Australian Government

Department of Health

Approval processes for new drugs and novel medical technologies

Submission from the Department of Health to the
House of Representatives Standing Committee
on Health, Aged Care and Sport

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Introduction

The Department of Health welcomes the opportunity to make a submission to the *House of Representatives Standing Committee on Health, Aged Care and Sport Inquiry* into the approval processes for new drugs and novel medical technologies in Australia, with a particular focus on those for the treatment of rare diseases and conditions where there is high and unmet clinical need.

This submission addresses the Inquiry's terms of reference in respect of the Department's various roles and responsibilities for medicines and medical technologies.

Therapeutic goods, including medicines and medical devices, are regulated by the Therapeutic Goods Administration (TGA), which is part of the Department. The TGA is responsible for ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose. Therapeutic goods must generally be entered on the Australian Register of Therapeutic Goods (ARTG) prior to import, export, supply or advertising, unless an exemption applies.

Medicines regulation

The TGA is responsible for evaluating, assessing and monitoring products that are defined as therapeutic goods. Therapeutic goods generally fall under three main categories:

- **Medicines** - including prescription, over-the-counter and complementary medicines, such as paracetamol and echinacea
- **Biologicals** - something made from or containing human cells or tissues, such as human stem cells or skin
- **Medical devices** - including instruments, implants and appliances, such as pacemakers and sterile bandages

The TGA also regulates 'other Therapeutic Goods', which include items such as tampons and disinfectants.

Therapeutic goods are broadly defined in Section 3 of the *Therapeutic Goods Act 1989* as products for use in humans in connection with:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury
- influencing, inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling or preventing conception
- testing for pregnancy.

This includes things that are used as an ingredient or component in the manufacture of therapeutic goods and/or to replace or modify parts of the anatomy.

Australia has a two-tiered system for the regulation of medicines, including complementary medicines. Higher risk medicines must be registered on the Australian Register of Therapeutic Goods (ARTG), which involves individually evaluating the quality, safety and effectiveness of the product. Registered medicines are assessed by the TGA for quality, safety and efficacy. All prescription medicines, most over-the-counter medicines and some complementary medicines are

registered. Lower risk medicines containing pre-approved, low-risk ingredients and that make limited claims can be listed on the ARTG.

Despite an increase in volume (from 349 in 2018-19 to 373 in 2019-20), there have been substantial improvements in the assessment times for Category 1 applications (new prescription medicine or major variation to an existing medicine e.g. extensions of indication and new routes of administration). Over the last financial year, the median assessment time has fallen from 182 working days to 162.

During the 2019/20 financial year the TGA:

- approved 29 medicines with an orphan drug designation and six medicines with a priority review approval for registration, with a median approval time of 133 working days
- approved 10 medicines given provisional determination for registration, with a median approval time of 135 working days
- approved two medicines for registration after undergoing Comparable Overseas Regulator (COR)-A review with a median approval time of 109 working days and approved eight medicines for registration after undergoing Comparable Overseas Regulator (COR)-B review with a median approval time of 161 working days
- reviewed four medicines collaboratively through work-sharing arrangements with the Australia-Canada-Singapore-Switzerland Consortium and four medicines collaboratively through the US Food and Drug Administration's Project Orbis.

Medicines Health Technology Assessment

The Department's Technology Assessment and Access Division (TAAD) is responsible for two program areas that are directly relevant to the Inquiry's Terms of Reference: the Pharmaceutical Benefits Scheme (PBS) and the Life Saving Drugs Program (LSDP).

The PBS provides Australians with reliable, timely and affordable access to a wide range of medicines. As of June 2020, there were 902 different types of medicines listed on the PBS. In 2019-20, the total PBS expense for the supply of medicines was $12.6 billion. The PBS operates under the Government's National Medicines Policy, in achieving the objective of 'timely access to the medicines that Australians need, at a cost individuals and the community can afford'. Legislation governing the PBS, including the functions and role of the Pharmaceutical Benefits Advisory Committee (PBAC) is prescribed under the *National Health Act 1953*.

From October 2013 to October 2020, 2,481 new or amended items (including those items where Budget funding is already provided and price changes) have been listed on the PBS. The Government has committed to listing all medicines that are recommended by the PBAC.

The LSDP is separate to the PBS and provides approximately 400 patients fully subsidised access to expensive and life-saving medicines for rare and life-threatening medical conditions. Medicines on the LSDP are available to eligible patients at no cost and for as long as clinically necessary. This program cost $133.6 million in 2018-19. There are currently sixteen medicines on the LSDP for the treatment of 10 conditions.

On 8 May 2018, the Department and Medicines Australia entered into a Compact[1] to facilitate and promote cooperation between the parties in respect to ensuring the future sustainability of the LSDP. The agreement is underpinned by the shared principles of:

- Stewardship of the Australian health system and a responsibility for its ongoing sustainability
- Patient access to clinically effective medicines for chronic progressive rare diseases
- Improved value of medicines available on the LSDP that enable ongoing sustainability of the program
- Stability and certainty for the investment in medicines for rare diseases, including recognition of the role that transparent and streamlined processes play in encouraging investment
- Transparency and efficiency of processes for listing medicines on the LSDP and for subsequent reviews of medicines

The Department in collaboration with the Rare Diseases Industry Working Group and Rare Voices Australia developed guidance to ensure transparency and associated timelines for consideration of medicines seeking funding through the LSDP. This guidance further delivers on the commitment to assist sponsors in preparing an application to make a rare disease medicine available on the LSDP; ensuring access to treatment for people with rare diseases is not unnecessarily delayed.

The Department also supports the two independent Committees and one Expert Panel that are integral to the Health Technology Assessment (HTA) approval processes for new medicines and novel medical technologies in Australia. These are PBAC, Life Saving Drugs Program Expert Panel and the Medical Services Advisory Committee.

Australia's regulatory and HTA processes continue to deliver good outcomes for Australians because they are subject to continuing review and improvement. Recent improvements to HTA processes include:

- greater collaboration across HTA committees and the Department to align regulatory and reimbursement processes;
- improved mechanisms for consumer involvement and engagement in HTA;
- a Strategic Agreement with Medicines Australia that has streamlined medicines listing processes and reduced the time to listing by an average of 3.5 months;
- the development of a Health Products Portal to reduce duplication and red tape through a digital solution for applicants engaging with both regulatory and reimbursement processes;
- the 2020-25 National Health Reform Agreement which provides specific arrangements to ensure Australians with some of the rarest conditions have access to new, life-saving highly-specialised therapies in public hospitals.
- the use of Managed Access Programs to provide early access to clinically important medicines; and

[1] Agreement between the Australian Government and Medicines Australia (MA). Ensuring the future sustainability of the Life Saving Drugs Program (LSDP). Accessed from: www1.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/$File/LSDP-compact-with-Medicines-Australia.pdf

- post-market reviews to inform optimal and sustainable use of listed medicines.

Australia's HTA systems have the capability, flexibility and expertise to assess new technologies and therapies. The current approach avoids fragmentation and minimises the need to create bespoke assessment and funding streams by disease type or technology type, supporting faster and fairer access and improved health outcomes for all Australians.

Medical technologies

Many medical technologies are regulated for safety, quality and efficacy as medical devices, however there are some technologies which fall outside the scope of the therapeutic goods framework, such as household and personal aids for people with disabilities. Medical devices generally have a physical or mechanical effect on the body or are used to measure or monitor functions of the body, have therapeutic benefits and are used for humans. This also includes *in vitro* diagnostic medical devices (IVDs).

There has been an increase in applications received by TGA for inclusion of medical devices in the ARTG, with a 10 percent increase from 2015-16 to 2019-20 in applications requiring assessment (excluding Class I medical devices). TGA received 3,085 applications for inclusion of medical devices on the ARTG in 2019-20, and a further 3,992 Class I applications were received in 2019-20 (that this figure was significantly inflated by COVID-19, for devices such as personal protective equipment). As at 10 September 2020, there are more than 61,000 ARTG entries for medical devices (including IVDs).

Applications to include a medical device on the ARTG usually rely on evidence of conformity from a comparable overseas regulator. However, the TGA also undertakes conformity assessment certification, which is the detailed evaluation of the manufacturer's quality management system and, for high-risk devices also a design examination. Any manufacturer wishing to supply in Australia can seek TGA conformity assessment certification, and for some high risk medical devices[2] TGA conformity assessment certification is required (even where already approved overseas). There has also been a 20% increase in applications received for conformity assessment certification from 257 applications received in 2015-16 to 308 in 2019-20.

Gene Technology Scheme

Some emerging medical technologies involve the administration of genetically modified organisms (GMOs) into patients. GMOs may also be used to synthesise new medicines or as a diagnostic tool. In Australia, activities with live and viable GMOs are regulated under the National Gene Technology Scheme, which is comprised of the *Gene Technology Act 2000* and corresponding state and territory legislation. The object of this Act is to protect the health and safety of people, and to protect the environment, by identifying risks posed by, or as a result of, gene technology, and by managing those risks through regulating 'dealings' (activities) with GMOs.

[2] The *Therapeutic Goods (Medical Devices) Regulations 2002* Regulation 4.1 requires TGA conformity assessment certification for medical devices containing medicines, materials of animal, microbial or recombinant origin, human blood or plasma derivatives, or Class 4 IVDs.

The Gene Technology Regulator is a statutory office holder who is supported in the performance of their functions by Department of Health staff within the Office of the Gene Technology Regulator (OGTR). Dealings with GMO therapeutics that are regulated under the Gene Technology Act include:

- developing the GMO
- manufacture of the GMO
- use of the GMO in the course of manufacture of a thing that is not the GMO (e.g. making insulin with a GMO)
- conduct experiments with the GMO (e.g. administering a GMO into a human in a clinical trial)
- import, transport and dispose of the GMO
- and the possession, supply, or use of the GMO in the course of these dealings.

The OGTR also monitors post-market activities with GMO therapeutics. Authorisations for commercial supply of GMOs include ongoing reporting and documentation requirements for licence holders.

While TGA and OGTR both regulate the manufacture of a GMO therapeutic, TGA focuses on making sure the manufactured GMO complies with quality standards and assesses the efficacy and clinical safety of the GMP. In contrast, OGTR is concerned about the containment of the GMO within a manufacturing facility, to avoid the release of the GMO into the environment, as well as the safety of workers in the facility.

