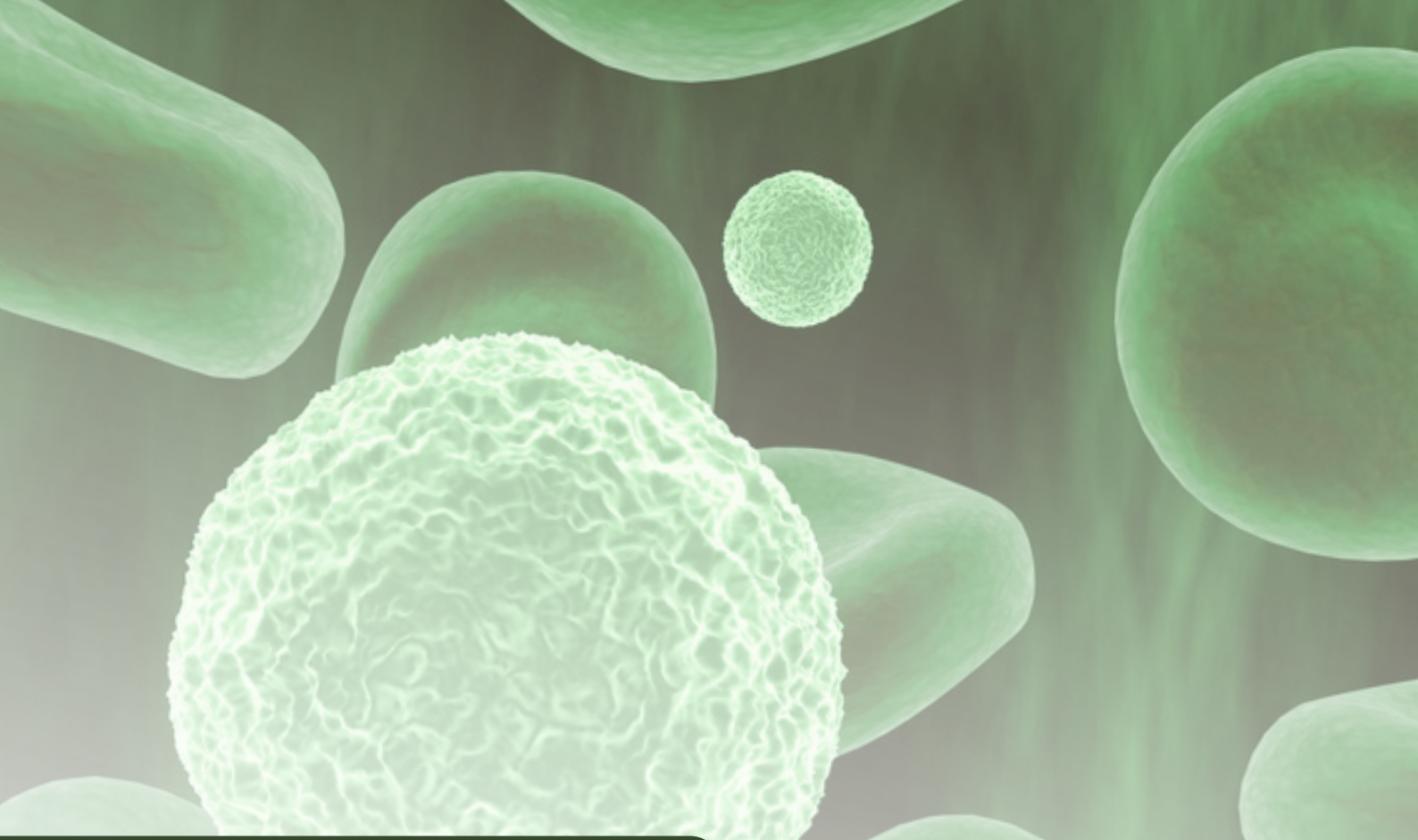

Australia's Regenerative Medicine Manufacturing Capacity & Capability

Prepared by Cell Therapies Pty Ltd

AusBiotech

Biointelect

cell therapies

Medicines Australia

Supported by MTPConnect MedTech and Pharma Growth Centre

NOVARTIS

RESEARCH STRATEGIES AUSTRALIA

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Disclaimer

Contents

Foreword

The Regenerative Medicine Catalyst Project has brought together seven partners in a consortium to build the foundations for a national regenerative medicines (RM) sector 'catalyst' collaboration body. The Regenerative Medicine Catalyst Project will address priority action areas including: workforce capabilities, collaboration, funding, regulation and policy infrastructure, and Australian manufacturing capability. The Catalyst Consortium and the subsequent Catalyst Body aim to support the Australian RM industry to see it thrive and drive benefits to the health of its people and Australia's economy. This Manufacturing Capacity and Capabilities Report forms a key part of the Regenerative Medicine Catalyst Project.

The significance and need for the Regenerative Medicine Catalyst Project was highlighted in a national, sector-wide report that assessed the current state of the Australian RM sector and made recommendations on the priorities and goals, see Regenerative Medicine: Opportunities for Australia (MTPConnect, LEK, 2018).

Major outcomes of the project include other reports and data that each add further to the body of evidence and understanding of the sector. The reports include:

- A researched, strategic roadmap for the RM sector's development in Australia, including sub-reports on skill and talent specific to the sector, determining a plan to attract patient venture capital investment and the role of Australian biotech companies partnering with global companies, and case studies;
- Determining a sustainable funding and model structure for an RM sector 'catalyst' collaboration body;
- A regulatory white paper;
- Establishing annual data points and information resources to: map/benchmark GMP manufacturing capability and capacity (this report), establish a model for an annual clinical trial database; and capture investments in Australian RM;
- Mapping the pathway for a typical product from early research to market, and patients receiving a therapy; and
- Mapping the global pipeline of gene and cell therapy products on the horizon.

Context

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 (B) in annual revenue, 6,000 new jobs for Australia by 2035 and earlier access to ground-breaking therapies for Australian patients[1].

RM is a multidisciplinary field that seeks to develop the science and tools that can help repair, augment, replace, or regenerate damaged or diseased human cells, tissues, genes, organs, or metabolic processes, to restore normal function. It may involve the transplantation of stem cells, progenitor cells, or tissue, stimulation of the body's own repair mechanisms, or the use of cells as delivery vehicles for therapeutic agents such as genes and cytokines.

RM includes gene therapies, cell therapies, and tissue-engineered products intended to regenerate or replace injured, diseased, or defective cells, tissues, or organs to restore or establish function and structure.

Globally, the growing sector has more than 1,200 clinical trials in progress, and attracted about AU$26.3B (or US$19.9B) in financing in 2020[2]. 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[3]. There are also increasing numbers of gene and cell therapies being developed in, and brought to, Australia for patient access.

