Business case for **onshore manufacturing of mRNA vaccines** in Australia

FINAL REPORT

Current as of 18 March 2021

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Executive Summary

The Australian Government seeks to understand options to onshore mRNA vaccine manufacturing capabilities to (1) increase Australia's COVID-19 vaccine supply in the near term, and (2) provide a 'platform' capability in mRNA vaccines for the longer term. This business case presents a current view of the feasibility, benefits, costs, and risks of options to onshore mRNA vaccine manufacturing capability to meet these objectives.

There are two potential paths for onshoring that the Government could pursue:

- **'Go now'.** A **~9 to 12-month path** with tech transfer from an **established IP partner** to an onshore **brownfield facility**.[1] This would provide a supply of COVID-19 vaccines for potential COVID-19 revaccination needs, as well as provide a 'platform' capability in mRNA technology.
- **'Go later'.** A **~3-year path** that allows for the additional flexibilities of a **greenfield approach** and/or use of **home-grown IP**. This would focus squarely on building long-term platform capability in the biopharmaceuticals sector.

The key benefit of the 'go now' path is the ability to provide earlier mRNA vaccine supply for COVID-19 revaccination, if a booster regimen and/or ongoing seasonal vaccination (e.g., for variants) is required. This may confer benefits to Australia of $1.2 billion to $7.9 billion. It could also provide an insurance policy against unanticipated challenges to the 2021 COVID-19 vaccine rollout. In the longer term, the 'go now' path could allow for a sovereign mRNA platform technology capability.

- **Meeting the timelines in this path requires an IP partner** to support a technology transfer. The two critical capabilities to onshore are those involved in the in vitro transcription (IVT) and lipid nanoparticle (LNP) formulation steps of mRNA manufacture, for which IP is currently concentrated in a small number of companies. The Government could explore arrangements with Pfizer/BioNTech[2] or Moderna (whose vaccines are approved/authorised in many countries), and also CureVac (whose candidate is in Phase 3 clinical trials).[3]

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- **Only a brownfield build could achieve near-term COVID-19 benefits.**[4] Timelines are contingent on favourable technical details emerging from the IP partner, and the existing capabilities of the brownfield facility. Under 'go now', there are three potential

1 Reflects critical path to onshoring discussed later in this document, reflecting maximal acceleration in an Australian context.

2 s47G(1)

3 s47G(1)

4 17 such mRNA vaccine manufacturing sites have been set up overseas, with the longest completion occurring within 10 months. s 47C

onshore partner arrangements that could provide a brownfield facility, delineated by the tech transfer archetype pursued.

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s 47C

The ultimate nature and cost of government supports required to attract and accelerate onshoring of mRNA vaccine capability will necessarily be subject to negotiation.

- **Pursuing this path will require urgent, concerted engagement of the IP partner's global leadership teams by the highest levels of the Australian Government.** This will act as a signal of genuine commitment, simplify communications, and enable rapid decision making across all parties. s47G(1), s 47C

  In its outreach, the Government must articulate Australia's attractiveness as a tech transfer investment destination. In particular, this value proposition could emphasise Australia's suitability as an export base, with the ability to credibly commit not to impose export controls, given the country's modest domestic needs relative to at-scale plant capacity.

The key benefit of the 'go later' path stems from added flexibility in the design of a long-term platform capability in mRNA technology for Australia. However, this path is unlikely to provide benefits in relation to COVID-19 (re)vaccination efforts in the short term.

- **A greenfield approach allows 'future-proofed' design**, including the build approach (e.g., flexible layouts), best-in-class equipment, and optimising site selection (e.g., co-location with local biopharma industry/ecosystem players). These flexibilities come at a greater CapEx, s 47C excluding tech transfer costs. To underwrite a break-even CapEx payback, the Government may need to guarantee offtake demand of up to s 47C doses in total[s4].
- **The most suitable 'anchor product' to generate sufficient baseload utilisation of an at-scale manufacturing facility is an mRNA vaccine for seasonal influenza**. If

5 s 47C, s47G(1)

6 s 47C

7 s 47C

COVID-19 is not the impetus for the build, an alternative product pipeline must be sourced to ensure both ongoing commercial viability of the facility, and maintenance of the know-how required for a sovereign capability. Other disease applications in the mRNA product pipeline are for currently sub-scale indications (e.g., Zika virus).

- **In sourcing the necessary IP under the 'go later' path, international tech transfer options may prove challenging** over a 3-year timeframe. Manufacturers have indicated that their mRNA manufacturing footprint decisions are currently under active consideration, resulting in a risk that potential IP partners will have already committed their global manufacturing footprints.
- **In addition to options to source IP from international owners, the 'go later' path allows for a fourth archetype where potential home-grown IP sources are utilised, though this carries the traditional risks associated with biopharma R&D.**

  Noting that the Government has an existing investment in CSL for future influenza vaccine production at a new facility in the Melbourne Airport Business Park, and that this production could be re-platformed onto mRNA technology, there are both capability and cost advantages to Australia in pursuing a 'home-grown' arrangement involving CSL. Alternatively, the Government could engage with other emerging, locally-led academic/private sector consortia, depending on their level of maturity. For home-grown IP owners, Australia has a limited track record in commercialisation.

Across both the 'go now' and 'go later' paths, an onshore capability in the mRNA technological platform could generate a number of additional benefits:

- **A speed advantage** in meeting demand shocks arising from future pandemics, potentially delivering a benefit of $10 billion to $80 billion in the event of a future pandemic.[8]
- **Greater efficacy** in treating seasonal influenza, delivering benefits of $0.1 billion to $1.3 billion per influenza season; via reduced illnesses and associated absenteeism, GP visits and hospitalisations.[9]
- **Security of supply** to novel 'blockbuster' vaccines, in the event relative global supply shortages persist.
- **Up to $1.3 billion in annual GDP**, and 1,700 ongoing jobs across the Australian economy, in addition to one off 12-month GDP benefit of $0.4 billion and 3,700 jobs (assuming a brownfield build).[10]

To onshore mRNA manufacturing capacity, it is likely that Australia's governments will need to play an active role to attract and accelerate onshoring and capture the associated benefits. In both a 'go now' and 'go later' path, partners are likely to require financial support (including capital contributions) and take-and/or-pay agreements for products produced. In the 'go now' scenario, there is likely to be additional direct government support required to accelerate the critical path to facility establishment (e.g., increasing resources for regulatory support). Governments could also intervene to increase the likelihood of capturing benefits. This could include ensuring access to the platform is

8 Future pandemics are considered to have a 1-2% chance of occurring per year (Chapter 17, Pandemics: Risks, Impacts and Mitigation https://www.ncbi.nlm.nih.gov/books/NBK525302/).

9 A successful switch from Australia's current onshore cell-based strategy to mRNA could yield significant healthcare cost savings, assuming the shorter lead times required for mRNA vaccine production allow strain-selection to occur closer to the start of winter (and thus for influenza vaccines, more closely match circulating strains).

10 Assuming full plant utilisation; and including the direct, indirect and induced multiplier effects on GDP. Multipliers have been calculated using OECD Australian pharmaceutical input output tables, refer to Chapter 3.4 for detailed analysis breakdown.

sufficiently flexible, purchasing COVID-19 vaccines, and reserving manufacturing capacity for future pandemics.

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1 Context and objectives

1.1 THE COVID-19 AND MRNA VACCINES CONTEXT

The ongoing COVID-19 pandemic has disrupted lives and livelihoods, communities, and economies, both at home and abroad. To protect the health of Australians, governments have deployed a wide range of public health measures, including movement restrictions and population-scale testing, tracing, and isolation activities. These measures have been broadly successful in containing the spread of COVID-19, when compared to many other countries. Australia has recorded some of the lowest infection and death rates across countries; less than 0.12% of the population has been infected and loss of life has been contained to less than 1,000, with Australia having one of the highest testing rates in the world.

Nevertheless, measures such as border restrictions and lockdowns are both imperfect and costly. Australia continues to see outbreaks, and now confronts the emerging challenge of new virus strains. The very same measures that save lives often disrupt livelihoods. Border restrictions and other disruptions have limited international commerce, with Australia's trade-exposed education and tourism industries particularly hard hit. In addition, domestic lockdowns have placed many local industries under significant strain and have had significant impact on the mental health of the Australian population, with up to a 7x increase in those exhibiting signs of clinical depression.

Hope has been placed in vaccines to provide a lasting reprieve. Notably, the promise of novel mRNA-based vaccine technology has been realised for the first time. Of over 80 countries who have launched vaccination campaigns, nearly half are using the mRNA vaccines from Pfizer/BioNTech[11] or Moderna. In contrast to traditional vaccines, mRNA-based vaccines are produced via chemical reactions, rather than more time-consuming biological processes (i.e., without the need to grow chicken, mammalian, or bacterial cells). The technology has supported the rapid development and manufacture of effective COVID-19 vaccines (with ~95% efficacy), and holds promise for similar advantages against other diseases.

The Australian Government has secured access to a diverse portfolio of COVID-19 vaccines, including the Pfizer and AstraZeneca/Oxford vaccines that have received provisional approval from the TGA. However, with the expectation of global supply constraints, in mid-2020 the Government undertook an audit of Australian vaccine and therapeutics manufacturing capability and capacity. This audit found limited existing capability in vaccines manufacturing, with no existing capability to produce mRNA vaccines.

Further information on mRNA vaccines and Australia's current vaccine manufacturing capabilities is included in Appendix A.

1.2 THE AUSTRALIAN GOVERNMENT'S OBJECTIVES

Recognising the immediate importance of mRNA vaccines to the fight against COVID-19, and the potential for mRNA as a platform technology for Australia's future, the Department

[11] The mRNA vaccine BNT162b2 for SARS-CoV-2 was developed using BioNTech's proprietary mRNA vaccine platform; Pfizer have partnered with BioNTech to jointly conduct clinical trials, scale up manufacturing capacity, and commercialise the vaccine worldwide. Pfizer Australia Pty Ltd will market this vaccine in Australia; as such, 'Pfizer' will frequently be used to refer to the Pfizer/BioNTech vaccine throughout this business case.

of Industry, Science, Energy and Resources (DISER) together with the Department of Health (DoH) now seek to better understand the options to onshore manufacturing capability for mRNA vaccines in Australia, in order to:

- **Increase Australia's COVID-19 vaccine supply**, to support potential needs for revaccination (e.g., due to waning immunity, new strains, or seasonality), and to provide an insurance policy against unanticipated delays or changes to the current (2021) COVID-19 vaccination program.
- **Provide a 'platform' technology capability** to capture other future benefits of mRNA vaccines (e.g., pandemic influenza preparedness, cancer vaccines), therapies and adjacent products.

This business case explores options to onshore mRNA manufacturing to meet the above two objectives. It provides an assessment of the feasibility and timelines of each option, and the relative benefits, costs, and risks of these options in the short and longer term. It also suggests the potential actions required (by stakeholders such as the Australian Government, state and territory governments, and other potential partners), for Australia to secure and capture benefits from that capability.

1.3 BUSINESS CASE FOCUS: CRITICAL MRNA CAPABILITIES TO ONSHORE

To successfully deliver mRNA vaccines purely onshore, Australia must possess the required capability and capacity across the end-to-end (E2E) value chain. Within this E2E value chain the business case focuses on manufacturing, where Australia has the most critical capability gaps in readiness. In contrast, other steps in the value chain are either complete or underway (e.g., regulatory approvals for specific vaccine candidates; logistics, distribution, and administration arrangements for the Pfizer COVID-19 mRNA vaccine).

To support Australia's COVID-19 vaccination program, the focus within manufacturing must be on bottlenecked steps in the process chain (see Figure 1). Currently, these are the mRNA in vitro transcription (IVT) step to produce bulk drug substance (DS), and the lipid nanoparticle (LNP) formulation step to produce bulk drug product (DP). Bottlenecks in these two steps are primarily due to tech transfer[12] constraints. The capability to address these bottlenecked steps is likely to be key to the attractiveness of Australia as a tech transfer destination for IP owners, and thus Australia's ability to secure extra doses of the finished product.

Furthermore, as IP is concentrated in a few players, holding capabilities in mRNA drug substance/drug product manufacturing is critical to building sovereign platform capabilities.