Term of Reference 1 - The range of new drugs and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies

Horizon scanning

In recent years, there has been an emergence of medicinal products based on genes, tissues or cells. Much of the current expansion in medical device technology is being driven by a range of broader technological developments, such as bioinformatics, artificial intelligence/machine learning, and emerging manufacturing technologies such as 3D printing. New areas of medical technology supported by these develops include genomics, personalised medicine including companion diagnostics, software as medical devices, and personalised medical devices.

These emerging technologies are providing promising new treatment options, including potential for patient-centric and preventative medical interventions. They potentially offer significant benefits for patients but also pose novel regulatory challenges and risks. This results in the need for new regulatory approaches to ensure the ongoing safety, quality and efficacy of these technologies. Horizon scanning to determine the therapies that are likely to be submitted for regulatory review in the short to medium term is important, so that the Department (through both the Therapeutic Goods Administration and the Health Resourcing Group) has the right capability and capacity to either review, or commission for review, products based on new technologies.

New medical technologies are also resulting in a range of new research organisations and companies entering the medicines and medical devices market place. This is changing the role of the regulator, as increasing support is needed for new entrants to the pharma and medical technology market to understand and comply with the regulatory obligations designed to ensure the safety, quality and performance of these products.

The Department regularly meets with researchers and industry sponsors to obtain information about developing therapies and their product pipelines. At these meetings, sponsors provide information on the stages of development of new medicines and novel technologies in Australia (and in the case of multinational companies, globally) as well as likely time for an application for registration. At these meetings, TGA also provides advice as to the regulatory requirements and pathways available under the existing regulatory framework.

Sponsors of new drugs and novel technologies are strongly encouraged to participate in formal pre-submission meetings with the TGA relating to their products prior to lodgement of an application. These scientific meetings increase the likelihood that a well-prepared application will be submitted for evaluation. Guidance for applicants requesting or preparing for pre-submission meetings is available on the TGA website. The OGTR website also has guidance for applicants on how to apply for authorisation for clinical trials involving GMO therapeutics.

TGA understands that knowing more about the pipeline of applications coming to it, the time for pre-submission preparation and potential TGA review time will help expedite the approval process where possible. This has been particularly useful in the current environment with the COVID-19 pandemic.

There has been a surge in biological medicine applications over the past 5-10 years, with the majority of New Chemical Entities (NCE) now biological medicines (such as engineered monoclonal

antibodies). Examples include rituximab and obinutuzumab for chronic lymphocytic leukaemia, daratumumab for multiple myeloma and trastuzumab for breast cancer.

Another contributor to the surge in biological medicine applications are those involving GMO therapeutics. GMO therapeutics are regulated by both TGA and the Gene Technology Regulator.

Research activities involving development of potential GMO therapeutics conducted in Australia are regulated by the Gene Technology Regulator during the pre-clinical phases. The OGTR maintains communication with applicants who are active in the field of GMO therapeutics, in order to learn about applications before they are submitted to the OGTR.

GMO therapeutics, CAR-T cells, Faecal microbiota transplant (FMT) and other advanced therapies

GMO therapeutics are biological medicines that are derived from living genetically modified organisms. There are multiple novel GMO therapeutics being developed, including:

- **Gene therapies** - use a GM virus to introduce a gene into patients to replace a non-functional or missing gene. Examples currently being trialled in Australia include introducing clotting factors into patients with haemophilia.
- **GMO vaccines** - are live, attenuated viruses that produce antigens to stimulate an immune response and prevent infection. Examples in the pipeline include certain vaccines for COVID-19 and dual vaccines for both Zika and Chikungunya.
- **GMO antimicrobial treatments -** Cocktails of live GM bacteriophage that are specific for multi drug resistant pathogenic bacteria can be used to treat bacterial infections in patients when antibiotics have failed.
- **GMO diagnostics** – Still in the research stage, GMOs could be potentially be used as diagnostic tools to detect disease.
- **GMO oncolytic viruses and immunotherapy -** GMO oncolytic viruses are designed to selectively replicate in and destroy cancer cells. They can be further modified to act as an immunotherapy by producing proteins that stimulate the immune system to target and destroy cancer cells. Examples include GM Herpes Simplex Viruses expressing human interleukin-12 to treat solid tumours.
- **CAR-T cells -** CAR-T cells are human T-cells (a type of immune cell) that have been genetically modified to target cancer cells. In order to create CAR-T cells, T-cells are harvested and purified from a patient's blood. The T-cells are then genetically modified using a GM virus to create T-cells that express CAR proteins on the surface of the cells (CAR-T cells). CAR proteins allow the cells to recognise and target tumours. The GM virus is removed from the CAR-T cells, and the cells are then put back into the patient to treat cancer. Examples of CAR-T cell therapies include Kymriah® and Yescarta®.

Use of gene technology enables the development of GMO therapeutics that are personalised medicines. CAR-T cells are considered personalised medicines, as they are created from cells extracted from an individual patient, modified and then administered back into the same patient to achieve a very specific outcome.

The field of GMO therapeutics is striving more than ever to define a path to the clinic and the market with over two thousand human clinical trials involving GMO therapeutics reported worldwide. The increasing number of GMO therapeutics being developed and substantial commitment from pharmaceutical companies to build manufacturing infrastructure for these

products makes it likely that regulators and funders will face an exponential increase in applications. Indeed the US FDA anticipates that by 2025 they will be approving 10-20 cell and gene therapy products per year, and it is likely that Australia will receive a similar number of applications annually by the mid-2020s.

The first two CAR-T cell therapies (Kymriah® and Yescarta® for certain lymphomas and leukaemias) have been approved by the TGA. Treatment of patients with CAR-T cell therapies does not require licensing by the GT Regulator.

There is a strong pipeline of other types of GMO therapeutics in clinical development. Gene therapies (Luxturna® for inherited retinal dystrophy), live GMO vaccines (FluMist® quadrivalent vaccine for Influenza, Dengvaxia® for Dengue and IMOJEV® for Japanese encephalitis) and oncolytic immunotherapies (Imlygic® for melanoma) have been approved by both the TGA and the OGTR. The OGTR has issued a licence authorising import, transport, disposal and supply of the gene therapy Zolgensma® for spinal muscular atrophy.

Gene therapies can be more expensive to manufacture than conventional treatments due to the cost of vector production and the often personalised nature of these therapies As automation and scale up capacity increases, and the possibility of using cells from donor banks (allogenic therapies) the costs may drop.

National Health Reform Agreement (NHRA)

The 2020-25 National Health Reform Agreement (NHRA) Addendum commenced on 1 July 2020. It sets out the financial and governance arrangements for Australia's public hospital system for the next five years, including funding for medicines and other therapies for patients treated in public hospitals. It commits all Australian governments to work in partnership to improve health outcomes for Australians and ensure the sustainability of the Australian health system.

This includes a shared commitment by all Australian governments to long-term system-wide health reforms to improve health outcomes for all Australians, and create a more efficient and sustainable health system. The Nationally Cohesive Health Technology Assessment reform will support improved and timely patient access to health technologies that add value, are financially viable, and improve population health.

The 2020-25 NHRA Addendum provides specific arrangements to ensure Australians with some of the rarest conditions have access to new, life-saving highly-specialised therapies in public hospitals. These funding arrangements (50 percent Australian Government, 50 percent state and territory governments) apply to high cost therapies recommended by the MSAC to be used in Australia and delivered in a public hospital. State and territory governments, as system managers of public hospitals, will determine if, when and where these treatments are delivered. All governments have agreed to greater transparency and improved consultation processes so all jurisdictions can be engaged and informed in technology assessment processes.

The Australian Government, together with the states and territories, jointly fund access to CAR-T cell therapy for patients with relapsed or refractory acute lymphoblastic leukaemia and diffuse large B-cell lymphoma, through the NHRA. This has included all governments working together to ensure a small number of advanced hospital units are equipped to deliver access to CAR-T cell therapy, as it is a highly specialised treatment that can only be delivered in hospitals that have the right expertise and infrastructure.

Improving patient access to CAR-T cell therapies has been further enabled through the Government's provision of $80 million to establish a Centre for Excellence in Cellular Immunotherapy at the Peter MacCallum Cancer Centre. This investment will enable end-to-end treatment delivery at the Centre – with the ability to manufacture cell therapies locally, and the presence of a dedicated clinical unit to support cell therapy treatment delivery. This investment has seen Australia become one of the few countries in the world that will manufacture CAR-T cell therapies, and will support Australian research in this area of revolutionary cancer treatment approaches for certain types of cancer. Securing access and funding for Kymriah® has meant that around 30 Australian children and young adults with ALL, and between 200 and 250 additional adult cancer patients with DLBCL are expected to benefit from access to this treatment each year.

National Blood Agreement

The emergence of new and innovative treatments is rapidly evolving in the area of blood related diseases. The use of blood products in Australia is managed cooperatively through the National Blood Authority (NBA) and includes extensive assessment processes for new products. Internationally, there are many clinical trials underway which are relevant to the national blood arrangements.

The primary objectives under the National Blood Agreement (NBA) are to provide an adequate, safe, secure, and affordable supply of blood products, blood related products and blood related services and promote safe, high quality management and use of blood products, blood related products and blood related services in Australia. All governments must approve the supply and funding of products under Schedule 4 of the National Blood Agreement, with 63 per cent of the funding provided by the Australian Government and the remaining 37 per cent provided by state and territory governments. The funding covers both the national blood supply and the operations of the NBA.

State and territory governments work within the frameworks established under this agreement, even when new, high cost therapies emerge, as they may have different risks. An example is emicizumab (Hemlibra®), a recombinant, humanised, bispecific monoclonal antibody that mimics the function of factor VIII. Emicizumab is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and paediatric patients with haemophilia A with or without factor VIII inhibitors. The MSAC supported funding of emicizumab via the NBA based on acceptable clinical effectiveness and safety compared with Factor VIII for haemophilia A patients with FVIII inhibitors, and patients with moderate or severe haemophilia A without FVIII inhibitors. All governments have agreed to supply the product under the national blood arrangements. This example illustrates that both Commonwealth and state and territories governments must work co-operatively to ensure our processes adapt and respond as more and more synthetic products and gene therapies become available.