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 in progress[4].

[1] MTP Connect, LEK Consulting. (2018). Regenerative Medicine - Opportunities for Australia
[2] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021
[3] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021
[4] AusBiotech. (2021). Australia's Regenerative Medicine Clinical Trials Database. ausbiotech.org

Executive Summary

Regenerative Medicine (RM) represents the possibility of revolutionary, lifelong, and curative therapies to meet some of the most pressing unmet medical needs. RM therapies (RMTs) include gene therapies, cell therapies (such as CAR-T), and tissue-engineered products (TEPs), to regenerate or replace injured, diseased, or defective cells, tissues, or organs to restore or establish function and structure. It is essential that Australians have access to RMTs.

The RM sector globally is growing rapidly. Despite the COVID-19 pandemic, 2020 saw US$19.9b investment in advanced therapy developers[5]. Globally, there were 1,200 RMT products at various stages of clinical trials in 2020[6] and the FDA predicts that by 2025, 10 to 20 products will be approved each year in the USA[7].

RMTs require specialised Good Manufacturing Practice (GMP) manufacturing capabilities and infrastructure, a highly-skilled workforce, and complex supply chains. There are significant benefits to having manufacturing facilities located onshore in Australia, for patients as well as RMT developers. For example, the patient pathway for many RMTs will require an integrated delivery network of clinicians, hospitals, supply chain logistics and manufacturing facilities. Local manufacturing will build resilience for the sector and ensure equitable access to cutting-edge therapies for all Australians. Sovereign capability facilitates access not only to early phase trials for Australian patients for locally developed products but also supports access to innovative and cutting-edge international trials.

This report presents the results of the inaugural Catalyst Consortium survey of RM GMP manufacturers within Australia. The aim of this survey is to provide a benchmark to map the growth of the RM GMP manufacturing sector over time and provide the basis on which to build and strengthen Australia's sovereign manufacturing capability and capacity.

The report provides metrics on GMP manufacturing facilities that produce cell and gene therapies, TEPs, and pivotal GMP-grade starting material and components required for RMT manufacture. Australia has a total of 7 RMT GMP manufacturers with TGA licences and these are manufacturing for commercial supply and for clinical trials. These facilities are located across three States: Queensland, Victoria and Western Australia.

There are a total of 34 cleanrooms, the combined cleanroom and QC footprint is ~2,982m^2, and the sector employs 231 full-time and 45 part-time/casual employees.

Early phase clinical trials are integral to the growth of the RM sector as they support the translation of research to the clinic. However, in Australia, RMTs specifically for early phase clinical trials (0-I) do not need to be manufactured in a TGA-licenced GMP facility. Australia has five non-TGA licenced facilities that manufacture RMTs for early-phase clinical trials and these are located across four states: Queensland, New South Wales, Victoria and Western Australia. There are a total of 15 cleanrooms, the combined cleanroom and QC footprint is ~1,577m^2, and the sector employs 24 full-time and 10 part-time/casual employees.

Of the TGA-licenced manufacturers, three have dedicated cell therapy capabilities, one has cell therapy and TEP capabilities, two manufacture GMP-grade nucleotides, and one manufactures peptides and proteins for biomaterials. All the non-TGA licenced manufacturers have cell therapy capabilities.

Currently, Australia has no facilities with the capability to manufacture GMP-grade viral vectors, however this is set to change later this year. The Westmead Viral Vector Manufacturing Facility (NSW, non-TGA licenced) has cell therapy capabilities and can manufacture viral vectors such as gamma retroviruses, adeno-associated virus (AAV), and lentivirus, on small scale for early phase clinical trials. In 2019, this facility received a $25 million investment from the NSW Government for the expansion of their viral vector manufacturing capacity. The expanded facility will seek a TGA GMP manufacturing licence and it is intended to serve local and international gene therapy markets. Although this represents a significant investment in Australia's GMP manufacturing sector, there remains a major gap in large-scale GMP manufacture of viral vectors (such as lentivirus required for CAR-T therapies) to serve late-stage clinical trials and commercial supply needs.

The potential of the RM manufacturing sector is large, and with investment in sovereign GMP manufacturing, Australia will be well positioned to capture high-value opportunities now and in the future.

[5] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021

[6] Regenerative Medicine Opportunities and Challenges in APAC, Special Report, LEK 2020.

[7] U.S. Food and Drug Administration https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

Introduction

Regenerative Medicine (RM) encompasses gene and cell therapies, and tissue-engineered products (TEP) and the advanced manufacturing that supports this sector 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 (RMT) represent the apex of "personalised medicine". Personalised RMTs (e.g. CAR-T therapy) may use a patient's own (autologous) cells. This 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 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$19.9b investment globally in advanced therapy developers – a 100% increase on 2019 figures[8]. There is a robust pipeline of RM products at various phases of clinical trials[9] 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[10].

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 internationally recognised. More than 40 companies in Australia are developing products and more than 65 clinical trials are in progress.

The demand for RMT manufacturers is growing and a major bottleneck exists at the GMP manufacturing phase of product development, both in Australia and globally. Australian based manufacturers are required to hold a GMP manufacturing licence to manufacture RMTs commercially and for late phase (II-IV) clinical trials. To obtain a GMP manufacturing licence, manufacturers must be GMP-compliant, as assessed by the TGA. Further, the manufacture of RMTs generally requires GMP-grade starting material such as viral vector (e.g., adeno-associated virus [AAV], lentivirus), nucleotides (e.g., plasmid DNA), and biomaterials (e.g., peptides and proteins). For early phase clinical trials (0-I), RMTs do not need to be manufactured in a TGA GMP licenced facility.

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.

[8] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021
[9] Regenerative Medicine Opportunities and Challenges in APAC, Special Report, LEK 2020.
[10] U.S. Food and Drug Administration https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

Aim

The results of the inaugural Catalyst Consortium survey of RM GMP manufacturing facilities within Australia are here presented. The aim of the report is 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 in the survey will provide a benchmark against which growth of Australia's sovereign GMP manufacturing sector can be measured and tracked.

Methodology

RM manufacturers across Australia were surveyed to benchmark their current capabilities and assess their capacity to support growth in the next 12 months. This inaugural survey constitutes the Catalyst Consortium's model to track growth in the sector and will serve as a resource for the annual assessment of the RM GMP manufacturing sector within Australia.

The survey was deployed to TGA-licenced (GMP-compliant) RM manufacturers of cell therapies (including genetically-modified cell therapies) and TEPs, as well as manufacturers of key components or starting materials for RMTs including viral vectors, nucleotides and biomaterials. RM manufacturers that do not currently hold a TGA licence, but manufacture RM products for early-phase clinical trials were also surveyed. These facilities are actively working toward a TGA licence for GMP manufacture, and their current services and capabilities are integral for the translation of RM in Australia. Non-TGA licenced RM manufacturers were surveyed to fully capture the current capabilities as well as the potential of the RM GMP manufacturing sector in Australia.

