Australia: The Regulatory and Reimbursement Environment

Third in a Three-Part Series

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This article is the third in a three-part series that aims to provide sponsors with information about Australia as a highly attractive option for drug research and development. Australia offers a mature infrastructure and experienced, capable local resources, especially important given global geopolitical uncertainties. Here, we examine the clinical trial start-up processes, regulatory pathway, market access, pricing system, and pricing control, with particular emphasis on cell and gene therapy with a case study to illustrate.

Compared to the approval process in other countries, Australia has a streamlined and transparent regulatory setup that allows for rapid approval timelines. In the U.S., on the other hand, the sponsor must submit an IND to FDA and sometimes hold a pre-IND meeting with the agency in order to conduct clinical trials. The FDA review timeline from IND submission to activation is typically 30 days. In Australia, regulatory approval timelines average five to ten days for most interventional trials via the Clinical Trial Notification (CTN) scheme.

Overview of Clinical Trial Start-up Process in Australia

All clinical trials conducted in Australia are required to have a "local" sponsor. The sponsor of the trial must be a legal Australian entity such as an appointed CRO. An overseas company, person, or entity, for the purpose of the Australian legislation, cannot legally be the sponsor of the trial in Australia. The sponsor takes responsibility for the initiation, management, and/or financing of a clinical trial, and for regulatory submissions and safety reporting to the Australian Therapeutic Goods Administration (TGA).

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A series of steps and procedures must be undertaken before a clinical trial can be initiated in Australia (Figure 1).

Documents required for trial start-up:

- Local sponsor confirmation
- Protocol
- Global/ trial ICF
- IB (and SmPC/PIS for marketed products)
- If Phase I, pre-clinical data including GLP toxicology, integrity of investigational product, stability, Certificate of Analysis (indicative of actual)
- Site budget
- Insurance/indemnification
- Patient-facing materials (Note that draft laboratory and pharmacy manuals are requested at HREC submission and are integral for budget negotiation.)

The Australian TGA provides two approval channels for clinical trials: Clinical Trial Notification (CTN) and Clinical Trial Application (CTA).

CTN: CTN is a process involving notification of the TGA regarding unapproved therapeutics. The CTN channel is generally used for clinical trials of chemical drugs and biological products considered low to medium risk. (For example, these products pose a low risk to public health, have appropriate means of oversight, have been subjected to only minimal manipulation, and are for homologous use.) The advantage of the CTN channel lies in its speed of approval. After approval by the Human Research Ethics Committee (HREC), the TGA is notified of the clinical trial at sites via the online CTN process scheme. The timeline from initial submission to TGA acknowledgement is five to ten days. The