International and domestic regulator networks

The TGA plays a lead role in a global network of regulators who meet regularly through a number of standing and ad hoc fora to discuss new and emerging therapies, regulatory challenges and the harmonisation of international approaches. This also ensures that we can develop our staff to ensure they have both the capability and capacity to assess these new therapies. For example, the TGA is the current chair of the Scientific Advisory Council of the Centre for Innovation for Regulatory Science, a global non-profit alliance of academia, regulators and HTA bodies and industry that meets several times a year to consider new technologies. In addition medical and scientific staff

attend major international meeting e.g. on the rapidly advancing field of oncology and haematology drug development either in person or virtually, and are part of global networks e.g. such as those established by the US FDA that meet monthly by teleconference to discuss new technologies in paediatric medicine.

These approaches have enabled the TGA to keep actively informed and engaged in relevant technological developments. Increased interactions with MTPConnect, Cooperative Research Centres and a number of universities has occurred as regulatory requirements are seen as a pivotal component to design, development and manufacturing preparedness.

Following a recent internal review, in recognition of the increasing prominence of novel cell and tissue and biological medicine therapies, a new advanced therapeutic evaluation unit led by a senior medical officer has been introduced to manage these regulatory applications and build regulatory capability. The TGA has also established an internal working group looking at advancements in gene therapies and seeking to address the challenges Australia may face in regulating these products and developing the skills of departmental evaluators.

Earlier guidance for industry on regulatory submissions

Therapeutic goods legislation was recently changed through the Therapeutic Goods Amendment (2020 Measures No. 1) Bill 2020 (given Royal Assent on 25 Jun 2020) to allow the TGA to provide formal cost-recovered scientific advice on higher risk medicines prior to the submission of an application for registration. Initially, this service will provide advice on the suitability of a sponsor's biowaiver justifications for generic prescription medicines, but it will subsequently be expanded to other application types such as New Chemical Entities (NCEs) and Extensions of Indication. This provides a customised service for complex applications to increase the quality and speed of applications and their subsequent evaluation.

For medical devices, pre-submission meetings are also available to potential applicants. Since May 2019, the TGA has conducted or provided specialist advice to 18 medical device manufacturers and applicants who requested pre-submission meetings on a range of products. Products include surgical mesh, orthopaedic systems, trans-catheter heart valves and more recently COVID-19 test kits and ventilators. Where applicants are making parallel submissions for reimbursement under the Prostheses List, there is provision for pre-submission meetings to be conducted jointly to facilitate the parallel assessments.

Through SME Assist, an initiative launched by the Minister for Health in June 2017, the TGA also helps small to medium enterprises (SMEs), researchers, start-ups and those unfamiliar with regulation to understand their regulatory and legislative obligations. In addition to a range of on-line resources, this has included face to face and webinar workshops. Fourteen workshops have been conducted around the country since August 2017, with more than 1,000 participants.

Prospective applicants for GMO therapeutics are strongly encouraged to contact the OGTR to discuss what type of authorisations they might require and data requirements for applications. There are currently no fees associated with these services, noting that OGTR is funded through a government appropriation.

Determining a HTA Pathway

The Department also works with applicants through the PBAC and MSAC pre-submission processes to provide advice on the most appropriate HTA pathway for consideration for public funding. This

advice is informed by the available information on the appropriate clinical setting for a patient to access the therapy.

The pre-submission meetings are intended to support applicants in the development of their submissions; provide applicants with experienced departmental advice on understanding the PBAC or MSAC guidelines and relevant previous recommendations; and supporting identification of any other system issues that may arise during the PBAC's or MSAC's consideration of the submission.

Medical devices technological capacity

In 2020, TGA established a dedicated Devices Emerging Technology and Diagnostics team to address medical device emerging technologies. Work in this area includes development and implementation of new regulatory frameworks, guidance to industry and supporting regulatory review of products on software as a medical device, cybersecurity, personalised (including 3D printed medical devices), companion diagnostics and IVDs for self-testing.

The creation of the dedicated team anticipates significant increase in the number and variety of medical devices involving emerging technologies entering the market in coming years:

- Companion diagnostics: A companion diagnostic is an *in vitro* diagnostic, which provides information that is essential for the safe and effective use of a corresponding medicine or biological. This technology is being driven by the emergence of personalised medicines and biologicals. Regulatory changes and new regulatory guidance for companion diagnostics came into effect in Australia in February 2020;
- Personalised medical devices: This term describes medical devices that are designed and/or manufactured to suit an individual. From 25 February 2021 a new framework for the regulation of these kinds of devices will commence, ensuring appropriate regulation and oversight; and
- Software as medical devices: While certain software has long been regulated as medical devices (for example software used as part of medical devices such as MRI machines), software is becoming increasingly important, and is also emerging as a medical device in its own right (such as various medical 'apps').

In other areas, the development of many medical device technologies is iterative, with novel breakthrough technologies the exception. The practical limits on clinical trials for medical devices compared with medicines (lower numbers of participants, inability to blind / double blind many technologies) for some emerging technologies can lead to caution in their deployment, especially invasive or implantable medical devices. Examples in recent years include heart valves such as transcatheter aortic valve implants and glucose sensors that can control the amount of insulin delivered to diabetics. Some of these are now publicly funded through hospitals, the private health insurance Prostheses List or the National Diabetes Services Scheme.

Term of Reference 2 - Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions

Regulatory incentives

The TGA does not initiate applications for new medicines or medical devices. An Australian sponsor must be willing to supply the medicine or medical device and, in the case of the latter, the manufacturer must seek conformity assessment certification (or its overseas equivalent). This can mean that consumers are seeking technologies not approved for the Australian market (such as smart watch medical functionality like ECG monitoring).

Orphan Drugs

The orphan drug program aims to incentivise sponsors to bring medicines for serious and rare conditions to market that would otherwise not be financially viable. The program offers a 100% waiver of TGA fees for application and registration to help offset orphan drug development costs. Similar arrangements operate with respect to reimbursement applications.

In July 2017, changes to the orphan drug program were implemented to create a fairer program that aligns more closely with international criteria without impeding the availability of drugs for rare diseases. In particular the new program provides a more generous orphan disease prevalence threshold (fewer than 5 in 10,000 individuals in Australia), potentially allowing a larger number of medicines to classify as orphan. However, following approval, the decision to supply the product remains at the discretion of the sponsor.

The eligibility criteria for orphan determination focus on the greatest unmet clinical need and include:

- the medicine is for the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition
- the condition affects fewer than 5 in 10,000 individuals in Australia
- it is not likely to be financially viable for the sponsor to market the medicine in Australia
- There are no other medicines to treat the condition marketed in Australia; or the medicine provides a significant benefit in relation to efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to existing marketed products.

The number of orphan drug registrations since 2017 are below:

	2017-18	2018-19	2019-20	2020-21 (to 30/9)
Number of orphan approvals	21	22	21	9

The orphan drugs approved in 2019/20 were:

- DIACOMIT (stiripentol) - generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy
- NPLATE (romiplostim) - thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura
- FIRAZYR (icatibant) - acute attacks of hereditary angioedema in patients with C1-esterase-inhibitor deficiency
- UVADEX (methoxsalen) - steroid-refractory and steroid-intolerant chronic graft versus host disease
- INCRELEX (mecasermin) - long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor 1 deficiency
- TECENTRIQ (atezolizumab) - non-small cell lung cancer and small cell lung cancer
- OXERVATE (cenegermin) - neurotrophic keratitis in adults
- IDHIFA (enasidenib) - adults with relapsed or refractory acute myeloid leukaemia who are ineligible for haematopoietic stem cell transplant, and have an isocitrate dehydrogenase-2 mutation
- ULTOMIRIS (ravulizumab) - treatment of adult patients with paroxysmal nocturnal haemoglobinuria
- VYNDAMAX (tafamidis) - transthyretin amyloid cardiomyopathy
- OFEV; VARGATEF (nintedanib esilate) - non-small cell lung cancer; idiopathic pulmonary fibrosis; systemic sclerosis-associated interstitial lung disease
- REVESTIVE (teduglutide) - short bowel syndrome
- VYNDAQEL (tafamidis meglumine) - transthyretin amyloid cardiomyopathy
- CABLIVI (caplacizumab) - acquired thrombotic thrombocytopenic purpura
- SARCLISA (isatuximab) - multiple myeloma
- QARZIBA (dinutuximab beta) - high-risk neuroblastoma
- XOSPATA (gilteritinib fumarate) - relapsed or refractory acute myeloid leukaemia with a FLT3 mutation
- VENCLEXTA (venetoclax) - acute myeloid leukaemia; chronic lymphocytic leukaemia
- SOLIRIS (eculizumab) - neuromyelitis optica spectrum disorder

Personalised Medicines

Personalised medicine has the potential to optimise health care targeted to the genetic and other characteristic of individual patients but is a complex area for regulators. In most cases, the personalised therapy is reliant on a companion diagnostic test and thus an integrated regulatory approach is crucial. The identification of subpopulations, e.g. of tumours with particular biomarkers, has led to the greater ability to personalise a medicine leading to more targeted and effective treatment.

Recent examples include:

- Rozlytrek (entrectinib) for treatment of advanced non-small cell lung cancer where tumours are ROS1-positive and solid tumours that have a neurotrophic tyrosine receptor kinase gene fusion without a known acquired resistance mutation.
- Other medicines approved that rely on a genetic diagnosis include cystic fibrosis transmembrane conductance regulator (CFTR) modulators (Orkambi, Symdeko, Kalydeco).

Use of autologous (the individual's own) cells and tissues can result in improved outcomes for patients, and reduced adverse events, complications, or difficulties that stem from rejection of foreign material. However, the shift towards the use of personalised therapeutics brings with it significant complexity and novel risks.

Research support

NHMRC Funding

The National Health and Medical Research Council (NHMRC) is the Australian Government's main health and medical research funding body. NHMRC supports excellence in research that meets the health needs of Australians, from basic science through to clinical, public health and health services research and research that reflects national, state and territory and community priorities. One of NHMRC's key objectives is to support the translation of health and medical research into better health outcomes. Details on schemes that may be particularly relevant for the Inquiry are outlined below.

