Joint submission to the Economics References Committee's Inquiry into the Australian Manufacturing Industry

To: Committee Secretary
Economics References Committee
Department of the Senate
PO Box 6100
Parliament House
CANBERRA ACT 2600
AUSTRALIA
Via email: seniorclerk.committees.sen@aph.gov.au

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From: AusBiotech Ltd
[redacted]

Introduction

As Australia's peak industry body for one of the most innovative industries - biotechnologies – AusBiotech, in collaboration with Cell Therapies Pty Ltd, MTPConnect and Research Strategies Australia, is pleased to have the opportunity to contribute comment and recommendations to the Inquiry into the Australian Manufacturing Industry. Our submission is specifically in regard to gene and cell therapies or regenerative medicines (RM), an important and emerging sector of medicine.

AusBiotech is a well-connected network of over 3,000 members across the medical and biotechnology industry, which includes bio-therapeutics, medical technology (devices and diagnostics) and agricultural biotechnology sectors.

Cell Therapies Pty Ltd is a Victorian-based Contract Development and Manufacturing Organisation (CDMO) which manufactures and deploys advanced cell-based therapies to the global cell and gene therapy market. For almost twenty years, Cell Therapies Pty Ltd has actively developed and manufactured cutting-edge therapeutics for cancer, rare diseases, and other serious medical conditions on behalf of local and international clients.

Established by the Federal Government in 2015 as an independent, not-for-profit organisation, **MTPConnect** is Australia's Medical Technologies and Pharmaceuticals (MTP) Industry Growth Centre, championing the growth of Australia's vibrant MTP ecosystem.

Research Strategies Australia is a consulting firm with the mission of maximising the benefits of publicly funded research. We work with government, universities non-profits and the private sector to plan, manage and monitor research investments.

With more than 1,852 organisations and 240,000 employees, Australia has a substantial life sciences and biotechnology sector, which is consistently ranked as one of the top countries for biotechnology innovation globally when adjusted for population. However, it is estimated that 86 percent of the sector is in the SME category, the majority of which is yet to reach commercialisation or earn revenue. Featuring heavily in this cohort are companies developing new and novel technologies.

This submission addresses the terms of reference (TORs) noted below in regard to the Australian manufacturing industry in gene and cell therapies or regenerative medicines, with specific regard to:

- TOR a) what manufacturing capacities Australia requires for economic growth, national resilience, rising living standards for all Australians and security in our region;
- TOR b) the role that the Australian manufacturing industry has played, is playing and will play in the future;
- TOR c) the strengths of Australia's existing manufacturing industry and opportunities for its development and expansion;
- TOR d) identifying new areas in which the Australian manufacturing industry can establish itself as a global leader;
- TOR f) the role that government can play in assisting our domestic manufacturing industry, with specific regard to:
    - research and development;
    - attracting investment;

- supply chain support;
- government procurement;
- trade policy;
- skills and training.

Regenerative medicines (RM) and the opportunity

RM encompasses gene and cell therapies, and tissue-engineered products (TEP), and the advanced manufacturing that underpins and supports this sector, which is unique. RMs are complex and nuanced, based on cutting-edge science and the manufacturing processes required for these products are a crucial part of the value chain. Sophisticated advanced manufacturing is required to generate these products including expensive equipment and technologies, high levels of quality assurance and quality control, and a highly-skilled workforce. Further, the delivery of RM to the patient often requires an integrated network of entities with which manufacturing facilities are inextricably linked: hospitals, clinicians, supply chain logistics, and a highly skilled workforce pipeline.

Many regenerative medicine therapies (RMTs) represent the apex of "personalised medicine". Personalised RMTs (e.g. chimeric antigen receptor T cell (CAR-T) therapies) may use a patient's own cells, termed autologous cell therapy. This currently limits the ability of manufacturers to take advantage of scale-up efficiencies and requires facilities to accommodate scale-out manufacturing processes. Additionally, given the complexities of RM manufacture, the sector will continue to be workforce-intensive, requiring scarce highly-skilled personnel.