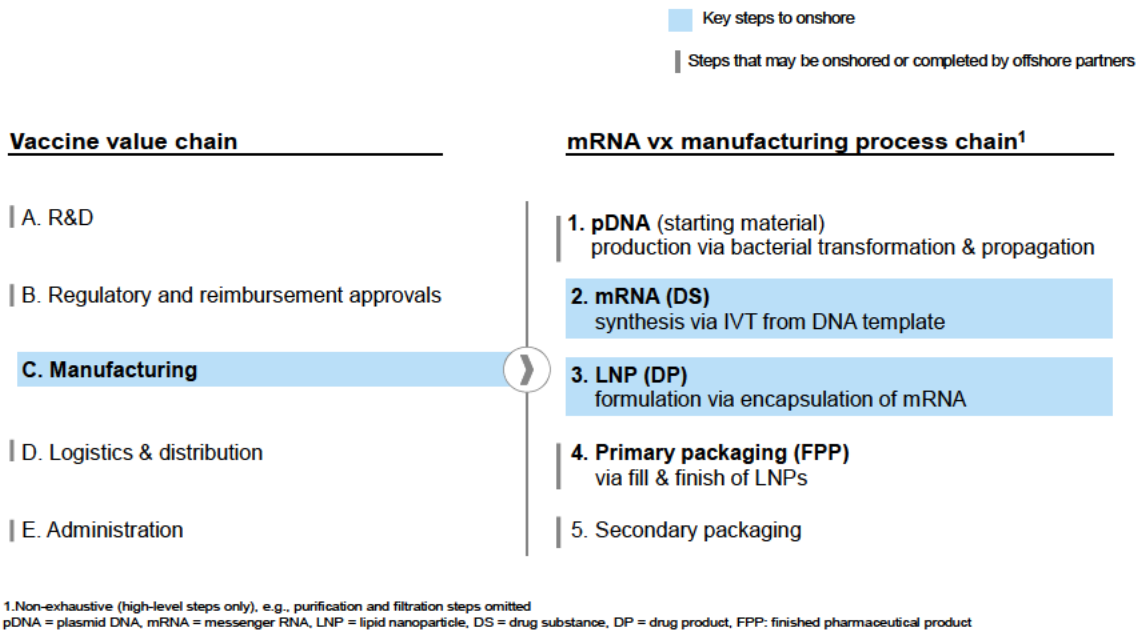
In contrast, plasmid DNA (pDNA) production and packaging steps are unlikely to be supply constrained, and Australia's biotechnology sector already has existing capabilities in pDNA production, as well as in fill-and-finish (FF) steps.

Acknowledging this context, this business case focuses on identifying and assessing options to onshore new IVT and LNP formulation capabilities. The business case also assesses the feasibility and desirability of including the remaining two steps (pDNA and FF) in the

[12] The process of transferring the technology and relevant know-how from the IP owner to the production facility, ensuring the local manufacturing processes and facilities are aligned with the IP owner's direction and quality requirements.

potential arrangements. Further details on the assessment of capability gaps across the end-to-end value chain are included in Attachment 1.

FIGURE 1: Critical activities to onshore within the end-to-end mRNA vaccine value chain



1.Non-exhaustive (high-level steps only), e.g., purification and filtration steps omitted
pDNA = plasmid DNA, mRNA = messenger RNA, LNP = lipid nanoparticle, DS = drug substance, DP = drug product, FPP: finished pharmaceutical product

2 Options for onshoring mRNA vaccine manufacturing capabilities

There are two principal requirements to onshoring an mRNA vaccine manufacturing capability: a source of **intellectual property** (IP – the proprietary know-how to manufacture a product), and a suitable **manufacturing facility**.

The decisions on solving for these two requirements will be informed by whether the Government pursues a 'go now' or a 'go later' path:

1. **A 'go now' path** rapidly establishes capability within a ~9 to 12-month timeframe. This timeframe requires **partnering with an IP owner** that brings a TGA-approved mRNA vaccine product (or a late-stage vaccine candidate that could be approved in the near term), and **repurposing an export-scale brownfield facility** (or facilities). This path delivers on a scenario in which revaccination is required for COVID-19.
2. **A 'go later' path** to establish capability within a ~3-year timeframe. This timeframe allows a broader set of options, including options to pursue a **home-grown IP** owner and/or a **greenfield facility**. This path potentially delivers a more flexible, purpose built on shore mRNA technology platform.

To determine which of these paths to follow, the Government should consider the feasibility and likely timelines involved (covered in this chapter), as well as the relative benefits, costs and risks relating to each path (covered in Chapter 3).

Section 2.1.1 provides an actions checklist should Government pursue the 'go now' path, while Section 2.1.2 provides a checklist for Government to pursue the 'go later' path.

Section 2.2 presents an assessment of each of the leading IP owners (further details are available in Attachment 2), while Section 2.3 presents an assessment of the choices for a manufacturing facility (further details are available in Attachment 3).

Further details on the feasibility of IP partner options are included in Attachment 2.

2.1 ACTIONS REQUIRED TO SECURE TWO KEY REQUIREMENTS (AN IP OWNER AND A SUITABLE MANUFACTURING FACILITY)

For each path, the Government should consider taking the following (non-exhaustive) sets of actions. These should be refined and further specified based on evolving stakeholder and expert engagement. Sequencing of individual steps may shift based on negotiation analysis.

2.1.1 Actions Checklist for the 'go now' path

1. **Stand-up an Execution Taskforce**, commencing with a fully resourced 'deal team' with the necessary delegations and commercial capabilities to engage partners:
   a. s 47C
   . s 47C

[13] BATNA = best alternative to negotiated agreement. This represents the counterparty's 'next best option' in a negotiation, and often sets the floor price.

s 47C

b. s 47C

c. s 47C

2. s47G(1)

a. s 47C

b. Demonstrate Australia's genuine commitment to proceeding with a 'go now' path, through outreach to potential IP owners by representatives at the highest levels of the Australian Government, and confirm the potential IP owner's interest.

c. s 47C

d. s 47C

3. s 47C

At a minimum, the Australian Government should maintain the necessary involvement to ensure it is in the flow of information, and can shape the evolving arrangements to protect the ability for Australia to capture value from the onshoring arrangements. For example, to ensure a guarantee of dose availability to Australia, and to ensure IP arrangements allow for a lasting onshore platform capability in mRNA technology (beyond the production of immediate products such as COVID-19 vaccines).

5. **Plan and execute the necessary government supports** to accelerate the scale-up of tech transfer, informed by the initial discussions. For example, depending on the brownfield facility chosen, there may be a requirement for early and intensive s 47C

s 47C

6. s 47C

7. **Coordinate interdependent activities**, including ensuring the manufacturing timeline is integrated with broader supply chain arrangements to deliver and administer vaccines.

2.1.2 Actions Checklist for the 'go later' path

1. **Conduct further assessment to confirm the longer-term target state** of capabilities in Australia.
2. s 47C

   b. Determine whether to pursue a brownfield re-development or a greenfield development in order to establish the required manufacturing facility.
3. s 47C

4. s 47C

s 47C

b. However, a broader set of potential IP owners could be engaged. s47G(1), s 47C

5. **If pursuing a home-grown IP owner**, then the Government should:
   a. **Determine the preferred home-grown IP approach** i.e., whether to anchor on a seasonal influenza product; s 47C
   or to engage other emerging, locally-led academic/private sector consortia.
   b. **Engage preferred home-grown IP owner**(s) to further understand the necessary commercial arrangements and government supports.
   c. **Negotiate in-principle partnerships** with the necessary IP/facility partners.
   d. **Facilitate the necessary commercial arrangements**, including the arrangements necessary for Australia to capture value from the onshore capability.
   e. Plan and execute the necessary government supports.
   f. **Monitor progress,** against milestones and timelines overseen by the Execution Taskforce; with aims as per the 'go now' checklist.

2.2 OPTIONS FOR SOURCING IP

Standing up an mRNA vaccine manufacturing facility requires an IP partner to provide the proprietary know-how, both for the technology platform (manufacturing methods) and for the resultant products produced. There are two major options for sourcing the relevant IP to produce an mRNA vaccine – seeking tech transfer from a partner with existing IP s47G(1)
or from the development of 'home-grown' IP *(de novo)*.

A 'go now' path requires tech transfer of the know-how for an existing manufacturing process (i.e., for a (near) approved mRNA vaccine product from an established IP partner).

- The IP required to manufacture mRNA vaccines is novel and concentrated in a small number of innovators. Tech transfer of this IP is the rate-limiting factor in the global expansion of mRNA manufacturing in the near term, driven by constraints on personnel with the required know-how to meet both ongoing production and scale-up demands to respond to the pandemic. Australia's challenge is likely to be in securing tech transfer from an innovator/IP partner s47G(1) who are only willing to invest in a limited number of tech transfers across the globe, given each carries a large and fixed opportunity cost. Australia would need to present a brownfield option of sufficient speed, scale, and quality to be attractive to the innovator/IP partner in the context of their *global* production strategy.

A 'go later' path allows additional tech transfer partners and the option of awaiting home-grown IP. IP owners with less mature platforms s47G(1) may be viable tech

s47G(1), s 47C

transfer partners over the longer term, and may bring technological advantages. Home-grown IP could be built from the ground up by relying on the development and commercialisation of a local new product by local innovator manufacturers. These options are unlikely to meet the objective to increase Australia's COVID-19 vaccine supply in the near term, due to long lead times and research uncertainty, and is thus only an option under the 'go later' path.

To successfully onshore the right IP, Australia will have to identify an appropriate IP partner option to meet its objectives and to articulate an attractive value proposition to them s 47C, s47G(1)

2.2.1 Australia's value proposition to IP partners

IP owners signalled that they had limited tech transfer capacity, and face considerable international demand for such tech transfers. As such, Australia will need to articulate an attractive value proposition to secure a tech transfer. This could include four elements:

- **A suitable brownfield site can be identified with sufficient capability**/capacity to provide speed-to-scale, meeting quality standards for both TGA and export markets overseas.
- **Australia is a safe and stable country to invest in**. We have a credible regulator, stable democratic government and economy, a skilled workforce, and track record of responsible global engagement.
- **Australia will rapidly saturate domestic demand,** and have no rational incentive to impose export controls. This could make Australia a more reliable partner within s47G(1) global supply network.
- **Australia offers an Asia-Pacific manufacturing base for export,** with geographic proximity, free trade agreements, high-quality standards, and close governmental relationships.

2.2.2 Overall comparison of IP partner options

There are three key factors that Government could consider in selecting an IP partner. These are:

1. **Advantage on speed-to-scale of onshoring**. Considerations include the potential partner's experience and capacity for tech transfer, scale, and any existing onshore manufacturing, licensing, and authorisation footprint.
2. **Advantages of the technology platform**. Considerations include the adaptability of the underlying manufacturing process/technology 'platform' to produce new products (whether in the product pipeline of the original IP partner, or in switching to products developed by other innovators), the strength of the potential IP partner's mRNA product pipeline, the quality and characteristics of the resultant mRNA products (e.g., thermostability advantages, mode of administration), and the cost of production.

3. **Advantage to economic development more broadly in Australia**. Considerations include the potential contribution to the growth and sustainability of the Australian biopharmaceuticals industry, and the Australian economy more broadly.[15]

IP partner options have been considered in reference to these factors, informed by both publicly available information and interviews conducted with multiple stakeholders.

s47G(1), s 47C

[15] Advanced manufacturing (including biopharmaceuticals) is an important area of potential economic opportunity for Australia. Onshoring of mRNA vaccine manufacturing capabilities in Australia is likely to constitute a significant government investment. s 47C, s47G(1)

s47G(1)

s 47C

s47G(1), s 47C

s47G(1), s 47C

s47G(1)

Moderna has an extensive mRNA product pipeline. Moderna is currently developing mRNA vaccines for new SARS-CoV-2 variants, including a vaccine to target the B.1.351 variant (first identified in South Africa). Beyond COVID-19, Moderna has four products in Phase 2 clinical trials, eight products in Phase 1 clinical trials, and an additional 11 products in preclinical development. These cover other infectious diseases (e.g., influenza and CMV), chronic diseases (e.g., heart failure), cancer (e.g., ovarian cancer), regenerative medicine (myocardial ischemia), and genetic disorders (phenylketonuria).

s47G(1), s 47C

[20] These CMOs/CDMOs typically provide the tech transfer expertise. s47G(1), s 47C

s47G(1), s 47C

s47G(1)

s47G(1), s 47C

s 47C, s47G(1)

[20] CMO and CDMO refer to pharmaceutical contract (development and) manufacturing organisations. Innovator pharmaceutical companies outsource the development (e.g., clinical trials) and/or manufacturing of their products to these companies.

[21] Moderna have publicly announced a target of 0.6 to 1 billion doses delivered by the end of 2021. s47G(1)

[22] s47G(1), s 47C

s 47C

s 47C, s47G(1)

s 47C, s47G(1)

2.2.6 Detail of home-grown IP owner option

The development of home-grown IP to support mRNA vaccine manufacturing is only viable for the 'go later' path due to the required lead time. While establishing home-grown IP may confer benefit to the local biopharmaceutical industry and promote platform adaptability, a number of trade-offs should be considered:

Firstly, speed-to-scale for home-grown IP relies on commercial investment to support an uncertain R&D process.

a. **Commercial attractiveness of product pipeline drives product and IP development.** There is a high degree of research uncertainty in the development and commercialisation of mRNA platform IP. Depending on the therapeutic area, the probability of entry to market for a pipeline product is low – it is approximately ~3% for oncology therapies and 33% for infectious diseases vaccines, which represent two primary use-cases for mRNA technology. Additionally, the average cost is ~US$1.3 billion.[24] Accordingly, this requires sufficient commercial attractiveness to encourage investment and support translation of research expertise into end product.

   s47G(1), s 47C

   s47G(1), s 47C

   The ARPC cite that limited number and risk averse domestic investors have prevented commercialisation of their research

23 s 47C

24 https://jamanetwork.com/journals/jama/fullarticle/2762311.