NHMRC's Development Grants scheme supports the commercial development of a product, process, procedure or service that, if applied, would result in improved health care, disease prevention or provide health cost savings. Research supported by this scheme have, via a commercial business plan, detailed feasible strategies for commercialisation that take into account the regulatory pathway, protectable intellectual property, commercial barriers and potential routes to market. In 2019, NHMRC funded 14 Development Grants to a total value of approximately $14.5 m.

NHMRC also provides funding for clinical trials and/or cohort studies, irrespective of their scale and scope, through the Clinical Trials and Cohort Studies scheme. The intended outcomes of the scheme are improvements in health and well-being, health care practice or policy, as a result of high-quality:

- clinical trials that provide reliable evidence of the effects of health-related interventions on health outcomes (or appropriate surrogates)
- cohort studies that provide reliable evidence on the relation of important risk factors and other exposures to health-related outcomes
- retrospective cohort studies that provide reliable evidence on the relation of important risk factors and other exposures to health-related outcomes

In 2019, NHMRC funded 31 of these grants to a total value of approximately $75 m.

NHMRC's Ideas Grant scheme funds innovative and creative research in any area of health and medical science from discovery to implementation. This scheme focuses on funding research that aims to challenge and shift current paradigms and/or have a major impact on a health research area through one or more studies that creatively:

- develop or use novel research concepts, approaches, methodologies, technologies or interventions,
- propose a reinterpretation, refinement, improvement or new application of existing theoretical concepts, approaches, methodologies, technologies or interventions, or
- integrate and adapt concepts, approaches, methodologies, technologies or interventions from other research fields or disciplines for a new purpose or in a new way.

In 2019, NHMRC funded 293 Ideas Grants to a total value of approximately $240m.

Medical Research Future Fund (MRFF)

The Medical Research Future Fund (MRFF), established under the Medical Research Future Fund Act 2015, provides a long-term sustainable source of funding for Australian health and medical research that aims to improve health outcomes, quality of life and health system sustainability. The MRFF has now reached maturity at $20 billion.

The net interest from the fund is available to health and medical researchers across a range of 20 initiatives under four themes: patients, researchers, research missions and research translation. The Australian Government's $5 billion, 10-year investment plan for the MRFF, announced in the 2019-20 budget, outlines how health and medical research will be funded over the next decade. In total, the MRFF has expended and committed in contracts over $1 billion across all themes and initiatives.

The Global Health initiative will invest $28.4m over 10 years to fund projects on understanding global health threats, including tackling antimicrobial resistance and drug-resistant tuberculosis.

The Frontier Health and Medical Research initiative is a program that will provide $570m over 10 years to enable researcher collaborations to explore bold, innovative ideas and/or make discoveries of great potential and global impact, through research relevant to any area of healthcare. The intended outcome of research funded by Frontiers is to enable innovative research projects that have the potential to extend existing knowledge and transform health care in Australia and globally; stimulate the creation of new research and industries; deliver new health care methods that will impact on an area or areas of the health care continuum; accelerate new technological advances in health care; and promote multi-disciplinary partnerships and approaches that enable transformative research and innovation.

The Million Minds Mental Health Mission aims to support a million Australians with mental health issues access new approaches to prevention, diagnosis, treatment and recovery. The MRFF has allocated $125m over 10 years for this mission.

The Genomics Health Futures Mission has been allocated $500m from the MRFF over ten years and aims to improve the lives of Australians by accelerating research that delivers more effective testing, diagnosis and treatment; facilitates the adoption of new interventions; and consolidates Australia's international leadership in genomics. Through research, it will improve testing and diagnosis for many diseases, help personalise treatment options to better target and improve health outcomes, and reduce unnecessary interventions and associated health costs. There are other genomic research initiatives that are funded separately, including the $50m Australian Genomic Cancer Medicine Program, the $67m Zero Childhood Cancer Precision Medicine Program and the $11.7m ASPiRATION study (co-funded by the Australian Government and Roche Pharmaceuticals), which aims to investigate the clinical impact of delivering comprehensive tumour genomic profiling to guide therapeutic decision making.

The Indigenous Health Research Fund is investing in Indigenous-led research to tackle health issues facing Aboriginal and Torres Strait Islander people. It will provide $160 m over 10 years. The Stem Cell Therapies Mission will invest $150m as part of the 10-year plan, to develop innovative, safe and effective treatments and to translate stem cell innovations into commercial products. Recently $5.9m has been allocated to eight projects to find new innovative treatments for diseases. The Cardiovascular Health Mission will invest $220m over 10 years to make transformative improvements in heart and vascular health, and stroke for all Australians.

The Medical Research Commercialisation initiative aims to support early-stage health and medical research and innovation in Australia through to proof-of-concept and beyond, providing opportunities for commercialisation. It will provide $311m over 10 years. Two programs have been established under the Medical Research Commercialisation initiative to date – BioMedTech Horizons and Biomedical Translation Bridge. The Biomedical Translation Fund is a $500 m equity co-investment venture capital program to support the development of biomedical ventures in Australia. The BTF aims to help translate biomedical discoveries into high growth potential companies that are improving long term health benefits and national economic outcomes. It specifically targets the ‘second valley of death’ along the research pipeline - that area in drug, device and therapy development where research ideas can fail due to lack of funding.

Term of Reference 3 - Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies

Australia as a destination for clinical trials

The Australian Government is leading a body of work to improve the Australian clinical trials environment with a view to improving health outcomes and increasing international investment and the objective of being a preferred destination for clinical trials. This is being progressed in collaboration with all jurisdictions, building on International evidence that jurisdictional collaboration and congruence is critical to success in federated clinical trials systems.

MRFF Clinical Trials Activity initiative

Under the MRFF 10 Year Plan, $614m has been committed to the Clinical Trials Activity initiative. Programs funded under MRFF Clinical Trials Activity initiative include Rare Cancers, Rare Diseases and Unmet need (RCRDUN) and International Clinical Trial Collaborations (ICTC).

RCRDUN supports clinical trials research that investigate new drugs, devices or treatments for rare cancers/diseases or for areas of unmet medical need. Examples of funded grants include studies on larotrectinib (a new drug) for children with newly diagnosed high-grade glioma; treating mitochondrial dysfunction with a novel form of anaplerosis; and clinical trial combining azacitidine and defactinib for high-risk myelodysplastic syndrome patients who fail to respond to azacitidine alone.

In 2020-21, there will be two grant opportunities under the Clinical Trials Activity Initiative including $25m for ‘Rare Cancers, Rare Diseases and Unmet Need for COVID-19’ and $25m for ‘Rare Cancers, Rare Diseases and Unmet Need’.

MRFF Emerging Priorities and Consumer Driven Research Initiative

Under the MRFF 10 Year Plan, $633m has been committed to the ‘Emerging Priorities and Consumer Driven Research’ initiative to support high quality research that improves patient care, translation of new discoveries and encourages joint collaboration of consumers and researchers in undertaking research in emerging priority areas. By doing so, it will nurture the development of new treatments and cures, providing hope for many Australians with debilitating conditions. Examples of funded grants include four projects that will investigate how pharmacogenomics can be used to tailor mental health prescriptions to the needs of each individual and improve health outcomes, and a project that aims to find a cure for bone marrow failure syndromes.

Other relevant MRFF funding initiatives

The National Critical Research Infrastructure initiative provides funding for research infrastructure that will be used to conduct world-class health and medical research. Over $19m was awarded for five grants using applied artificial intelligence (AI) technologies, to improve the ways we prevent, diagnose and treat a wide range of health conditions.

$5 m over four years was awarded to the Australian Clinical Trials Alliance (ACTA) to be a national partner providing specialised leadership and support to both investigator-led and industry clinical trials, and to Clinical Quality Registries with the aim to promote a more effective clinical trials sector in Australia. As part of the Government’s Coronavirus Research Response, $95m from the MRFF has been invested in COVID-19 research including for diagnostics, vaccine development, antiviral

development, clinical trials, digital health research infrastructure, studies on the human immune response to COVID-19 infection, community information needs and behavioural responses during outbreaks.

Streamlined process for clinical trial notification to the TGA

Australia has a fast and pragmatic regulatory pathway for clinical trials. To enable the lawful supply of medicines not included in the Australian Register of Therapeutic Goods (ARTG) (known as 'unapproved' medicines) for the purposes of a clinical trial, the TGA operates the Clinical Trial Notification (CTN) and a Clinical Trial Exemption (CTX) schemes.

Clinical trials of unapproved medicines in Australia are conducted by a trial sponsor with oversight by a Human Research Ethics Committee (HREC). For the vast majority of trials that are notified through a CTN, the TGA does not (re-)evaluate the trial. Clinical trials that do not involve the use of 'unapproved' therapeutic goods (including placebos) are not subject to CTN or CTX requirements. However, all clinical trials require HREC approval before the clinical trial can commence.

The number of notifications for new clinical trials involving unapproved therapeutic goods received for the past few years include:

	2017-18	2018-19	2019-20
Number of new clinical trial notifications	920	1059	984

The CTX route is generally designed for high-risk or novel treatments where there is no or limited knowledge of safety. For medical device trials, the CTX scheme may be more appropriate where the experimental device introduces new technology, new material or a new treatment concept, which has not been evaluated previously in clinical trials in any country. The CTX scheme should also be considered for medical devices that pose a risk of serious patient harm.

In many cases, a HREC recommends that the CTX scheme is used and this will depend on whether the committee has access to appropriate scientific and technical expertise in order to assess the safety of the product. However, certain Class 4 biologicals must be submitted under the CTX scheme.

Clinical trials involving GMOs

Before a clinical trial involving GMOs can proceed, it must be appropriately authorised under both the *Gene Technology Act* and the *Therapeutic Goods Act 1989*. Each approval process is independent and typically occurs in parallel. As risks to trial participants are addressed through oversight by TGA and HRECs, the Gene Technology Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GMO therapeutic, and risks associated with import, transport and disposal of the GMO. Clinical trials with CAR-T cells are Exempt Dealings (no licensing required under the GT Act).

Commonwealth / State collaboration on clinical trials

In March 2017, all Commonwealth, state and territory Health Ministers agreed to a revitalised clinical trials agenda to further strengthen Australia's clinical trials sector, using stimulus from the

Commonwealth's $7m 'Encouraging more clinical trials in Australia' initiative aimed at supporting jurisdictions in redesigning clinical trial operations around coordination hubs. Activities are improving trial sponsor, participant and investigator navigation and trial start-up times and outcomes.

