MTP Connect
MedTech and Pharma Growth Centre

Cell, Gene and Tissue Regulatory Framework in Australia: Stakeholder Perspectives

A stakeholder engagement report on Advanced Therapies prepared for the Therapeutic Goods Administration

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Australian Government
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CONTENTS

PROJECT BACKGROUND

The Therapeutic Goods Administration (TGA) is responsible for regulating therapeutic goods in Australia under the provisions of the *Therapeutic Goods Act 1989* (TGA, 2021c). First introduced in May 2011, the regulatory framework for biologicals provides the legislative basis for the regulation of human tissue and cell-derived products as well as live animal cell, tissues or organs that are supplied, in or exported from, Australia (TGA, 2017, 2021b). For those therapeutic goods, regulated by the TGA, and which are produced by genetic manipulation (GM), the TGA is required to seek advice from Office of the Gene Technology Regulator (OGTR) (TGA, 2004).

Indications from international regulators on submissions, as well as the sheer number of trials currently being undertaken in this space, suggest that Australia will see significant increases in the number of applications for these types of therapies over the next decade (Department of Health, 2020; FDA, 2019; Regenerative Medicine Catalyst Project consortium, 2021).

House of Representatives Inquiry

The current House of Representatives "Inquiry into approval processes for new drugs and novel medical technologies in Australia" ("the Inquiry") received multiple submissions that voiced concerns with aspects of the current regulatory framework, in particular pertaining to gene therapies. These included concerns regarding the communication of the different processes, parallel regulation and reimbursement processes, the TGA-OGTR interface and clinical trial pathways, as well as priority and provisional access pathways.

Following on from these submissions and acknowledging the rapidly changing landscape of therapeutics, the TGA is seeking stakeholder input on:

- whether there is opportunity for improving TGA communication of the regulatory framework, in particular, for biologicals; or
- whether there could be modifications to some aspects of the regulatory framework, such as review of mechanisms of TGA-OGTR interface, and priority, provisional and parallel application pathways.

Scope and approach

MTPConnect has been invited by the TGA to conduct a stakeholder consultation to review Australia's regulatory framework for gene, cell and tissue therapies. Working with Evohealth, the review involved individual interviews and group sessions with key stakeholders from across the sector, including from:

- Pharmaceutical and biotechnology industry
- Clinical trials
- Regulatory
- Clinicians
- Researchers
- Ethics committee
- Manufacturing
- Patient advocacy/consumer groups.

Questions were tailored to each stakeholder. A full list of stakeholder groups and the questions categorised by stakeholder type is provided in Appendix A.1 and Appendix A.2, respectively. A total of 17 one-hour individual stakeholder interviews were carried out, with two stakeholders requesting follow-up interviews to provide additional feedback. Additionally, five two-hour workshops were undertaken with:

1. Researchers
2. Clinical trial experts
3. Regulatory experts
4. Manufacturing
5. Clinicians

This report summarises the consultation outcomes within the context of background information provided to the stakeholders and is categorised based on the following themes:

- Terms and definitions
- Clinical trial pathways
    - Ethics approval
- GMP
- OGTR-TGA interface
- TGA registration pathway
- PBAC/MSAC interface with the TGA
- Other considerations

REPORTS AND OTHER REFERENCES

Throughout the consultation process, several stakeholders noted that there were reports available representing broader views surrounding cell and gene therapies. MTPConnect's Regenerative Medicine Opportunities report explores regulation and policy challenges. Clinicians cited the Andrew Spencer review, noting that this was representative of many of their field's views. Industry stakeholders and clinicians often commended and cited Project Orbis and the Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium as key examples of international harmonisation. Industry stakeholders and regulatory experts cited key documents that they would recommend the TGA consider including: The European Federation of Pharmaceutical Industries and Associations (EFPIA)'s position on RWE; the Medicines and Healthcare products Regulatory Agency (MHRA) consultation paper on developing a regulatory framework for manufacturing at point of care; as well as the MHRA's delivery plan which has stated the ambition of considering joint clinical trial approvals and advice across ACCESS countries.

KEY THEMES

Following these conversations, core themes were distilled from the consultation notes associated with the questions and detailed below. Key themes to emerge from the consultations to ensure Australia is competitive and patients have access to these new medicines with fit for purpose and harmonised processes include:

1. The flexibility of the TGA and their willingness to engage with stakeholders and seek feedback was commended however it was suggested that the TGA could be more proactive.

2. Better communication by the TGA. This included feedback with regards to plain language and contemporary information being available on the website, supporting better understanding of the clinical trial and regulatory pathways as well as interactions/interdependencies with other agencies (defined timelines and greater clarity around requirements at each step of the process). Several stakeholders suggested there was a need for flowcharts and diagrams, webinars with Q&A guidance and tailored communications (e.g. via SME Assist, specific newsletters or otherwise).

3. Alignment with comparable overseas regulators (CORs) is recommended with respect to definitions and classifications, dossiers, pathways and data requirements. Industry stakeholders in particular noted there had been significant improvements with evaluating dossiers which had previously been submitted to CORs.
4. While the Clinical Trial Notification (CTN) pathway is an advantage for conducting trials in Australia in a timely manner, process improvements were noted for the Clinical Trial Approval (CTA) process. Clinical trial experts, researchers, clinicians and industry stakeholders all noted that the CTA process needed improvement and timelines needed to be equivalent to international benchmarks "at the minimum". There was a general perception that the CTA process was resource intensive and had substantially lengthier timelines when compared to key international jurisdictions and that the TGA had less experience in evaluating Advanced Therapies (ATs) in particular.
5. Process improvements for biologicals. It was noted that the biologicals pathway was less well-defined relative to the prescription medicines pathway and that this was unique to Australia. Ensuring that these therapies had appropriate designations in terms of orphan drug status as well as expedited pathways based on need, rather than classifications, was a key theme across all stakeholder groups.
6. Reduced duplication of effort across key agencies. Industry stakeholders and patient advocacy group representatives in particular suggested that there should be a single point of entry for data requirements and a more streamlined and holistic approach to enabling patient access to new therapies. Industry stakeholders noted that at times they were submitting near identical information to separate agencies and that there was seemingly little communication across these agencies.

TERMS AND DEFINITIONS

Classifications and management

Products which are regulated as biologicals in Australia include human cell or tissue-based products; products which contain live animal cells, tissues or organs; and combination products (TGA, 2021b). First introduced in May 2011, the regulatory framework for biologicals provides the legislative basis for the regulation of human tissue and cell-derived products as well as live animal cell, tissues or organs that are supplied, in or exported from, Australia (TGA, 2021b; TGA, 2017).

These Class 4 biologicals are managed by the Biological Sciences Section (BSS), Scientific Evaluation Branch (SEB) of the TGA. This includes therapies where the gene is delivered to cells outside of the body, which are then transferred back into the body (e.g., CAR-T cells). Other cell and tissue therapies are also managed by BSS.

Therapies which involve *ex vivo* manipulation of genetic material are classified as gene modified cell therapies. The TGA's current working definition is provided below:

> *A Gene Therapy is a therapeutic good that contains an active substance used in, or administered to, humans with a view of regulating, repairing, replacing, adding or deleting a genetic sequence, and for which the therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant genetic sequence or gene product consequent to its action. These are regulated as medicines. CAR-T cells which involve the genetic manipulation of an autologous cell that is then reinfused is regulated as a biological as it is seen as a genetically modified cell therapy.*

Gene therapies that involve *in vivo* manipulation of genetic material [e.g., the gene is transferred to cells inside the patient's body (e.g. Luxturna®, Zolgensma®)] are regulated as prescription medicines and are

managed through Prescription Medicines Authorisation Branch (PMAB) (TGA, 2019). An overview is provided in Figure 1.

Figure 1 – Regulation pathways for Advanced Therapies

ADVANCED THERAPIES			
Type	Cell therapies including *ex vivo* genetically modified cell therapies	Tissue Therapies	*In vivo* gene therapies
Regulation managed by	Biological Sciences Section	Biological Sciences Section	Prescription Medicines Authorisation Branch

Stakeholder feedback

During consultation, stakeholders provided feedback on definitions used by the TGA, as presented below:

THEME	DESCRIPTION
Biological classifications are out-of-step with Comparable Overseas Regulators (CORs)	The TGA classification of biologicals for these therapies is an anomaly and distinct from CORs. Most stakeholders did not understand why this distinction existed and did not understand the need for it. *"Why do these classifications exist, is it because the science is too complex? What is the rationale? Is it hampered by the complexities of state and federal funding?" – Patient advocacy group representative* Stakeholders from multinational pharmaceutical companies in particular noted that this also made things difficult when communicating within their own companies, including global colleagues. Definitions and classifications need to have global consistency and a global approach. All stakeholders felt that the rationale behind this required better communication and justification. *"These classifications lead to misunderstanding and a lack of understanding internally [within industry]; having asset teams as biological vs cell therapies… no one knows what we're talking about and this feeds into our global systems which are not set up to cope with this. It's a real disincentive for clinical trials or indeed the global filing strategy." – Industry stakeholder* *"There is nothing like [the distinction between Class 4 vs other biologicals] in other major markets. It seems a bit strange to introduce complexity that doesn't exist elsewhere." – Industry stakeholder* *"Why is there biovigilance if we have pharmacovigilance? The same general principles still apply" – Industry stakeholder* *"I understand from a safety point of view, there may be a*