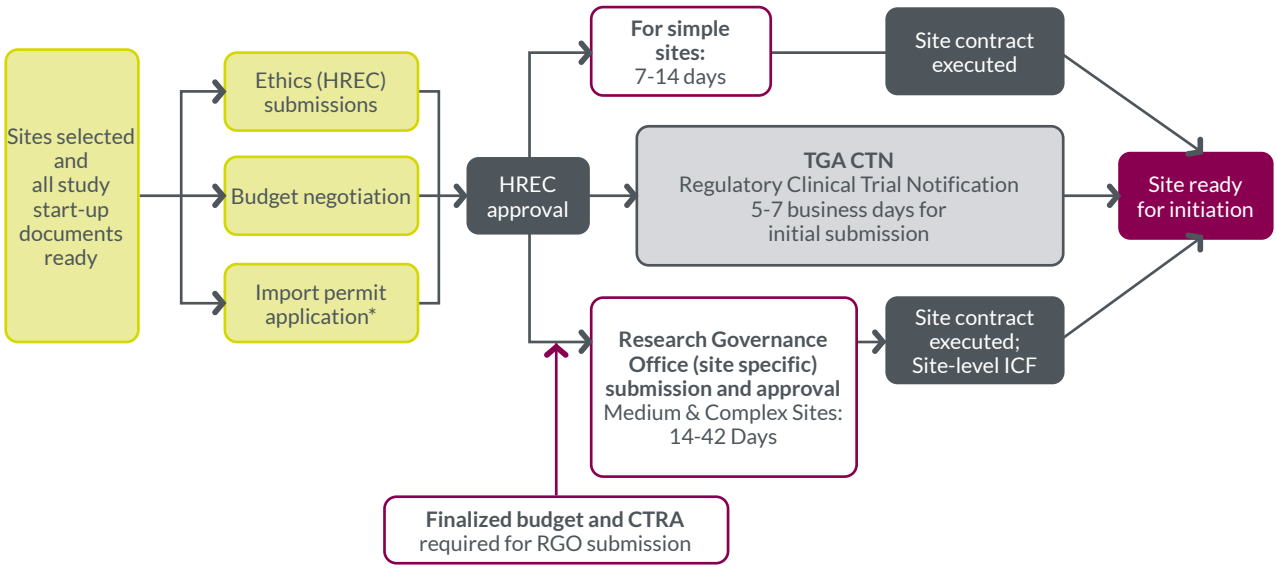

Figure 1: General Timeline for CTN-based Trial Start-Up

TGA is not required to perform full regulatory review of protocols, only review of a seven-page CTN form submitted by the local sponsor. No dossier, protocol, IB, or other trial-related documents are required to be submitted. However, these core documents are needed for the local sponsor to be able to complete the CTN form.

CTA: The CTA route is generally designed for high-risk or novel treatments where there is no or limited knowledge of safety. If the drug is classified by the TGA as a Class 4 biological (e.g., cell therapies such as CAR-T and iPSCs), the clinical trial needs to be reviewed through the CTA channel. In short, the CTA needs to be approved by two parties, namely, the Ethics Committee from an ethical perspective, and the TGA from a scientific/regulatory perspective. The approval timeline of the CTA is relatively long, generally several months. However, if the sponsor has conducted clinical trials for its "Class 4 biological" product and has complete data, or the product has been approved by another regulatory authority of similar level as TGA in the same indication, the product can go through the CTN channel for clinical trial authorization in Australia.

Each clinical trial is subject to the review and approval of the relevant HREC. Typically, the HREC review cycle takes only four to six weeks, based on the submission of protocols, the investigator's brochure, patient-facing materials, and independent toxicology reports (if required).*

Note that at the site level, approval is required from the Research Governance Office (RGO), which does contribute to some variability in the overall timeline.

For studies involving Genetically Modified Organisms (GMO), independent review by an Institutional Biosafety Committee (IBC) and licensed by the Office of Gene Technology Regulatory (OGTR) is required. The IBC approval process is independent from clinical trial regulatory approval and can run in parallel. An application for a GMO license for a clinical trial can be submitted to the OGTR in parallel with applications to the HREC (and RGO) and the TGA. However, each site has a specific process, and some may require site IBC approval before HREC approval will be granted.

Under the 1989 Therapeutic Goods Act and associated regulations, ICH-GCP standards are mandatory for all Australian clinical trials. Many Australian researchers have international experience and are familiar with GCP and other guidelines. Data from Australian clinical trials are recognized and accepted by other regulatory authorities, including FDA, EMA, and NMPA.

For First in Human (FIH) studies, sponsors need to start up their studies quickly to establish optimum doses. At Parexel, we use our network of sites for early engagement on the feasibility of the compound and protocol design in Australia. As an example, we initiated a first site within two months of HREC submission for a complex oncology FIH study, with the first patient enrolled within three months. This

* Australia has developed the single ethical review approach for multi-center research, the National Mutual Acceptance (NMA), a national system for mutual acceptance of scientific and ethical review of multi-center clinical trials undertaken in publicly funded health services. The NMA aims to enable the acceptance of a single ethical and scientific review of human research projects in participating jurisdictions.

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was a combination study protocol involving dose escalation in a 3+3 design, followed by dose expansion. The key success factors were close collaboration between the sponsor/site and Parexel, using standardized clinical trial agreements.

In many cases, the Phase 2 part of dose expansion studies needs to expand into additional countries. Parexel has successfully been able to offer best-suited countries for the expansion phase for multiple projects to ensure that the sponsor is able to meet recruitment targets.

Market Access and Pricing

After collecting data from pivotal clinical trials conducted in or outside Australia to support entry into the Australian market, pharmaceutical companies must go through the TGA regulatory approval process. As shown in Figure 2, the standard pathway typically takes about one year from dossier submission to drug listing on the Australian Register of Therapeutic Goods (ARTG).

It is important to note that the process timeline can be shortened by up to three months under the Priority Review pathway if a drug is indicated for serious and life-threatening conditions. Cell and Gene Therapy (CGT) products are good candidates for this pathway. Figure 3 shows the regulatory pathway for CGT products in Australia, which differs by administration method. Ex vivo CGT will be treated as a Class 4 Biological while in vivo CGT will be handled as a Prescription Medicine. Based on the three historical TGA-approved CGT products, the average evaluation time is ~180 working days (~9 months), or ~75 working days (~3 months) shorter, compared to a standard application. That said, CGT products do require additional approval from the Office of the Gene Technology Regulator before being allowed on the market.