25 ARPC is a consortia of domestic researchers with RNA expertise. ANU are believed to have the largest group of researchers in the field.

skillset. Further consideration of specific levers to attract increased investment in the Australian biopharmaceutical industry is outside the scope of this report.

b. **Smaller scale home-grown IP owners may have limited manufacturing scale.** s 47C, s47G(1)

Secondly, global IP owners may have relative advantage in breadth of platform pipeline and favourable mRNA technology characteristics (vs. home-grown IP).

4. **Future platform adaptability may require partnership with global innovator manufacturers.** Use of a home-grown mRNA platform to support multiple IP holders and capitalise on the breadth of product pipelines of global innovator manufacturers (i.e., s47G(1) etc.) requires entering a CMO/CDMO arrangement. Potential at-scale home-grown IP owners (s47G(1) could be viewed as a competitive threat by global players compared to smaller scale options (s47G(1)). However, while this could limit future platform adaptability in some instances, global IP owners may also prefer at-scale partners due to ease of technology transfer.
5. **Lack of domestic mRNA expertise could lead to suboptimal platform technical characteristics.** Incumbent global innovator manufacturers may maintain a relative advantage in mRNA platform technology if home-grown IP owners are unable to develop comparable technology (i.e., product thermostability, clinical efficacy etc.) – this could have broader supply chain implications (i.e. increased cold-chain complexity). s47G(1)

Thirdly, development of home-grown IP may have limited benefit in supporting economic development. While home-grown IP could improve the technical and commercial capabilities of Australia's biopharmaceutical industry, it may not provide a sustainable platform for economic development outside of use for seasonal influenza and pandemic insurance. This is due to the product pipeline of emerging oligonucleotide therapies being generally focused on niche markets, making supply shortages unlikely in the context of rapidly mRNA manufacturing capability rapidly expands in response to COVID-19 demand.

Finally, in addition to the above three considerations, the nature and extent of government supports[26] required for the development of a home-grown IP option could vary in view of existing arrangements. s47G(1), s 47C

[26] See Chapter 4 for detail on potential government supports required.

FIGURE 2: ARPC has significant capability gaps across the drug development value-chain s47G(1)

s47G(1), s 47C

Phase	Sub-phase	Activity
Research		Basic research
		Discovery research
Development	Pre-clinical	Pre-clinical testing
	Clinical	Phase 1
		Phase 2
		Phase 3
Product Launch		Regulatory
		Manufacturing
		Sales & Marketing
		Logistics & Distribution

2.3 OPTIONS FOR ESTABLISHING A MANUFACTURING FACILITY

In parallel with a decision made regarding to 'go now' or 'go later', and potential IP owner(s) selection, a decision needs to be made on the approach to establishing a manufacturing facility, and the archetype of any associated tech transfer (see Figure 3 below).

s 47C

There will need to be a commercial agreement between the IP Partner and the manufacturing site, and therefore the IP Partner's preferences will have significant influence on the final decision.

There are two major options for establishing a manufacturing facility in Australia.

A 'go now' path requires a brownfield approach (retooling an existing facility). This provides the fastest possible timeframe to first dose production.

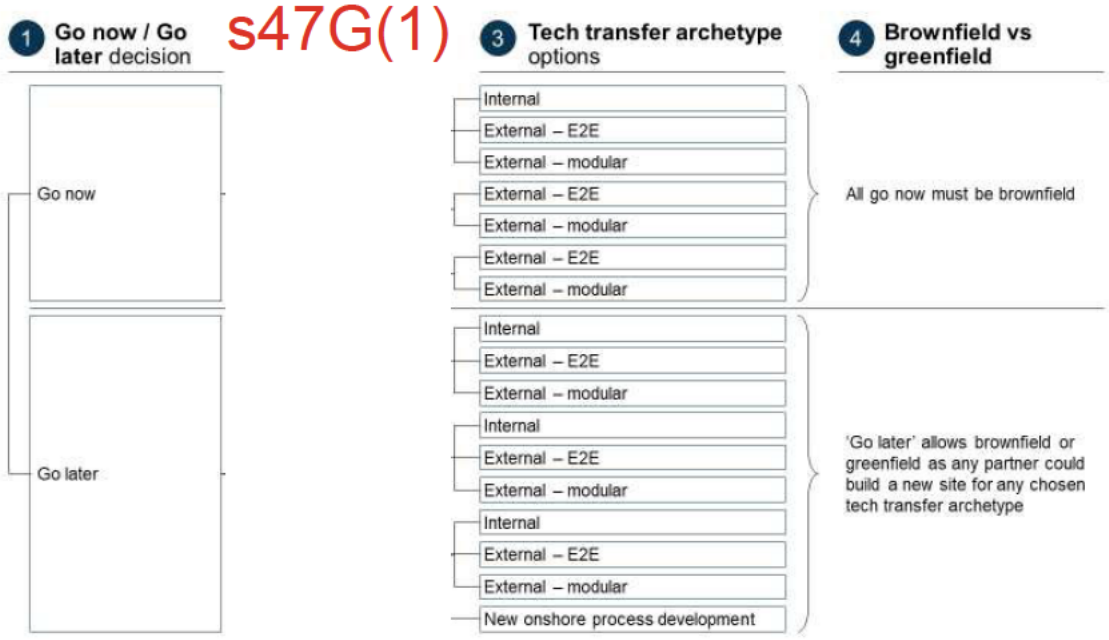
A 'go later' path allows the additional option of pursuing a greenfield approach (i.e., commissioning a new facility). A greenfield site has long lead times, ~2 years longer than brownfield, due to the need to seek a suitable site and associated permits, construct the building, and seek GMP licensing. As such, a greenfield approach is significantly less likely

to reach the speed-to-scale required to meet the Government's first objective (to increase Australia's COVID-19 vaccine supply), and is not suitable for the 'go now' approach.

Under either approach, four archetypes exist for establishing capability at the selected brownfield or greenfield facility:

1. **Internal tech transfer** (from the IP partner to a self-operated facility).
2. **External tech transfer – end-to-end** (to a manufacturing partner with E2E capability i.e., s47G(1)).
3. **External tech transfer – modular** (to a consortium of partners, e.g., involving a set of CMOs/CDMOs).
4. **New process development** using home-grown IP (only in the 'go later' path).

FIGURE 3: The are s47G steps in the decision pathway for onshore mRNA manufacturing



Section 2.3.1 presents an overall assessment of the feasibility and critical path for a brownfield approach and a greenfield approach; while Section 2.3.2 presents an assessment of specific potential brownfield facilities, delineated by the archetype of tech transfer/IP sourcing approach used. Further details are available in Attachment 3.

2.3.1 Overall perspective on feasibility and critical path assessments

Australia has the basic capabilities required to stand up either a brownfield or a greenfield site for mRNA product manufacturing.

- **In an accelerated case, a brownfield facility could be operational in Australia within 9 to 12 months**, and may meet both of the Australian Government's objectives (i.e., may both increase Australia's COVID-19 vaccine supply, and provide a longer-term capability in the mRNA technology platform), although it may not have all of the platform benefits of the newest technology.

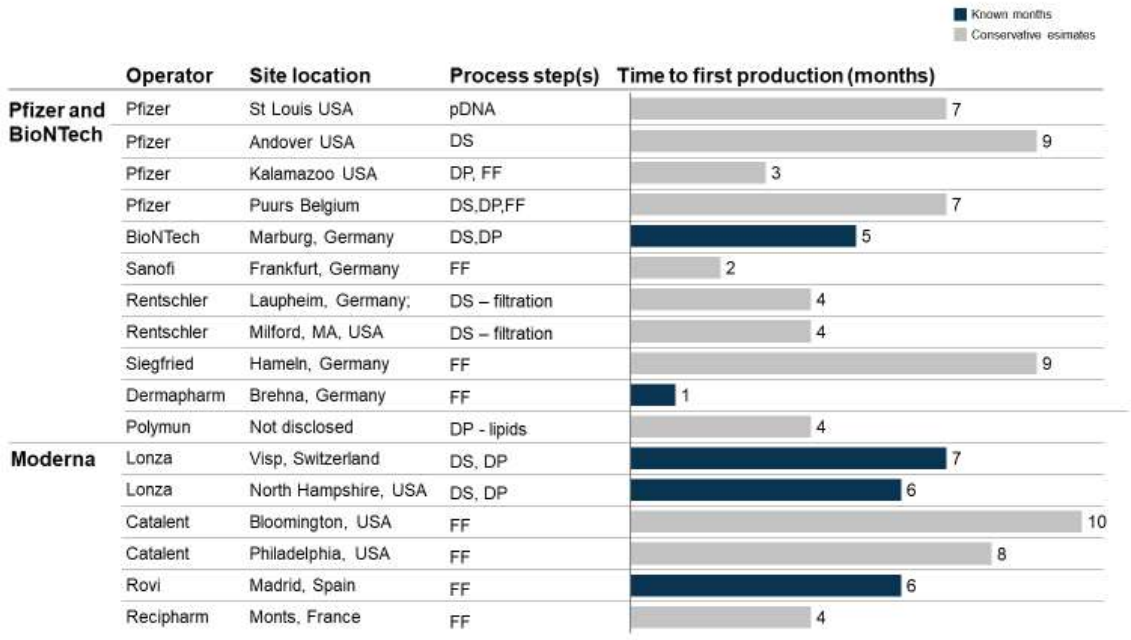
- **A greenfield facility likely requires 2-to-3 years longer lead time**, in the most accelerated case. This could potentially meet the second objective (to provide a platform capability), but is less likely to deliver the benefits under the first objective (to increase Australia's COVID-19 vaccine supply).

Brownfield facilities could be operational for mRNA production in Australia in 9 to 12 months.

Completing a tech transfer, retooling, and adjusting the license for an mRNA vaccine brownfield manufacturing site in Australia within 9 to 12 months is theoretically feasible, based on a review of retooling for mRNA overseas, and critical path analysis; although achievability in the Australian context requires further validation with input from the IP partner on the exact requirements of their specific manufacturing process.

As of early February 2021, 17 mRNA vaccine associated manufacturing sites have been set up globally between Pfizer, BioNTech, Moderna, and their CMO/CDMO partners.[27] All of these sites were brownfield projects, utilizing existing sites and retooling them, although none were complete end-to-end sites (i.e., they only addressed part of the process). Given the timeline of the emergence of COVID-19, the retooling of these sites was completed in a maximum of 12 months, and in some reported cases as few as 4 months (Figure 4).

FIGURE 4: 17 sites have begun production for mRNA vaccine



A review of the capability of these 17 sites demonstrated that they all had significant strengths in the same, or highly adjacent, technologies prior to the tech transfer and setting up mRNA vaccine production processes. Initial, outside-in, analysis suggests that Australian sites have moderate capabilities in highly adjacent technologies, but not the same level of capabilities as the 17 sites utilised by s47G(1) (see 2.3.2 and Attachment 3).

27 Information and data on time to first production sourced from public announcements by the relevant IP Partner and manufacturing companies.

Analysis of the critical path processes to establish mRNA vaccine manufacturing sites in Australia indicates accelerated timeframes under 'business as usual' (pre-COVID-19) contexts of ~18 months to retool a brownfield site. However, the theoretical limit of establishing a brownfield mRNA manufacturing site in the COVID-19 context in Australia appears to be ~9 months (Figure 5, detailed version in Attachment 3, Section D).[28]

s47G(1), s 47C

The theoretical limit of the time taken to retool a brownfield site for mRNA production must then be compared to the existing capabilities of individual sites (see Section 2.3.2) on a site by site basis. For example, if a site does not have an existing sterile injectables license, implementation and TGA validation of sterile processes may add considerable lead time. It is possible that no site in Australia has all the requirements to complete the theoretically fastest possible tech transfer and regulatory approval process.

Even if local sites meet these requirements, significant delivery risks remain. Due to the short timeframes, if any critical path activity is delayed the entire project will be delayed, and four specific steps on the critical path (negotiations, purchasing equipment, setting up new processes, and regulatory approval) have been identified as high risk of delay or failure.

Supply constraints in the 'go now' scenario are unlikely to impact timelines.

Initial concerns were raised that shortages of supply in raw materials and equipment may occur, however this is unlikely to be an issue for COVID-19 commercial manufacturers in a year's time. In examining this concern, industry stakeholders and experts have consistently advised that supply constraints are very unlikely to be ongoing by the time a brownfield mRNA manufacturing facility is operational in Australia (i.e., in late 2021 or early 2022).[29] This reflects two factors: first, that suppliers prioritise commercial COVID-19 products above

[28] Critical path analysis was completed by interviewing experts in each component of the process to understand accelerated timelines. The overall timeline been confirmed in interviews with engineering firms, pharmaceutical executives, and equipment suppliers, who gave estimates ranging from 6 to 10 months in the COVID-19 context, in Australia.