THEME	DESCRIPTION
	need to classify these products differently if there are different safety procedural approaches required for different classes. But I sometimes think, if other countries do not need these distinctions, is it really necessary?" – Researcher *"No one else in the world understands what we are talking about when we say [biologicals]… If you become an expert in Class 4 biologicals [global colleagues] will not have foggiest clue what you are talking about." – Industry stakeholder* Industry stakeholders also noted that the biologicals pathway was significantly more difficult and complex to navigate relative to the medicines pathway and therefore the classifications and definitions were very important. It was perceived by industry stakeholders that these different pathways were also somewhat siloed.
'Advanced Therapies' (AT) definition require international alignment and examples	Stakeholder views on AT definition were variable, with some noting the definition was reasonable and others seeing room for improvement. Some researchers specifically voiced concerns around whether synthetic oligos and RNA products would be captured within this definition. Overall however, industry stakeholders and patient groups felt that the definitions needed to align with CORs. *"Why not adopt the universal definition accepting that there are risks and attributes of product that are clearly defined, included in all guidelines and registrations and so on so that there's global consistency and a global approach?... Noting that these are global companies." – Industry stakeholder* Some suggested that definitions needed 'official' and 'consumer-ready' versions and that lots of examples (not just CAR-T) would be useful. Patient advocacy groups felt that having simple definitions would help consumers better understand the therapies and more readily enable trial participation. *"Compared to the international definitions, why is ours so complicated? From the consumer perspective, it's so hard to get understanding around what this means and what the pathways are." – Patient advocacy group representative* Researchers as well as several stakeholders from industry and manufacturing also recommended that the term Advanced Therapeutic Medicinal Products (ATMPs) as applied in the UK and Europe should be used rather than ATs. Particularly, researchers felt that the boundary between prescription medicines and cell/gene therapies (and tissue therapies and medical devices) was blurring, and that there could be an opportunity to broaden the definition to "medicinal products" as per the European Medicine Agency (EMA) framework. They noted that the United States (US) was also shifting towards this term. *"ATMPs at least has historical use and has been consistently recognised in the EU and maybe even the US is shifting in that*

THEME	DESCRIPTION
	direction. There's an opportunity to make the terminology consistent. One minor step towards international harmonisation." – Manufacturing stakeholder
It is not clear why classifications affect orphan drug designation	Industry understands that Class 4 biologicals cannot get orphan drug designation in Australia and was confused by the rationale behind this. Industry stakeholders mentioned that they had liaised with the TGA regarding this and the TGA indicated that it was a legislative anomaly but that "was just the way it is". *"Our product is a Class 4 biological and has orphan designation for the FDA [meaning that we] qualify for US Food and Drug Administration (FDA) regenerative medicine AT designation and get benefits of breakthrough and FastTrack designation. [These designations mean] there are different pathways there compared to in Australia." – Industry stakeholder* Industry stakeholders also noted that although they had no issues with the general approval process, the orphan drug issue was perplexing and there didn't seem to be logic or rationale provided.

Suggested improvements

A summary of suggested improvements from stakeholders:

- TGA should align definitions and classifications with international regulators
- TGA to communicate the rationale behind the perceived intersection between orphan drug status and Class 4 biologicals

CLINICAL TRIAL PATHWAYS FOR ADVANCED THERAPIES

Clinical trials that involve 'unapproved' therapeutic goods are subject to regulatory controls via the CTN scheme and the CTA scheme [previously known as the Clinical Trial Exemption (CTX) scheme]. The CTN scheme is a notification process where the trial sponsor notifies the TGA of the intent to sponsor a trial utilising an unapproved therapeutic good. The scheme defers the review and oversight of the clinical trial to the relevant Human Research Ethics Committee (HREC). The CTA scheme involves sponsors applying for the TGA's approval to supply unapproved therapeutic goods via a clinical trial {TGA, 2020 #27}.

As part of the CTA scheme, the TGA evaluates summary information about the product including relevant scientific data (which may be preclinical and early clinical data). The HREC is still responsible for considering the scientific and ethical issues of the proposed trial protocol. Currently, genetically modified human cells (Class 4 biologicals) are not able to be supplied under the CTN scheme and must be submitted under the CTA scheme {TGA, 2019 #25} unless exempt (clinical trials for genetically modified cell therapies approved in a comparable jurisdiction may not need to go via CTA). There is currently no maximum review time stipulated once a CTA is filed.

The majority of clinical trials for unapproved therapeutic goods in Australia are conducted under the CTN scheme and the CTA scheme is infrequently used. Other than the situation described above with Class 4

biologicals, it is ultimately the trial sponsor, in consultation with the HREC, who determines which scheme is used.

Questions put to stakeholders pertaining to clinical trials included the following:

1. Have you notified under the CTN or applied under the CTA for a clinical trial of an Advanced Therapy product?
2. Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?
3. Can you tell us about your experience with the CTA/CTN schemes, including utilising comparable overseas regulator approvals?
4. How can the TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?
5. Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?
6. What are your views on enhancing the role of the TGA in the development process of these products e.g. like EMA, FDA?
7. Describe any opportunities that exist to improve CTA/CTN regulatory guidance and/or communication for researchers, Human Research Ethics Committees and industry?
8. What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme? What IT or infrastructure would support these improvements?

Stakeholder feedback

THEME	DESCRIPTION
CTNs provide Australia with competitive advantage	All stakeholders commended the CTN pathway in Australia and noted that this process was a distinct advantage to help get clinical trials, particularly first in human trials, running quickly. *"TGA's willingness to recognise international agencies as competent authorities is a great thing" – Clinician*
Confusion between CTN and CTA pathways and when they should be used	All stakeholders felt that better education and guidance to aid in decision making around when the CTA process should be used was necessary. It was noted that as CTA applications were very rare, there was a need to "re-educate oneself" when going through the process. Enhanced communication around these pathways was noted as a mechanism to improve awareness across different groups. Website content, webinars, conference presentations and livestream videos of talks and associated Q&A sessions were all suggested as potential ways to better communicate this information. Targeted email lists and newsletters to relevant stakeholders were also suggested. The majority of stakeholders, including researchers, SMEs, and clinical trial experts in industry, noted the difficulties in seeking information on the TGA website. Commentary from researchers included that "they were certain that the information was there, but they didn't know where to find it." Other stakeholders also noted that different information was provided depending on

THEME	DESCRIPTION
	who they spoke with at the TGA. An industry clinical trials expert noted that after extensive research on their part, when seeking clarification from the TGA on the most appropriate pathway to utilise there was a four-month delay before receiving a response. This timeline gave them significant uncertainty as to the process involved in arriving at that answer.
CTN vs CTA pathway – who decides?	Understanding varied across stakeholders on who determined whether a product should proceed down the CTN or CTA pathway. Some groups, particularly researchers, SMEs, and clinicians, believed that this was the sponsor's decision, some thought it was down to the ethics committees, and others believed this was a decision made by specific site personnel. Clinicians, clinical trial experts and some industry stakeholders noted that industry would always try to go down the CTN pathway ("the path of least resistance") and if the ethics committee was uncomfortable or unsure on this they could seek advice from the TGA. *"What's happening is that the ethics committees and investigators are de facto making decisions [about CTN vs CTA] which to my mind should be made by the national regulator" – Clinician* *"The FDA has specific streams to provide advice on implementation… This from the TGA doesn't exist. They say what the outcome should be but leave the hospital and labs in limbo so they come to us. Small wins and improvements though; the TGO 88 is very old [but they're] trying to improve it. We acknowledge their willingness to change. Institutes are not prepared for clinical trials. The TGA doesn't work with the hospital like the FDA does in the US." – Industry stakeholder* *"The TGA should consider whether education and communications [are needed] to make sure stakeholders understand when CTN can be used and what constitutes a CTA application as there are infrequent numbers of these." – Industry stakeholder*
CTA pathways are uncertain, resource intensive and have long timelines	Both clinicians and industry stakeholders raised several concerns regarding the CTA process. There was a general perception that the TGA timelines were less reliable than the FDA, noting in particular that the TGA 'stop the clock' process without time limits was concerning. Clinicians noted that the 'stop the clock' process was a strategic disaster for industry and trial participants. Additionally, there was a perception among SMEs that there were no timelines for CTA stated on the website and that this information was essential in the first place for decision making re filing Investigational New Drug (IND) first or a CTA. It also made it difficult to work with investigators, who without structured timelines, would already be drawn across to another study while waiting for the TGA. Some industry stakeholders noted that the stated timelines for CTA were in reality much longer due to the 'stop the clock' process. *"For a company that's dependent on funding, you can't turn*

THEME	DESCRIPTION
	company off while waiting for things to happen. So much better to know the timeframes or have some idea of it. Being held up causes problems." – Industry stakeholder Researchers, clinicians and industry stakeholders noted several instances where trials set to be conducted in Australia only, ultimately ended up including trial sites outside of Australia. This was due to the uncertainty surrounding the CTA timelines and processes, and the comparable predictability in the US, resulting in IND applications being made to the FDA. For those researchers conducting trials in the UK, it was noted that a UK site is required in order to get trial approval which led to sponsors including additional trial sites outside of Australia. Researchers in particular felt that this was a shame as it hindered Australia's capacity to grow capability for these trials locally and affected developing Australian innovations in Australia. *"We know with the FDA that if the application is not back within 30 days, you can start your trial. There is no 'stop the clock' there." – Industry stakeholder* *"There is a perception (perhaps now historical) that timelines for review [via CTA] are slow, or not fixed, within the TGA…Timelines are not trusted. [From my experience] working with industry, they often have a strategy that includes the US or other sites. So even if they had an Australia first strategy, if they have a 'US ever' strategy, the IND process is [seen to be] more reliable and advantageous. So many small biotech companies put their resources into one or two assets, a six-month review is untenable… The problem is that this incentivises them to consider the US earlier than they would have." – Clinician* Industry stakeholders also noted that the FDA had pre-IND meetings with Standard Operating Procedures and Policies (SOPP) available which helped sponsors know what to submit for each meeting. The information from these meetings could then be shared with company stakeholders and potential investors. There was a perception that there were no analogous formal meeting processes specified in the TGA like there were for the FDA and that the CTA process was more opaque. Other sponsors noted similar approaches were available in the UK: *"In the UK, they have a section for scientific advice requests [and] there are timelines for meetings etc. There's nothing similar [with the] TGA. Although they were willing to meet with us and give guidance, this only worked by us getting proactively in touch with them." – Industry stakeholder* Industry stakeholders noted that the CTA process would need to be significantly faster and better than the IND process for it to be competitive. *"The processes need to proceed at the same pace [relative to*