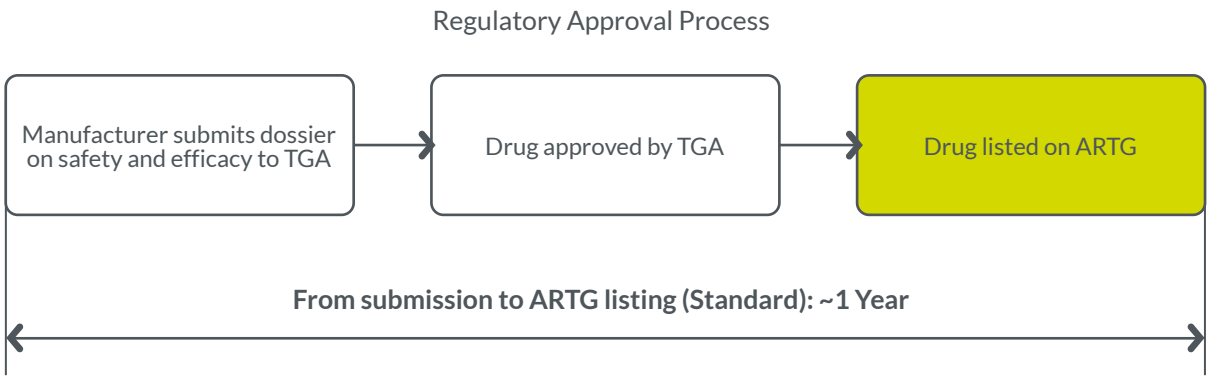


Figure 2: Overview of Regulatory Approval Process

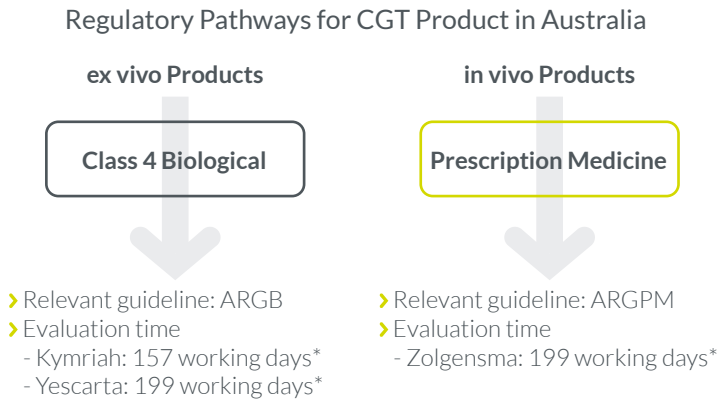


Figure 3: Regulatory Pathway for CGT Product in Australia. Ex vivo product: Genetic modification of patient cells happens outside the body before being transferred back into the body. In vivo product: Gene product is directly transferred into cells in a patient's body. Number of working days is from submission dossier acceptance to registration decision. Statutory timeframe for standard application is 255 working days.*

After the listing on ARTG, pharmaceutical companies can apply for inclusion in the Pharmaceutical Benefits Scheme (PBS), where the Australian government provides subsidies for most prescription drugs to reduce patients' out-of-pocket spending. The PBS schedule lists all medicines available to be dispensed to patients at a government-subsidized price. The schedule is part of the wider Pharmaceutical Benefits Scheme managed by the Department of Health and Aged Care and is administered by Services Australia.

The Pharmaceutical Benefits Advisory Committee (PBAC) and the Medical Services Advisory Committee (MSAC) are the two major health technology advisory committees assessing whether medicines qualify for Australian government subsidies. The following section outlines the key steps in the PBAC health technology assessment (HTA) process, as illustrated in Figure 4, and a high-level overview of pricing and reimbursement systems in Australia.