The pilot and finalisation of the National Clinical Trials Governance Framework is an important element of the clinical trials reform agenda to ensure nationally consistent accreditation of health services undertaking trials. In November 2019, all Health Ministers endorsed the Governance Framework and the national pilot commenced on 1 September 2020 following a COVID-19 suspension. Pilot outcomes will be evaluated in early-mid 2021.

Repurposing

Repurposing 'old' drugs to treat new conditions is a regulatory challenge. There are two possible circumstances: a) the medicine has broader regulatory approval in other countries than in Australia and the only limitation is an Australian sponsor's willingness to pursue an application to match the TGA approval with the overseas one by collating existing evidence; and b) the formal evidence to support a broadening of the registration needs to be generated.

There may be little incentive for a sponsor to generate the data required to support an application to register a new indication, and to pay regulatory fees for extension of indications to cover an additional indication. This is because some medicines are routinely used 'off-label' for other conditions, and have become part of the standard clinical paradigm without having formal regulatory approval. If the medicine is cheap, or used in in-patient situations there may not be sufficient incentive to seek TGA registration for the particular indication (and thus possible PBS reimbursement).

While TGA will accept literature-based submissions and observational studies, there still may be challenges in assembling 'regulatory quality' data to support an application to register a new indication. There may be an actual evidence gap. For generic medicines with several sponsors, a lack of a unique incentive for any one company to take the initiative may also be cited as a concern – if one company gets approval for an extension of an indication then if the product is already off patent, in many cases then other generic companies can apply for the same indication especially if the application is based on literature submissions.

Following requests from patient groups in 2014/15, the TGA met several times with medical professional groups and sponsors about three medicines for potential repurposing. These included:

- Ramipril (an ACE-inhibitor approved for the treatment of high blood pressure) - new research supported a new use for the medicine to address intermittent claudication in patients with peripheral artery disease
- Darcarbazine (chemotherapy for metastatic melanoma and various sarcomas) - the current indication that was not consistent with current standard of care for early stage Hodgkin Lymphoma.
- Tamoxifen (approved for the treatment of breast cancer) – there was solid evidence that it could also be used as a primary prevention in women at high risk of developing breast cancer and increasingly used 'off-label' for this.

The TGA worked with the original sponsor of tamoxifen (AstraZeneca), who developed a literature based submission to streamline the application process with a focus on safety and efficacy without

the requirement for quality or nonclinical information (as this was already established). In parallel with the TGA assessment of the regulatory submission for tamoxifen, the PBAC undertook an assessment of its suitability for subsidy under the PBS. Tamoxifen was PBS-subsidised for prevention of breast cancer from 1 October 2016.

While the TGA very actively pursued repurposing the two other products (ramipril and darcarbazine), no applications from these sponsors were put forward. The Australian Government is unable to compel a sponsor to make an application under the current provisions of the *Therapeutic Goods Act 1989*. It is possible for non-commercial entities, such as clinical colleges or patient organisations to become a sponsor of a product but they would need to take on the medico-legal responsibilities for product stewardship that sponsorship of a particular medicine involves.

The TGA has also contributed to the MTP Connect project on drug repurposing which was one of the areas of focus identified in MRFF research priorities. This work also includes drug re-purposing for COVID-19. A report is expected in 2020-21. The TGA actively encourages sponsors to discuss repurposing regulatory options. For older medicines which have many generics, the innovator sponsor may no longer supply the medicine in Australia. In these situations, the TGA can work with sponsors to develop a regulatory approach to extend indications.

TGA Cost recovery model

Where specific demand for a government activity is created by identifiable individuals or groups, Australian Government policy is that they should be charged for it unless the Government has decided to fund that activity. The Australian Government's overarching cost recovery policy promotes consistent, transparent and accountable charging for government activities and supports the proper use of public resources. The Cost Recovery Guidelines set out the overarching framework under which government entities design, implement and review cost recovered activities. In the 1997–98 Budget, it was stated that the TGA would fully recover all costs from industry from 1998–99.

As the TGA operates on a cost recovery basis, to enable pre- and post-market regulatory activity, there are a number of fees and charges for therapeutic goods. These include annual charges, application and evaluation fees, conformity assessment fees and inspection fees which are imposed on sponsors and manufacturers of medicines and medical devices. The *Therapeutic Goods Act 1989* provides a legal authority for the TGA to charge for its regulatory activities within the scope of the Act. The *Therapeutic Goods (Charges) Act 1989* provides a legal authority to levy annual charges (a type of tax) on sponsors and manufacturers of medicines and medical devices. Applicable fees and charges are prescribed in the subordinate regulations made under these Acts.

Each year the TGA is required to consult with industry representative bodies in relation to proposed changes to fees and charges and publish a Cost Recovery Implementation Statement (CRIS). The CRIS provides information on how the TGA implements cost recovery activities associated with the registration and listing of medicines and inclusion of medical devices, including IVD devices, and biologicals onto the ARTG and the ongoing monitoring and surveillance of them. After the consultation, proposed fees and charges are submitted to Government for endorsement, and if endorsed charging regulations are submitted to the Executive Council for approval.

Most years fees and charges are adjusted in line with the average of the Consumer Price Index and Wage Price Index, but where effort has been shown to be reduced, fees and or charges are reduced. For example, in 2020/21 in recognition of the impact of pauses in elective surgery due to the COVID-19 pandemic, annual charges for a large number of medium and high risk medical devices were

halved. In recent years, fees or charges have been decreased for export only medical devices, and fees for regulatory assessment for medical devices can be reduced for applicants where less work is required by TGA. For example, where conformity assessment is abridged due to use of information from overseas approvals, the TGA's evaluation fees are abridged by up to 85%. Applications to include multiple related medical devices in the ARTG, where submitted at the same time, may also save on audit fees if the application is supported by the same conformity assessment certification.

A number of other reductions have been made to the TGA fees and charges in the last five years. In 2015-16, annual charges were reduced by 23% for generic medicines and by 5% for other prescription medicines and medical devices Class IIa and above. Additionally, the fee for extensions of indications for generic medicines (to align with the parent drug) was reduced significantly to $5,155 (previously more than $130,000). In 2017-18, the fee for minor variations to registered medicines was more than halved where variation to the entry was made by notification. Additionally, annual charges for medical devices (other than Class I) were reduced by 6.5%.

While some funding is provided by the Government for meeting the cost of medicines and chemicals scheduling activity, and partial funding of orphan drug and special access schemes, and an interest equivalency payment against the special account reserves, approximately 94% of funding for TGA operation is generated through industry fees and charges set under cost recovery arrangements.

In conjunction with the Department of Finance, and supported by PWC, a review of all TGA fees and charges is currently underway, with results anticipated to be provided to government in early 2021. The purpose of the review is to provide Government with options for a sustainable funding model that enables TGA's regulatory and public health responsibilities. The review will include consultation with industry.

Funding of, and fees and charges of comparable overseas regulators

In late 2019 an external consultancy (by Noetic Pty Ltd) obtained information on the levels of government funding of major comparable regulators. A summary of the results is in the table below, noting that while the TGA exclusively regulates human therapeutic goods, whereas the European Medicines Agency (EMA) and Health Canada also regulate veterinary drugs and medical devices. The United States FDA undertakes regulatory activities for food and food products, human drugs and medical devices, and veterinary drugs and medical devices. The scope of the UK regulator MHRA is the same as TGA.

Regulator	Industry fees & charges	Government funding
Therapeutic Goods Administration (TGA)	>99%	<1%
European Medicines Agency (EMA)	90%	10%#
UK Medicines and Health products Regulatory Agency (MHRA)	87%	15%
Health Canada	43%	57%
United States Food and Drug Administration (FDA)	45%	55%

Data as of October 2019 - there has been a slight increase in government funding to the TGA since that time.

Note - this is an under-estimate as the initial evaluation of medicines in the EMA system is done by scientists and medical officers from EU member states, a function which is partly subsidised by member state government budgets.

TGA's fees and charges are also in general somewhat lower than those of comparable regulators (see below), even though the work to evaluate a submission is the same. The table below shows application/evaluation fees and annual charges for new prescription medicines.

Regulator	Application/Evaluation fee as of 30/9/20	Annual charge as of 30/9/20
Therapeutic Goods Administration (TGA)	AUD 249,300	AUD 3430 (chemical) AUD 7410 (biological)
European Medicines Agency (EMA)	AUD 490,000 (Eur 296,500)	AUD 175,000 (Eur 106,300)
Health Canada	AUD 428,000 (CAD 400,288)	AUD 1920 (CAD 1836)
United States Food and Drug Administration (FDA)	AUD 4.13 million (USD 2,942,965)	AUD 460,000 (USD 325,424)

Currency conversions as of 30/9/20.

Term of Reference 4 - Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment

National Medicines Policy

The National Medicines Policy provides an overarching strategy for the management of medicines and the pharmaceutical sector. The Department's regulatory and reimbursement assessment processes deliver on the principles outlined in the policy. These processes have demonstrated flexibility and the capacity to expedite the assessments of new technologies and therapies, and to secure agreements with sponsor companies to enable expanded access, especially in areas of high unmet clinical need.

The Department remains committed to continuous improvement of HTA processes with recent improvements including:

- greater collaboration across HTA committees and the Department to align regulatory and reimbursement processes
- improved mechanisms for consumer involvement and engagement in HTA
- a Strategic Agreement with Medicines Australia that has streamlined medicines listing processes
- the development of a Health Products Portal to reduce duplication and administrative burden
- the use of Managed Access Programs to provide early access to medicines.

In recognition of the changing medicines landscape over the past 20 years, the Minister for Health made an election commitment in 2019 to review the National Medicines Policy. The aim of the review is to identify any gaps in the policy's objectives, partnership approach and accountabilities. The Review will be inclusive of the community and supported by a consultation process that ensures the diversity of views are captured. Initial stakeholder meetings about the Review occurred in late January 2020, with the Review scheduled to commence in March 2020 over a six-month period. However further consultations were delayed due to the COVID-19 pandemic. The Department is currently considering revised timeframes for this review.

Benchmarking against comparable regulators and funding bodies

The TGA has a strong reputation as a medicines regulator internationally and benchmarks well against comparable overseas regulators. A 2019 study by the Centre for Innovation in Regulatory Science (CIRS) found that the TGA's assessment timeframes are comparable to six major regulatory agencies: the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada and Swissmedic.