The emerging RMTs market is delivering ground-breaking results. To date, five CAR-T therapy products have reached the market, all of which are approved for the treatment of specific subsets of blood cancers. These cell therapies are achieving astounding results with complete remission rates of up to 90 percent. Currently used as third-line treatments, after two or more previous standard treatment lines, these therapies are showing comparable results to earlier treatments. It is expected that CAR-T therapies will transition up the treatment pathway and displace other expensive medicines and treatment regimes. In 2021 we have seen positive Phase 1 clinical trial results from the in vivo use of CRISPR gene editing to treat transthyretin amyloidosis - a world first.

Though these are complex therapies, they have the potential to reduce the burden of disease significantly, leading to better health outcomes for Australians, higher participation rates in the workforce, and impacting the economy on a large scale.

The potential of the RM manufacturing sector is large, and Australia is well positioned to capture the high-value opportunities that exist now, and in the future. Despite the COVID-19 pandemic, 2020 saw US$19.9 billion investment globally in advanced therapy developers[1]. This year's investment to date is on a trajectory to beat last year's financing with US$14 billion already raised in the first half of the year.[2]. There is a robust pipeline of RM products at various phases of clinical trials and the FDA predicted in 2019 that by 2025, 10 to 20 cell and gene therapy products will be approved each year in the USA[3].

Globally, the growing sector has more than 1,200 clinical trials in progress, with 97 ongoing RM Phase III clinical trials or products awaiting regulatory decisions in the coming months, therapeutics companies are turning their attention to the RM sector[4]. There are also increasing numbers of gene and cell therapies being developed in, and brought to, Australia for patient access.

Australia has an opportunity to harness and leverage a growing and active global RM industry. If we get this right, success could be worth at least $6 billion in annual revenue, 6,000 new jobs across the sector for Australia by 2035 and earlier access to ground-breaking therapies for Australian patients.[5]

Australia has a strong and active RM industry eco-system with basic and translational research capabilities, a clinical trials framework and clinical centres that are all internationally-recognised. More than 40 companies in Australia are developing RM products and more than 65 clinical trials are in progress[6].

Building Australia's sovereign manufacturing capability for complex and advanced RMTs will ensure equitable access to cutting-edge treatments for Australian patients, create new jobs now and for the future, and develop a highly skilled workforce. Commercially scaled resources will also build new export markets and deflect the prevailing trend of establishing advanced manufacturing in lower cost markets. By leveraging Australia's reputation for delivering high-quality, complex, and safe medical products, as well as our highly-skilled workforce, we can become the manufacturing hub for the region and deliver potentially life-changing treatments to patients, both in Australia, and the broader Asia Pacific region.

Why manufacturing regenerative medicines is unique

RMTs are based on cutting-edge science and require specialised Good Manufacturing Practice (GMP) manufacturing capabilities and infrastructure. To deliver these therapies to the patient often requires an integrated network of entities including advanced manufacturing facilities, hospitals, clinicians, supply chain logistics, and a highly trained workforce pipeline.

Capital infrastructure to support RM GMP manufacturing requires significant investment and unlike other medical manufacturing sectors such as biologics, manufacturing scale-up efficiencies can be difficult to capitalise on, such as within the autologous cell therapy paradigm where each production batch represents one dose for one patient. GMP infrastructure investment must be timely. The substantial growth in the RM sector has revealed a significant manufacturing capacity shortage. Right now, global manufacturing capacity is not meeting demand and it is approximated that five - times the current capacity is required[7].