[29] Based on expert interviews with current and ex-executives at mRNA producing pharmaceutical companies, non-mRNA pharmaceutical companies; executives of companies which supply materials and equipment to pharmaceutical companies, and consultants who serve pharmaceutical companies.

all other products; and second, that unprecedented industry collaboration has resulted in rapid ramp up of production across all input materials. These two factors mean that while non-COVID-19 applications have seen significant delays/shortages in supplies, this is not the case for commercial production of COVID-19 mRNA vaccines.

Development of a greenfield site is less likely reach speed-to-scale for onshore manufacturing, but will have more flexibility in platform possibilities.

A greenfield site is likely to require an additional 2 years of development, in comparison to a brownfield approach (i.e., 3 or more years in total). In addition to the requirements for brownfield sites (such as equipment purchase), a greenfield site requires identification of a location, design of a site from scratch, build of the physical facility, its infrastructure, and then application and approval of GMP licensing. None of the pharmaceutical or engineering experts interviewed believed a greenfield site could be completed in less than 2 years, with the most accelerated possible timeline estimated at approximately 3 years. e.g. Some of the time required to build a greenfield facility could possibly be removed if an early stage design or build is repurposed, such as the s47G(1) site, but the process remains significantly longer than brownfield.

A greenfield site does provide flexibility in platform possibilities, allowing the integration of the most recent technology and processes; opening more future options for the site's usage, and in some cases optimising ongoing costs (see Section 3.5).[30]

Further details on the overall assessment of feasibility and critical path possibilities are included in Attachment 3.

2.3.2 Overall comparison of tech transfer approaches and potential facilities

A shortlist of brownfield sites that may be able to produce doses onshore within 9 to 12 months was assessed. There is no perfect pre-existing facility, with at-scale capability in both IVT and LNP. Each potential facility poses their own set of challenges that must be overcome, against the context of ongoing rationalisation of multi-national manufacturers' footprints in Australia, s47G(1) , and the limited scale and mRNA experience of other potential sites.

There are s 47C tech transfer archetypes to support a mRNA product manufacturing facility. s47G(1), s 47C

s47G(1), s 47C

[30] Manufacturers may also prefer to establish capabilities for other technologies in the same facility.

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s47G(1), s 47C

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31 s47G(1), s 47C

s47G(1), s 47C

3 Benefits and costs

This chapter outlines the benefits to the Australian society that may arise from an onshore mRNA manufacturing capability with a capacity of 100 million+ doses per annum. It covers benefits related to COVID-19, other illnesses, and the potential benefits for Australia's biopharmaceutical industry. This chapter also includes estimates of the likely costs, including the capital investment required to set up onshore mRNA vaccination manufacturing capacity in Australia, together with ongoing operating costs.

The major sources of benefit of onshore manufacturing are anticipated to be:

1. **Benefits related to COVID-19.** The near-term benefit of availability of onshore mRNA vaccines to revaccinate Australia's population (in the event that SARS-CoV-2 continues to mutate, or immunity conferred by 1st-generation vaccines diminishes over time), and to enable additional vaccines for donations to other countries.
2. **Benefits related to other illness.** Beyond COVID-19, benefits connected with speed of access to vaccines in the event of another pandemic, together with benefits associated with onshore mRNA vaccines for seasonal influenza, which are anticipated to be more efficacious than alternative vaccines.
3. **Benefits for Australia's biopharmaceutical industry.** Economic benefits related to onshore mRNA vaccination, including 'multiplier' effects from spillover economic stimulation, and benefits related to increased capability and capacity in the Australian biopharmaceutical manufacturing sector.

Realisation of each of these benefits varies by path chosen ('go now' or 'go later') and by tech transfer archetype. Different benefits are also realised if a greenfield build is chosen under a 'go later' path, versus a brownfield build under either a 'go now' or 'go later' path.

3.1 SUMMARY OF BENEFITS BY PATH, IP OWNER, TECH TRANSFER ARCHETYPE AND BUILD TYPE

Across the 'go now' and 'go later' paths, an onshore capability in mRNA platform technology could generate several common benefits:

- A speed advantage in meeting demand shocks arising from future pandemics,[32] potentially delivering a benefit of $10 billion to $80 billion in the event of a future pandemic. Future pandemics are considered to have a 1-2% chance of occurring each year.[33]
- Greater efficacy in treating seasonal influenza, delivering benefits of $0.1 billion to $1.3 billion per influenza season via reduced illnesses and associated absenteeism, GP visits and hospitalisations.[34]
- Security of supply to novel 'blockbuster' vaccines, in the event relative global supply shortages persist.

32 During the current COVID-19 pandemic, countries with onshore manufacturing generally accessed vaccines earlier than other comparable countries.
33 Chapter 17 Pandemics: Risks, Impacts and Mitigation https://www.ncbi.nlm.nih.gov/books/NBK525302/
34 A successful switch from Australia's current onshore cell-based strategy to mRNA could yield significant healthcare cost savings, assuming the shorter lead times required for mRNA vaccine production allow strain-selection to occur closer to the start of winter (and thus for influenza vaccines, more closely match circulating strains).

- Up to $1.3 billion in annual GDP, and 1,700 ongoing jobs across the Australian economy, in addition to one off 12-month GDP benefit of $0.4 billion and 3,700 jobs (assuming a brownfield build).[35]

The path chosen determines whether near-term benefits related to COVID-19 are delivered and the degree of flexibility in selecting build type, IP partner and tech transfer archetype:

- **Under a 'go now' path,** there is an opportunity to realise *Benefits related to COVID-19*, which could deliver $1.2 billion to $7.9 billion in benefits related to revaccination, together with intangible benefits around global health diplomacy through regional vaccination.
- **Under a 'go later path'***, Benefits related to COVID-19*[36] are closed off, but realisation of *Benefits related to other illnesses* as well as *Benefits for Australia's biopharmaceutical industry* may be enhanced, due to flexibility in IP partnerships and build type.

Tech transfer archetype chosen within a given path determines which *Benefits related to other illnesses*, and which *Benefits for Australia's biopharmaceutical industry* are realised (and to what magnitude, see Figure 8 below):

- s47G(1), s 47C

- **An internal tech transfer** potentially limits the facility to future pipelines of the IP originator.
- **External modular tech transfer,** while highly flexible, poses a risk of not receiving future tech transfers from IP owner, due to sub-scale nature of consortium members.
- **New onshore process development** has the greatest potential for cascading spill over benefits to the biopharmaceutical ecosystem. However, long timelines for IP development result in no COVID-19 pandemic benefit and significant hurdles to achieving benefits for other illnesses (e.g., influenza). This risk can be mitigated via the involvement of CSL due to their skill, experience and R&D pipeline.

Refer to Attachment B for further details on tech transfer archetype benefits.

IP owner chosen will in turn impact the ability to capture these benefits. If a global IP owner s47G(1) is chosen for onshoring, then the key benefit that differs by source is *Benefits related to other illnesses* due to differences in the mRNA technology platform and associated product development pipelines (assuming similar efficacy and safety profiles for COVID-19 vaccines, and therefore similar *Benefits related to COVID-19*). All three major players have seasonal influenza vaccines in development: Moderna has the strongest pipeline in other mRNA therapeutics, especially for infectious

35 Assuming full plant utilisation; and including the direct, indirect and induced multiplier effects on GDP. Multipliers have been calculated using OECD Australian pharmaceutical input output tables, refer to Chapter 3.4 for detailed analysis breakdown or Attachment 4.

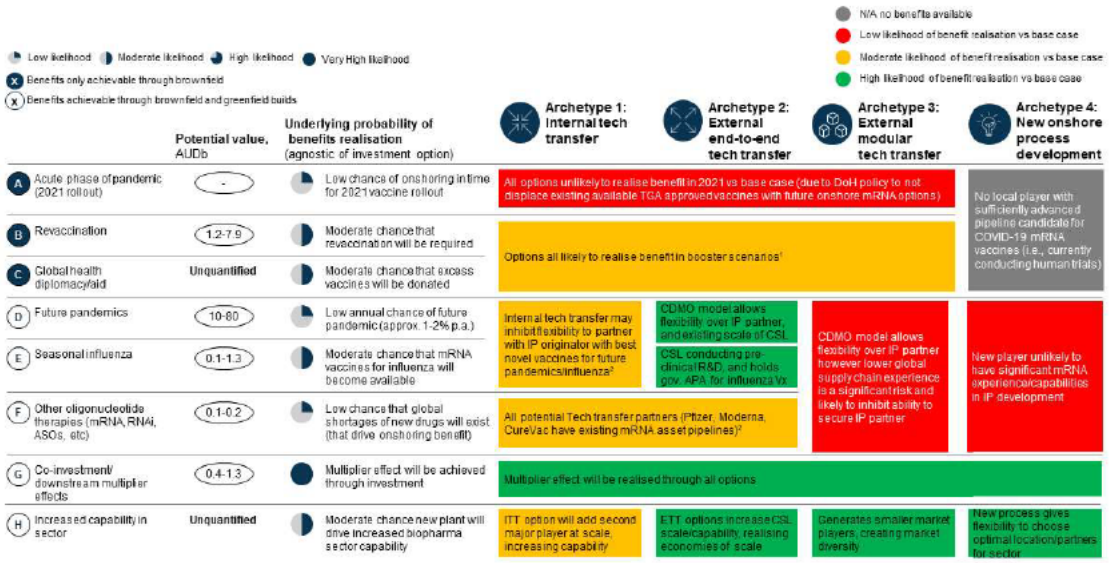
36 s 47C

disease (e.g., their Phase 2 cytomegalovirus vaccine, which could become a 'blockbuster' drug).

Build type will also determine type and magnitude of benefits. A 'go now' path will require a brownfield development s 47C , while 'go-later' has the optionality of adopting either a brownfield or greenfield build. The strategic benefits related to a greenfield build include 'future-proofed' design, including the build approach (e.g., flexible layouts), best-in-class equipment, and the opportunity to optimise site selection (e.g., co-location with local biopharma industry/ecosystem players). These will in turn drive greater *Benefits for Australia's biopharmaceutical industry* given the additional upfront investment required (which will increase the multiplier effect) and create greater capability than a brownfield option.

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FIGURE 8: Estimated realisation of benefits by archetype option



s47G(1), s 47C

Further details on the assessment of benefits, costs and risks are included in Attachment 4.

3.2 BENEFITS RELATED TO COVID-19

Benefits are unlikely to be realised during Australia's initial COVID-19 vaccination program; however, significant benefits may be realised if there is a need for ongoing COVID-19 vaccinations following the first national vaccination campaign.

3.2.1 Acute phase of the pandemic (2021 initial vaccine rollout)

A domestic mRNA manufacturing facility is unlikely to commence production in time to make a material contribution to Australia's initial vaccination program in 2021. Benefits would only be realised in the event of disruptive events such as:

- s47G(1), s 47C

- s47G(1), s 47C

- **A change in vaccination strategy** to include a higher portion of mRNA vaccine in the overall mix, potentially in response to new information about efficacy against mutations.
- **Significant rollout delays** to the population, resulting in a policy decision to allow citizens awaiting vaccination at the time of onshore mRNA production commencing to choose whether to receive an onshore mRNA vaccine instead of alternative vaccines scheduled in the rollout.

At this point in time, these events appear unlikely. If such events occur, the benefits would be similar to those described in the next section.

3.2.2 Revaccination

From 2022 onwards, if boosters or regular revaccinations are required to address mutating SARS-CoV-2 strains or improve waning immunity, onshore mRNA may provide a benefit through delivery of up-to-date mRNA vaccines targeting the latest strains.

While the uncertainty regarding the need for revaccination persists, many experts believe given the prevalence of SARS-CoV-2 variants and reduced efficacy of existing 1st-generation vaccines to these variants, revaccination may be required in the future.

The ongoing cost of restrictions to Australian society, including international and domestic border closures, venue capacity restrictions, and lost productivity due to illness, are estimated at ~$5 billion per month (see Figure 9)[37] based on the current costs of COVID-19 to the Australian society. A 10% saving in these costs for one month would exceed the estimated capital cost of s 47C to establish an onshore mRNA facility.