THEME	DESCRIPTION
	CORs] at a minimum" – Industry stakeholder Finally, several industry stakeholders that had been through the CTA process noted that it was more resource intensive compared with CORs. *"[We don't go down the CTA pathway] due to resources and timelines. For the resources required to support a CTA-type package, [we] may as well go to the UK or France or have more sites in US." – Industry stakeholder*
Recommendations to bolster the CTN process	A handful of industry stakeholders suggested that there may be some scope to improve what is listed on the CTN form. One perceived that in order to add an additional site they had to submit the first CTN form and then wait for the site to be approved before they could re-submit for the second site. They noted that if the TGA could enable the process to list additional sites in parallel this would make the CTN process even more attractive to industry and help get trials up and running faster. Other industry stakeholders felt that the information required in the CTN form had increased substantially over the past decades and it was not clear the extent to which all the additional information was needed. They cited Good Manufacturing Practice (GMP) changes to sites needed to be updated in the CTN, which often required multiple updates and there was uncertainty as to the rationale of why manufacturing site changes needed to be included in the CTN.
Resourcing and capability in evaluating ATs through CTA	Several sponsors noted that when clarifying whether to progress down the CTN or CTA pathway, their interactions with the TGA were less than ideal, which led them to question if the TGA had the expertise required to appropriately evaluate these therapies through a CTA process. *"The advice [the TGA] gave us was not possible and at odds with the US advice. We decided then to focus on the FDA and some in Europe… We decided to go with a regulator who had some idea of what we were trying to do and had some experience with stem cells and gene editing. The FDA were much more open, they've seen them [and] approved similar products." – Industry stakeholder* Several industry stakeholders noted that trying to have an initial discussion with the TGA was difficult, with many having multiple correspondences over email and limited opportunity for a two-way discussion. One industry representative noted a call with the TGA: *"We provided [the TGA] with background documentation for the call and clearly they hadn't read it or didn't understand it. Some of the questions they asked [in the call] told us they had little comprehension… [we] thought in the TGA route of CTA we would spend more time educating them than other way around. So, our strategy became to file IND with FDA then*

THEME	DESCRIPTION
	come back to Australia under CTN." – Industry stakeholder Industry and manufacturing stakeholders, that had been through the CTA process, also noted the volume of follow up questions from the TGA reflected more a lack of knowledge rather than problems with the actual application. *"Responses or requests by the TGA are often out of date or stem from a lack of understanding." – Manufacturing stakeholder* Industry generally thought that there should be more guidance and education around the technology to the TGA itself to ensure that they could provide appropriate and tailored advice.
Disproportionate relationship with the FDA which affects trials in Australia	Several clinicians noted that FDA processes and the size of the US market disproportionately affects trial design. To this end, there is a perception that it is difficult for the TGA to influence even what happens in Australia. Clinicians felt that in order to compete for trials on an international scale they needed to tell industry to go to the US for regulatory advice and rely on the clinicians for in house processes, including ethics. Having the IND in place then going through to TGA via CTN works well but it was perceived this doesn't go both ways (i.e., industry cannot go through CTA then gain reciprocal approval in the US). *"The TGA needs to think about what their function is and where they see themselves positioned internationally for trials This is a competitive landscape, even as a regulator." – Clinician* *"There's no reciprocal arrangement with the FDA of having recognition of approvals in this jurisdiction so balance is lopsided in terms of TGA vs FDA route." – Clinician*
Support equitable and timely access to clinical trials	Clinicians and patient advocacy groups noted that due to a lack of awareness of clinical trial activity in Australia, there may be inequitable access to potentially life-saving therapies. It was noted that there are a handful of 'centres of excellence' for gene therapy clinical trials. Building capability takes time. Clinicians observed that to make it attractive for other states to engage in these trials, the governance and standard operating procedures (which are extensive) need to be shared across multiple sites and states, particularly given the complexities of GMOs. It was suggested by industry stakeholders that the TGA could play a role in helping sites, and specific cell labs, with their capabilities and governance. In particular, it was felt that centres of excellence needed to be supported to develop their capability for ATs. Clinicians noted that they needed to do a lot of education with sponsors when trying to get access to clinical trials in Australia relative to overseas. This was in

THEME	DESCRIPTION
	part attributable to a lack of clarity around timelines and the perception by industry that it is slow to get clinical trials up and running in Australia. *"There is a perception that Australia is slow in clinical trials start up. The questions to us are always "what's your turnaround for ethics", "your turnaround for OGTR". They look at the whole journey. They think it's slow so Australia is not a destination. My colleagues were not selected for a particular trial on that perception and had to fight hard with the sponsor to educate them on that and undo that decision. There is work to be done [by the TGA] on communicating what the timelines are so that we can conduct clinical trials." – Clinician*

Suggested improvements

A summary of suggested improvements from stakeholders:

- Enhanced communication about when CTN vs CTA pathway should be used
- Timelines for CTA process to be published on the TGA website
- Education around ATs for the TGA personnel to support CTA process improvements
- TGA to continue to work with CORs to ensure CTA can be recognised in other jurisdictions
- TGA to consider supporting centres in developing capacity to run trials for Ats

Ethics approval

Stakeholder feedback

THEME	DESCRIPTION
Variable capability of ethics committees for considering ATs	Many stakeholders from industry, clinical trials experts, and ethics bodies, noted concern regarding variability in the capability of ethics committees to review clinical trials for ATs. Some committees were very well resourced and capable of making decisions, such as those located at tertiary hospitals with centres of excellence. Ethics committees with specific input from scientific advisory committees, or dedicated ethics bodies like Bellberry, were also viewed positively. Most stakeholders felt that other "less well-resourced" ethics committees did not have access to the required expertise. This variability was noted to be not only risky for patients but could also lead to inconsistency in decisions. *"It's a better look for the country to have a single national committee overseeing this rather than individual ethics committees making these decisions in an anxious state." – Clinician*

THEME	DESCRIPTION
	It was highlighted by clinicians that this variability was distinct from the UK where there was one national Human Research Ethics Committee (HREC). One industry stakeholder noted that they had the same ethics application approved in one site but not another. As a result, their entire clinical trials strategy shifted and they were required to run the trial at another site. The clarification questions they received indicated to them that the ethics committee did not have the necessary expertise to evaluate their application. Specific training for ethics committees around OGTR was also recommended by researchers.
Uncertain of TGA role in ethics approval	Opinion varied as to TGA involvement in ethics through the CTN pathway, with industry stakeholders generally believing that the TGA already played an appropriate role. Both clinicians and industry stakeholders acknowledged that the variability in ethics committees' expertise may necessitate some oversight from other experts and national coordination. Stakeholders were unsure whether this was a role for the TGA, or if the TGA had the capability to do this. Many noted that if they were to take more of a role, e.g., through accreditation of ethics committees or otherwise, that they would need to be adequately resourced to do so and ensure timelines, and patients, were not impacted. Clinicians and industry sponsors who believed their ethics committees were very well placed to evaluate trial applications, or believed that adequate processes and frameworks were already in place (e.g., the NHMRC framework or engagement with scientific advisory committees) were adamant that the TGA should not play a role. *"The TGA has no role [in ethics]. They don't have the expertise. We need to trust local ethics committees to make the right decisions. The NHMRC framework is pretty good. We can influence trial design significantly and the trials get a good review here. The TGA shouldn't overstep… having another layer of guidance/rules will be a huge mistake and impair our ability to compete internationally. We are routinely first in human dosing and that is hugely academically advantageous." – Clinician* *"I would prefer to go to Medicines Australia or the NHMRC before going to the TGA [for guidance on ethics]" – Industry stakeholder* *"There shouldn't be more of a role for the regulator in initial ethics. It's not a good use of their resources. We need them to provide more comprehensive advice generally and as cases come through; to provide examples… to make it easier for the ethics committee to make those decisions"– Manufacturing stakeholder*

Suggested improvements

No improvements for the TGA were noted under this section.

GMP

Class 4 biologicals require GMP approval, quality dossier and biovigilance activities including a Risk Management Plan (RMP). While there is no requirement for these therapies to submit an Electronic Common Technical Document (eCTD), most applications are received in this format. Other ATs, managed by PMAB require eCTD and streamline submission processes where there is a statutory defined period for evaluation. RMP are also required. Questions asked pertaining to GMP included:

1. What opportunities are there to improve the regulatory framework with respect to GMP requirements for Advanced Therapies?
2. Is guidance clear around GMP requirements for these therapies? If not, what opportunities are there to improve guidance?

