressive advance in levels of product expression and

recovery. Such improvements increase productivity in existing capacity, and therefore reduce the perception of capacity limitation.

Total global industry capacity (all cell types), is currently perceived to be 70% utilised, compared to 79% in 2003. CMOs perceived a higher global industry utilisation rate (73%) than did biotherapeutic manufacturers (68%). These figures are broadly in-line with forecasts by Frost and Sullivan in 2003(1) , which predicted capacity utilisation to be at 70.5% by 2006 after a drop to 59.5% in 2005 as new tankage came on stream.

However, at the individual enterprise level, biotherapeutic developers were twice as likely versus CMOs to report that they were currently experiencing capacity constraints. This presumably reflects the tendency for the former to install dedicated in-house capacity, which should be fully utilised, all other things being equal.

It is worth noting that capacity constraints emerge at less than 100% of theoretical full utilisation due to inefficiencies created by scheduling, product, mix, and line changeovers. These factors impact more on CMOs with multiple clients than they do on big pharma, with in-house capacity which is likely to be dedicated to a single product or a few products only. This creates a heightened sensitivity in CMOs to capacity issues, and may explain the lower in-house utilisation rates perceived by CMOs when compared with biotherapeutic developers(1).

Mammalian Cell Capacity

In the case of mammalian cell capacity, global industry utilisation has fallen slightly from 69% in 2003 to 64% in 2005 according to a recent industry survey by BioProcess Technology consultants(4). This trend to a slight fall in overall utilisation mirrored the BioPlan data for biotherapeutics in general (see above).

At the individual company level, the BioPlan 2005 study indicated that CMOs reported themselves to be at 64% utilisation, whilst biotherapeutics developers claimed 83%.

Microbial Cell Capacity

The BioPlan survey indicated that CMOs saw themselves operating at 58% of capacity for bacterial products, versus 77% for big pharma. Again this is consistent with a picture of dedicated in-house capacity purpose-designed for particular products and production volumes.

Future trends – Capacity

Notwithstanding current perceptions of global utilisation levels, 42% of the companies surveyed predicted that they will experience capacity constraints by 2010 (48% CMOs and 45% biotherapeutics developers). In fact, the companies surveyed by Bio Plan expected, on average, to increase mammalian cell capacity by 54% and microbial capacity by 40% by 2010. 28% of respondents expected to double mammalian capacity in the next 5 years.

Therefore it seems clear that whilst significant new capacity has come on-line in 2004-2005, the industry overall maintains a very strongly optimistic perception

regarding growth in biopharmaceuticals over the next 5 years. Frost and Sullivan's(1) forecasts indicated capacity utilisation at over 80% by 2008, rising to 85% by 2010.

The key reasons identified for likely constraints on capacity were lack of trained production staff, lack of finance for expansion, and physical limitations of existing equipment. Against this backdrop, key business strategy responses were to optimise expression levels and to balance downstream recovery steps with upstream improvements (ie improve internal efficiencies). Heightened efforts to increase the availability of training and education were also seen as important to avoid future resource problems.

Another factor influencing production capacity will be the increased use of disposable scalable equipment (rather than larger capacity fixed equipment) and process-standardized high-yield cell lines.

Trend to CMOs

The growth rate of biopharma CMO's revenues has followed that of the biopharmaceutical sector in general. Revenue growth (actual and forecast) from 2002 to 2006 averaged 20% per annum (5).

CMO's represent an attractive route to market which, for the client, offsets product failure risk and reduces need to raise capital to fund new facilities. Time-to-market is reduced because the period associated with building proprietary capabilities is by-passed. Until the advent of CMOs, in-house developers essentially were required to build their full-scale production facility, then await final regulatory approval before commercial sales could begin and investment recovered. The non-productive downtime following submission of the clinical and technical data package could amount to 1-3 years (depending upon jurisdiction and product). Only the largest companies could afford this approach.

Increasingly, even big pharma will outsource production of new products until the market and the economic viability of manufacture has been established. Some products are then brought back in-house into purpose-built facilities which offer optimal processing and economies of scale.

e. Driving Forces – Biotherapeutics Supply Side

- The leading CMOs possess the "first mover" advantage and have created formidable barriers to entry in the form of facility investments (of the order of US$300 – 500M in the case of the category leaders(1)), and a high level of technical experience and "GMP-compliance credibility". New entrants cannot hope to compete at the same level initially; rather a staged program over 10 years at minimum would be required.
- The importance of "industry credibility" cannot be over-emphasised in terms of attractiveness to clients. This credibility is garnered by maintaining a significant presence as a reliable, financially sound, and technically excellent provider over a period of years.
- Capacity utilisation has fallen recently as large investments in new tankage have come on line. However, continued industry growth is forecast to