PBAC HTA Process – from Dossier Submission to PBS Inclusion

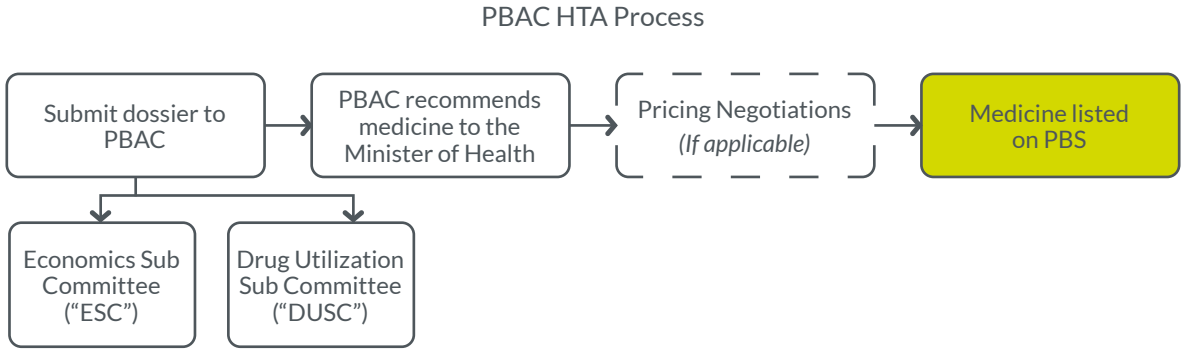


Figure 4: Overall PBAC HTA Process Timeline

Figure 5 illustrates the general timeline for the PBAC HTA process. It is important to note that PBAC meets three times per year in March, July, and November[1]. As a conservative estimate, the process will take at least six months, contingent on the requirement of pricing negotiations.

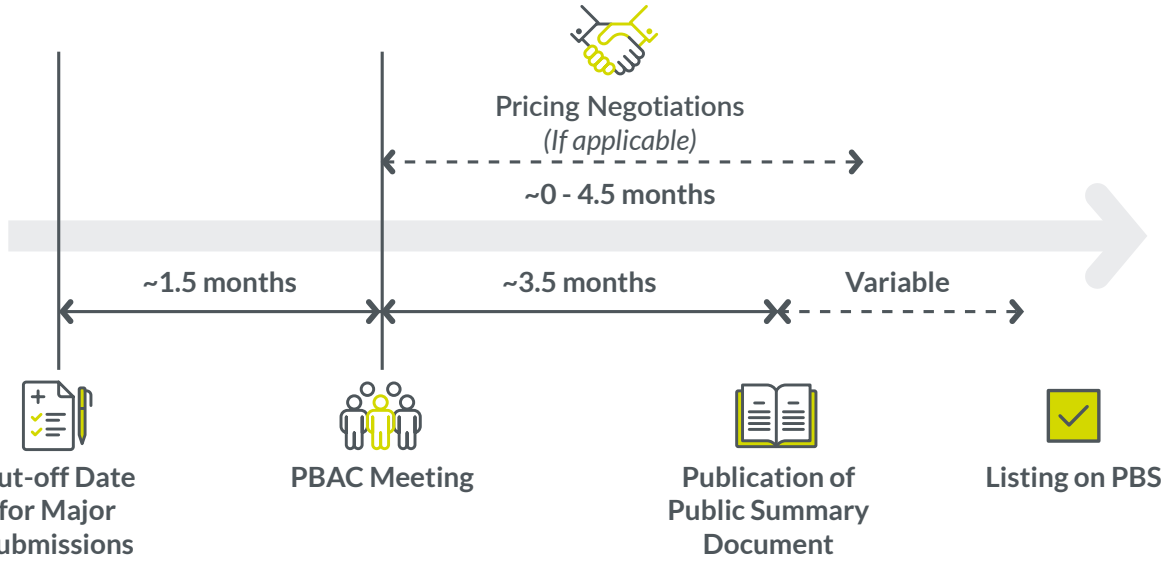


Figure 5: General Timeline for PBAC HTA Process. Note: All submissions related to a new medicine are categorized as a major submission.

Upon dossier submission, the Economics Sub Committee (ESC) and the Drug Utilization Sub Committee (DUSC) under PBAC will review the dossier. ESC reviews the economic submission, whereas DUSC collects and analyzes data on anticipated drug utilization.

Recommendation and Pricing Negotiations

In deciding whether to recommend a medicine to the Department of Health, PBAC considers the quantitative and qualitative factors listed in Table 1.

Table 1: Major Quantitative and Qualitative Factors considered by PBAC

Quantitative Factors	Qualitative Factors
› Comparative health gain › Comparative cost-effectiveness › Patient affordability in the absence of PBS inclusion › Financial implications for PBS and the Australian government health budget	› Disease severity › Effectiveness of alternative treatments › Ability to target the ideal patient population › Public health concerns › Equity concerns

Figure 6 illustrates how PBAC evaluates the cost-effectiveness of a new medicine depending on the existence of treatment alternatives.