Stakeholder feedback

THEME	DESCRIPTION
Opportunities to provide guidance for GMP requirements for ATs	Manufacturing stakeholders noted the guidance for GMP was unclear and how it was applicable across multiple stages (all phases of clinical trials, commercial, and manufacturing). This was compounded by clinical trials for ATs not always fitting into standard phases. They felt there was an opportunity to provide clearer guidance on what is appropriate.
Leveraging overseas accreditation	It was suggested that the TGA should rely on overseas GMP accreditation for sites located outside of Australia and not insist on additional evaluation of audit reports or request review of technical agreements between manufacturers. One industry stakeholder noted that they initially did not have mutual recognition of GMP from the TGA and the FDA and therefore required a TGA inspection which took six months to book in. In one instance both the FDA and the TGA performed the inspections at the same time. This stakeholder believed that the TGA now had mutual recognition and saw this as positive, demonstrating a willingness to listen to feedback.
Disconnect between GMP and pre-market processes	Industry stakeholders noted a lack of effective communication between the different branches responsible for GMP (pre-market, post-market pharmacovigilance and the sections providing inspections, licenses, etc.). Because the GMP database was standalone relative to the pre-market information, industry found it difficult to make an accurate assessment on where they were up to in the various processes; e.g., whether clearance was submitted, underway, or close to finalisation etc. It was felt that there were no formal timelines available around the GMP assessment compared to the pre-market processes and that stakeholders could not provide what information was missing if there was no transparency around this. Industry stakeholders commented that knowing how they were tracking through the GMP process would be useful and that IT infrastructure could support this.

Suggested improvements

A summary of suggested improvements from stakeholders:

- TGA to provide more guidance around when GMP is applicable across the different stages
- TGA to improve communication between the different branches responsible for GMP

OGTR-TGA INTERFACE

Some Advanced Therapies are involved in administration of GMO into patients. The OGTR administers the *Gene Technology Act 2000* and is responsible for managing health and environmental risks of genetically modified organisms (GMOs) (Tribe, 2012). As well as providing information to other regulatory agencies about GMOs and GM products, the OGTR has roles in monitoring international practice pertaining to regulation of GMOs and promoting the harmonisation of risk assessments relating to GMOs and GM products across regulatory agencies (OGTR, 2021).

Questions that were asked of stakeholders pertaining to the OGTR-TGA interface are summarised below:

1. What are the impacts of inconsistencies in definition of gene therapies between the OGTR and TGA?
2. Are there overlaps or gaps in the regulatory requirements imposed by the TGA and OGTR for Advanced Therapies (for both clinical trials and commercial applications)?
3. Are you aware that joint TGA-OGTR pre-submission meetings are available? If not, how could this have been more effectively communicated?
4. What other challenges have you faced with the OGTR-TGA interface? What would improve the situation?

Stakeholder feedback

THEME	DESCRIPTION
Variable awareness of requirement to engage with OGTR	Some industry stakeholders were uncertain when they were required to consult with the OGTR, and at which stage of the development cycle, and sought independent guidance or legal advice as it was not explicitly clear (for their specific product) from the TGA website and documentation. Several industry stakeholders from major global companies mentioned that they started to write their own guidance documents about the OGTR-TGA interface across different stages. *"Getting this information is certainly not easy, especially when you're a novice" – Industry stakeholder* Manufacturing stakeholders also noted the need to make the interaction between the OGTR and TGA more transparent, particularly as this appeared to be unique to Australia (and Brazil). The OGTR acknowledged that there was more confusion at the moment as the Australian Government Department of Health (DoH) were updating their systems and that this was not currently linking properly with the OGTR webpages. It was recommended that having the same information on the TGA and OGTR websites would be beneficial. *"People need to understand whether they have to engage*

THEME	DESCRIPTION
	with OGTR or not. The technology is so complex and bespoke so many people struggle to make the decision themselves. They're looking for guidance and not finding it." – Clinician Researchers suggested that education around the OGTR-TGA interface should come from the TGA as they were better resourced than the OGTR.
OGTR processes can negatively impact on clinical trial timelines	Manufacturing stakeholders noted that the benefits of the short timelines for the CTN pathway can be dampened by the OGTR process and that their 90-day application process adds to the time to set up clinical trials. Researchers and clinical trials experts suggested they could do OGTR and ethics in parallel but usually waited to understand the OGTR issues before submitting ethics which adds to time. Some ethics committees wanted to see OGTR outcome before considering application. It was suggested that this could potentially be rectified in future with a review of gene technology regulators to make these processes more efficient.
OGTR role and TGA interface seems opaque and can be duplicative	Many stakeholders had a view that there was an opportunity to enhance and streamline the interactions between the TGA and OGTR. Stakeholders felt that the TGA-OGTR interactions were quite *ad hoc* and that it was not clear when the OGTR should be consulting with the TGA and *vice versa*. There are challenges navigating between the TGA and OGTR website. Web pages sit in the DoH website and there were challenges associated with DoH shifting to a different platform which doesn't (yet) link with the OGTR's sites. Many web pages were noted to be out of date. A handful of stakeholders highlighted there were inconsistencies with timeframes in reporting to each agency. Some felt that feeding information into any one of those regulators led to duplication of effort with the same data packages being sent to both the TGA and OGTR. *"Having separate submissions of identical information is cumbersome, clunky and unnecessary." – Industry stakeholder* Several clinicians and industry stakeholders noted that there were aspects of the OGTR processes that seemed to be over-reaching and were already considered through the TGA. One stakeholder noted that this was specific for their trial with the OGTR coming back to ask questions about the trial that were not a part of the OGTR remit. *"There is a disconnect between the different regulatory agencies and how they interact. It strikes me that the current relationship is untenable. The OGTR is more about preventing GMOs getting into community and crops than human biologics. There needs to be closer decision making for the TGA and OGTR and clear guidance… all things should be mirrored." – Clinician*

THEME	DESCRIPTION
	"There is overlap… the Gene Technology Act explicitly says that humans can't be GMOs. The Act doesn't cover gene therapy or ATs actually. The OGTR has to think about population harm but not think they have any responsibility with respect to individual patients being treated; that is ethics, physicians and the TGA. OGTR's singular concerns should be the environment and the community but now they want to know about when we've commenced the trial and other things. To be frank, adverse events are reported to other agencies and they don't need to go back to the OGTR. The OGTR are trying to regulate things outside of the Act. There are duplication of requirements." – Clinician Patient advocacy groups also had some concerns around the timelines associated with the OGTR and TGA interaction. They noted that displaying the timelines relative to COR might not be fully transparent if the separate/additional OGTR-related timelines were omitted. *"It seems like additional step most other jurisdictions don't have. It is not clear what value it adds and why that work is not being done by the TGA, given [the TGA] is purpose built for evaluating… from the patient perspective [why couldn't] any specific OGTR expertise be incorporated into the TGA to eliminate an additional step in the process?" – Patient advocacy group representative* It was noted that in other jurisdictions (e.g. in the UK and the FDA), the OGTR equivalent was consulted directly through the comparative registration body.
TGA-OGTR joint pre-submission meetings known by those who have been through the process	Stakeholders that had gone through the journey with the TGA and OGTR were aware of the TGA-OGTR joint pre-submission meetings however those that were not yet at that stage had little awareness of this, or how the TGA and OGTR worked together more broadly. In addition, those who had exclusively worked with the OGTR indicated they were also not aware of pre-submission meetings even though they would soon be at that stage of their processes.
Definitions of gene therapies between OGTR and TGA and overall classifications	None of the interviewed stakeholders noted that the definitional differences across the OGTR and TGA had impacted their path to registration *per se*. However, stakeholders from manufacturing noted that there were differences in nomenclature citing that the OGTR frequently mention "dealings" but the TGA does not. Generally, stakeholders agreed that there should be standardisation of terminology. More broadly in terms of classifications, researchers felt that there was little sense that oversight by the OGTR was required for gene therapy but not for gene-modified cell therapies and that this separation was "completely artificial."

Suggested improvements

A summary of suggested improvements from stakeholders:

- Opportunity to enhance and streamline the interactions between the TGA and OGTR, with many industry and patient advocacy group stakeholders recommending that the interactions with the OGTR be done directly by the TGA themselves
- TGA to provide more guidance about when industry should interact with the OGTR across each stage of the development cycle, and better communicate why there are distinctions for gene-modified cell therapies vs gene therapies
- TGA and the OGTR to apply consistent terminology

TGA REGISTRATION PATHWAY

Therapeutic goods that are regulated as a prescription medicines for serious or life-threatening conditions may be eligible, subject to determination, for the priority review or provisional approval pathways to make them available to patients sooner (TGA, 2021a). Eligibility for the Priority Review pathway is based on "substantial evidence" of a major therapeutic advance while the Provisional Approval pathway is based on "promising evidence from early clinical data" when compared with existing therapeutic goods on the Australian Register of Therapeutic Goods (ARTG) (TGA, 2017). Advanced Therapies regulated as biologicals are not currently eligible for the priority review or provisional approval pathways.

Questions that were asked of stakeholders pertaining to the TGA registration pathway are summarised below:

1. Have you applied to the TGA to register an Advanced Therapy product?
2. Are there opportunities for the TGA to better communicate classification of Advanced Therapies vs international jurisdictions?
3. Are there concerns around the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?
4. What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?
5. What is your understanding of how the TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?
6. What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?
7. Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?