Should one-off or multiple instances of revaccination be required to improve overall population immunity to SARS-CoV-2 or its variants, there will be two key drivers of benefits, assuming earlier relaxation of policies by 1 to 3 months in the setting of revaccination:

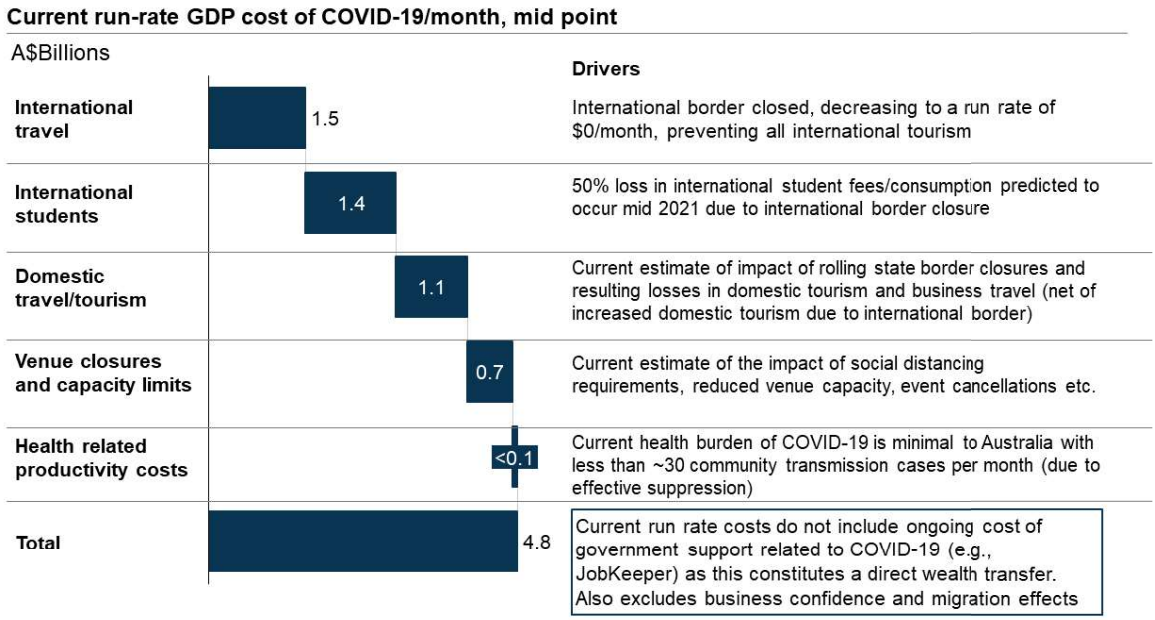
- Earlier re-opening of international travel arrangements with certain countries, based on vaccination status and/or COVID-19 prevalence, unlocking benefits to the Australian economy of ~$0.3 billion for a 1-month advantage, up to $2.5 billion for a 3-month advantage.[38]
- Earlier removal of restrictions on both domestic travel and venue closures/capacity limits (including lockdown induced measures), unlocking benefits to the Australian

[37] Expected costs of COVID-19 are variable. Costs may decline if contact tracing further improves, however they may also escalate if further mutations with increased transmissibility are seen.

[38] Assuming in the low case this allows international travel to resume with countries with less than 1-daily case per million population who have the vaccine program rolled out by mid-2022 (1-month earlier). High case allows opening to countries with less than 1-daily case per million people OR countries with less than 15-daily cases per million people who have the vaccine program rolled out by mid-2022. (3-months earlier). 50% travel/international students don't return in both cases.

economy of ~$0.9 billion for a 1-month advantage, up to ~$5.4 billion for a 3-month advantage.[39]

FIGURE 9: Ongoing costs of COVID-19 to Australian society[40]



Other, highly valuable unquantified benefits from increased freedom of movement (e.g., mental health benefits, decreased government financial support) would be realised in addition to the quantified benefits.

Given the likelihood of some form of revaccination being required,[41] there are three key preconditions for value to be achieved in the setting of revaccination:

1. That certain ongoing costs related to COVID-19 restrictions identified above are still being incurred during 2022.
2. That improved population immunity through earlier revaccination will result in Australian governments relaxing these restrictions (in whole or in part), which will directly unlock these economic benefits earlier.
3. Onshore manufacturing allows earlier Australian public access to mRNA vaccines than international procurement.

3.2.3 Global health diplomacy/aid

Australia has committed to s 47C mechanisms that will facilitate access to COVID-19 vaccines for lower-income countries globally:

s 47C

39 Low case assumes 50% of domestic travel and venue closure/capacity limit costs are removed 1-month earlier. High case assumes 100% of domestic travel and venue closure/capacity costs are removed 3-months earlier.

40 Treasury, ABS, Department of home affairs, Department of Prime Minister and Cabinet (Office of best practice Regulation), Mitchell University.

41 As discussed earlier due to antigenic drift or waning immunity as discussed by leading health experts, including Professor David Heymann, WHO's strategic and technical advisory group for infectious hazards (Chair).

s 47C

For in-kind donation, it is not anticipated that onshoring of mRNA production would directly lead to provision of doses of mRNA vaccines to lower-income countries in the Asia-Pacific region. This is for two reasons: firstly, many of Australia's lower-income regional neighbours lack the requisite cold chain capacity to safely store and administer mRNA vaccines;[42] and secondly, any mRNA vaccines would likely be purchased through the Regional COVID-19 Vaccine Access and Health Security Initiative via multilateral implementing partners.

Instead, there is a stronger likelihood that onshore mRNA vaccine production could enable additional viral vector or protein subunit vaccines for in-kind donation that might otherwise have been stockpiled or used for revaccination of the population where indicated.

3.3 BENEFITS RELATED TO OTHER ILLNESSES

Potential benefits that may arise from applications of mRNA technology to illnesses other than COVID-19 have also been considered within this business case. Including applications of mRNA vaccines for future pandemics and seasonal influenza, applications of mRNA and other oligonucleotide therapies for both infectious and non-infectious disease.

The use of mRNA vaccines for seasonal influenza remains one of the most likely disease applications for which a substantial benefit may be realised in the next decade. However, mRNA vaccines use for influenza is not expected to reach market until 2024 onwards. Other mRNA and related oligonucleotide drugs (such as ASO, RNAi and others) are also anticipated to deliver significant healthcare benefits to target populations. However, the incremental benefit of onshore manufacture in relation to this remains doubtful, given these drugs will likely be widely available on the global market.

The benefits related to other illnesses will vary depending on tech transfer archetype, and on the selected IP owner if a tech transfer occurs, with archetypes 2 and 4 s 47C) likely providing the greatest opportunity to realise benefits around future pandemics and seasonal influenza in particular.

The benefits related to other illnesses may also vary depending on IP owner. s47G(1), s 47C

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- s47G(1), s 47C

[42] As required by current mRNA vaccines being rolled out for vaccinations.

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- s47G(1), s 47C

3.3.1 Future pandemics

While the absolute risk of a new pandemic may appear low at 1 to 2% per annum, onshore mRNA vaccination manufacture could potentially save an estimated cost of $10 billion to $80 billion if it hastens Australia's vaccine rollout by 1 to 3 months. It is important to note that onshore domestic production capacity is only one step towards pandemic preparedness. Consideration should also be given to how Australia can further build on its learnings in COVID-19 to better contain outbreaks.

The ongoing pandemic risk is expected to continue to increase in the future due to four key factors: return of global travel, ongoing urbanisation, climate change increasing the risk of waterborne diseases, and increased human-to-animal contact (increasing the risk of zoonotic disease transmission).[43]

The most likely driver of value from onshore mRNA production in a future pandemic is that Australia will be able to produce and roll out future mRNA vaccines quicker than onshore viral vector vaccines, given mRNA has been shown to have a ~1 to 3 month time advantage in vaccine production and manufacturing. However, the virulence and morbidity/mortality associated with a future pandemic is unknown, as are the commensurate policy responses to attempt to contain loss of life. As such, in sizing the benefit of more rapid access to mRNA vaccines through onshoring versus global procurement, the following scenarios have been modelled:

- In the event Australia experiences another pandemic similar to COVID-19 and is able to supress it in a similar fashion, with minimal community transmission and short, targeted regional lockdowns, onshore mRNA would potentially drive a benefit of $10 billion, based on the scenario that Australia could begin relaxing international travel policies and domestic restrictions 3 months earlier (than in a situation where mRNA were procured offshore).
- In the event the next pandemic is similar to COVID-19, but Australia is unable to suppress the spread of the virus and instead ends up in a position similar to the United Kingdom with national lockdowns and substantial community transmission (e.g., over 25,000 cases per month), onshore mRNA would potentially drive a benefit of $80 billion based on the scenario Australia could begin relaxing international travel policies and the more restrictive domestic restrictions 3 months earlier.

[43] Disease control priorities: improving Health and Reducing Poverty: Chapter 17 Pandemics: Risks, Impacts and Mitigation https://www.ncbi.nlm.nih.gov/books/NBK525302/.

An additional benefit of pandemic preparedness is the ability of Australia to play a lead role in the Asia-Pacific region in the distribution of vital vaccines to neighbouring countries that may otherwise struggle to access sufficient supplies of vaccinations.

3.3.2 Endemic infectious disease (e.g., seasonal influenza)

The application of mRNA technology to produce vaccines against seasonal influenza within Australia may potentially deliver a benefit of $0.1 billion to $1.3 billion per influenza season, once mRNA becomes commercially viable and approved[44]. At this stage, however, no mRNA influenza vaccines have been approved for use globally – experts expect vaccines may become commercially available from 2024 to 2026, with s47G(1), s 47C

The value of mRNA technology is the potential to improve the highly variable vaccine efficacy seen in inactivated virus-based influenza vaccines. This is a result of the increased speed of asset development post pathogen identification. This speed advantage may allow mRNA vaccine manufacturers to commence vaccine development closer to the influenza season than alternative technologies, facilitating a more accurate selection of endemic influenza strains and delivering a higher-efficacy vaccine. This increased efficacy may in turn reduce costs associated with illnesses, GP visits and hospitalisations, alongside economic benefits related to reduced workplace absences due to illness.

Australia has recently entered into a 10-year agreement with CSL for the purchase of influenza vaccines (and antivenoms) from 2026 to 2036, with a $1 billion pre purchasing agreement. As a result, any potential future benefits from onshore mRNA vaccine availability must be considered in light of this existing commitment. There is potential that, under an external tech transfer archetype s47G(1), s 47C

3.3.3 Other oligonucleotide therapies (e.g., mRNA, RNAi, ASOs)

Aside from mRNA technology, other oligonucleotide therapies are also coming online which offer new ways to treat both common and rare diseases. In particular, antisense (ASO) and RNAi are particularly advanced in the development pipeline, with multiple instances of both drug classes already available in various markets. Additionally, experts note that it is not difficult to retool mRNA vaccination plants to produce these related pharmaceuticals, offering long-term flexibility for manufacturers who do not want to be reliant solely on COVID-19 mRNA vaccine demand.

For the purposes of this business case, however, the benefits of onshore manufacturing are likely limited for other oligonucleotide therapies beyond influenza and COVID-19, notwithstanding the exciting applications of these new technologies. Given the arrival of products reaching market in Australia is frequently determined by timelines around market authorisation or reimbursement, not global supply constraints, onshore manufacturing provides minimal benefit versus simply sourcing these drugs on the global market.

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44 Assumed Australia will maintain its policy of self-sufficiency for seasonal influenza vaccines.

45 CSL (2021). Product pipeline. https://www.csl.com/research-and-development/product-pipeline.

46 s47G(1), s 47C

Additionally, in a non-pandemic context, product and manufacturing related regulatory pathways may not benefit from acceleration mechanisms adopted during COVID-19 due to a relatively lower public health priority and expected scale. While in such instances, regulatory timelines can be protracted, presence of onshore manufacturing may permit more regular TGA engagement and confer minor lead-time benefit. For cGMP licensing, realising this benefit would require the manufacturer to apply for only limited variations to their existing license. From a product approval standpoint, market authorisation timelines are more affected by availability of clinical data and timing of sponsor engagement compared to location of manufacturing. Ultimately, the TGA adjusts its approach in response to public health need – accordingly, shifts in accrual of potential benefits is unlikely to be affected in a non-pandemic context.

However, there are instances where global supply shortages have played a role in 'blockbuster' drugs or vaccines – for example, global supply shortages impacted Gardasil 9, which is used in adolescents to confer protection against human papillomavirus which causes various cancers, including cervical cancer. s47G(1), s 47C

In such instances, the regulatory pathways are unlikely to be a bottleneck.

3.4 POTENTIAL BENEFITS AND IMPLICATIONS FOR AUSTRALIA'S BIOPHARMACEUTICAL INDUSTRY

Several positive externalities are expected to arise from onshore mRNA production in addition to the direct benefits above. These benefits include (but are not limited to) increased output, GDP and jobs in both the broader biopharmaceutical industry and the wider economy. This investment may also serve as a strategic unlock to assist Australia in developing its capabilities to commercialise local R&D onshore.

The biopharmaceutical industry is an attractive industry within which Australia can look to advance economic development. Within the industry, mRNA and the broader RNA market is forecasted to experience substantial growth over the next 5 years, making it a potential entry point for a country looking to expand its pharmaceutical capacity and capabilities.

Globally recognised biopharmaceuticals ecosystems typically have five characteristics that enable their success. These are: access to human capital and talent, a network of industries (including establish players, earlier stage start-ups, and the interactions between these entities); access to funding and investment, enabling regulation and policy (including IP protection, taxation, and pharmaceuticals regulation); and enabling infrastructure (including research infrastructure, clinical trial networks, and access to public health data). It is important to meet these requirements in thinking about how Australia could support a biopharmaceuticals ecosystem. Interviews with stakeholders suggested that access to at-risk capital was a significant problem in Australia, which has prevented previous research commercialisation efforts from progressing.