Survey

The survey was designed to capture the national capabilities and prospective capacity in the RM manufacturing sector.

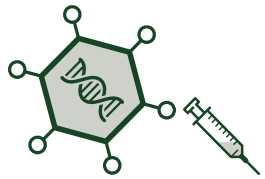
Seven Australian RM TGA-licenced GMP manufacturing facilities were identified by the Catalyst Consortium. A further five RM manufacturers of products for early phase (O-I) clinical trials and that do not currently hold TGA licences, were identified and surveyed. These facilities are actively working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

Surveys were deployed to all 12 identified RM manufacturers for participation between April-May 2021 and 10 full responses (1 partial response) were received, a 92% response rate. Table 1 lists the survey questions. The following report collates data for all survey respondents. A complete list of facilities can be found in Appendix 1. The Westmead Viral Vector Manufacturing Facility (NSW, non-TGA licenced) expansion of viral vector manufacturing capability will be functional by late 2021 and their current and prospective data was included in the report.

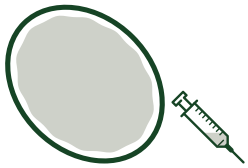
Key Definitions

RM is the branch of medicine that develops methods to regrow, repair or replace damaged or diseased cells, organs or tissues. RM includes the generation and use of therapeutic stem cells, tissue engineering and the production of artificial organs." - Nature[11]

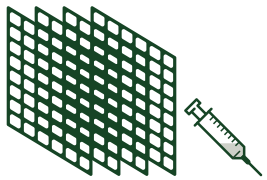
The following definitions are used in this report:



Gene therapy is the introduction, removal or change in the content of a patient's genetic code, with the goal of treating or curing a disease[12]. "Gene therapy" as used in this report is delivered *in vivo* (where the genetic modification occurs inside the patiet). Gene therapies are delivered to specific cells of interest, and includes gene transfer, gene replacement and genome editing.



Cell therapy is the transfer of intact, live cells into a patient. It may be used to replace cells that are missing or non-functional, or to provide cells that have improved functionality. Cell therapies may include cells that originate from the patient themselves (autologous), or from a human (allogeneic) or animal (xenogeneic) donor. This now often includes genetically modified cell therapies, which can also accurately be referred to as "*ex vivo* gene therapies".



Tissue engineering combines biomaterial scaffolds with cells and/or biologically active molecules. Scaffolds are supporting materials that may be populated or "seeded" with cells before they are implanted or may be implanted without cells (acellular) and interact with cells *in vivo*.

Statement on definitions used in this report

RM therapeutic approaches are complex and may include concepts that fit under two or even all three of the definitions in this section. The groupings and definitions used here have been pragmatically chosen based on the similarities and differences in the value chains of various therapeutic approaches[13]. Future innovations are likely to introduce further complexity.

Further description of the RM therapies can be found in the *AusBiotech Regenerative Medicine Value Chain, Pathway from Discovery to Patient Delivery Report*[14].

[11] https://www.nature.com/subjects/regenerative-medicine
[12] Only somatic gene therapies discussed in this report. Genetic modification of "germline" cells that would contribute to the next generation (i.e. sperm and eggs) is currently illegal in Australia and is not discussed in this report.
[13] RNA blocking technologies (small interfering RNA and antisense oligonucleotides [siRNAs and ASOs]) have been omitted. Although they fit definitions of gene therapies, their value chains (from reimbursement, to manufacturing, to patient delivery) are relatively comparable to traditional pharmaceutical value chains.
[14] AusBiotech. (2021). Regenerative Medicine Value Chain, Pathway from Discovery to Patient Delivery Report. ausbiotech.org

Table 1. RM GMP manufacturing in Australia: capability and capacity survey

Facility Type
What client types does the facility service?
What accreditation or licenses are held by the facility?
What Cell Therapy process capabilities exist at the facility?
What Gene Therapy process capabilities exist at the facility?
What other Regenerative Medicine capabilities exist at the facility
Types of processing equipment used?
Types of analytical equipment used?
Number of GMP laboratories?
What is the certified classification of the cleanrooms?
What is the total cleanroom footprint?
What is the quality control footprint?
How many parallel manufacturing processes can be performed in the facility?
Over the past 12 months, what was the average booked capacity of the facility?
Could you have taken on further work if you had larger capacity?
How many early-phase (Phase I-II) clinical trial, late-phase (Phase III-IV) clinical trial, and commercial projects have been conducted in the last 12 months?
Number of Full-Time staff are currently employed?
Number of Part Time/Casual staff are currently employed?
Number of Manufacturing staff?
Number of Quality Assurance/Quality Control staff?
Has the facility hired new staff in the past 12 months?
If new staff were hired in the past 12 months, on average how long did it take to fill the role?
Is the facility planning to expand to other types of Regenerative Medicine product manufacture? If so, what products?
What are some of the limitations to growing manufacturing output?
Would you like to comment further on the capability or capacity of the Regenerative Medicine manufacturing sector in Australia?

National Regenerative Medicine GMP Manufacture

NATIONAL SITE LOCATIONS

A total of seven RM TGA-licenced GMP manufacturing facilities were identified in three states across Australia: QLD, VIC and WA (Figure 1). Five facilities manufacturing RMTs for early phase clinical trials, and that do not currently hold TGA licences for GMP manufacture were identified in NSW and VIC. There were no facilities identified in ACT, SA, TAS or NT. Six out of seven TGA-licenced facilities responded in full to the survey, four non-TGA-licenced facilities out of five responded in full to the survey.

State/Territory	# TGA licenced GMP Sites	# Non-TGA licenced Sites
NSW	–	3
VIC	2	2
QLD	3	–
WA	2	–
TOTAL	7	5
# Survey responses (full)	6	4

Figure 1. Locations of RM manufacturing sites within Australia including TGA licenced and non-TGA licenced manufacturers.