Stakeholder feedback

THEME	DESCRIPTION
The TGA registration timelines are not necessarily an issue	TGA registration timelines were not seen to be a significant issue and more concerns were expressed around the CTA and Health Technology Assessment (HTA) timelines. The detail provided on how the TGA performed compared to

THEME	DESCRIPTION
	international regulators in the consultation briefing document was commended and it was suggested that this information be made available through the website in similarly digestible formats. Patient advocacy groups noted that while the TGA wasn't currently on the consumer's radar, "the train is on the tracks" and patients will become increasingly aware that if they speed up TGA processes, it can get to the reimbursement step more quickly.
ATs need to access expedited pathways based on need	There was a lot of confusion around why biologicals were not able to access expedited pathways based upon a specific classification. Clinicians, patient advocacy groups and industry stakeholders in particular did not understand the logic behind this. An industry stakeholder noted that some products had gone through 'unofficial' priority reviews, but that this approach was not sustainable and that a specific 'needs-based' mechanism through which to expedite therapies was needed. *"If [the TGA] has the resources to [conduct a priority] review unofficially do they need a formal process? At the end of the day, when you look at those pathways for ATs, the key question is 'will it provide increased access to patients?' or are there other ways [to ensure this] that don't involve legislative changes?" – Industry stakeholder* It was felt unanimously, that whatever the classification, it should not impact timelines and that the focus needed to be on the potential outcomes for patients, and in particular those groups with severe unmet need. Stakeholders ultimately wished that biologics had the same access to accelerated pathways. *"Consumers want a level playing field. They just see it as a treatment or a cure and, [to them], just the outcomes matter… There should be no difference… From the consumer's point of view, just make it work."– Patient advocacy group representative* *"I understand these things are new. [But] for the consumer it's just another bureaucratic hurdle… just sort it out. If a patient's life is coming to end, it's black and white." – Patient advocacy group representative* *"All pathways should be available to all therapies; no special cases and categories. [This is] in no one's interest, adds complexity and time, and lacks transparency about what's going to happen. [Means that companies will] prioritise Australia lower as a market because they expect pathway to be difficult."– Patient advocacy group representative*
The TGA should be proactive rather	An underlying theme across many of the conversations around ATs was a need for the TGA to be proactive and flexible with their regulatory responses, with ATs

THEME	DESCRIPTION
than reactive when it comes to new therapies	and 'n=1 trials' in particular. Industry stakeholders understood that the original biologicals framework was set up to help with registration of blood products and that ATs have subsequently been included. This has led to a perception that the TGA was ultimately trying to apply existing outdated frameworks to therapies they were never set up for. Industry stakeholders noted that they had pipeline discussions with the TGA every year but it was unclear how this information was being utilised. It was felt that the TGA were not proactive until the sponsor submitted and by the time issues were raised at the pre-submission meeting it was "too late." *"These medicines are being developed at faster pace than 20 years ago. The process was ok 20 years ago when incremental advancements were marginal. These medicines can change every six months."- Industry stakeholder* Some industry stakeholders and clinicians felt that the TGA should be adaptable to better accommodate the therapies coming through now and in the near future, with fit for purpose regulation and less focus on trying to retrofit old models. *"Whatever [the TGA] does, it needs to be nimble and acknowledge that the landscape is changing quickly. Concrete recommendations are useful but there needs to be ongoing discussion, not just once every five years through a Senate inquiry." – Clinician* Industry stakeholders that had been through the registration process noted that the TGA was flexible, but many *ad hoc* processes and communications were necessary to get products across. Many felt this was not sustainable.
International collaboration on regulatory frameworks is to be commended	Industry and regulatory stakeholders felt that there should be better alignment with international regulators and cited key examples such as the FDA's Project Orbis which provides a framework for concurrent submission and review of oncology products among international partners, and the Access Consortium, a collaboration of regulatory authorities from Australia, Canada, Singapore, Switzerland and the UK which is supported by industry, academia, government, and patients.
TGA requires consistent, transparent and broad consultation with experts	Sponsors which had been through the registration and reimbursement process for ATs noted that sometimes the decisions appeared highly reliant on the advice from a single expert and that more extensive consultation was required. In some instances, a single specialist disagreed with recommendations and processes that were standardised across international jurisdictions. Sponsors suggested that this was another example of where regulation in Australia was seemingly different to everywhere else in the world. Although there is only a small pool of experts with very specialised ATs, stakeholders felt it is important to get representative and consensus views from other specialists in this area. More

THEME	DESCRIPTION
	transparency regarding Advisory Committee on Medicines (ACMs) was also recommended. *"ACM is the last bastion within the TGA framework that has somehow avoided any kind of transparency reform. Unlike advisory committees in the US or Europe, ACM has remained a closed shop. The only industry engagement is through written response." – Industry stakeholder*
It's not just communication	Industry stakeholders, researchers, and clinicians all raised concerns that the TGA may be focusing too heavily on communication and wanted to highlight that there were genuine structural issues associated with the regulatory frameworks and the interface across different bodies. They noted that the TGA's responses needed to go beyond mere "tweaks" and take a holistic approach to ensure patient access was front of mind. This was cited at great length via the 'single point of entry' discussions.

Suggested improvements

A summary of suggested improvements from stakeholders:

- Irrespective of their classification, expedited pathways should be available for all therapies and based on patient need
- TGA to make proactive adaptions to regulatory frameworks and communicate how they use horizon scanning to implement these changes
- International collaboration on regulatory frameworks to be continued and expanded
- TGA to gather representative expert advisory views when appraising ATs and provide more transparency around ACM discussions
- TGA to consider a holistic approach and a single point of entry for data input when working with other agencies in the patient access pathway

PBAC/MSAC INTERFACE WITH THE TGA

The TGA and Health Technology Assessment (HTA) Committees, namely the Pharmaceutical Benefits Advisory Committee (PBAC) and the Medical Services Advisory Committee (MSAC), have established parallel process arrangements. Parallel processing allows sponsor companies to submit to the PBAC or MSAC, in parallel with the application to the TGA, prior to registration on the ARTG.

Questions asked of stakeholders regarding the TGA-HTA interface are presented below:

1. What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?
2. What opportunities are there for the TGA to enhance flexibility in parallel applications to TGA/PBAC for Managed Entry Schemes?

Stakeholder feedback

THEME	DESCRIPTION
TGA and HTA interface could be streamlined	While many stakeholders acknowledged the importance of the distinct processes, it was felt they could be better aligned and that communication could be enhanced. While parallel processes were considered to be a positive step, industry stakeholders noted that they had to follow-up themselves to ensure that the delegate had passed on the information to the relevant HTA committee. Stakeholders hoped that by interacting more closely in the future each side would have a better understanding of the other's needs and the milestones required for each step of the process. *"The intersection between PBAC/TGA is quasi-connected. The ACM meeting cycle and PBAC meeting cycle is out of sync. Three for PBAC, six for ACM and all at different times. The critical piece where we're meant to dovetail [the registration] with reimbursement comes down to me making a call and asking for a favour. [We] need a holistic approach to the whole process." – Industry stakeholder* Other stakeholders noted that there were *ad hoc* concessions made to facilitate parallel processing, with the TGA making allowances for the sponsors to adjust their MSAC timelines to align with TGA (so that ideally, they could submit with similar timeframes). A sponsor who had been through the process with an AT noted that in that instance, the TGA-HTA interface worked for them but it was bespoke and would not be sustainable at scale. With some of these therapies requiring inpatient admission, it was also thought that the TGA-HTA interface should encompass aspects required by states and territories and that the TGA should engage more broadly with the various agencies, including the OGTR. There were divergent views on how the HTA committees dealt with delays to the Delegate's decision from the TGA. Researchers noted that the HTA committees were able to deal with the situation where the decision was not available at time of reimbursement review. Other industry stakeholders who attempted to use the parallel processing pathway experienced the opposite situation whereby the PBAC would not make a recommendation until the TGA indication had been finalised.

Suggested improvements

A summary of suggested improvements from stakeholders are:

- TGA to work more closely with the relevant HTA bodies

OTHER CONSIDERATIONS

Other aspects of the regulatory process as a whole, as well as broader factors are provided in this section. Some of the questions asked broadly are provided below:

1. Is there an opportunity for the TGA to embed advances in regulatory assessments into processes, e.g., allow dynamic labelling updates and cloud- based dossiers?
2. Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?
3. What opportunities are there to formalise/improve guidance on submission of real-world evidence to the TGA?

In addition to these questions, many stakeholders provided commentary about the overall trial through to access pathway. These views as well as the responses to the above questions are distilled in the table below.

THEME	DESCRIPTION
Communication in general could be improved	Communication at a broader level was raised by a number of stakeholders, with some specialist stakeholders not being aware of SME Assist. For investigator-led trials specifically it was noted that academics cannot afford a regulatory expert so the communication and guidance needed to be clear. Several industry stakeholders noted that at times the guidance could vary depending on who they spoke with at the TGA so internal communication and consistency was also recommended. Stakeholders suggested that information could be tailored to different groups depending on where they were at in their journey; e.g., at the CTN/CTA stage through to registration. Numerous suggestions were posed such as email newsletters, flowcharts, webinars, and the opportunity for stakeholders to register interest for specific aspects which would cater for different levels of expertise or areas of interest. It was also suggested that education materials could be developed in consultation with the TGA by other groups in the sector such as AusBiotech or CCRM Australia. Industry stakeholders cited specific instances where communication was greatly appreciated and informative: *"pre-COVID, the TGA did workshops and Tony Manderson would come to conferences and do Q&A sessions. This went a long way in educating… this helped speeds things up and [enabled us to] spend less time looking at documents that don't address what we need"– Industry stakeholder* *"There needs to be much more attention paid to communication, It's just difficult to find your way. No one can say 'start here' for most of us its trivial and we know but many of us spend endless hours with every sponsor or single investigator explaining the intricacies of the process which is so time wasting. Something should be done by government to improve. clarity in feedback and generally improve communication around the process." – Manufacturing stakeholder*