The CIRS report showed that where 'parallel processing' of regulatory and reimbursement submissions is sought the delay between the two was a matter of weeks. Australia had the shortest

overall median time between regulatory approval and health technology assessment (HTA) recommendation, suggesting the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory recommendation is achieving its purpose. For example, the median time between regulatory approval and HTA recommendation for Australia was 24 days in 2015-19, followed by Germany with a median of 132 days.

The report highlighted Australia's proactive approach to streamlining processes for the PBS listing of medicines. It noted the benefits and significant utilisation of the parallel process pathway (parallel consideration of submissions by the TGA for registration and the PBAC for PBS listing) for the assessment of medicines. 65% of medicines were assessed through the parallel process pathway, with companies taking advantage of this mechanism in Australia to submit to PBAC approximately 4 months before TGA approval.

To illustrate, the parallel process pathway was successfully used to expedite the PBS listing of lorlatinib for the treatment of patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer, who have disease progression following treatment with a prior ALK inhibitor. The submission of lorlatinib was made under the TGA/PBAC parallel processing arrangements and enabled the respective registration and reimbursement evaluation and assessment process to be undertaken in parallel.

Despite an increase in volume in Category 1 submissions (from 349 in 2018-19 to 373 in 2019-20), there have been substantial improvements in the TGA's assessment times. Category 1 applications are those to register a new prescription medicine (other than an additional trade name) or to make a variation to an existing medicine that involves the evaluation of clinical, pre- clinical or bio-equivalence data (e.g. new chemical entities, extensions of indication and new routes of administration). In 2019-20 the median assessment time has fallen from 182 working days to 162. This is in part due to the implementation of new pathways recommended by the MMDR Review, including priority review and provisional registration, to support timely approval and early access to new prescription medicines.

The TGA is also a key player in international regulatory cooperation activities for prescription medicines, and since 2017 has worked to increase reliance on assessments of overseas regulatory agencies and partners. These changes provide greater incentive for product sponsors to coordinate global filing strategies.

However, the CIRS report found significant delays in companies bringing new medicines to Australia. In the CIRS study, 84% of the new medicine approvals surveyed in 2019 were approved by FDA, EMA, PMDA, Health Canada or Swissmedic before being approved by the TGA. The median 'submission gap' between the first regulatory submission to the US FDA and regulatory submission and approval by the TGA was 535 days.

Expedited pathways to provide earlier patient access to medicines

The release of the Australian Government Response to the Medicines and Medical Devices Regulation (MMDR) Review in September 2016, initiated a significant reform program to improve access to therapeutic goods and decrease regulatory burden whilst maintaining the safety of therapeutic goods in Australia.

The objective of the expedited pathways is to facilitate earlier availability of medicines that address unmet clinical needs for Australian patients, without compromising strict standards for safety, efficacy and quality.

The number of medicines approved via the introduction of the expedited pathways include:

	2017-18	2018-19	2019-20	2020-21 (to 30/9/20)
Number of provisional approvals	0	0	10	3
Number of priority approval	5	11	6	3

Priority review for medicines

The Department implemented the Priority Review pathway in July 2017. The eligibility criteria for priority determination are designed to ensure that only medicines providing the most benefit to patients are eligible. The criteria are:

- New prescription medicine or new indication
- Serious condition; and
- Comparison against registered therapeutic goods; and
- Major therapeutic advance.

The priority registration pathway provides consumers and health professionals with faster access to new medicines for serious and life-threatening conditions. The target timeframe of 150 working days to decision is up to three months shorter than the standard prescription medicines registration process. The priority review process provides greater alignment with comparable overseas regulators that offer expedited pathways for prescription medicines. In 2019-20 the median priority approval time was 133 working days.

Provisional registration of medicines

The Department implemented the provisional registration pathway for prescription medicines in March 2018. Approval through the provisional pathway is based on preliminary clinical data where there is the potential for a substantial benefit to Australian patients.

The provisional pathway provides access to certain promising new medicines where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional clinical data are still required. Eligible medicines could be registered up to two years earlier than under the standard prescription medicines registration process.

Provisional registration of prescription medicines is limited to two years but up to two extensions of two years each can be applied for, subject to evidence of progress being made in collection of further patient safety and efficacy data by the sponsor, resulting in provisional registration for a maximum of six years. In 2019-20, 10 medicines were provisionally registered by the TGA, with a median approval time of 135 working days.

This mechanism provides patients with privately funded access to an approved medicine earlier than under normal assessment processes and timeframes. However, this does not automatically mean subsidy through the PBS. A critical step is a determination by the PBAC on a price commensurate with the level of evidence of the clinical effectiveness, safety and cost-effectiveness of a medicine. This includes determining if a PBS Managed Access Program arrangement is appropriate to manage any uncertainty.

Managed Access Program

The Managed Access Program (MAP) (formerly the Managed Entry Scheme (MES)) Framework was developed in consultation with representatives of applicants for PBS listing, and came into effect in 2011 as part of the response to the trend for applications for new medicines in rare diseases based on relatively preliminary evidence. The Department is undertaking further consultation with the pharmaceutical industry in the context of the Strategic Agreement with Medicines Australia on this program.

The MAP enables the PBS listing of products, under special circumstances of high unmet clinical need, on terms that allow for the resolution of otherwise unacceptable clinical or economic uncertainty for the PBAC. A submission that would not normally be recommended for listing by the PBAC because of unacceptable clinical and/or economic uncertainty could be recommended under a MAP. The MAP mechanism means:

- earlier access to the medicines by patients;
- earlier access to a subsidised market for the sponsor whilst acknowledging that some form of confidential discount may be required in recognition that the initial evidence is less convincing;
- clear articulation of the evidence required to resolve the identified area of uncertainty and the consequences of potential outcomes from the additional evidence;
- agreement by the PBAC to review a submission once the additional evidence becomes available and to reconsider the listing in light of the new evidence; and
- appropriate sharing of risk.

Two examples of medicines where earlier patient access was made possible by use of a MAP/MES are lumacaftor with ivacaftor (Orkambi®) and crizotinib (Xalkori®).

Lumacaftor with ivacaftor is a treatment for cystic fibrosis that slows the rate of decline in lung function in patients with cystic fibrosis. However, clinical trial data was only available for up to 24 months of treatment, a short period in the context of a life-long condition. The PBAC recommended a MAP to allow access to subsidised treatment, whilst providing the sponsor the opportunity to demonstrate that the medicine's effects on lung function are sustained over a longer time period. As part of the MAP, the sponsor is required to make a further submission to the PBAC which will inform whether the price of lumacaftor with ivacaftor should remain the same or be reduced based on all of the available evidence[3].

Crizotinib is a treatment for advanced non-small cell lung cancer in patients who have a particular genetic mutation in their tumour. Crizotinib had a promising early indication that it improved survival over standard treatments by 12 months. The PBAC recommended a managed entry type of arrangement as a mechanism to address the uncertainty related to the magnitude of clinical benefit while providing early access to those patients for whom there is a high clinical need. The managed access program required the collection of further information on the benefits of crizotinib and linked the future subsidy price of the medicine to the outcome[4].

[3] www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-07/files/lumacaftor-with-ivacaftor-age-12-over-psd-july-2018.docx.pdf

[4] www.pbs.gov.a/industry/listing/elements/pbac-meetings/psd/2014-11/files/crizotinib-psd-11-2014.pdf

International regulatory reliance practices for medicines

There are many efficiencies able to be gained from the alignment of international regulatory frameworks as well as the use of assessments from comparable regulators (where available) in making regulatory decisions in Australia. Work sharing opportunities also reduce duplication of effort and improve approval timeframes for some products.

The TGA actively participates in three reliance pathways to make greater use of assessments from overseas regulators:

- The Comparable Overseas Regulator (COR) pathway makes use of overseas regulatory assessments in lieu of a full TGA evaluation report.
- Work-sharing through the Australia-Canada-Singapore-Switzerland Consortium (ACSS) involves divided or shared review of different parts the submission with a high level of interaction between regulators throughout the process.
- Participation in the US FDA's Project Orbis involves parallel and collaborative review of new oncology medicines.

However, under each of these pathways the TGA continues to make independent decisions about the registration of the medicine. Reliance does not represent a less robust form of regulation, rather it is a way to have a more efficient regulatory system.

Comparable Overseas Regulator Pathway for medicines

The COR report-based process was implemented in January 2018. Under the COR process, assessments from comparable overseas regulators are used in Australian regulatory decision making. Reports are currently accepted from seven overseas regulatory authorities: Health Canada, Health Science Authority Singapore, Swissmedic, UK Medicines and Healthcare products Regulatory Agency, United States Food and Drug Administration, European Medicines Agency and the Pharmaceuticals and Medical Devices Agency of Japan.

The process involves the submission of un-redacted COR assessments by medicine sponsors. There are two approaches depending on the amount of Australian-specific evaluation required:

  - COR-A: Evaluation and decision timeframe of 120 working days
  - COR-B: Evaluation and decision timeframe of 175 working days.

The COR report-based process is open to prescription medicine registration applications where the medicine has been comprehensively evaluated before receiving full overseas marketing approval. As at 30 September 2020, there have been 16 medicines approved via the COR pathways (5 via COR-A and 11 via COR-B).

Work-sharing with the Australia-Canada-Singapore-Switzerland (ACSS) Consortium

The Australia-Canada-Singapore-Switzerland (ACSS) Consortium is a collaborative initiative of medium-sized regulatory authorities between the TGA, Health Canada, Singapore's Health Sciences Authority and Swissmedic. The ACSS New Active Substance work sharing initiative has aligned regulatory approaches and technical requirements. ACSS work-sharing involves the coordinated assessment of new medicine applications that are filed within two or more ACSS jurisdictions. ACSS Consortium Regulators undertake a single assessment for new products that will support decision-making within each jurisdiction.

The ACSS partnership benefits the Australian community by improving access to the most recent and innovative treatment options. The ACSS partnership maximises the use of up-to-date technical expertise and brings greater alignment of regulatory approaches, technical requirements, knowledge sharing and better use of resources. ACSS also facilitates cooperation and collaboration, reduces duplication, and increases each regulator's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products.