6

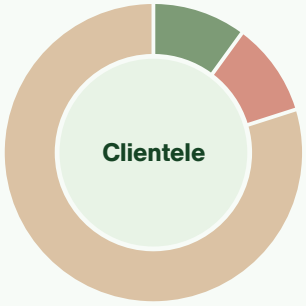
TGA licenced GMP manufacturing sites

(survey respondents, 7 in total)

4

Number of non-TGA licenced manufacturing sites

(survey respondents, 5 in total)



6

Number of dedicated cell therapy manufacturing sites

(3 TGA licenced)

1

Number of viral vector manufacturing sites

(none TGA licenced)

1

Number of plasmid DNA manufacturing sites

(TGA licenced)

2

Number of TEP and Biomaterial manufacturing sites

(2 TGA licenced)

2

Number of multifunctional RM manufacturers

RM MANUFACTURER OVERVIEW

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 for-profit or not-for-profit. 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 the Westmead Viral Vector Manufacturing Facility (NSW, non-TGA-licenced) manufactures 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 investment in Australia's viral vector GMP manufacturing sector with the potential to supply the global market.

Manufacturing Capacity

SUMMARY

6

TGA Licenced facilities

4

Average number of cleanrooms

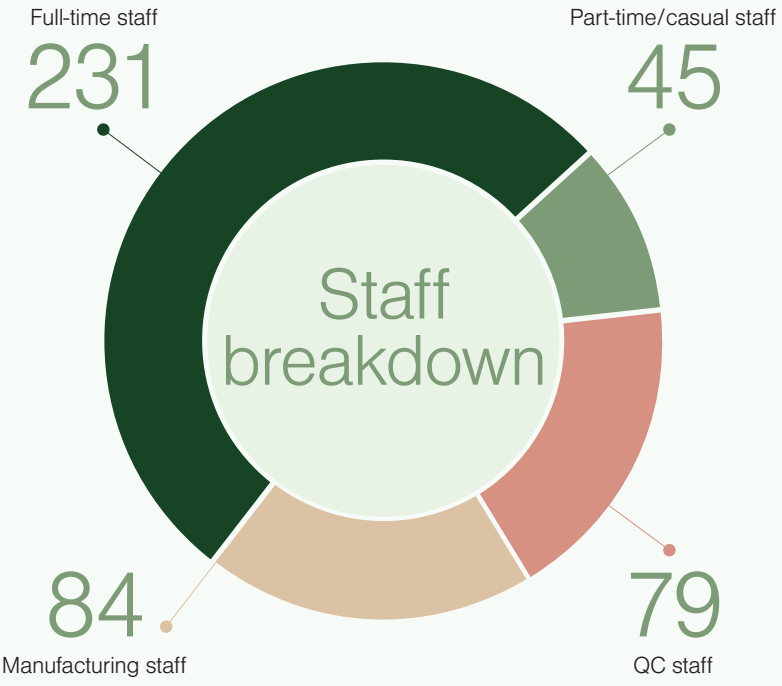
(median 3.5 per facility)

2,472m²

Total cleanroom footprint

510m²

Total in-house QC footprint



90%

Facilities hired new employees in the last 12 months

Table 2 summarises the total cleanroom footprint, in-house Quality Control (QC) footprint, and staffing requirements by role (manufacturing, QC) and the nature of their employment (full-time, part-time, casual) in TGA- licenced manufacturing facilities, as well as those without a TGA licence.

Table 2. Manufacturing capacity in TGA licenced facilities and non-TGA licenced facilities including cleanroom footprint, QC footprint and staff.

Facility	# Sites	# Cleanrooms	Cleanroom footprint (m^2)	In-house QC footprint (m^2)	# Full-time staff	# Part-time & casual staff	# Manufacturing staff	# QC staff
TGA Licenced	6	34	2472*	510	231	45	84	79
Non-TGA licenced	4	15	1228	349	24	10	9	11
TOTAL	10	49	3700	859	255	55	93	90

Includes Luina Bio Pty Ltd combined footprint for cleanrooms and QC, 1,200m^2

CLEANROOMS AND ACCREDITATION

Of the surveyed RMT manufacturers, six are TGA-licenced and four do not hold TGA GMP manufacturing licences. Of the four non-TGA-licenced facilities, all are actively working toward GMP certification by the TGA. In total there are 49 cleanrooms: 34 in TGA licenced facilities (median 3.5) and 15 in non-TGA licenced facilities (median four). The largest number of cleanrooms (15) are housed at Q-Gen Cell Therapeutics (QLD, TGA licenced). The total cleanroom footprint for TGA licenced facilities is ~2,472m2 (includes Luina Bio Pty Ltd combined footprint for cleanrooms and QC, 1,200m2) and 1,228m2 in non-TGA-licenced facilities. The total in-house QC footprint for TGA-licenced facilities is approximately ~510m2 and 349m2 for non-TGA-licenced facilities.

Cleanroom certified classifications across all facilities include ISO7 (4), ISO8 (2), Grade B (4), Grade C (2), Grade D (2). Accreditations included the Foundation for the Accreditation of Cellular Therapy (FACT) (2), National Association of testing Authorities (NATA) (1), Office of the Gene Technology regulator (OGTR) (3), and International Organisation for Standardisation (ISO) (3).

EMPLOYEES

The TGA licenced manufacturers employ a total of 231 full-time staff and 45 part-time or casual staff. Manufacturers that do not currently hold a TGA licence employ a total of 24 full-time staff and 10 part-time or casual staff. The ratio of manufacturing staff to QC staff in TGA licenced facilities is nearly 1:1, with 84 staff dedicated to manufacturing and 79 to QC, demonstrating that these two components of RM GMP manufacture is similarly workforce intensive. Similarly, the non-TGA-licenced manufacturers employ nine staff dedicated to manufacturing and 11 to QC. The largest employers are TGA-licenced manufacturers Cell Therapies Pty Ltd (VIC) and Luina Bio Pty Ltd (QLD), who respectively employ 90 and 85 employees. Cell Therapies Pty Ltd is a contract development and manufacturing organisation (CDMO) for cell and gene therapies across the development pipeline from translational studies and clinical trials through to commercial supply. Luina Bio Pty Ltd is a CDMO for biopharmaceuticals including plasmid DNA, however RM is not their core focus. Therefore, the reported workforce for Luina Bio Pty Ltd is not solely dedicated to GMP manufacture of RMT/key GMP-grade components, as is the case for other facilities.

Ninety percent of the surveyed manufacturers hired new employees in the last 12 months and most facilities (eight out of nine) were able to fill the role/s within an average of 0 - 4 months. One facility noted that the average time to fill roles was five months and over.

PROJECT ACTIVITY

Across six TGA-licenced facilities there were a total of 32 parallel manufacturing processes (median six, maximum >10, one facility answered 'depends on process') that could be undertaken. A total of seven parallel manufacturing processes (median 3.5, maximum four, two facilities answered 'depends on process') that could be undertaken in non-TGA-licenced facilities.

Cell and gene therapy manufacturers have conducted 51 clinical trials (early and late phase) in the last year and 16 commercial projects (Table 3). These clinical trials and commercial projects may include the manufacturing of the cell and gene therapies or the storage and deployment of RMTs (without in-house manufacture).