Australia remains neither cost advantaged nor disadvantaged relative to peers in other high-cost jurisdictions (e.g., Switzerland, the US), and possesses many strategic advantages

relevant to the industry such as high levels of human capital (though focused on earlier stage research rather than commercial/GMP contexts), sophisticated logistics and infrastructure networks, and a stable political climate. Nevertheless, multinational pharmaceutical companies (s47G(1)) have been consolidating operations into geographical biopharma hubs overseas (e.g., Europe and the US), s 47C This is due to many factors (e.g., attractive regulatory settings in certain jurisdictions abroad). s47G(1), s 47C

3.5 ECONOMIC BENEFITS OF MANUFACTURING MRNA PRODUCTS ONSHORE

The benefit of accelerating onshore development of an mRNA facility include the economic impact of both once-off and recurring GDP and jobs creation, and the cascading benefits generated. A brownfield site development is estimated to generate benefits of $0.4 billion GDP and 3,700 jobs[47] for a 12-month development period;[48] subsequent ongoing operation (assuming full plant utilisation) could generate up to $1.3 billion in GDP per annum, and 1,700 ongoing jobs.[49] If a greenfield development was pursued the one-off benefit for development would increase to $0.8 billion GDP and 7,700 jobs.[50] GDP and job creation has been determined using input-output based multipliers derived using OECD tables for Australian Pharmaceutical goods. The multipliers have subsequently been adjusted using expert knowledge of likely job creation for mRNA specific manufacturing.[51] Please see Attachment 4 for further details on the multiplier analysis.

In addition to the GDP and jobs created by this investment, there may be further cascading benefits seen throughout the biopharmaceutical industry in Australia; in particular, the facilitation of at-scale clinical trials (enabled through availability of trial doses) and associated increased ability to commercialise Australian R&D.

Finally, in respect of the benefits associated with increased competition, the global market for pharmaceutical goods, and vaccines, remains highly globalised in nature. There are few use cases where onshore production of a pharmaceutical is necessary. Thus, it remains unlikely in most situations the addition of another manufacturer into the domestic market will have a marked effect on competition and pricing. It may, however, increase competitive tensions when government finds itself in need of local sourcing e.g., where domestic supply is required through legislation.

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47 These include both the direct, indirect and induced multiplier effects on GDP and Jobs.

48 Assuming a s 47C CapEx build (s 47C).

49 Assuming s 47C

50 Jobs refers to job years created (i.e., one job is the equivalent of one FTE for 12 months), s 47C

51 Induced multipliers may be higher or lower due to shifts in consumption and saving behaviours during COVID-19. Multipliers may also be unaffected for this industry due to the high skilled nature of workers, therefore having a more robust consumption demand.

3.6 BENEFITS RELATED TO A GREENFIELD BUILD

Three key benefits are potentially available in the scenario of a greenfield build being selected over a brownfield development:

1. **Modular design of the facility,** facilitating rapid and cost-effective retooling, increasing speed of switching between different technologies and reducing risk of assets becoming stranded.
2. **Freedom in geographical selection,** increasing the ability to optimise spillover effects within the broader biopharma ecosystem via positioning of manufacturing sites proximate to relevant upstream/downstream players.
3. **Integrated design with non-manufacturing facilities,** enabling facility design to incorporate early stage R&D requirements (further amplifying network effects).

The ability to realise these benefits will be constrained or vary by the IP owner/manufacturing archetype selected. Global IP originators may anchor location selection based on their existing asset network, versus a new entrant (e.g., Moderna or a home-grown IP player) being more flexible as to greenfield site selection.

3.7 COSTS AND RISKS

3.7.1 Financial cost – plant development

Preliminary estimates suggest development of a facility with capacity of 100 million+ doses per annum will require a capital investment of s 47C for a brownfield facility.[52] This entails the estimated cost to take a GMP certified 'shell' of a building with clean rooms and to subsequently develop the required:

- Storage facilities for raw materials and the handling of buffer liquids.
- Processing facilities.
- Formulation, fill-and-finish lines.
- Final packaging lines.
- Soft costs[53] required to facilitate technology transfer and regulatory approval.

The key factors that can lead to cost escalation are the appropriateness of the brownfield site, the experience of the manufacturer, the level of automation sought, and the development speed required.

It should be noted that commercial mRNA production technology is relatively new and we would expect the CapEx cost of both brownfield and greenfield developments to reduce over time. This is likely to result as the number of suppliers increase, and as innovation drives down the cost to produce relevant equipment (which contributes 30-50% of the total CapEx required for site development). The capital estimates made earlier have been developed on

[52] An additional $10 million in 'soft costs' are also expected for tech transfer and regulatory approval proceedings.

[53] 'Soft costs' refer to ancillary costs not directly related to construction (e.g., legal costs, tech transfer resourcing costs, financing, regulatory costs).

a current cost estimate basis and are thus potentially conservative. Under a 'go later' path it is likely some costs will come down (potentially quite significantly).

For a greenfield development the build cost can be expected to increase by s 47C This includes the cost of developing the shell of the building (including the connection to required utilities and development of cleanrooms with HVAC), the GMP certification, and the fit-out costs (as discussed in the brownfield estimations).

Based on outside-in market available information and industry expert assessments, s 47C, s47G(1)

s 47C

See Attachment 4 for more details on the brownfield and greenfield development cost breakdowns.

3.7.2 Ongoing costs

Beyond immediate COVID-19 vaccine production, the ongoing costs of the plant will depend on the future utilisation and subsequent labour and sustaining CapEx requirements. In the event all production is ceased, and the plant can be put into care and maintenance, the ongoing costs are expected to be less than s 47C per annum.

Ongoing cost of operations are anticipated to closely resemble those of European and US counterparts, but a cost premium will continue to be seen in comparison to lower cost country manufacturers (e.g., China, India, Eastern Europe). This is due to labour costs comprising a significant proportion of the unit costs, with Australia generally recognised as a high cost labour location. However, this is offset by the quality standards seen in Australian manufacturing that are sought out by end markets, which is the reason operations continue in high cost countries.

Additional factors such as manufacturing efficiency (primarily driven through Overall Equipment Effectiveness (OEE), Right First Time (RFT)) and the IP advantages (e.g., in IVT,

54 Cost of goods sold (COGS).

55 This also includes an assumed company tax rate of 30% and a WACC of 10%.

s 47C

capping yield, and self-replicating technology) are key determinants of the unit costs and subsequent plant profitability. These factors are heavily influenced by the capabilities of the operating party and the IP advantage of the originator.

3.7.3 Risks

Development of an onshore mRNA manufacturing facility involves multiple risks which can be considered across three dimensions: plant commissioning, ongoing production/asset utilisation, and risks arising outside the project.

Plant commissioning risks to be considered and mitigated include (but not limited to):

- Delays in the modification/delivery of new processes for a brownfield site, equipment procurement, and commissioning the facility (including regulatory approvals).
- Capital expenditure overruns.
- Delays or quality issues related to lack of available human capital.

Ongoing production/asset utilisation risks to be considered include (but not limited to):

- Disruption to supply of inputs (consumables).
- Insufficient global demand for mRNA and adjacent oligonucleotide products (e.g., ASO, RNAi).
  - A key driver of global demand is whether influenza vaccines are successfully re-platformed to mRNA, which is likely the largest potential demand for a single mRNA vaccine product. Even if successful, only partial utilisation of an onshore facility is likely from domestic demand (i.e., for influenza vaccines procured for use in Australia), with significant risk remaining that insufficient overseas offtake will materialise to run an onshore plant with high utilisation.
  - Global demand for mRNA also faces a 'bridging risk' for the period between COVID-19 vaccine demand subsidising and influenza re-platforming. This is likely to occur the scenario where COVID-19 vaccine demand subsides, but there are no other -at-scale mRNA products yet approved for use.
- The asset being unable to be retooled in the event demand is no longer present and production ceases.
- Other risks related to the COVID-19 vaccine rollout may arise that are created by establishing onshore mRNA manufacturing (e.g., the risk of stretching resources devoted to the provision and rollout of existing vaccines).[58]

Risk comparison across paths, IP partners and archetypes

- In the 'go now' path risks are heightened by the uncertain nature of the global manufacturing landscape in the setting of the acute COVID-19 response, and the compressed timelines involved in standing up manufacturing capability to secure short

s47G(1), s 47C

term benefits. In juxtaposition the 'go later' path involves less commissioning risk but faces increased risk of insufficient local and global demand in the 3+ year timeframe.

- While risks are present across all tech transfer archetypes, specific risks are more likely to be realised in certain combinations of IP owner and tech transfer archetype. These differential risk levels are detailed in Figure 10 and 11 for the 'go now' and 'go later' path respectively. Overall, a greater risk level is demonstrated in the case of a modular/multi-partner external tech transfer partnership, compared to relatively consistent levels across an E2E internal tech transfer investment option, or an external tech transfer to an E2E partner.
- s47G(1), s 47C

Outside of project-induced risks, the Australian Government should also consider any impacts/risks to Australia's pandemic preparedness across the country's full portfolio of strategic investments. s47G(1), s 47C

s 47C

s 47C

s 47C

4 Government roles and next steps

Establishing onshore mRNA vaccine manufacturing capacity has the potential to deliver significant benefits for Australia and the region. However, in order to establish this capability, stakeholders have uniformly highlighted that strong sponsorship of the effort from federal, state, and territory governments is critical to success. Furthermore, these governments have a central role in ensuring that the facility can make a positive contribution to Australia by capturing the associated benefits.

To s 47C

The levers described below represent an initial perspective on the roles governments could play. Consultation and coordination across governments would be beneficial, should the Government choose to proceed with an onshoring path.

Further details on governments' roles and next steps are included in Attachment 5.

4.1 GOVERNMENT LEVERS TO ATTRACT AND ACCELERATE ONSHORING

There is a very high level of global demand to establish new mRNA vaccine manufacturing facilities, with manufacturers trying to grow footprints to meet ambitious COVID-19 vaccine production commitments and many countries considering their sovereign capabilities. s 47C

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4.1.1 Governments' role in facilitating scale-up

In the context of high global demand for COVID-19 vaccines and ambitious production targets, product IP owners are looking to rapidly scale their global manufacturing footprints. s47G(1), s 47C

Significant orchestration and support will likely be required to accelerate timelines from 'fast' pre-COVID-19 timelines (~18 months) towards the best-in-class ~6 to 9-month timelines seen in more mature vaccine manufacturing ecosystems (EU and US).

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[59] s 47C

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- s 47C

This could support two outcomes:

[60] E.g., Italy prompted the European Union to block the export of ~250,000 doses of AstraZeneca's COVID-19 vaccine to Australian in March 2021.

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- s 47C

4.1.2 Governments' role in ensuring long term sustainability of operations

To be commercially attractive to both international IP owners and domestic manufacturers, operations in Australia must be sustainable in the long term. s 47C

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- s 47C

Beyond the levers outlined above, governments could strive to grow a broader biopharmaceuticals ecosystem by offering a package of interventions. As detailed in Section 3.4, such ecosystems tend to be mutually self-reinforcing – requiring a set of interdependent supports, underpinned by appropriate policy and infrastructure to sustain the industry. s 47C

s 47C

4.2 GOVERNMENT LEVERS TO ENSURE VALUE CAPTURE

Establishing onshore mRNA vaccine manufacturing capacity is likely to require substantial investment from governments. While it is anticipated that significant benefits could also come from this facility, governments have the ability to take actions that increase the likelihood of benefit capture. s 47C

Governments have a number of levers to capture benefits associated with onshoring mRNA vaccine manufacturing capability in the near- and longer-term. s 47C

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61 Subject to ensuring such access is in Australia's national interest and consistent with relevant privacy protections.
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63 The Department of Health recently entered into a $1 billion 10 year agreement with CSL for the offtake of various products, notably flu vaccine. s 47C

64 E.g.; European Union holds capacity reservations with Seqirus for production of pandemic flu vaccine.

Appendix A: background information – mRNA technology and Australia's current position

I. THE PROMISE OF MRNA VACCINES

How mRNA differs from traditional vaccines

All vaccines work by stimulating a person's immune system with a foreign pathogen (e.g., a virus or bacteria). If the vaccine is effective, the immune system 'remembers' the part of the pathogen it has recognised (the 'antigen'), conferring immunity that strengthens the immune response in the event of encountering the pathogen in the future.

Traditional vaccines either presented the whole pathogen in weakened (attenuated) or killed (inactivated) form, or used a part of the pathogen (e.g., protein subunit vaccines). More recently, some vaccines have introduced the genetic code (nucleic acid) of a pathogen. The body then uses this introduced genetic code to self-manufacture the antigen, and subsequently develops an immune response.

The production process for these three major types of vaccines is relatively time consuming. For example, requiring the gradual replication of a viral pathogen (e.g., influenza virus) or the viral vector in chicken eggs or mammalian cells, or requiring the production of protein subunits by biological processes (e.g., using bacteria as a biological factory).