As of 30 September 2020, seven medicines have been approved for registration after undergoing ACSS work-sharing review.

On 12 October 2020, it was announced that the UK Medicines and Health Products Regulatory Agency would join the ACSS Consortium (which will be renamed 'ACCESS'). Inclusion of the UK regulator, which is one of the world's larger and most technically competent regulators, will transform ACCESS into the third largest developed country regulatory entity at a global level (the other two being the US FDA and the EMA). The five member countries provide a population of 150 million, and its attractiveness as a group of markets should stimulate earlier submissions to ACCESS members from major pharmaceutical companies.

Participation in the US FDA's Project Orbis

In mid-2019, the FDA Oncology Center of Excellence launched Project Orbis to facilitate faster patient access to innovative cancer therapies across multiple countries. Project Orbis aims for concurrent submission, review, and regulatory approval for highly clinically significant products among the participating partner countries. TGA has been an active participant in the project with other international regulatory partners including Brazil, Canada, Singapore, and Switzerland.

Australia's participation in Project Orbis leverages our existing scientific and regulatory partnerships with the FDA and other health authorities under mutual confidentiality agreements. As of 30 September 2020, nine medicines have been approved for registration as part of Project Orbis since the program began just over a year ago.

Significantly, in contrast to the CIRS data, participation in Project Orbis has allowed TGA to achieve parity or near-parity with FDA timelines. Three quarters of the Australian submissions and approvals have occurred within 6 weeks of the corresponding FDA timeline for the same application. All medicines approved under Project Orbis have had accelerated assessment timeframes. Apart from this benefit for cancer patients, benefits for the pharmaceutical industry include reducing duplication and regulatory burden and increasing the possibility of simultaneous access to multiple international markets.

PBS process improvements

The Department, in collaboration with Medicines Australia, has been working since late 2017 to deliver on commitments to streamline medicines listing processes as set out under the Strategic Agreement between the Australian Government and Medicines Australia. These process improvements support the Government's commitment under the Strategic Agreement to improve the transparency, timeliness and efficiency of the PBS listing processes. These changes ensure that all Australians will continue to be able to receive timely and affordable access to necessary medicines.

PBS process improvements commenced from 1 July 2019 and are being implemented in a two-staged process. A major objective of the Stage 1 improvements was to reduce the time from PBAC

consideration to PBS listing by an average of two months. This was achieved within 12 months of Stage 1 measures being in place, with the average time to listing reduced by an average of 3.5 months. The changes made in Stage 1 included:

- Changes to pre-submission meetings to improve guidance and support and submission quality for complex submissions
- Introduction of a compulsory 'intent to apply' step to enable effective resource planning for submissions coming forward to the PBAC
- Introduction of four transparent pricing pathways following a positive PBAC recommendation to assist with reducing the time to listing on the PBS
- Revised cost recovery arrangements to better align fees with the cost of services provided
- Establishment of a medicine status website, which enables consumers to track a medicines progress through the PBS listing process.
- There has also been a demonstrated improvement in timeliness for applicants lodging their notice of intent for the time from PBAC minutes to PBS listing date. Following stage 1 improvements, it was an average (mean) of 105 days (approx. 3.5 months) and a median of 93 days (approx. 3.1 months). Prior to Stage 1 improvements, this was 7.1 months (216 days).

The Department's ability to support timely PBS listing is reliant on cooperation, information and securing agreements with industry. Currently, the Stage 1 metrics show that less than 20 per cent of applicants are utilising the earliest timelines to commence pricing services. This presents opportunities to further improve listing timeframes, with increased use of the new services and pathways by industry.

The implementation of Stage 2 PBS process improvements will commence from 1 January 2021, and will include:

- Changes to initial submission categories including introduction of a single submission date
- Introduction of resubmission pathways for submissions not recommended by the PBAC
- Revised cost recovery arrangements
- IT system changes.

These process improvements will benefit consumers, industry and the PBAC and the Department.

These benefits include:

- For consumers – improved transparency of submissions considered by PBAC, and supporting access to medicines by enabling faster resolution of issues (when possible)
- For industry – increased clarity and transparency of activities required to assess submission types, reduced cross-subsidisation of evaluation fees, continued effective handling of submissions
- For PBAC and the Department of Health – increased transparency regarding amount and complexity of activities required to assess the range of submissions coming forward for PBAC consideration, streamlining of internal processes and resourcing to support the PBAC

HTA Assessment and listing of co-dependent and hybrid technologies

The enhancements to the HTA assessment process for co-dependent and hybrid technologies have focused on supporting an integrated approach to reduce duplication of effort across the respective committees, and to minimise potential barriers to patient access. This is demonstrated through the PBAC-MSAC co-dependent submission process, which includes an integrated approach for a subsidy submission for a medicine and co-dependent test by a sponsor. A feature of the integrated co-dependent approach includes the preparation of a single evaluation document for use by MSAC and the PBAC. This evaluation document is then considered by the economic subcommittees of PBAC and MSAC at a joint meeting, and a joint ESC Advice document prepared for the PBAC and MSAC. The integrated co-dependent submission process was successfully used to support MSAC and PBAC's recent consideration of BRCA mutation testing to determine eligibility for olaparib maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer.

Health Products Portal (HPP) Program

The Department is also improving the efficiency of the regulatory and technology assessment process through the development of a Health Product Portal (HPP). The HPP program strongly aligns to the Government's commitments to reduction of regulatory burden, congestion busting and the digital transformation agenda. This will actively address the concerns and needs of industry stakeholders.

The HPP Program vision is to realise a single, secure and easy to use place where industry can interact with Government to apply, track, pay and manage listings for regulated and subsidised health-related goods and services. The aim of the HPP is to create consistent and simplified business processes through a digital solution that supports legislative compliance and evidence-based policy and decision making.

This digital solution will provide a consistent user experience for sponsors and other stakeholders, reducing duplication of effort and enabling a single, digital and trackable user journey through the regulatory and subsidisation lifecycle. Further, it will create a cohesive end-to-end HTA process, where information is gathered at any stage of the process with a view to its purpose, its use and reuse throughout, and availability at the right time. This will streamline and improve the process and efficiency in which medicines and medical devices enter the Australian market. The HPP has already enabled a streamlined approach for PBAC submissions, and over time, will link data and services to include other areas including TGA, PLAC and MSAC. This will be supported by whole-of-government authentication services and data asset management solutions.

Post-market monitoring for medicines

The TGA takes a lifecycle approach to product vigilance, taking account of the entire body of evidence that accumulates from drug development to post-registration to inform a product's safety profile. Post market assessment of the safety and efficacy of provisionally registered products is crucial as there is less opportunity for this information to be generated prior to registration.

The TGA uses a variety of tools for assessing safety, quality and efficacy following registration, including analysis of adverse drug reaction reports, evaluation of periodic safety evaluation reports and post-market safety studies, review of the scientific literature, and collaboration with international regulatory counterparts. Different thresholds for investigation in response to adverse event reporting are used according to a risk stratification for therapeutic goods, with provisionally registered products being subject to more frequent review.

Risk Management Plans (RMPs) are completed by sponsors as part of the registration process for high-risk medicines and biologicals (e.g. registration of new chemical entities, provisional registration of a medicine, and some extensions of indications) and outline the risk management system for a product once it is available on the market in Australia. RMPs are living documents that cover the lifecycle of a product and are updated as the product's safety profile changes over time.

To enhance public and health professional awareness of the importance of adverse event reporting, particularly for new medicines or those extended into very different populations for example a different medical condition or from an adult to a paediatric population, the Black Triangle scheme was introduced in January 2018 in response to the Expert Panel Review of Medicines and Medical Devices Regulation. Those medicines in the Black Triangle scheme are required to include information at the top of the Product Information (PI) and Consumer medicine Information (CMI) about the scheme and how to report. The use of the Black Triangle does not mean that the medicine has significant safety issues rather that its use in the general population is yet to be fully characterised.

The OGTR also monitors post-market activities with GMO therapeutics. These requirements include mandatory reporting of any additional information as to any risks to the health and safety of people, or to the environment or any unintended effects caused by the GMO

The PBS post market review and monitoring activities contribute to the quality use of medicines objective of the National Medicines Policy framework. The post-market review processes involves consultation with all stakeholders including the pharmaceutical industry, prescribers and has a strong focus on consumers.

The Drug Utilisation Subcommittee (DUSC) undertakes routine assessments of PBS medicines 24 months after their first listing. Based on these reviews, the DUSC provides advice to the PBAC on the current utilisation of newly listed medicines compared with the use as recommended by the PBAC. The DUSC Utilisation Analysis Public Release Documents provide public access to these utilisation analysis reports. DUSC considers the reports assist stakeholders to better understand how PBS medicines are currently being used and may be informative to pharmaceutical sponsors in the development of new medicines.

All PBS Post Market reviews are conducted within a framework agreed with the pharmaceutical industry, and provide a mechanism for medicines to be reconsidered in the current treatment context to ensure that the clinical and cost-effectiveness of medicines is maintained following PBS listing. These reviews support the ongoing sustainability of the PBS, ensure access to medicines remains consistent with contemporary clinical practice, and allows for new medicines to be listed on the PBS. In 2018-19, 96% of all Government-accepted recommendations from the PBAC related to PMRs of PBS medicines were implemented within agreed timeframes

Further, a cross-program review of the Life Saving Drugs Program is currently underway with recommendations due to be agreed by Government. The implementation of supported review recommendations is anticipated to commence in early 2021.