THEME	DESCRIPTION
	Regulatory experts recognised that the SME Assist education systems were useful but more was required. Other researchers and regulatory experts were not even aware of the SME Assist service and resources.
TGA's willingness to engage and seek feedback was commended	All stakeholders noted that it was a good sign that the TGA was conducting these, and other, stakeholder consultations. Industry stakeholders in particular had noted that their previous feedback had sometimes been implemented, albeit noting that these changes generally required approval from higher levels of leadership.
TGA could play more of a role in early development conditional on local and international harmonisation	Industry stakeholders noted that it would be useful to have the TGA involved with early development and aspects of trial design (particularly given provisional approval pathways), albeit with a few caveats. It was noted that if they were involved, the TGA would need to apply a 'whole of system' lens to ensure that the correct data were being collected across all stages from registration through to reimbursement. One industry stakeholder noted that, in one instance, they were required to run separate additional trials to fulfil the data requirements for the HTA process. *"[early advice needs to consider] all decision makers in the access chain and think about the end game. Registration is great, it's like a trophy on a shelf, but unless it reaches the patient as fast as possible it doesn't mean much. Need to look at fundamental legislation and impact in 5-10-20 years' time, rather than TGA088 and little stop gap measures on the way." – Industry stakeholder* Recognising that trials were often conducted on the global stage and that companies generally sought international approval prior to Australia, industry stakeholders also noted that alignment with international regulators' scientific advice would be essential. *"In development programs, major pharmaceutical companies get advice from the FDA and the EMA routinely. The concern with the TGA is that if their advice differed to the advice of FDA/EMA, we would be in a quandary" – Industry stakeholder* A regulatory expert felt that whilst TGA involvement would be useful, it was unlikely to be adequately resourced to do this.
A single point of entry	There was strong sentiment from both industry stakeholders and patient advocacy groups that there should be a single point of entry for all decision makers in the clinical trials, TGA, OGTR, HTA, state/territory processes. Industry stakeholders were hoping that the 'one stop shop' for clinical trials would also embed other processes more holistically and whilst they understood that the TGA was involved, they were unsure to what, and if at all the other agencies, such as the OGTR, were involved.

THEME	DESCRIPTION
	Sponsors noted that there was overlapping information required for each of the processes (trials-TGA-OGTR, TGA-HTA, TGA-HTA-State/Territory) and that it would be useful to understand what each decision maker needs at different stages of the pathway. Broader pre-submission meetings and a single point of entry for data input through an integrated system were suggested to help facilitate such a holistic approach. Some industry stakeholders cited the UK as leading the way with this, citing the Innovative Licensing and Access Pathway (ILAP) as a novel holistic process that embeds connections throughout horizon scanning to trials being done in parallel with the real world evidence (RWE) framework, and through to registration and reimbursement. Digital infrastructure was recommended as the key way to achieve this single point of entry process. *"There is an opportunity to streamline clinical trials applications into a single application. A single portal for clinical trials across states and Australia-wide means this is a good time to do it." – Researcher* *"The pathway to commercialisation requires a coordinated view across the states and the Commonwealth and various agencies" – Industry stakeholder* One sponsor noted that in the UK there was a single entry point through the TGA-equivalent for ethics and regulation and that this body would liaise with the OGTR-equivalent and other relevant bodies where necessary: *"In the UK, there is an integrated system [which has] ethics and regulation all done through one online form. It goes both through NHMRA and relevant ethics committees and has separate reviews [for specific aspects] which require different perspectives but it's just one application and everything is standardised." – Industry stakeholder* The distinct processes were thought to create duplication of effort in some instances: *"The OGTR was set up for specific areas related to GMO crops and their impact on the environment. In Europe and the US, the risks associated with gene therapies are dealt with within the regulatory process. [There is] extraordinary duplication of activities here. The same submissions essentially sent to both the OGTR and the TGA... The information we provide to the OGTR is from regulatory dossier anyway… OGTR approval provides a series of conditions that the site has to meet … [and] a lot are the same requirements as per the TGA. It's just over regulation"– Industry stakeholder* *"We would like to see more consistency in terms of public outlook from those government authorities [TGA-OGTR] that work pretty much independently (though they meet*

THEME	DESCRIPTION
	regularly)." – Manufacturing stakeholder
More guidance on RWE	Both patient advocacy groups and industry stakeholders noted that a lot of information is being collected from patients in not only clinical trials but for ongoing treatment and monitoring. It was felt that there was more momentum in the post-market field and there was an opportunity to formalise pre-market RWE collection to understand what would be useful in the TGA registration process. Patient advocacy groups also felt that there needed to be more guidance on RWE and an ownership of what should be included in registries, particularly as many of these were industry-funded. However, representatives from large multi-national companies noted that what was collected was often done so in alignment with companies' international strategy. Patient advocacy groups noted that the formalisation of RWE also needed to consider CORs. Clinicians also noted that historically there has been an over-emphasis on Australia-specific data and there was a perception that this had skewed TGA/PBAC decisions. They noted there should be some collection of data to ensure outcomes were 'ballpark' to help give confidence to approvers to make quick decisions but that specific RWE for Australia was not always clinically relevant.
There is pressure on the system to collect RWE	The resourcing necessary for hospital staff or otherwise to collect and maintain registries is substantial. *"Resources are not flowing to sites to provide boots on the ground to collect the RWE" – Clinician* *"If a contract between the Commonwealth and sponsors for ongoing data collection for some years [is necessary]. Funding is required for ongoing collection… it's a huge burden." – Researcher and Clinician*
There are opportunities to improve dynamic labelling updates and cloud-based dossiers	Industry stakeholders suggested that enhancing direct electronic submissions would be well received by everyone. Sponsors felt that some simple changes, (e.g., changes in salt formulations) should be streamlined and triaged to determine the level of regulatory involvement required, if any. *"Submission portals, it is time to come to the 21st Century; everyone wants that." – Industry stakeholder* *"The bigger regulators are looking at real time data submission and review. Colleagues in the manufacturing side are sharing batch analysis data direct to the regulator. Integrating all of this to facilitate more rapid reviews is key. For labelling, everything is still paper based. Electronic labels that can be accessed would be so much easier. Label would be a dynamic document (with links) to help patient better*

THEME	DESCRIPTION
	understand. More education for patients about use of products. Minor changes could be more easily captured too. How the TGA sets up the IT systems and how they can be interacted with is key." – Regulatory expert and researcher
The TGA website needs to be improved and have plain language information	All stakeholders had experienced difficulties in navigating the TGA website and finding out where to go to seek the right information. Industry stakeholders noted that the comparable FDA guidance were much easier to navigate. *"The TGA website is nightmare. You're better off ringing a TGA person and asking them where to click." – Industry stakeholder* It was also noted that aspects of the website were outdated (for e.g., some documents still saying CTX) and that there also needed to be more consumer-friendly language. Many industry stakeholders had developed their own internal documentation to help navigate the website and to compile their own relevant information for understanding the legislative processes. The ARTG was not considered to be very consumer friendly. *"There needs to be plain language information as there is an assumed level of knowledge." – Patient advocacy group representative* *"[Information needs to be] in plain English rather than 50 pages of legislative nonsense" – Industry stakeholder*
It would be useful to make the stakeholder consultation documents or subsequent report made available	Many stakeholders stated that they would like to see the outcomes of this consultation and that it would be useful to have access to the report. The consultation document itself was viewed as being very useful, with many commenting this is the type of information they would like to receive/have made available on the website.
A role for TGA in imports?	Clinicians noted that patients and patient groups were importing treatments from overseas to try to get access (for example, getting Orkambi® from Argentina). They noted a particular group had the product tested by an academic institute to make sure it was actually the active product and wondered whether the TGA could play a role in this, noting it "was GMP through and through."
Questions about molecular indications indicate progressive thinking but require more thought	Industry stakeholders and patient advocacy groups felt that questions around molecular indications were very pertinent to the ATs space and personalised medicine. *"[Molecular indications] will be more and more important, around general prescription medications too. Molecular definition of diseases is where we will see things going more*

THEME	DESCRIPTION
	and more." – Regulatory expert and researcher Some noted that the FDA had taken this approach with cancers but that ultimately any considerations regarding this needed to be in the best interest of the patient and aligned with international regulators. *"The reality is that the shift has to come as otherwise they can't do what they're meant to do. This is already happening with cancers already doing it; take the SMA drug before symptomatic, the outcome is significantly better. This is where natural history and registries would help us. The mindset should be applied as with newborn screening. We have to find a way to do that." – Patient advocacy group representative*

Suggested improvements

A summary of suggested improvements from stakeholders:

- TGA to align with international regulators' scientific advice
- The TGA website needs to be improved, contemporary, and have plain language information
- TGA to consider dynamic labelling updates and cloud-based dossiers
- TGA to consider a 'whole of system' lens to ensure that the correct data is collected across all stages from registration through to reimbursement
- Enhanced communication of the regulatory frameworks and the different stages of interactions with other agencies. Webinars, website improvements, newsletters, flowcharts were all suggested as useful options.
- Enhanced communication between agencies as well as within the TGA itself to ensure information provided to stakeholders was consistent

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APPENDIX

A.1. Stakeholders consulted

Individual meetings:

	CATEGORY	ORGANISATION
1	Industry	Novartis Cheryl Maley, Nicole Johnston, George Lillis, Othon Gervasio, Mitch Kirkman, Nick Hagan
2	Industry	Gilead Andrew Notley, Kim Mitchell
3	Industry	GSK Dr Mark McDonald
4	SME	Prescient Therapeutics Dr Rebecca Lim, Leanne West, Steven Yatomi-Clarke
5	SME	Cynata Therapeutics Dr Ross Macdonald, Dr Kilian Kelly
6	Researcher	Centre for Molecular Medicine + Innovative Therapeutics, Prof Steve Wilton
7	SME	PYC Therapeutics, Dr Sue Fletcher
8	SME	Cartherics, Dr Alan Trounson, Dr Ian Nisbet
9	Patient/Consumer	Rare Cancers Australia, Dr Amanda Ruth
10	Patient/Consumer	Rare Voices Australia, Louise Healy
11	Patient/Consumer	Cystic Fibrosis Australia, Nettie Burke
12	Clinician/Researchers	Peter MacCallum Cancer Centre Prof Simon Harrison and A/Prof Michael Dickinson
13	Ethics	Bellberry, Kylie Sproston
14	Clinician/Researchers	Children's Medical Research Institute (CMRI) Prof Ian Alexander, Sydney Children's Hospitals Network and CMRI, Westmead A/Prof Leszek Lisowski, CMRI and The University of Sydney Jo Karra, Sydney Children's Hospitals Network and CMRI
15	Regulatory	PharmMed, Dr Orin Chisholm
16	Clinician/Researchers	Royal Prince Alfred Hospital, Prof Joy Ho
17	Researcher	The University of Melbourne, Prof Megan Munsie

Workshop groups:

WORKSHOP CATEGORY	PARTICIPANTS
Clinical trial experts	R&D taskforce • GSK, Carrie Bloomfield, Dr Karen Leskie • Roche, Helen Aunedi • Paradigm Biopharma, Sharon Charles • Medicines Australia, Eric Johnsson
Regulatory experts	• Medicines Australia Regulatory Working Group (Sanofi, Amgen, Novartis, Pfizer, BMS, Bayer, J&J, Commercial Eyes, AstraZeneca, Roche, Abbvie, Medicines Australia) • Judy Bingham, Easington Pty Ltd
Clinicians	• Prof Ian Alexander, CMRI • A/Prof Michelle Farrar, UNSW, Sydney Children's Hospital • Prof Robyn Jamieson, USyd, Children's Hospital Westmead • Prof Adam Jaffe, UNSW, Sydney Children's Hospital • Prof Andrew Davidson, Royal Children's Hospital Melbourne • Prof Martin Delatycki, Victorian Clinical Genetics Service • Dianne Tucker, Royal Children's Hospital Melbourne
Researchers	• Prof Melissa Little, Murdoch Children's Research Institute • Prof Graham Jenkin, Hudson Institute • Prof Simon Barry, University of Adelaide
Manufacturing	• Therapeutic Innovations Australia Dr Stuart Newman, Dr Heather Donoghy • Cell and Molecular Therapies, Royal Prince Alfred Hospital Dr Zlatibor Velickovic, Prof John Rasko, Luigia Manzoni, Dr Sharon Sagnella • Royal Prince Alfred Hospital Dr Gabrielle O'Sullivan • Cell and Tissue Therapies WA Leon Brownrigg, Janice Fogarty • Q-Gen Cell Therapeutics (within QIMR-Berghofer Institute) Dr Leon Scott, Darron Laing • Cell Therapies Pty Ltd Dr Jennifer Hollands, Nathan Smith, Gerry McKiernan

A.2. Stakeholder group questions

	INDUSTRY	REGULATORY	CLINICIANS	RESEARCHERS	MANUFACTURING	PATIENT ADVOCACY/ CONSUMER GROUPS
Clinical trial pathwaysfor Advanced Therapies	Have you notified under the CTN or applied under the CTA for a clinical trial of an Advanced Therapy product?	Have you notified under the CTN or applied under the CTA for a clinical trial of an Advanced Therapy product?				
	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?	Thinking about clinical trial regulatory pathways for Advanced Therapies (CTA/CTN), what are the current barriers for your sector?
	Can you tell us about your experience with the CTA/CTN schemes, including utilising comparable overseas regulator approvals?	Can you tell us about your experience with the CTA/CTN schemes, including utilising comparable overseas regulator approvals?	Can you tell us about your experience with the CTA/CTN schemes, including utilising comparable overseas regulator approvals?	Can you tell us about your experience with the CTA/CTN schemes, including utilising comparable overseas regulator approvals?		
	How can TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?	How can TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?	How can TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?	How can TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?		How can TGA communicate more effectively which clinical trials require to use CTA pathway or not, depending on overseas regulatory approval status?
	Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?	Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?	Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?	Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?		Should the TGA play a role in how ethics approval is sought, if at all, via HRECs?

	INDUSTRY	REGULATORY	CLINICIANS	RESEARCHERS	MANUFACTURING	PATIENT ADVOCACY/ CONSUMER GROUPS
	What are your views on enhancing the role of the TGA in the development process of these products e.g. like EMA, FDA?	What are your views on enhancing the role of the TGA in the development process of these products e.g. like EMA, FDA?	What are your views on enhancing the role of the TGA in the development process of these products e.g. like EMA, FDA?	What are your views on enhancing the role of the TGA in the development process of these products e.g. like EMA, FDA?		
	Describe any opportunities that exist to improve CTA/CTN regulatory guidance and/or communication for researchers, Human Research Ethics Committees and industry?	Describe any opportunities that exist to improve CTA/CTN regulatory guidance and/or communication for researchers, Human Research Ethics Committees and industry?	Describe any opportunities that exist to improve CTA/CTN regulatory guidance and/or communication for researchers, Human Research Ethics Committees and industry?	Describe any opportunities that exist to improve CTA/CTN regulatory guidance and/or communication for researchers, Human Research Ethics Committees and industry?		
	What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme?	What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme?	What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme?	What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme?		What is your knowledge and experience of CTA timelines relative to overseas regulatory schemes e.g., FDA CTX scheme?
	What IT or infrastructure would support these improvements?	What IT or infrastructure would support these improvements?	What IT or infrastructure would support these improvements?	What IT or infrastructure would support these improvements?		What IT or infrastructure would support these improvements?
GMP	What opportunities are there to improve the regulatory framework with respect to GMP requirements for Advanced Therapies?	What opportunities are there to improve the regulatory framework with respect to GMP requirements for Advanced Therapies?		What opportunities are there to improve the regulatory framework with respect to GMP requirements for Advanced Therapies?	What opportunities are there to improve the regulatory framework with respect to GMP requirements for Advanced Therapies?	

	INDUSTRY	REGULATORY	CLINICIANS	RESEARCHERS	MANUFACTURING	PATIENT ADVOCACY/ CONSUMER GROUPS
	Is guidance clear around GMP requirements for these therapies? If not, what opportunities are there to improve guidance?	Is guidance clear around GMP requirements for these therapies? If not, what opportunities are there to improve guidance?		Is guidance clear around GMP requirements for these therapies? If not, what opportunities are there to improve guidance?	Is guidance clear around GMP requirements for these therapies? If not, what opportunities are there to improve guidance?	
OGTR-TGA interface	What are the impacts of inconsistencies in definition of gene therapies between OGTR andTGA?	What are the impacts of inconsistencies in definition of gene therapies between OGTR andTGA?	What are the impacts of inconsistencies in definition of gene therapies between OGTR andTGA?	What are the impacts of inconsistencies in definition of gene therapies between OGTR andTGA?	What are the impacts of inconsistencies in definition of gene therapies between OGTR and TGA?	What are the impacts of inconsistencies in definition of gene therapies between OGTR and TGA?
	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?	Are there overlaps or gaps in the regulatory requirements imposed by the TGA and the OGTR for Advanced Therapies (for both clinical trials and commercial applications)?
	Are you aware of that joint TGA-OGTR pre-submissions meetings are available? If not, how could this have been more effectively communicated?	Are you aware of that joint TGA-OGTR pre-submissions meetings are available? If not, how could this have been more effectively communicated?		Are you aware of that joint TGA-OGTR pre-submissions meetings are available? If not, how could this have been more effectively communicated?		
	What other challenges have you faced with OGTR and TGA interface? What would improve the situation?	What other challenges have you faced with OGTR and TGA interface? What would improve the situation?		What other challenges have you faced with OGTR and TGA interface? What would improve the situation?	What other challenges have you faced with OGTR and TGA interface? What would improve the situation?	
TGA/PBAC/MSAC parallel processing	Have you applied to the TGA to register an Advanced Therapy product?	Have you applied to the TGA to register an Advanced Therapy product?				

	INDUSTRY	REGULATORY	CLINICIANS	RESEARCHERS	MANUFACTURING	PATIENT ADVOCACY/ CONSUMER GROUPS
	What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?	What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?	What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?	What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?		What opportunities exist to improve and enhance efficiencies of the interface between regulation and reimbursement for Advanced Therapies?
	What opportunities are there for TGA to enhance flexibility in parallel applications to TGA/PBAC for Managed Entry Schemes?	What opportunities are there for TGA to enhance flexibility in parallel applications to TGA/PBAC for Managed Entry Schemes?				What opportunities are there for TGA to enhance flexibility in parallel applications to TGA/PBAC for Managed Entry Schemes?
Priority + provisional pathways (including CORP)	What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?	What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?	What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?	What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?		What opportunities exist to improve and harmonise regulation with overseas regulators, for Advanced Therapies?
	What is your understanding of howthe TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?	What is your understanding of howthe TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?	What is your understanding of howthe TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?	What is your understanding of howthe TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?		What is your understanding of how the TGA leverages international assessments (evaluation reports)? Are there more opportunities for the use of comparable overseas reports in Advanced Therapies?
	Are there concernsaround the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?	Are there concernsaround the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?	Are there concernsaround the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?	Are there concerns around the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?		Are there concerns around the available TGA regulatory pathways and/or timeframes for Advanced Therapies? If so, what?