An added complexity to the production and delivery of sophisticated products such as RMTs is their inextricable link to upstream and downstream value chain activities. Key components and starting materials such as GMP-grade viral vector, plasmid DNA, and mRNA are also in high demand and represent major bottlenecks in the RMT value chain. For example, some cell therapies require GMP-grade viral vector for ex vivo gene editing. mRNA vaccines such as those to protect against severe COVID-19 require plasmid DNA for upstream processes, and lipid nanoparticles for vaccine

formulation. As such, supply chain security is key to building and growing a thriving RM advanced manufacturing ecosystem.

To support the growth of the RM GMP manufacturing ecosystem, we need to build a high performing workforce pipeline. The GMP manufacturing process for RMTs is sophisticated and requires a highly skilled workforce engaging with novel technology and processes not generally found elsewhere. Access to a skilled workforce is a recognised barrier in Australia, and indeed globally, for the RM sector. The sector has not benefited from existing academic programs as these graduates have no exposure to true commercial-scale GMP manufacturing, nor have they experienced the operational overlay of the prevailing quality assurance and quality control systems. There is global competition for this talent, and one cannot deploy a new RM advanced manufacturing industry without a training pipeline to develop talent and skill with workforce-ready capabilities.

Current manufacturing capability and capacity

The results of the inaugural survey of RM GMP (Good Manufacturing Practice) manufacturing facilities within Australia are captured in a report[8], released in early September 2021. The aim of the report – *Australian Regenerative Medicine Manufacturing Capability and Capacity*[8] - was to establish Australia's present GMP manufacturing capability and capacity and develop a model for tracking change in the sector in the future. The data collected provides a benchmark against which growth of Australia's sovereign RM GMP manufacturing sector can be measured and tracked.

Seven Australian RM TGA-licenced GMP manufacturing facilities were identified. A further five RM manufacturers of products for early phase (O-I) clinical trials and that do not currently hold TGA licences, were identified and surveyed. These facilities are actively working toward TGA GMP manufacturing licences.

Surveys were deployed to all 12 identified RM manufacturers for participation between April-May 2021 and 10 full responses (one partial response) were received, a 92 percent response rate. A complete list of facilities can be found in the Report.

Of the 10 facilities across Australia that responded to the survey questions, four facilities are for-profit organisations, five are not-for-profit, and one facility identified as neither. The majority of facilities serve both academic and commercial clients (eight out of 10).

There are six dedicated cell therapy (including genetically modified cell therapy) manufacturers, three of which hold TGA licences. Nucleotides such as plasmid DNA can be used as starting material for the development of cell and gene therapies. Luina Bio Pty Ltd (QLD) is the only TGA-licenced manufacturer with the capability to manufacture GMP-grade plasmid DNA. Auspep Holdings Ltd (VIC) holds a TGA licence for the manufacture of GMP-grade APIs (Active Pharmaceutical Ingredients) such as peptides and proteins, which can be used as starting material for TEPs and biomaterials.

There are two multifunctional manufacturers: Orthocell Ltd (WA) manufactures cell therapies and TEPs and is TGA licenced for manufacturing autologous cells, and when it comes online later this year, the Westmead Viral Vector Manufacturing Facility (NSW, non-TGA-licenced) will manufacture cell therapies, and viral vectors at small scale for early phase clinical trials including for gene therapies.

Viral vectors can be used in the manufacture of cell therapies, such as lentivirus for CAR-T cell therapy manufacture, and AAV for gene therapies. Currently there are no TGA-licenced sites in Australia that manufacture GMP-grade viral vectors. This represents a significant gap in the value chain of sovereign manufacture of RMTs.

In 2019, the Westmead Viral Vector Manufacturing Facility (NSW) received a $25 million investment from the NSW Government for the expansion of their AAV vector manufacturing capacity. The facility expansion is expected to be completed by Q4 2021 and a TGA manufacturing licence will be sought. The facility will serve local and international cell and gene therapy markets for clinical-stage product. This represents a significant initial investment in Australia's viral vector GMP manufacturing sector, but the capacity is not sufficient to meet the current and future needs of the RM sector in Australia, nor the burgeoning APAC regional demand.