Table 3. Number of clinical trials and commercial projects undertaken by cell and gene therapy manufacturers in the last 12 months.

Facility	Early phase (I-II) clinical trial projects	Late phase (III-IV) clinical trial projects	Commercial projects	TOTAL
TGA licenced	25	1	11	37
Non-TGA licenced	21	4	5	30
TOTAL	46	5	16	67

BOOKING CAPACITY

The booked capacity over the last 12 months of TGA-licenced facilities ranged from 25-50% (one out of six survey respondents), to 50-75% (two out of six survey respondents), to 75-100% (four out of six survey responses) (Figure 3). Non-TGA-licenced facilities' booking capacity ranged from 0-25% (one out of four), 25-50% (two out of four) and 75-100% (one out of four).

CAPACITY IS A CONSTRAINT

When TGA-licenced facilities were asked if they could have taken on further work if they had larger capacity, 100% replied 'Yes'.

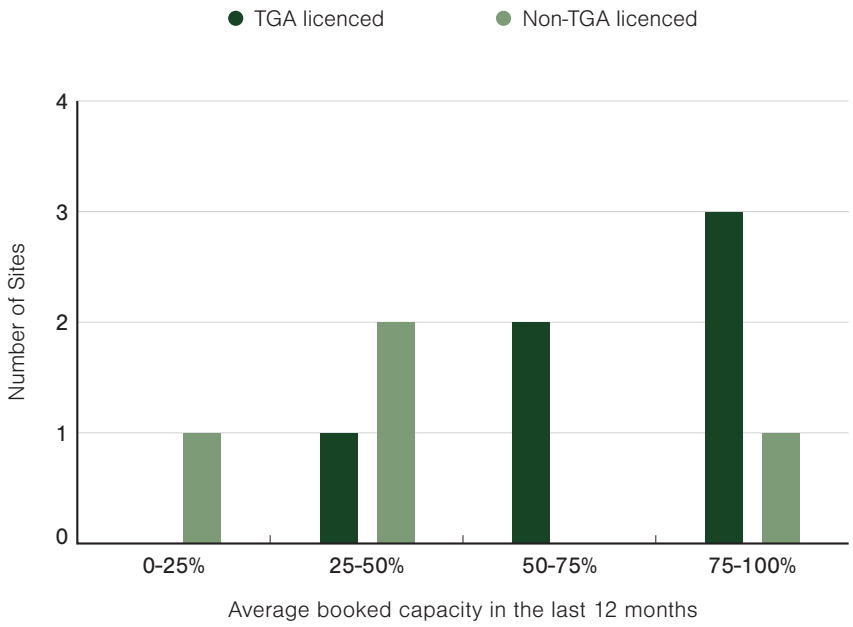


Figure 3. Average booked capacity of TGA licenced and non-TGA licenced manufacturers in the last 12 months.

Manufacturing Capabilities

To capture the RM manufacturing capabilities available around Australia the survey assessed cell therapy manufacturers' specific process capabilities related to three categories: 'Cell Therapy Process Capabilities', 'Gene Therapy Process Capabilities' and 'TEP and Biomaterial Process Capabilities (Figure 4). Figure 4 summarises the process capabilities across four TGA-licenced and four non-TGA licenced cell therapy manufacturers.

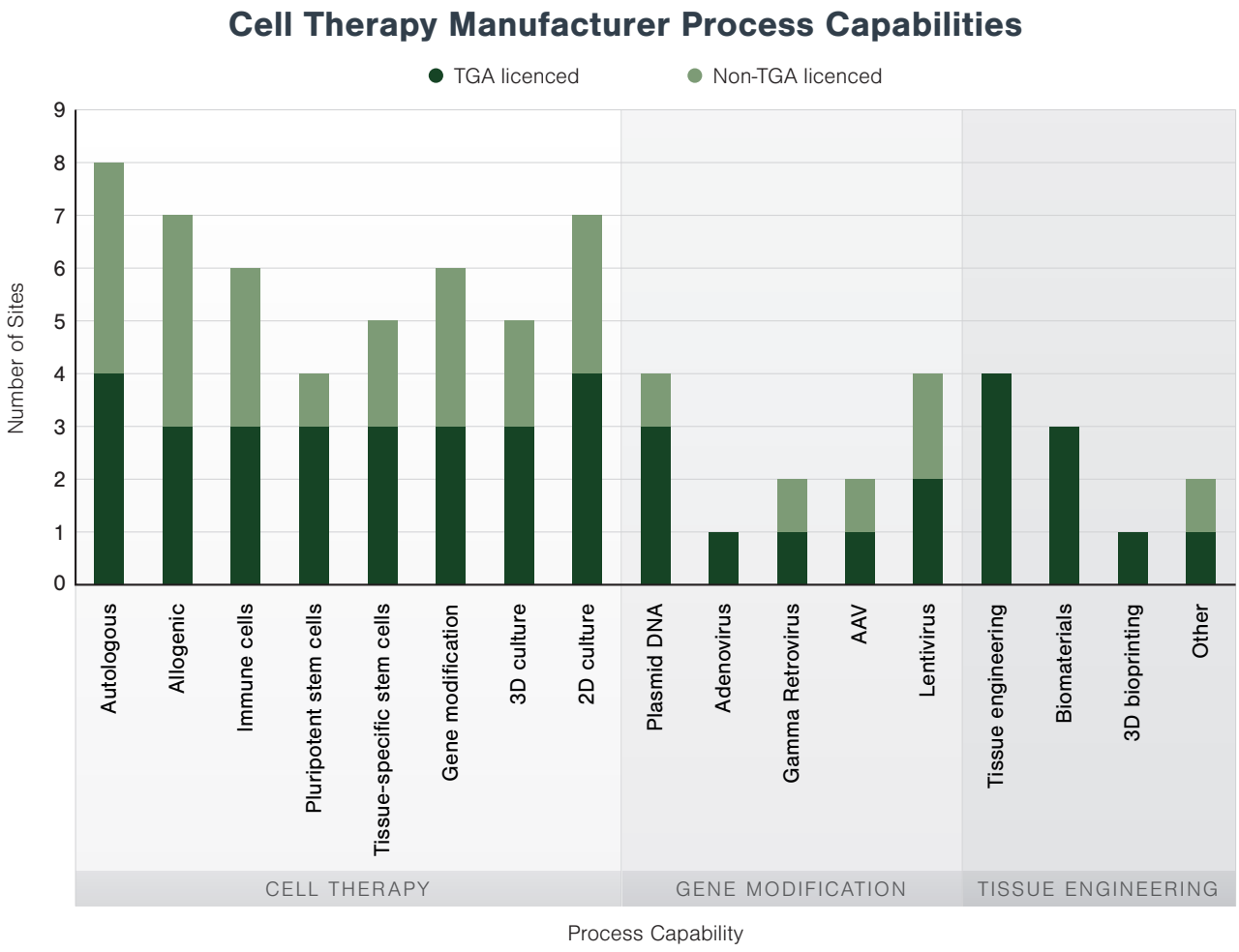


Figure 4. Summary of TGA-licenced and non-TGA-licenced cell therapy manufacturer capabilities. Four TGA-licenced and four non-TGA-licenced cell and gene therapy manufacturer survey responses.