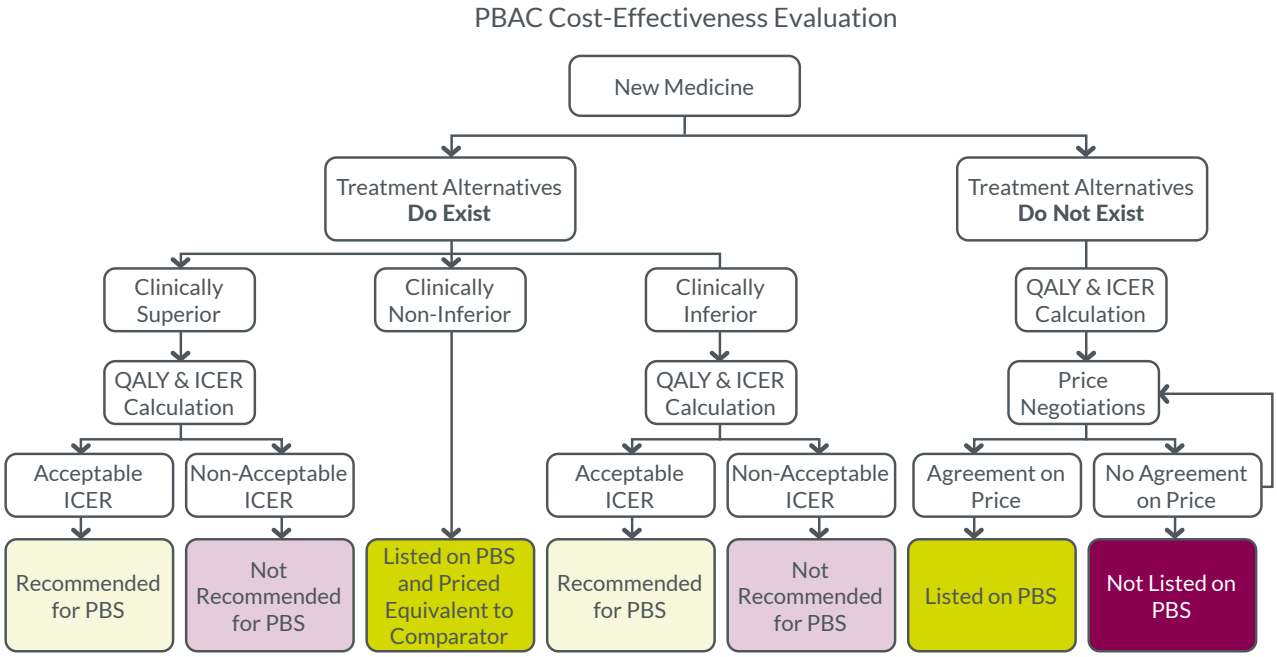


Figure 6: PBAC Cost-Effectiveness Evaluation Process. Note: Treatment alternatives can include surgery, ongoing care, or "doing nothing". QALY = quality-adjusted life years. ICER = incremental cost effectiveness ratio. ICER is calculated by Change in Cost / Change in QALY.

For a new medicine in the context of existing treatment alternatives, PBAC evaluates its cost-effectiveness relative to standard of care to determine a recommendation for the PBS listing. For a new medicine when there are no treatment alternatives, the Department of Health will enter pricing negotiations with the drug sponsor, and often tries to price products based on the methods listed in Table 2.

Table 2: Overview of Pricing Methods

Method	Description	Applicable Products
Cost-Plus	Calculated as cost of manufacturing plus a markup (typically ~30%)	Stand-alone products where there is no comparator
Reference Pricing	Benchmark price set by the lowest priced brand or medicine	Products with similar (non-inferior) safety and efficacy
Weighted Pricing	A single "weighted" price determined based on anticipated indication-specific usage of the medicine	Products with multiple indications
Combination Product Pricing	Calculated based on the sum of the prices of the individual components at the time of listing	Products with multiple active ingredients or components
Risk-sharing Agreement	Drug sponsor agreeing to rebate some part of the drug price	New and high-cost products with no comparators

PBS Inclusion

Medicines are listed on one of the two PBS formularies or can be covered by the Life Saving Drugs Program (LSDP), National Immunization Program (NIP), or Highly Specialized Drugs (HSD) Program. Innovative therapies where no alternatives exist are often listed on Formulary 1 (F1).