Case study
Cell Therapies Pty Ltd, Peter MacCallum Cancer Centre

A prime example of the need for sovereign advanced manufacturing for the RM sector is the production of chimeric antigen receptor T cell (CAR-T) therapies. CAR-T therapy is an innovative personalised immunotherapy that harnesses the innate power of a patients' own immune cells (T cells) by genetically engineering them to recognise and destroy cancer cells. A personalised one-time treatment, CAR-T is set to revolutionise cancer treatment and the healthcare system in Australia, where it has just been made available commercially, and globally, with access to these treatments in North America, Europe, and Japan.

The development of personalised CAR-T therapies involves several stages including the collection of T-cells from the patient via apheresis, genetic modification and re-programming **at a specialised advanced manufacturing facility**, and re-infusion of the modified cells. The manufacturing process for each patient is complex, nuanced and takes weeks. During the manufacturing time, patients are often placed on essential bridging therapy to carry them through this critical interim period.

Currently, Australia has only one GMP manufacturing facility equipped for commercial-scale CAR-T therapy manufacture, Cell Therapies Pty Ltd.

Cell Therapies Pty Ltd is a national leader in the cell and gene GMP manufacturing sector and is the only Australian CDMO with a TGA licence to manufacture T cell therapies for clinical and commercial supply. The GMP facility is located within the Peter MacCallum Cancer Centre, which has established itself as the Australian leader in cellular immunotherapy treatment and is in Australia's premier Biomedical Precinct in Parkville, Melbourne.

Novartis's Kymriah® (tisagenlecleucel) is the first CAR T-cell therapy to be approved in Australia, authorised by the TGA (Therapeutic Goods Administration) in 2018 for the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy, and paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse.

Though Kymriah® has been approved by the TGA since 2018, until recently there were no on-shore manufacturing facilities for commercial supply. Cell Therapies Pty Ltd was recently granted approval by the TGA to commercially manufacture Kymriah® for patients in Australia, making it the first of its kind in Australia, and one of only six locations in the world manufacturing Kymriah®. Beginning production early in 2021, the facility has been able to supply Kymriah® to other CAR T-cell cancer centres in Melbourne, Sydney, Brisbane and Perth that were previously relying on a manufacturing network stretching all the way to New Jersey, USA for processing.

Significant investment in the manufacturing capacity of Cell Therapies Pty Ltd has been instrumental to the onshore manufacture of Kymriah®. In 2019, the Commonwealth Government announced $80M funding to establish the Centre of Excellence in Cellular Immunotherapy at Peter Mac, co-funded by Peter Mac and the Peter MacCallum Cancer Foundation ($25M). This funding grant has supported an expansion of Cell Therapies Pty Ltd's facilities for large scale manufacturing of T-cell therapies, and as such, the commercial supply of Kymriah®.

Access to the local market is of course key to the onshore manufacturing of RMTs. However, for a sustainable and successful RM advanced manufacturing ecosystem it is imperative that increased manufacturing capacity is invested in to support export demand of the APAC market.

Barriers and opportunities

The key barriers for RM at this time are:

- Capacity constraints: Investment in GMP manufacturing infrastructure is needed to capitalise on the emerging and developing global opportunities;
- Capability lacking: Currently there are no TGA-licenced sites in Australia that manufacture GMP-grade viral vectors;
- Highly-skilled workforce pipeline;
- Key skills lacking within the manufacturing sector, such as GMP accreditation
- Ability to scale-up in Australia.

The opportunity for the Australian economy and patient access is to contribute to the development of infrastructure and capability across the entire RM value chain[9]. This will assist in taking advantage of the significant opportunities for Australian patients to access global therapies and products, as

well as for Australian companies to export novel RM therapies globally. We see that there is an opportunity for Australia to be a regional hub in the Asia Pacific region known for leading research, clinical trials, translational know-how, and manufacturing capabilities. It requires a significant uplift in our capabilities and capacity in order to service the opportunities.