	INDUSTRY	REGULATORY	CLINICIANS	RESEARCHERS	MANUFACTURING	PATIENT ADVOCACY/ CONSUMER GROUPS
	Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?	Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?	Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?	Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?		Would it be beneficial to explore the introduction of expedited pathways for non-medicine Advanced Therapies that mirror pathways for prescription medicines, such as priority review and provisional approval pathways? What does that look like?
	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?	Are there opportunities for TGA to better communicate classification of Advanced Therapies vs international jurisdictions?
Other regulatory framework?	What opportunities are there to formalise/ improve guidance on submission of real world evidence to the TGA?	What opportunities are there to formalise/ improve guidance on submission of real world evidence to the TGA?	What opportunities are there to formalise/ improve guidance on submission of real world evidence to the TGA?	What opportunities are there to formalise/ improve guidance on submission of real world evidence to the TGA?		What opportunities are there to formalise/ improve guidance on submission of real world evidence to the TGA?
	Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?	Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?	Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?	Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?		Does the regulatory framework enable sponsors to seek molecular indications vs disease specific indications?
	Is there an opportunityfor TGA to embed advances in reg assessments into processes, e.g., allow dynamic labelling updates and cloud- based dossiers?	Is there an opportunityfor TGA to embed advances in reg assessments into processes, e.g., allow dynamic labelling updates and cloud- based dossiers?		Is there an opportunityfor TGA to embed advances in reg assessments into processes, e.g., allow dynamic labelling updates and cloud- based dossiers?		

A.3. International regulatory processing and timelines for Advanced Therapies

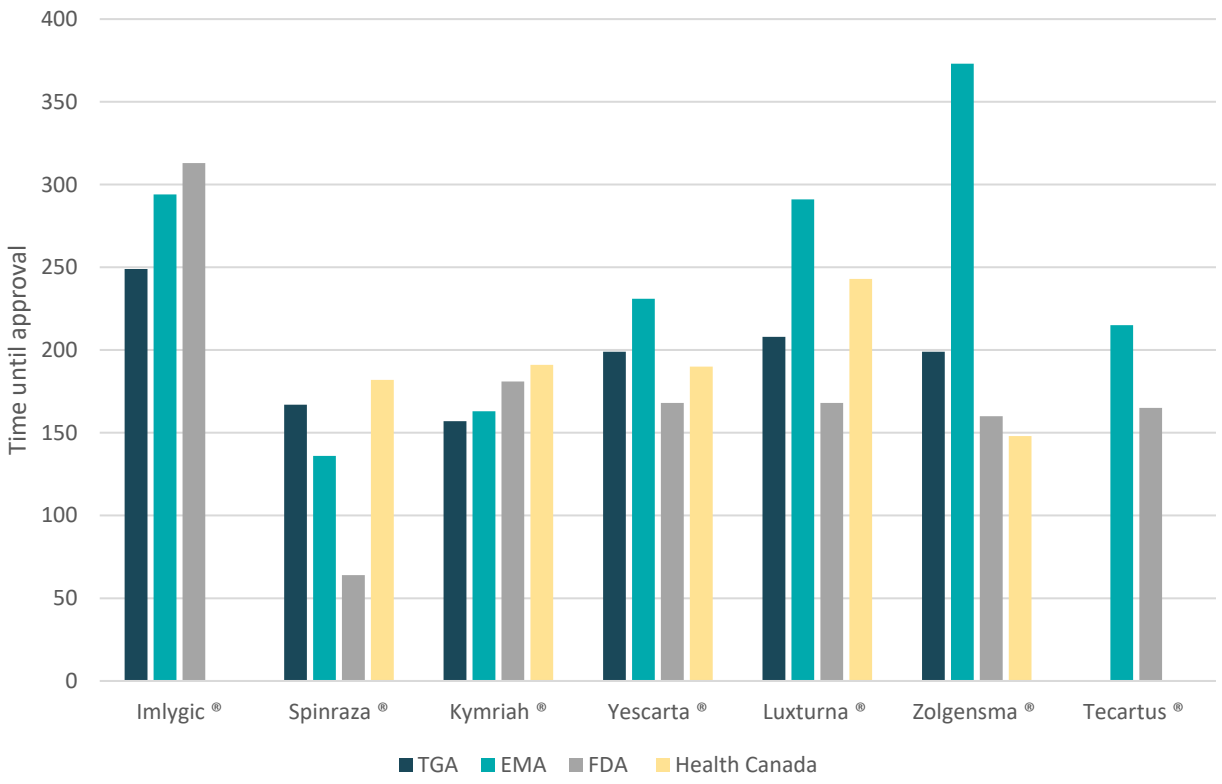
REGULATORY BODY	ADVANCED THERAPIES DEFINITION/SCOPE	TIME FOR REGULATORY PROCESS	SOURCE
TGA	Gene therapy that involves ex vivo manipulation (e.g., CAR-T cells) of genetic material are classified as biologicals and managed by Biological Sciences Section (BSS). Gene therapies that involve *in vivo* manipulation of genetic material (e.g., LUXTURNA) are classified as biological medicines and regulated through Prescription Medicines Authorisation Branch (PMAB). Cells and Tissues are regulated through the biological science section.	Standard medicines pathway: 255 days Priority Pathway: 150 days COR A: 120 days COB B: 175 days Biological application: 255 days	(TGA, 2021a, 2021b)
FDA	The Center for Biologics Evaluation and Research regulates cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy. Gene therapy is defined as that which seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. This includes all products that mediate their effect by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Gene therapies must meet the definition of a biological. Cellular Therapies include cellular immunotherapies, cancer vaccines, autologous and allogenic cells. Cell and tissue products that are more than minimally manipulated or for non homologous use or have a systemic effect or a metabolic activity are regulated as a biologic. Note: Articles containing human cells and tissues and cellular and tissue based products that are used for implantation, transplantation, infusion or transfer into a human recipient are regulated separately. Combination products are assessed by a committee and regulated by whichever pathway is deemed most appropriate.	Standard pathway: 10 months Priority review: 6 months Other pathways • Regenerative medicine Advanced Therapy • accelerated pathway • fast track • breakthrough therapy	(FDA, 2021a, 2021b, 2021c)

REGULATORY BODY	ADVANCED THERAPIES DEFINITION/SCOPE	TIME FOR REGULATORY PROCESS	SOURCE
EMA	The EU classify Advanced Therapies into 4 groups 1. Gene therapy 2. Somatic cell therapies (SCT) 3. Tissue engineered therapies (TEP) 4. Combination advanced products Both somatic cell therapies and tissue engineered products must fulfil the following criteria i) have been subject to substantial manipulation ii) are not intended to be used for the same essential function. However, for SCT the product is administered to human beings with the view to treat, prevent, or diagnose a disease through pharmacological, immunological or metabolic actions of its cells, where as in TEP the product regenerates, repairs or replaces human tissue.	Standard pathway: 210 days Accelerated pathway: 150 days	(EMA, 2021)
Health Canada	While Health Canada has no legislated definition of these products, all gene and cell therapies are classified as Drugs under the *Food and Drugs Act*. While whole allogeneic structural tissues that have not been more than minimally manipulated and are for homologous use are typically classified as devices at the level of the Act and regulated under the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*. Tissue engineered products are generally regulated as drugs by the Biologic and Radiopharmaceutical Drugs Directorate in the Health Products and Foods Branch of Health Canada. Drugs that are unable to be appropriately regulated by our existing frameworks may be eligible to be added to our schedule of Advanced Therapeutic Products (ATP) (e.g., products manufactured at the point-of-care, adaptive artificial intelligence/ machine learning, etc). This enables Health Canada to authorize ATPs in a flexible and risk-based manner - where 'regulatory sandboxes' can be created using tailored requirements for a product/class of products.	Standard pathway: 300 days Priority review: 180 days	(Health Canada, 2021a, 2021b)
Singapore Health Sciences Authority	In Singapore, cell, tissue or gene therapy (CTGTP) products are health products intended for use in humans for a therapeutic, preventive, palliative or diagnostic purpose. They can contain either • Viable or non-viable human cells or tissues • Viable animal cells or tissues • Recombinant nucleic acids	Full evaluation 270 working days	(Singapore Health Sciences Authority, 2021)

REGULATORY BODY	ADVANCED THERAPIES DEFINITION/SCOPE	TIME FOR REGULATORY PROCESS	SOURCE
	They achieve their intended action by pharmacological, immunological, physiological, metabolic or physical means. CTGTP do not include recombinant vaccines; in-vitro diagnostic products; bone marrow, peripheral blood, umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use; cells and tissues obtained from a patient that are minimally manipulated and reimplanted for homologous use into the same patient during the same surgical procedure; organs and tissues that are minimally manipulated and intended for transplant; reproductive cells (sperm, eggs) and embryos for assisted reproduction; whole blood.		
Japan Pharmaceuticals and Medical Devices Agency	In Japan, the PMDA ACT was revised to include regenerative medical products. These are defined as processed (more than minimal manipulation) live human/animal cells that are intended to be used either for the reconstruction, repair or formation of structures or functions of the human body OR for the treatment and prevention of human diseases for gene therapy .	Standard: 14 months Priority: 10 months Sakigake: 6 months	(PMDA, 2021)

Comparison of time from registration to regulatory approval across different countries for some Advanced Therapies is shown below.

Comparison of time from registration until approval across different countries for Advanced Therapies approved in Australia (Note: missing information for international CORs not shown).



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