Cell Therapy Process Capabilities refers to the capability to handle different cell types such as autologous, allogeneic, or pluripotent stem cells, as well as capabilities for genetic modification of cells, 3D culture and 2D culture platforms (Table 4).

Table 4. Cell therapy process capabilities of cell therapy manufacturers.

Facility	Cell Therapy Process Capabilities							
	Autologous	Allogeneic	Immune cells	Pluripotent stem cells	Tissue specific stem cells	Gene modification	3D cell culture	3D cell culture
Cell Therapies Pty Ltd*	✓	✓	✓	✓	✓	✓	✓	✓
Cell & Molecular Therapies	✓	✓	✓	✓	✓	✓	✓	✓
CTTWA*	✓	✓	✓	✓	✓	✓	✓	✓
Hudson Institute	-	✓	✓	-	✓	-	-	✓
Orthocell Ltd*	✓	-	-	-	-	-	-	✓
Q-Gen Cell Therapeutics*	✓	✓	✓	✓	✓	✓	✓	✓
Sydney Cell & Gene Therapies	✓	✓	✓	-	-	✓	-	-
Westmead Viral Vector Facility	✓	✓	✓	-	-	✓	✓	✓

TGA licenced GMP manufacturer

Gene Therapy Process Capabilities refers to the capability to utilise nucleotides (e.g. plasmid DNA) and viral vectors as starting material for the manufacture of genetically-modified cell therapies (Table 5).

Table 5. Gene therapy process capabilities for genetic modification of cells.

Facility	**Gene Therapy Process Capabilities**				
	Plasmid DNA	Adenovirus	Gamma Retrovirus	AAV	Lentivirus
Cell Therapies Pty Ltd*	✓	-	✓	-	✓
CTTWA*	✓	-	-	✓	✓
Cell & Molecular Therapies	✓	-	✓	✓	✓
Q-Gen Cell Therapeutics*	✓	✓	-	-	-
Westmead Viral Vector Facility	-	-	-	-	✓

TGA licenced GMP manufacturer

Tissue Engineering Process Capabilities refer to the ability to tissue engineer, utilise biomaterials, and conduct 3D bioprinting (Table 6).

Table 6. TEP and biomaterial process capabilities.

Facility	TEP and Biomaterial Process Capabilities			
	Tissue Engineering	Biomaterials	3D Bioprinting	Other
Orthocell Ltd*	✓	✓	-	-
Auspep Holdings Ltd*	-	✓	-	-
Cell Therapies Pty Ltd*	✓	✓	-	-
CTTWA*	✓	✓	✓	✓
Q-Gen Cell Therapeutics*	-	-	-	-
Sydney Cell & Gene Therapies	✓	-	-	✓

TGA licenced GMP manufacturer

Australia has one TGA-licenced facility that can manufacture GMP-grade plasmid DNA and one facility that has the capability to manufacture viral vectors (Table 7).

Table 7. Nucleotide and Viral Vector Manufacturing Capabilities.

Facility	Nucleotide and Viral Vector Manufacturing Capabilities				
	Plasmid DNA	Adenovirus	Gamma Retrovirus	AAV	Lentivirus
Luina Bio Pty Ltd*	✓	-	-	-	-
Westmead Viral Vector Facility	-	-	✓	✓	✓

TGA licenced GMP manufacturer

PROCESSING EQUIPMENT

Facilities manufacturing cell and gene therapies house key clinical-grade pieces of equipment for cell processing including cell therapy manufacturing platforms, cell expansion systems, cell separation systems, and electroporators, including Wave XURI, Prodigy, CliniMACS Sepax Bioreactor, Cocoon, Cell Saver, G-Rex Cell Factories, Rotea, Cobe, Elutra, MaxCyte, Optipress, TFF centrifuge. Key pieces of processing equipment for manufacturing nucleotides, TEPs and biomaterials include high 500L fermenters, homogenisers.

Analytical equipment used across the facilities includes FACSVerse, Nucleocounter NC-200, BacT/Alert 3D 240, ELISA plate reader, Quantstudio and Lightcycler RT-PCR, QIAgility and Automate express flow cytometry, quantitative polymerase chain reaction (qPCR), droplet digital PCR (ddPCR), portable endotoxin testing system, optical microscopes, and haemocytometers. Types of analytical methods include western blot, enzyme-linked immunosorbent assay (ELISA), performance liquid chromatography (HPLC) purification (small to large-scale), freeze drying, and mass spectroscopy.

Manufacturing Forecast and Limitations

RM GMP MANUFACTURING CAPACITY FORECAST

The prospective booking capacity of TGA-licenced facilities was 25-50% (one out of six), 75-100% (four out of six), and unsure (one out of six) (Figure 8). Non-TGA-licenced facilities forecast 25-50% (three out of four) and 75-100% (one out of four). Most facilities (eight out of ten) are planning to expand into manufacturing other RM-related products such as exosomes, bioengineered products, messenger RNAs (mRNAs), antisense oligonucleotides (ASOs) and lipid-based nanoparticles (LNPs)