We recommend doing this by:

- Mobilising resources, building stakeholder engagement, and advocating for mechanisms that provide researchers early access to clinical-grade cell lines;
- Mobilising resources and advocating for a national stem-cell registry for researchers;
- Advocating for ongoing and increased government investment in domestic manufacturing capability;
- Building stakeholder engagement and supporting activities aimed at improving health system readiness;
- Development of a highly-skilled advanced manufacturing workforce pipeline.

At the time of writing AusBiotech and Medicines Australia were co-leading an 'expression of interest' process to gather funding needed to progress the work above under the auspices of an RM Catalyst – as no single suitable organisation currently exists to drive this work. The RM Catalysts aim to support the Australian RM industry to see it thrive and drive benefits to the health of its people and Australia's economy.

The RM Catalyst would build on resources developed earlier this year when a Project brought together seven partners in a Consortium to build the foundations for RM in Australia. The Project addressed priority action areas including: workforce capabilities, collaboration, funding, regulation and policy infrastructure, and Australian manufacturing capability. The *Manufacturing Capacity and Capabilities Report*[8] noted above forms a key part of the RM Project.

The RM Project's Consortium holds extensive insight and experience in the life sciences and regenerative medicines landscape in Australia: AusBiotech, Medicines Australia, Cell Therapies Pty Ltd, Novartis Pharmaceuticals Australia Pty Ltd, Biointelect Pty Ltd, Research Strategies Australia and Australia's Industry Growth Centre, MTPConnect.

The RM Project is funded through MTPConnect's Growth Centre Project Fund Program, an Australian Government initiative supported by the Department of Industry, Science, Energy and Resources. It is a competitive matched funding program that aims to invest in ideas to boost the innovation, productivity, and competitiveness of Australia's MTP sector. Six consortium members are providing matched funding.

The RM Project resulted from a national, sector-wide report that assessed the current state of the Australian RM sector and made recommendations on the priorities and goals, *Regenerative Medicine: Opportunities for Australia*[10].

Government role in the future of RM manufacturing

Investing in advanced manufacturing sector for RMTs will lead to anchoring global biotechnology and pharmaceutical companies' cutting-edge RMT manufacture onshore. This will strengthen Australia's

supply chain resilience for these complex, sophisticated therapies, ensure equitable access to cutting-edge treatments for Australian patients, and attract high-value investment to the Australian economy. Such investment would also encourage and attract increased translational work, currently lost to North America, to be undertaken within Australia and help to position Australia as Southeast Asia's RMT manufacturing hub, forestalling strongly competing offers for hubs to be established elsewhere in the region. Further, growth of the Australian RM sector will require the development of a high performing workforce pipeline, leading to the generation of new, highly-skilled jobs.

In other jurisdictions there has been significant investment in manufacturing capability to overcome this 'chicken or egg' situation (i.e. we need manufacturers to have a local RM industry but manufacturers will not come until there is an established RM industry to service). And while the Australian government has made some investments in this respect (e.g. the Federal Government's investment of $80 million to establish the Centre for Excellence in Cellular Immunotherapy at the Peter MacCallum Cancer Centre to increase patient access to CAR-T, or the viral vector manufacturing facility at Westmead, NSW) this is still not at the scale of investment needed to keep pace with the diverse products on the horizon. Examples from other jurisdictions also point to the important role for PPPs, such as the Vaccines Manufacturing and Innovation Centre (VMiC) in the United Kingdom, the UK Cell and Gene therapy Catapult and the 'Cellicon Valley' concept in Philadelphia. Such approaches may have an important role to play in Australia.

The RM sector would welcome Government leadership and support to support the intended work of the RM Catalyst, specifically to initially establish much needed infrastructure for the breadth of gene and cell therapies in Australia. This will support important access to world-leading healthcare and related clinical trials, and support economic growth, national resilience, and better living standards for all Australians.

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