Table 3: Overview of Pricing / Reimbursement Schemes. PBS Formulary 1 and Formulary 2[2].
1 USD = 1.6 AUD

	PBS	
	Formulary 1 (F1)	Formulary 2 (F2)
Eligibility	No alternatives exist in class	Other generic/biosimilar or similar classes of therapies exist
Pricing Mechanism	Based on economic impact (ICER), often with risk-sharing and/or rebates to government	Priced referenced to existing therapy if not therapeutically superior
Copayment Amount	› Patient copayment up to - ~US$4 if patient has a concession card (low income) - ~US$27 for most PBS medicines › Some medicines may also require a premium, which is the difference between what PBS will reimburse and what the manufacturer is willing to sell (usually only when generic available). › A "safety net" exists as a cap on the total amount a patient can pay out-of-pocket - ~US$208 if patient has a concession card - ~US$980 for all other patients	

Table 4: Overview of Pricing / Reimbursement Schemes. LSDP, NIP, and HSD Program
Note: Rare condition is defined as one case per 50,000 people in the Australian population.
SMA = spinal muscular atrophy.

	LSDP	NIP	HSD Program
Eligibility	› Transformational high-cost therapies for life-threatening and rare conditions › Currently 16 products[3] for 10 rare conditions	› All vaccine products › Positive PBAC recommendation	› Medicines for the treatment of chronic conditions which, due to their clinical use, have restrictions on where they can be supplied › Notable example: Zolgensma for SMA
Pricing Mechanism	Independent agreement between government and product sponsors	Independent agreement between government and vaccine sponsors	Independent agreement between government and product sponsors
Copayment Amount	› Fully subsidized with no patient cost-sharing › Physicians must apply for patient access	No patient cost-sharing	PBS patient copayment (listed in Table 6)

Pricing Control

Like other APAC markets such as Japan, there are drug-pricing control mechanisms. The Australian government has instituted multiple compulsory price-reduction schemes to limit increases in pharmaceutical spending. Tables 6 and 7 outline the different pricing and reimbursement schemes under PBS.

Table 5: Drug Pricing Control Mechanisms

Automatic Periodic Price Reductions	› Regular price reductions at certain intervals after initial listing for therapies listed on the F1 formulary - Year 5: 5% price decrease - Year 10: 10% price decrease - Year 15: 5% price decrease
Price Reduction on a Drug Product after Listing of its Generic/Biosimilar	› Statutory 25% price reduction of a drug product upon the listing of its first bioequivalent or biosimilar
F2 Transparency Price Reductions	› Sponsors provide periodic data to the government to show discounts and other benefits (e.g., copay assistance) they provide to patients in association with supply of the medicine. › From this, the government determines the weighted average "effective price" and reduces the F2 listed price to meet the "effective price" over time.

Case Study: Market Access of CGT Product in Australia

Currently launched CGT products often target rare diseases with small patient populations. They are expensive and present reimbursement challenges. Nonetheless, CGT products are fully or largely reimbursed in Australia and can potentially go through an expedited regulatory pathway. In addition to its favorable market access, Australia has manufacturing capabilities and structured governance of product delivery, as well as regulatory filing requirements harmonized to EMA guidelines. Therefore, Australia is often considered an attractive market by CGT developers. As illustrated in Figure 7, TGA's approval of CGT products follows FDA's nod by 20 months, on average, and Australia is often the first APAC country in granting approval, sometimes before Japan.