In contrast, mRNA is a new vaccination technology. No mRNA vaccine had received approval for widespread human use until the advent of COVID-19 mRNA vaccines in 2020. mRNA vaccines deliver the genetic code directly into the body, without the aid of a viral vector. They are produced by chemical reactions, rather than biological processes (i.e., without the need to grow chicken, mammalian, or bacterial cells[65]). As a new technology, the true potential of mRNA vaccines remains uncertain. However, the mRNA technology has proven able to support rapid development and manufacture of effective COVID-19 vaccines, and it seems likely that a range of other applications will follow.

mRNA as the basis for a COVID-19 vaccine

Two mRNA vaccines have received authorisation for emergency use by several regulators globally, including by the US's FDA, UK's MHRA and EU's EMA: namely products from Pfizer and Moderna. A third vaccine, developed by CureVac, is in Phase 2b/3 trials. In Australia, Pfizer's vaccine has been provisionally approved by the TGA.

As demonstrated in the COVID-19 pandemic, the promise of mRNA vaccines is in the potential for faster development and production than traditional vaccines, and greater efficacy:

- **Shorter development time.** The time from pathogen (virus) identification to vaccine production is lower for mRNA vaccines; developing a new candidate takes ~3 weeks with mRNA versus 2 to 3-months with cell-based technologies (requiring a lengthy

[65] mRNA vaccines require plasmid DNA as raw material, which is produced via bacterial cell cultures.

process of virus selection, incubation, and fluid purification). For seasonal influenza, it takes roughly 6 months from identification of circulating influenza strains to produce traditional vaccines. For mRNA, once the genetic code is identified, vaccines can proceed straight to testing.

- **Shorter production time.** Traditional vaccines are grown using complex biological processes, such as egg or mammalian cell-based cultivation (where viruses are grown in living cells). In contrast, the RNA that forms the basis of mRNA vaccines can be synthesised from chemical reactions rather than biological processes. By removing the need to obtain/grow cells and then to grow/produce the antigen within them, this significantly shortens production times and complexity. The production process is also repeatable and scalable; once a process is established, it can be reused for multiple vaccine candidates.

- **Improved efficacy.** To date, clinical data has shown mRNA vaccines to be equally or more efficacious than traditional viral vector and protein vaccines. Pfizer[66] and Moderna's[67] mRNA vaccines have demonstrated efficacy levels of 95% in response to SARS-CoV-2, versus 95.6% for Novavax's protein-based vaccine[68] and an average of 70.4% for AstraZeneca/Oxford's viral vector vaccine.[69]

mRNA applications beyond COVID-19

mRNA has been discussed as a promising technology for the delivery of vaccines and pharmaceuticals for decades. The first successful animal trials involving transcribed mRNA were published in 1990, but delays in developing effective mRNA therapeutics transpired due to challenges such as mRNA instability and inefficient *in vivo* delivery/organ targeting.[70] However, in recent years significant advances have been made in the development of mRNA vaccine technology – in particular, around the delivery of mRNA into cells using technologies such as lipid nanoparticles.

Prior to COVID-19, a number of vaccines for HIV-1, rabies, Zika and influenza viruses had entered clinical trials. The arrival of COVID-19 dramatically accelerated progress, with vaccines to protect against disease becoming the first human applications of this new technology.

Some of the most promising applications of mRNA beyond COVID-19 are in vaccinations for other infectious diseases. These applications also do not require the targeting of specific cells or end organs within the human body (a key challenge in the development of mRNA-based therapeutics for other diseases). Rather, the apparatus of multiple cells can be used to produce the protein encoded by the mRNA, which prompts the immune response. The

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66 F Polack et. al., "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine". *N Engl J Med* 2020; 383:2603-2615. https://www.nejm.org/doi/full/10.1056/NEJMoa2034577.

67 L Baden et. al., "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine". *N Engl J Med* 2021; 384:403-416. https://www.nejm.org/doi/full/10.1056/NEJMoa2035389.

68 Efficacy of 95.6% was demonstrated against the original strain of COVID-19, with average efficacy of 89.3% across all variants in the study cohort in the UK (including >50% UK variant strain prevalence). E Mahase, "Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant". *BMJ* 2021;372:n296. https://www.bmj.com/content/372/bmj.n296.

69 M Voysey et. al., "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK". *Lancet* 2021; 397(10269) 99-111. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext.

70 See e.g., N Pardi et. al., "mRNA vaccines – a new era in vaccinology" *Nature Reviews Drug Discovery* 2018; 17, 261-279. https://www.nature.com/articles/nrd.2017.243.

recent success in COVID-19 mRNA vaccines opens the possibility for other infectious disease vaccines including influenza, Zika, HIV-1, and dengue fever.

mRNA cancer vaccines represent another exciting potential opportunity; most cancer vaccines are designed to treat established cancers rather than prevent them, and seek to stimulate cell-mediated responses to clear or reduce the burden of cancerous tumours.[71] A number of clinical trials have already commenced to test the application of these technologies. To date no successful candidates have reached market.

Additionally, therapeutics for the management and treatment of other diseases are under early-stage development. Including candidates for the treatment of diseases including myocardial ischaemia, autoimmune disorders, and rare metabolic diseases.[72] Additionally, some innovators are exploring alternate routes of administration for mRNA products (e.g. oral tablets), which could advance the technology.[73]

Likely evolution of the mRNA market

Vaccine supply is rapidly expanding

The pre-COVID-19 global vaccine market had capacity to produce approximately ~4.8 billion doses per annum; consisting of ~3.1 billion doses per annum of viral vector vaccines and ~1.7 billion doses per annum of protein-based vaccines. Prior to the pandemic, mRNA vaccine manufacturing capacity was restricted to clinical scale, with little to no commercial production capacity.

Since the onset of COVID-19, global vaccine manufacturing capacity has rapidly expanded. Latest estimates indicate global vaccine production capacity of ~13.5 billion doses per annum. mRNA vaccines represent a significant proportion of this growth, increasing from close to zero production capacity, up to 3.6 billion doses being produced in 2021 alone, with a further 0.5 billion doses capacity committed for 2022 thus far.

In order to meet rapid scale-up targets mRNA vaccine manufacturers have quickly scaled their footprints. To date, mRNA vaccines from both Pfizer and Moderna have been manufactured entirely in the USA and Europe. Both geographies were a natural choice, as they are global biopharmaceutical manufacturing hubs with high levels of skilled labour, established quality standards, and robust local supplier networks. In both cases, facility establishment and tech transfer has been accelerated from pre-COVID-19 timelines of 12 to 18 months, to <6 months in the most aggressive cases to allow rapid capacity expansion.

- s47G(1), s 47C

71 Ibid.

72 e.g., Moderna is developing therapies for myocardial ischaemia, autoimmune hepatitis, heart failure, generalised autoimmune disorders, propionic acidemia, methylmalonic acidemia, phenylketonuria, glycogen storage disorder type 1a.

73 E.g., Biotech Vaxart are working on an oral vaccine technology, s47G(1) are working on an intranasal vaccine technology.

- s 47C, s47G(1)

Supply side innovation is expected to drive further efficiency and capacity gains

Developments in mRNA vaccine manufacturing that are anticipated to drive efficiency and greater effective capacity include:

- **Process improvements.** As the manufacturing process for mRNA vaccines for COVID-19 continues to be refined, it is expected that ongoing process improvements will lead to greater vaccine production capacity coming online in 2022. To date, manufacturers have scaled clinical labs to commercial scale without the traditional lead time to design a 'for purpose' manufacturing facility. As a result, a cycle of continuous improvement across the industry is likely to play out in parallel to vaccine development, rather than in sequence. For example, s47G(1) has announced that its production time has almost halved since its mRNA vaccines were brought to market, decreasing from 110 days to 60 days per batch.
- **Major production technology innovation**. In additional to continuous improvement, there are multiple manufacturers who are developing next-generation mRNA manufacturing techniques. s 47C, s47G(1)

  s47G4 This could enable a distributed manufacturing network around the world, as opposed to relying on relatively few centralised sites. s 47C, s47G(1)

- **Manufacturing process scalability**. The mRNA vaccine manufacturing process is easier to scale than traditional cell- and egg- based techniques. Technical experts have indicated that *in vitro* transcription of mRNA is the scale-limiting step in production. This is a benchtop chemical process, and batch sizes can be easily scaled up – from a small volume producing a few doses to commercial scale – with batch sizes of millions of doses. This is far more flexible than traditional egg-based techniques, which require inoculation of chicken eggs to produce a vaccine; and newer mammalian cell-based techniques, which require cell colonies to be expanded and maintained.

Anticipated evolution of vaccine demand

The demand for other types of mRNA vaccines moving into the future is highly uncertain as the market shifts from supplying COVID-19 vaccines to other indications. For the next 2+

s 47C, s47G(1)

years, demand is likely to remain high as the effort to achieve global vaccination coverage against COVID-19 continues.[76]

Longer-term demand (beyond COVID-19) is expected to be determined by demand for future mRNA products, with ~25 products currently in clinical trials. The most significant at-scale demand for non-COVID-19 mRNA products is anticipated for seasonal influenza vaccinations, which experts in mRNA vaccine development believe may become commercially viable by 2024-26 at the earliest. However, this market is likely to comprise ~1.2 billion doses per annum, given that the current global influenza vaccination market is sized at 600 million doses.[77] Beyond influenza vaccines, there are no candidates identified that are likely to scale to a run-rate demand more than 100 million doses annually. It is therefore likely that demand for mRNA products falls short of the supply established for COVID-19 vaccine production, based on current pipelines. Importantly, the supply-demand balance in Australia is likely to be distinct and will depend on the scale of a facility established, and individual offtake agreements negotiated for domestic use and export. Further analysis of global supply-demand balance can be found in Attachment 4.

Demand for vaccines is the most uncertain in the medium term, where several factors will influence further COVID-19-related demand for mRNA vaccines, including:

- Duration of immunity resulting from vaccination.
- Prevalence of mutations which existing mRNA vaccines are no longer effective against.
- Extent to which thermostability is increased, facilitating broader adoption of mRNA COVID-19 vaccines globally.[78]

In light of uncertainties across these factors, two potential medium-term scenarios stand out:

- **No revaccination is required**, meaning COVID-19 mRNA vaccine demand could be met by late-2022. Beyond this, supply is likely to exceed demand until the market for other mRNA products matures.
- **At-scale revaccination is required** due to waning immunity or a high prevalence of vaccine-resistant SARS-CoV-2 variants. In this scenario, COVID-19 vaccine demand is likely to remain high and supply will be scarce, at least for 1 to 2 years.

II. AUSTRALIA'S CURRENT VACCINE MANUFACTURING CAPABILITIES

A recent audit of Australia's baseline domestic vaccine and therapeutics manufacturing capabilities identified key gaps across various vaccine technology platforms. While the audit highlighted Australia's potential to support protein-based or viral-vector vaccine manufacturing in the short term, it identified a paucity of domestic manufacturing capability beyond these platforms, particularly in nucleic acid vaccines (i.e., DNA and mRNA). Additionally, there are a select number of sites that possess adjacent capabilities (e.g.,

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76 Demand in the setting of COVID-19 will vary based on a number of factors, including but not limited to speed of mutations in SARS-Cov-2; further developments in vaccines (e.g., improvements in thermostability); and, further discoveries regarding vaccines efficacy (e.g., whether single-dose regimens are sufficiently efficacious, or certain vaccine types prove consistently less efficacious against SARS-Cov-2 and its variants).

77 Assumes two dose influenza mRNA vaccine displaces current influenza vaccine products.

78 Outside production timeframes, pharmaceutical companies are continuing to innovate and explore alternative formulations which allow for increased thermostability. s47G(1)

biologics manufacturing) that could support the establishment of broader vaccine manufacturing capability to address these gaps.

Vaccine manufacturing

Australia's current commercial scale vaccine manufacturing capability is limited to CSL's two domestic sites. CSL has two existing facilities in Victoria that possess vaccine manufacturing capabilities – currently CSL's Broadmeadows site is manufacturing AstraZeneca's viral vector vaccine, while CSL's Parkville site is manufacturing the seasonal flu vaccine and performing all fill-and-finish requirements (including for the AstraZeneca vaccine).

Prior to the Astra Zeneca vaccine, CSL focused on an egg-based vaccine manufacturing platform. CSL is building cell-based manufacturing capacity in its new $800 million facility to be based at Melbourne Airport Business Park, planned to open in 2026 – s 47C, s47G(1)

s47G(1), s 47C

Aside from s47G(1) have direct involvement in vaccine manufacturing – this is limited in scale and applies to select aspects of the manufacturing chain:

- **Luina Bio** is a small scale CDMO based in Brisbane, that specialises in the development and clinical scale manufacturing of biologics and small-molecule products. Luina Bio has clinical scale vaccine manufacturing experience and is licensed for commercial manufacturing of vaccines. Additionally, it produces plasmid DNA (pDNA) s 47C . s 47C, s47G(1)

- **Sypharma** is a small scale domestic CMO (Contract Manufacturing Organisation) involved in adjuvant and formulation manufacturing for protein-based vaccines used in clinical trials. Additionally, Sypharma manufactures intravenous solutions and veterinary products.