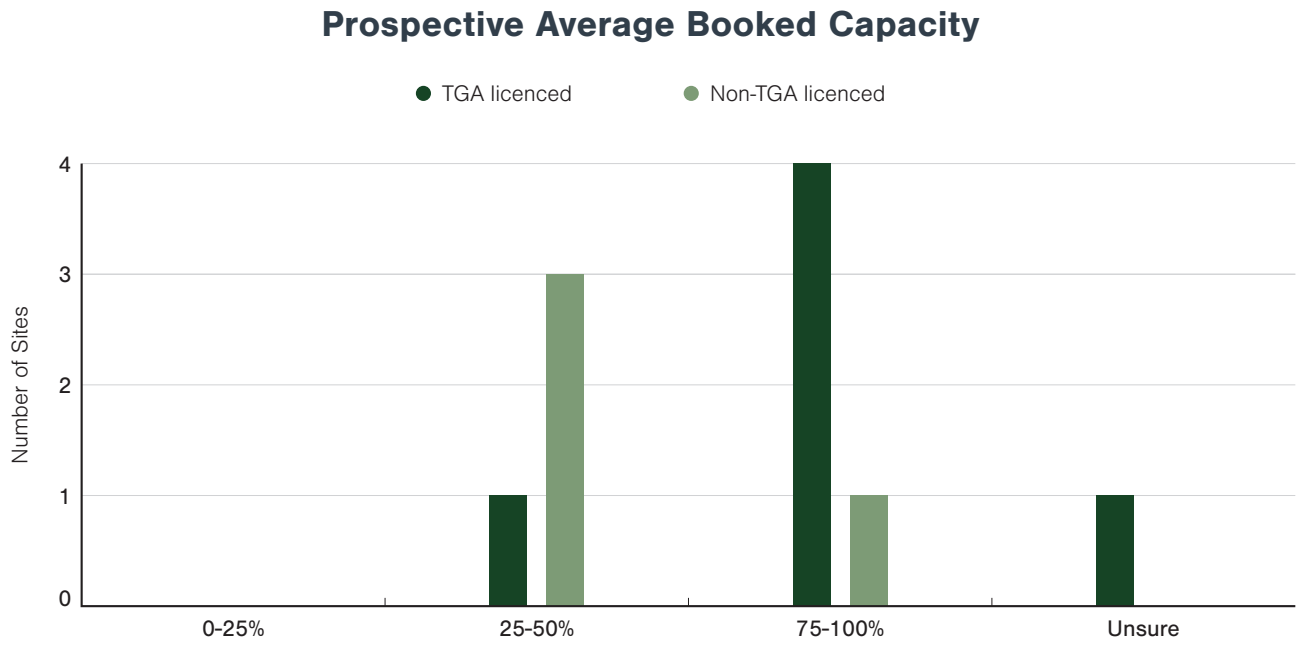


Figure 8: Prospective booked capacity of RMT manufacturers for the following 12 months.

LIMITATIONS TO MANUFACTURING OUTPUT GROWTH

Figure 9 summarises the most common limitations to growing GMP manufacturing output as identified by participating facilities.

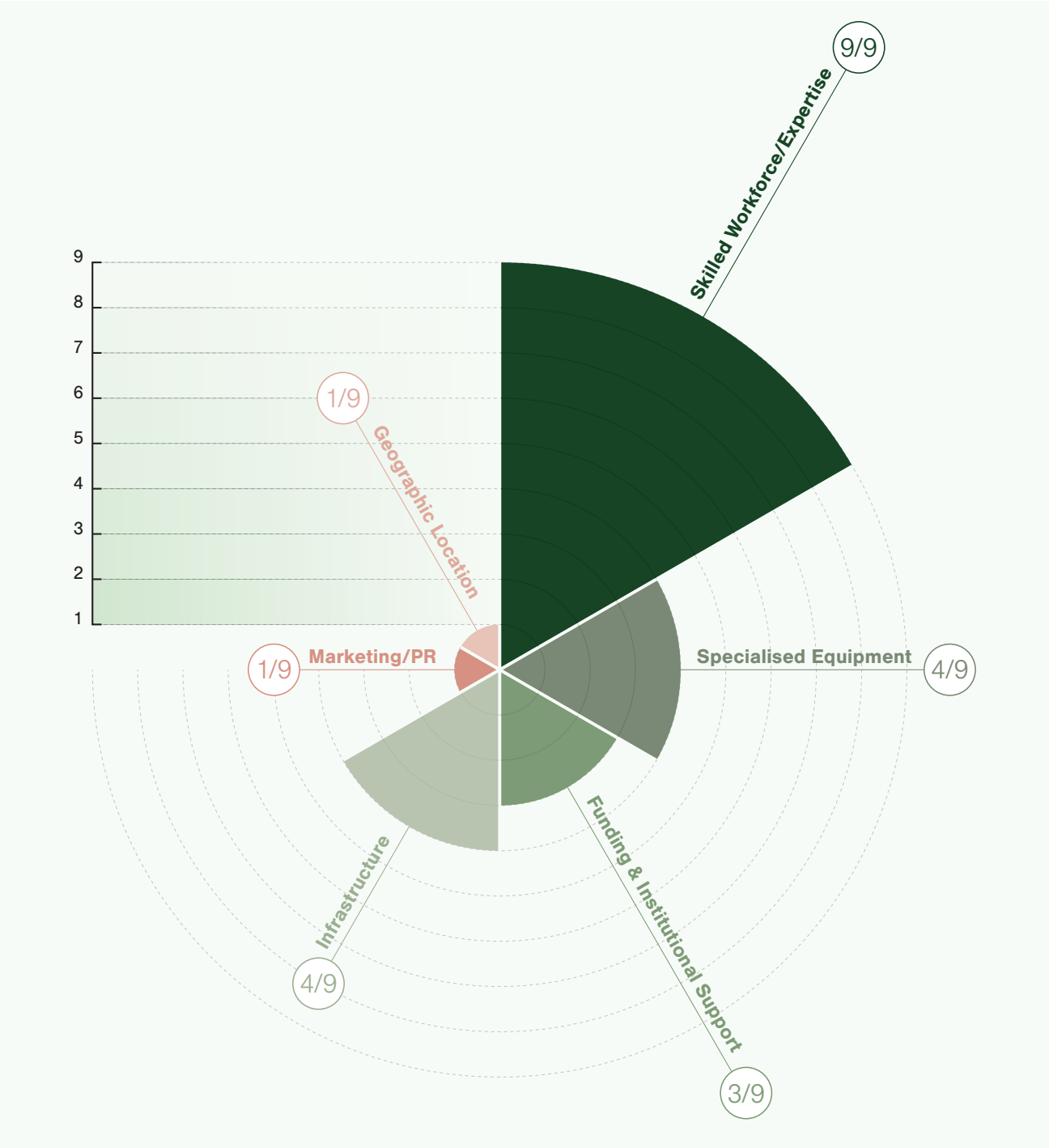


Figure 9. Prevalence of limitations to growth of GMP manufacturing facilities. Size of circle represents prevalence of identified limitation. Limitations cited include lack of skilled workforce, insufficient institutional infrastructure, access to funding and lack of appropriate institutional support, need for more specialised equipment, a need for marketing and public relations (PR), and geographic isolation from the rest of the world.

Key Contributors

The Australian RM manufacturing sector is growing, and every effort was made to identify all RM manufacturers. It is likely that the next annual data point for this survey will see an increase in the total number of RMT manufacturers, and an increase in the number of TGA-licenced manufacturers supplying product for late phase clinicals.