Approval Sequence of Notable CGT Products in APAC

As of Dec 2021

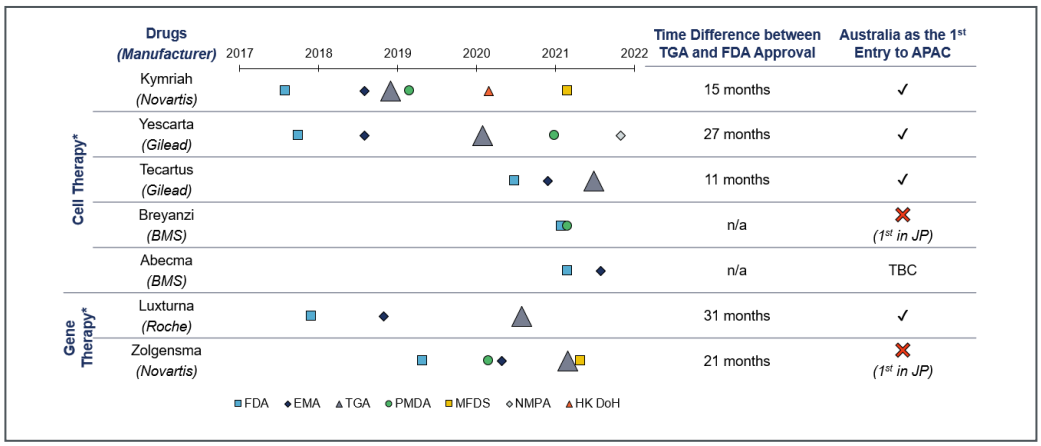
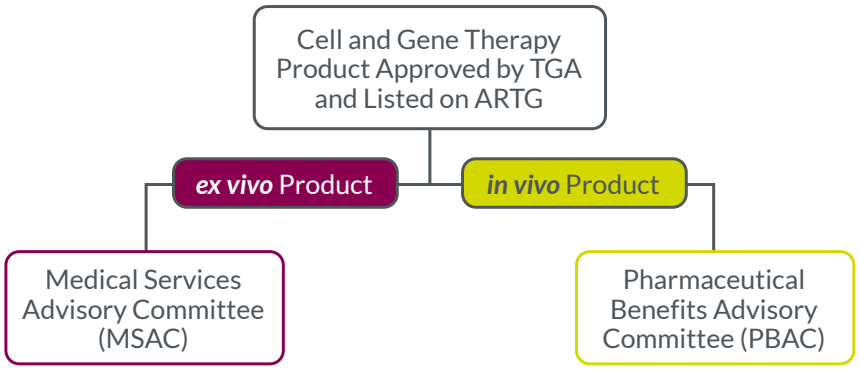


Figure 7: Approval Sequence of Notable CGT Products in APAC

Figure 8 outlines the HTA pathways for CGT products, which depend on the method of administration. Ex vivo CGT products, e.g., Kymriah (CAR-T), are assessed by MSAC, whereas in vivo CGT products, e.g., Zolgensma (gene therapy) are assessed by PBAC.

HTA Pathway for Cell and Gene Therapy Product in Australia



- Broader remit and less constrained by legislation
- Funding pathway include Federal schemes, e.g., Medicare Benefits Schedule, National Blood Authority or nationally coordinated funding allocated to State and Territory hospitals

- Funding pathway relatively well-defined
  - Listed on the Pharmaceutical Benefits Scheme (PBS) for Federal reimbursement

Figure 8: HTA Pathway for Cell and Gene Therapy Products in Australia[4]

Table 6 outlines the case of Kymriah, the first FDA-approved CAR-T cell therapy product introduced in the Australia, Japan, and Korea markets. In Australia, eligible leukemia and lymphoma patients are fully reimbursed; approximately 255 patients are covered.

Table 6: CGT Product Kymriah (CAR-T) Pricing and Reimbursement in Key APAC Markets

	Australia	Japan	Korea
Price to U.S. List Price	MSAC published a public summary document about its recommendation and considerations. Note that the negotiated price is redacted[5]	~70%	~70%
Insurance Coverage	**Fully covered**	Mostly covered	90-95% covered
Estimated Patients Covered	**~255 patients**	~216 patients	~180 patients
Remarks	› April 2019: ALL patients are fully reimbursed › Jan 2020: DLBCL, TFL. and PMBCL patients are fully reimbursed	› May 2019: Coverage approved at ~U.S. $305,800 › Effective from July 2021: 4.3% price cut by Chuikyo › Categorized as an H3 medicine, deemed eligible for CEA-based price cuts	› Oct. 2021: Novartis in negotiation stage with HIRA › Apr 2022: Coverage approved at ~US$296,000 › Performance-based risk-sharing agreement: DLBCL patients without treatment effect will receive additional refund

U.S. List Price: $424,000 (average of $373,000 for ALL and $475,000 for DLBCL). In Japan, Insured working-age patients typically have a co-pay of 30% on medical bills. There is also a cap on expensive treatments and the co-pays, which are loosely based on income. For example, a patient with an annual income of JPY5 million will only need to pay about JPY400,000 for Kymriah.
ALL = acute lymphoblastic leukemia, CEA = cost-effectiveness assessment, DLBCL = diffuse large B-cell lymphoma, HIRA = Health Insurance and Review Assessment, PMBCL = primary mediastinal B-cell lymphoma, TFL = transformed follicular lymphoma.