Therapeutics manufacturing

Additionally, Australia has a range of other sites that manufacture therapeutics which could provide synergies with vaccine manufacturing and be used to establish broader vaccine capabilities in a modular or end-to-end fashion:

- **Patheon** has existing biologics manufacturing capability s 47C

  s 47C, s47G(1)
  Nevertheless, Patheon is a global CDMO network and a subsidiary of

Thermo Fisher – globally, Patheon and Thermo Fisher provide expertise across viral vector vaccines, pDNA, fill-and-finish and procurement of raw materials/equipment.

- **IDT** is a small-scale manufacturer based in Melbourne that specialises in medical cannabis, chemical APIs, and finished dose forms (FDF) manufacturing at clinical scale. IDT is not currently licensed for commercial applications, but has established bulk liquid formulation and sterile fill-and-finish capabilities at large scale, s 47C

- **BioCina** is a single site based in Adelaide that specialises in development and manufacturing of microbial-based therapeutics and biologics. BioCina is part of the Bridgewest group and its Adelaide site was acquired from Pfizer in September 2020. BioCina does not have a sterile GMP license s 47C , and currently produces pDNA that s 47C .

- **Pfizer** has two domestic sites in Australia across Melbourne and Perth. The focus of Pfizer's Perth site is on the production of sterile injectables and oncology products, while its Melbourne facility is a large biologics formulation and fill-and-finish site, mainly for oncology products. Neither site manufactures active pharmaceutical ingredient (API).

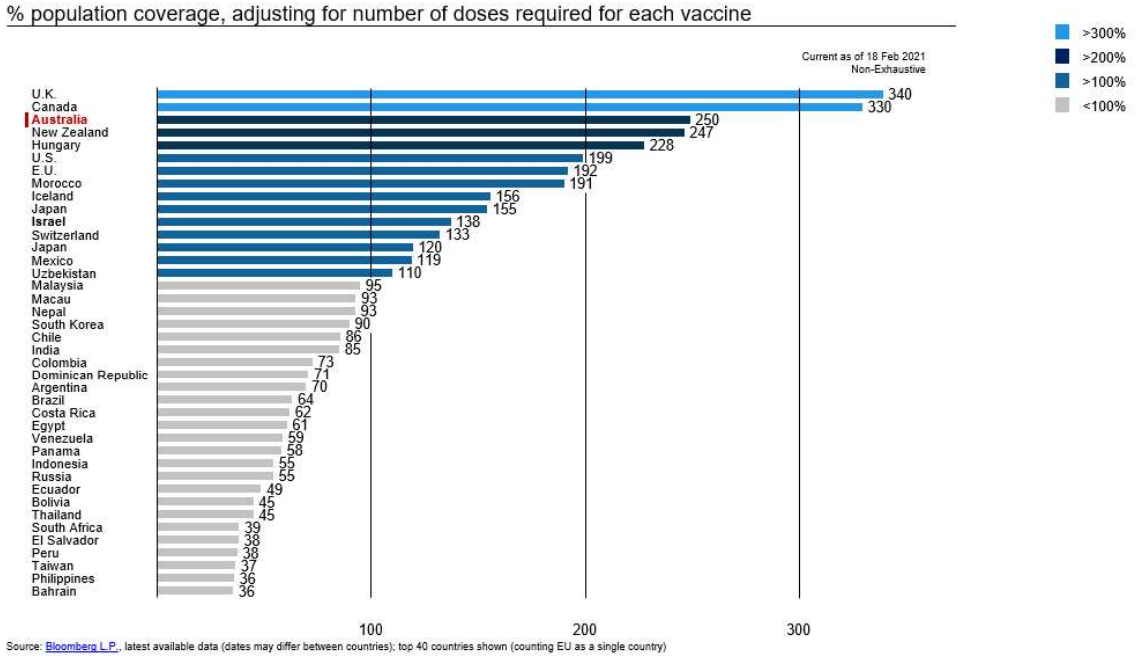
III. AUSTRALIA'S CURRENT COVID-19 VACCINE PORTFOLIO

Early access to a sufficient and secure supply of safe and effective COVID-19 vaccines is essential to the success of Australia's COVID-19 Vaccination Program, and the core goal of the COVID-19 Vaccine and Treatment Strategy. To this end, the Australian Government has made investments to secure access to a diverse portfolio of COVID-19 vaccine products/ candidates, both directly through advance purchase agreements and indirectly through COVAX participation.

s47G(1), s 47C

Assuming that Novavax is approved by the TGA, Australia will be in the fortunate position of having one of the highest levels of vaccines per head of population based on confirmed advance purchase agreements,[79] providing the ability to vaccinate our own population, and additionally support regional neighbours with their immunisation programs with any excess supply remaining (see Figure 13).

FIGURE 43: Population coverage levels of purchased COVID-19 vaccines



79 Australia has pre-ordered over 5 doses of COVID-19 vaccine per capita.

Appendix B: Business case methodology

I. A HUMANITARIAN CHALLENGE

The COVID-19 pandemic is, first and foremost, a humanitarian challenge; thousands of health professionals are heroically battling the virus, putting their own lives at risk. Governments and industry are working together to understand and address the challenge and bring effective treatments and vaccines to market.

This business case assesses how Government and industry can potentially work together to provide more effective, more timely, safe and high-quality vaccines for Australians, our regional neighbours and the world.

II. SOURCES OF UNCERTAINTY

In attempting to estimate the COVID-19 related benefits of an onshore mRNA vaccine manufacturing capability in Australia, it needs to be recognised that the impact of a fast-evolving virus differs in many ways from the better understood influenza (flu) virus and previous pandemics. As such, there are many uncertainties about how the SARS-Cov-2 virus will behave in the future, and how humans will mount an immune response.

Similarly, mRNA vaccines are a novel technology. The real-world effectiveness of mRNA products,[80] the extent of future demand (for SARS-CoV-2 and other applications), and the scale and location of global supply are all uncertain. There are also uncertainties around (i) government actions globally (e.g., export controls, approvals of different vaccines for different cohorts); (ii) the potential scale and impact of the public health response in Australia under different scenarios; and (iii) how Australian manufacturing may contribute to the challenge of vaccinating people in other nations, including those in the Asia-Pacific region.

Given the many uncertainties that exist, this business case seeks to make underlying drivers of costs and benefits transparent, rather than assuming these away with a traditional net present value (NPV) or benefit-cost ratio (BCR) analysis.

The nature of the benefits differs significantly between COVID-19 and non-COVID-19 applications, and are described in the next section. Many of the benefits relating to the current and potential future pandemics are akin to an insurance policy, with the possibility that onshore mRNA manufacturing does reduce the enormous health and economic costs of a pandemic. Rather than assuming a probability and multiplying by the potential benefit, the business case makes clear what is a low probability/very high consequence benefit versus a higher probability/lower consequence benefit.

Cost estimates are outside in, based on proprietary benchmarking, industry expert interviews and analyst reports, but depend ultimately on the parties selected and the scale of production. These estimates are expected to be clearer when the IP owner articulates the technology transfer requirements to the counterparty manufacturing the product.

80 Including uncertainty relating to mRNA vaccines' effectiveness in reducing transmission, in addition to effectiveness in reducing disease.

The analysis in this business case is current as of 12 March 2021 and the materials reflect the best understanding of the situation and business case drivers at that point in time.

III. COVID-19 RELATED BENEFITS

To date, Australia has performed well in supressing the spread of COVID-19, resulting in a relatively low rate of morbidity and mortality. This business case assumes Australian governments continue to achieve similar public health outcomes, adjusting restrictions on international borders, state borders, density limits, etc. when confident the combination of population immunity and better treatments will not significantly compromise those physical health outcomes.

More timely or effective COVID-19 vaccinations would allow faster or greater relaxation of those restrictions, increasing economic activity. As such, the quantifiable benefits within the business case are based on the difference in speed with which economic outcomes are enabled by onshoring mRNA vaccine manufacturing (i.e., a cost of delay approach).

There are three primary drivers – all of which need to be true – to realise economic benefits across each benefit category:

- **Technical or biological drivers**. These relate to factors such as the behaviour of the SARS-CoV-2 virus and its variants, and the effectiveness of mRNA vaccines versus viral vector or protein subunit vaccines. For example, after the first round of vaccinations is completed, revaccination with mRNA-based products may be needed to reduce ongoing health risks in Australia due to waning immunity or significant viral mutations.

- **Access drivers**. These relate to how quickly Australia accesses vaccines. This may be driven by differences in the vaccine development and production process which mean new mRNA vaccines can be available faster than traditional vaccines; or by a potential speed benefit from onshore manufacturing versus international procurement (e.g., an ongoing supply constraint for mRNA vaccines may make rapid onshore production advantageous during a revaccination period).

- **Policy drivers.** These relate to decisions by government to protect lives and livelihoods – for example, revaccination with mRNA-based products may reduce the economic cost of public health directives designed to protect Australians (e.g., border closure costs).

  To illustrate – economic benefits would accrue if an mRNA vaccine was significantly more effective against a future mutation of SARS-CoV-2, *and* onshore manufacturing gave Australia access to sufficient quantities of vaccine earlier than alternatives such as international procurement or onshore viral vector manufacturing, *and* the earlier deployment of that more effective vaccine allowed state and federal governments to adopt less onerous restrictions more quickly.

IV. OTHER BENEFITS

Beyond the immediate need to manage the ongoing COVID-19 crisis, onshoring of mRNA manufacturing may yield additional benefits in terms of access to other novel vaccines and pharmaceuticals, and other positive economic externalities from investment in the biopharmaceutical landscape in Australia. The most likely adjacent applications from a

disease perspective include future non-COVID-19 pandemics, seasonal influenza vaccines, and applications of oligonucleotide[81] technology to other infectious and non-infectious diseases.

In determining the likely source of benefits and sizing them:

- **For future pandemics**, benefits estimation requires consideration of the same three categories of primary drivers as per the COVID-19 benefits analysis; specifically, that mRNA will be a high-potential platform for vaccination development in future pandemics, benefits will largely accrue from quicker access to vaccines enabling lifting of restrictions, and policy settings to contain harms related to a future pandemic will be similar to that of the COVID-19 pandemic (noting that a future pandemic is a low absolute likelihood event).
- **For seasonal influenza**, it is assumed that benefits will accrue from more efficacious mRNA vaccines being developed. This benefit may arise because reduced mRNA production lead times allow strain selection to occur closer to the start of the influenza season, and thus for mRNA vaccines (which contain predicted strains) to more closely match actual circulating influenza strains. This may reduce healthcare costs associated with current lower-efficacy influenza vaccines (assuming Australia's policy of domestic influenza vaccine production remains the same).
- **For other disease applications**, it is assumed that benefits will accrue from expedited access to 'blockbuster' mRNA vaccines for which global supply shortages may be seen (noting that this is a low likelihood event) – but that for other new drugs, no benefit in terms of speed of access will be seen.

Other benefits come from the 'multiplier effect' of investment in a new plant spilling over into other areas of the value chain, including the second and third order benefits for suppliers and surrounding communities of investment, and the cascading benefits of improved capability within the biopharmaceuticals industry.

V. TECH TRANSFER ARCHETYPE DEEP DIVE

s47G(1), s 47C, s 45(1)

[81] mRNA is a member of the drug 'family' called therapeutic oligonucleotides, which also encompasses other therapies including RNAi, antisense (ASO), aptamers, and others. Oligonucleotides are nucleic acid polymers with the potential to treat or manage a wide range of diseases.

s47G(1), s 47C, s 45(1)

VI. INDUSTRY ENGAGEMENT IN FEASIBILITY ASSESSMENTS

This business case is informed by extensive industry engagement through the following means.

First, a detailed review of findings from the 2020 audit of Australian vaccine and therapeutics manufacturing capability and capacity, conducted by DISER and the Department of Health. This included more than 64 industry responses to an RFI.

Second, regular and wide-ranging interviews and discussions with 40+ industry experts connected with development and manufacturing of mRNA, and associated technologies. This included experts based in Australia and overseas (e.g., European and North American); commercial, operational, scientific and advisory stakeholders; R&D experts; suppliers of equipment and materials; pharmaceutical manufacturing and operations experts; logistics experts, and greenfield and brownfield development engineers.

Third, direct engagement with industry participants: both mRNA vaccine product/IP owners, and potential mRNA manufacturing sites in Australia (detailed in Sections 4.2 and 4.3 respectively). These discussions were undertaken to understand interest, feasibility and timelines, as well as risks and necessary supports to onshoring mRNA manufacturing in Australia; including to assess the stakeholders' relevant tech transfer and manufacturing capabilities. Engagement with these stakeholders is ongoing.

In addition, regular feedback was sought from the Expert Advisory Group convened by DISER.

s 47C

The information contained in these documents is commercial-in-confidence and not publicly available; comparing the specification and costs in these documents to the capabilities of Australian manufacturing sites is the critical remaining step to move from an 'outside-in' evaluation of feasibility based on general industry standards, to a company and site specific review of what can be done in Australia.