The Regenerative Medicine Catalyst Project would like to recognise and thank all participating RMT manufacturers for their assistance and contribution to the inaugural *Australia's Regenerative Medicine Manufacturing Capacity & Capability Report*, including: Cell & Molecular Therapies, Royal Prince Alfred Hospital, NSW, Sydney Cell & Gene Therapy, Westmead Institute of Medical Research, NSW, Westmead Viral Vector Manufacturing Facility, Westmead Health Precinct, NSW, Luina Bio Pty Ltd, QLD, Q-Gen Cell Therapeutics, QIMR Berghofer Medical Research Institute, QLD, Auspep Holdings Ltd, VIC, Cell Therapies Pty Ltd, Peter MacCallum Cancer Centre, VIC, Hudson Institute Cell Therapy and Regenerative Medicine Platform (Hudson Institute), Translational Research Facility of the Monash Health Translation Precinct, VIC, Magellan Stem Cells, VIC, Cell & Tissue Therapies Western Australia (CTTWA), Royal Perth Hospital, WA, and OrthoCell Ltd, WA.

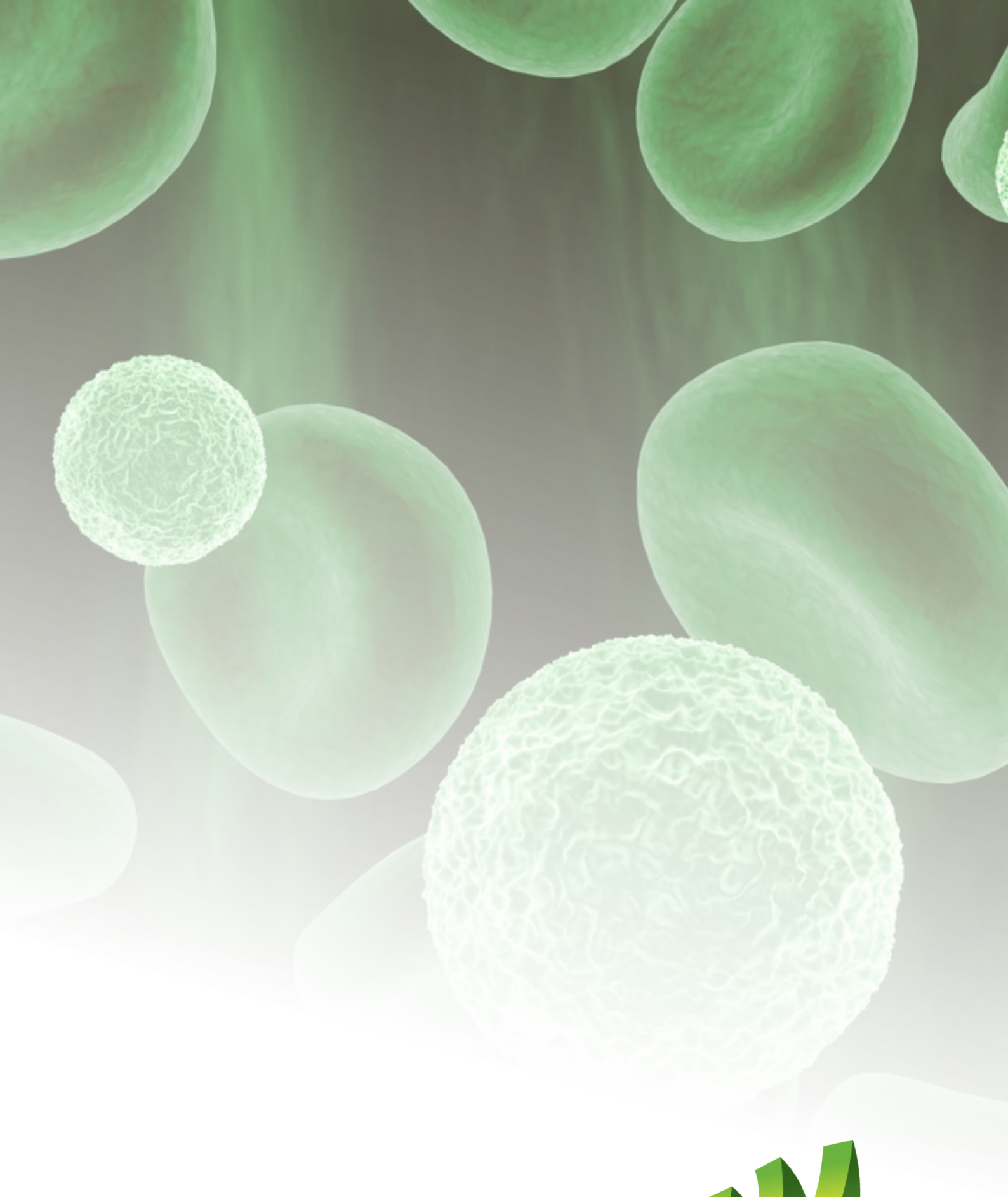
Appendix

1. AUSTRALIAN RM GMP MANUFACTURING FACILITIES

Australian RM GMP Manufacturing Facilities		
Facility	**TGA Licence**	**Survey Participation**
Cell & Molecular Therapies, Royal Prince Alfred Hospital, NSW	-	✓
Sydney Cell & Gene Therapy, Westmead Institute of Medical Research, NSW	-	✓
Westmead Viral Vector Manufacturing Facility, Westmead Health Precinct, NSW	-	✓
Luina Bio Pty Ltd, QLD	✓	✓
Patheon by Thermo Fisher Scientific, QLD	✓	-
Q-Gen Cell Therapeutics, QIMR Berghofer Medical Research Institute, QLD	✓	✓
Auspep Holdings Ltd, VIC	✓	✓
Cell Therapies Pty Ltd, Peter MacCallum Cancer Centre, VIC	✓	✓
Hudson Institute Cell Therapy and Regenerative Medicine Platform (Hudson Institute), Translational Research Facility of the Monash Health Translation Precinct, VIC	-	✓
Magellan Stem Cells, VIC	-	✓ partial
Cell & Tissue Therapies Western Australia (CTTWA), Royal Perth Hospital, WA	✓	✓
OrthoCell Ltd, WA	✓	✓

2. GLOSSARY OF TERMS

AAV	Adeno-associated virus
ACT	Australian Capital Territory
ASO	Antisense oligonucleotides
CAR	Chimeric antigen receptor
CDMO	Contract development and manufacturing organisation
DNA	Deoxyribonucleic Acid
GMP	Good manufacturing practice
LNP	Lipid-based nanoparticles
NT	Northern Territory
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
QC	Quality Control
QLD	Queensland
RM	Regenerative medicine
RMT	Regenerative medicine therapeutic
RNA	Ribonucleic acid
SA	South Australia
TAS	Tasmania
TGA	Therapeutic Goods Administration
TEP	Tissue engineering product
VIC	Victoria
WA	Western Australia



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