This concludes our three-part series about Australia's environment for drug development. With its global presence, extensive knowledge of the APAC market, and highly experienced Australia-based team, Parexel is ready to support your initiatives with our comprehensive services.

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About Parexel: At the Heart of Getting Medicines to Those Who Need Them

Parexel is among the world's largest clinical research organizations (CROs), providing the full range of Phase I to IV clinical development services to help life-saving treatments reach patients faster. Leveraging the breadth of our clinical, regulatory, and therapeutic expertise, our team of more than 20,000 global professionals work in partnership with biopharmaceutical leaders, emerging innovators, and sites to design and deliver clinical trials with patients in mind, increasing access and participation to make clinical research a care option for anyone, anywhere.

In the past five years, our team in Australia has supported more than 300 clinical trial notification (CTN) submissions and nearly 400 clinical projects, offering expertise in regulatory consulting, clinical operations, and market access. These include more than 100 projects in oncology, as well as hematology, dermatology, rheumatology, neurology, and more.

Our depth of industry knowledge and strong track record gained over the past 40 years is moving the industry forward and advancing clinical research in healthcare's most complex areas, while our innovation ecosystem offers the best solutions to make every phase of the clinical trial process more efficient. With the people, insight, and focus on operational excellence. We work *With Heart*™ every day to treat patients with dignity and continuously learn from their experiences, so every trial makes a difference.

Parexel worldwide project experience
Region - Australia all projects - past 5 years (as of 13-Apr-2023)

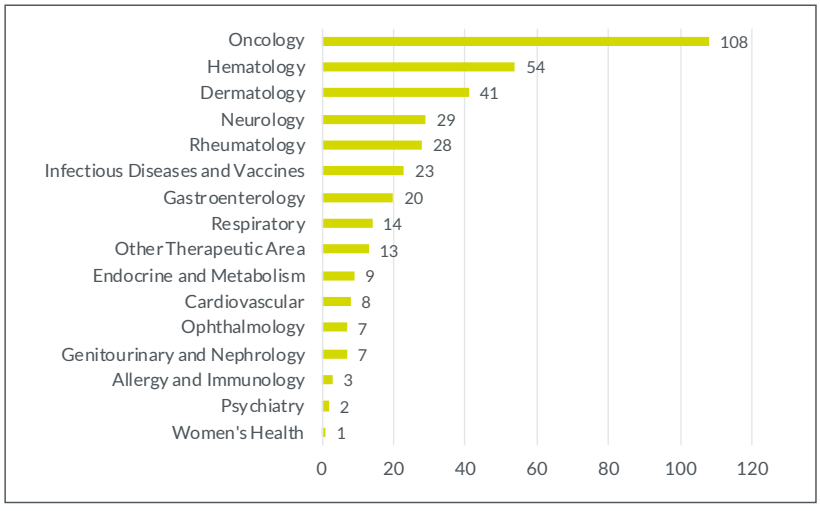

Figure 9: Parexel Project Experience in Australia in the Past 5 Years

1 Australian Government, Department of Health and Aged Care, The Pharmaceutical Benefits Scheme.
2 Australian Government, Department of Health and Aged Care, The Pharmaceutical Benefits Scheme.
3 Australian Government, Department of Health and Aged Care, About the Life Saving Drugs Program.
4 Health Advances analysis, Evohealth 2021, p 14-15
5. Source:MSAC

About the Authors

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Natasha is the regional head for Southeast Asia, Pacific, Africa, Australia, and New Zealand, responsible for oversight of clinical deliverables in these regions. She also oversees general administration and legal requirements in Australia and Vietnam. Natasha has more than 20 years of experience in the pharmaceutical field and has spent most of her career at Parexel, covering roles in clinical research, project leadership, and line management. She earned a BSc in Human Physiology and Psychology from the University of Pretoria, South Africa.

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As regional network manager for the APAC region, Stella plays a key role in delivery of Parexel trials, focusing on site selection – the cornerstone of more predictable recruitment. She has extensive experience in building working relationships with institutions, investigators, and research teams for better data organization that improves efficiency, knowledge sharing, and ultimately brings life-changing treatments to patients. With over 15 years of experience in clinical research at Parexel, Stella has held various roles including clinical research associate (CRA), clinical operations leader, project leader, and CRA line management. Stella holds a BS in Medical Science from Macquarie University in Sydney.