Greater collaboration to further align regulatory and reimbursement processes in Australia

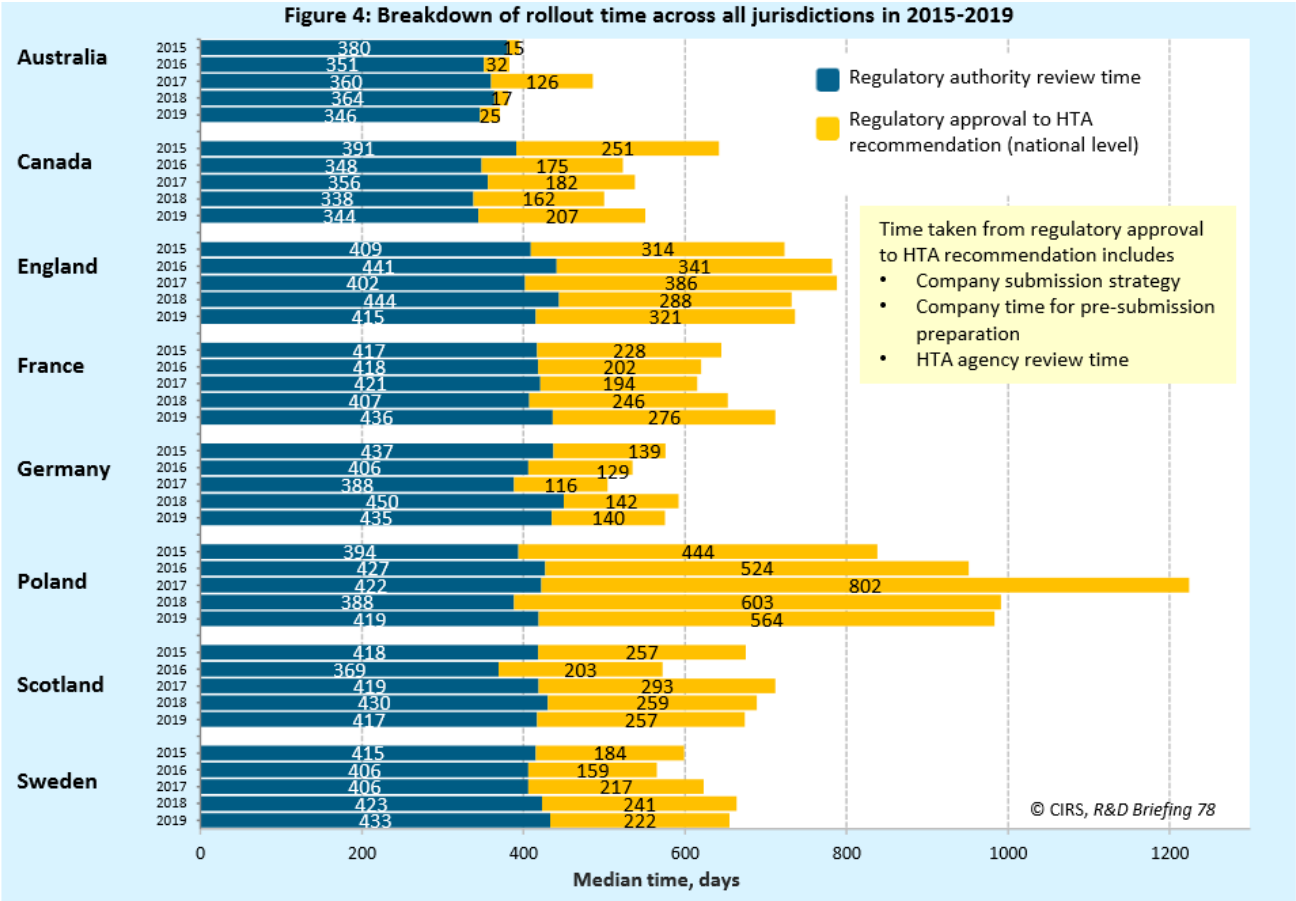
The National HTA Chairs Committee was formed in August 2017 to facilitate the development of coordinated approaches to issues common to the deliberations of the HTA committees for medicines and medical devices, and tap into the accumulated wisdom of these HTA leaders. The HTA Chairs Committee is chaired by the Chief Medical Officer, with membership inclusive of the

Chairs of the PBAC, MSAC, Prosthesis List Advisory Committee, Advisory Committee on Medical Devices, Advisory Committee on Medicines, and the Consumer Consultative Committee. The Chairs Committee promotes regular HTA policy level discussion and coordination between the Chairs of medicines and medical devices committees. This enables a coordinated approach to the development of evidence based processes, promote learnings from international experience and ensure Commonwealth HTA adapts to new challenges, new technology and medical service innovations.

As part of an ongoing study to monitor regulatory and HTA performance, the CIRS has been collecting data on new active substances appraised between 2015 and 2019 by eight health technology assessment (HTA) agencies, analysing synchronisation between the regulatory decision and first HTA recommendation in timing and outcome.

The CIRS report showed that there is currently a well aligned process in Australia and that compared to other jurisdictions, and as noted above, Australia had the shortest overall median time between regulatory approval and HTA recommendation. This suggests that the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory recommendation is achieving its purpose.

This is highlighted in the figure below from the CIRS report.



The Department is working to further improve the flow of applications through the regulation and reimbursement processes. In the first instance, work is underway focussing on aligning administrative processes to ensure timely access to information required to inform regulation decisions and reimbursement consideration. The second stage of this work is to explore further efficiencies through joint evaluation and increased information sharing.

It is anticipated that this future work will reduce duplication and increase certainty for sponsors about the timeframes for approval and re-imbursement decisions.

Approval of GMO therapeutics for commercialisation

Authorisation is required from both the TGA and the GT Regulator before commercial supply of a GMO therapeutic. Assessments by the TGA and the GT Regulator are independent, and applicants are able to apply to both regulators at the same time. TGA and OGTR share information and seek advice from each other as necessary while assessing applications.

Assessment of Medical Devices

TGA has undertaken an international benchmarking exercise to compare timeframes for conformity assessment and inclusion of medical devices in the ARTG. Conformity assessment (or equivalent) Australian timeframes are comparable with other overseas regulators, noting that timeframes do vary between jurisdictions, and in many jurisdictions they also vary in line with the risk of the medical device being assessed.

No other jurisdiction examined splits the conformity assessment (or equivalent) and market authorisation steps (i.e. inclusion in the ARTG), as we do in Australia. This split in Australia relates to the extensive use of approvals from comparable overseas regulators, with other jurisdictions using fewer or no overseas approvals.

Post-market monitoring for medical devices

The TGA's post-market monitoring and vigilance system for medical devices aims to maintain the safety of patients and, through the collection, analysis, and action taken in response to adverse event reports, reduce the likelihood of adverse events recurring.

The iterative nature of medical devices means that many are approved on the basis of their design and the manufacturer's compliance with quality standards, rather than on the basis of detailed clinical trials as are required for medicines. As a result, timely and effective post-market monitoring of the performance of medical devices in the real world is an essential element of an effective regulatory system. Post-market monitoring of medical devices poses particular challenges compared to medicines due to the greater diversity and complexity of medical devices, the learning curve associated with health practitioners and consumers adopting new technologies, and the short lifecycle and iterative nature of medical devices.

The TGA has made a number of recent changes to strengthen the post-market monitoring and vigilance of medical devices. These include:

- Requiring sponsors of certain high-risk devices to provide more frequent adverse event reports to the TGA
- Changing online adverse event reporting forms to make it simpler for consumers and healthcare professionals to report
- Consulting on introducing a unique medical device identification system in Australia, assisting more accurate reporting and efficient analysis of adverse events, recalls, and better international device information sharing
- Implementing new risk analysis tools and improved data analytics for early signal detection

- Actively engaging consumer groups, healthcare professionals and hospitals to explain the system, improve awareness, and encourage increased adverse event reporting
- Co-leading a national project to identify ways for rapid information sharing between states, territories and the TGA
- Undertaking targeted consultation with stakeholders to identify additional ways to improve data collection and sharing between the TGA and hospital systems.

Consultation will also be undertaken later this year on further proposed changes to post market monitoring and adverse event reporting for medical devices.

Medical device comparable overseas regulators

From October 2018 the TGA expanded the range of international assessments and approvals from comparable overseas regulators that can be used to support marketing approval in Australia. This includes using overseas approvals to support the vast majority of applications for inclusion of medical devices in the Australian Register of Therapeutic Goods (ARTG), or to abridge conformity assessment applications (in-depth evaluation) by the TGA where this is required. As outlined above, where conformity assessment is abridged due to overseas approvals, the TGA's evaluation fees can also be abridged.

The TGA has accepted certification from European notified bodies as evidence of compliance with the conformity assessment procedures since the introduction of the medical devices framework in 2002, as an alternative to the conformity assessment certificates issued by the TGA. These changes formalised and expanded these arrangements so applicants can also use approvals from the USFDA, Health Canada, Japanese medical device regulators, and certification issued under the Medical Device Single Audit Program (MDSAP - a joint program between the USA, Canada, Japan, Brazil and Australia).

There is already extensive use of approvals from comparable overseas regulators to support market approval for medical devices in Australia. More than 90 percent of the nearly 28,000 ARTG medical device entries requiring certification or comparable evidence (all but the lowest risk Class I medical devices) are supported by overseas approvals.

Medical device priority review

A new pathway for priority review for novel medical devices was introduced from July 2018. Medical device applications which are granted a Priority Review designation of either TGA conformity assessment, or inclusion in the Australian Register of Therapeutic Goods (ARTG) will be allocated 'front-of-queue' priority throughout the relevant assessment process.

To be eligible, devices must meet three specific criteria.

- The device addresses a life threatening or seriously debilitating condition, and;
- Either no devices are already approved for the same purpose in Australia, or the new device has substantially better safety or performance than approved devices, and;
- At least one of the following applies:
  - the new device is a breakthrough technology with substantially better safety or performance than existing devices

- there is evidence that the device offers a major clinical advantage over existing alternatives included in the Register
- the new device is an IVD which will provide a major public health benefit.

Since introduction of the pathway eight applications for priority review of medical devices have been submitted with six designated for priority review. Five of those six priority assessments have been completed and one is in progress. Four of the approvals expand an existing device to a new patient group based on emerging safety and efficacy data. The average number time taken to complete the conformity assessment application was 67 TGA days, compared with average of 143 TGA days for non-priority device reviews.

The five assessments completed include a new hepatitis C in vitro diagnostic critical as a companion test for newly developed drug regimens, four aortic transcatheter heart valve bioprostheses. Another application currently under assessment is for a bioresorbable hydrogel coating intended to create a temporary barrier against the bacteria adhesion onto the surfaces of orthopaedic and dental implants.

Improved mechanisms for consumer and stakeholder involvement and engagement in HTA

There is a wide and diverse range of expertise across the Department and the HTA committees and expert panels. Their collective experience and expertise, particularly in relation to rare diseases, has been built up over the years through involvement across various programs and on emerging technologies. This is complemented by consumer and stakeholder engagement throughout the HTA cycle, through mechanisms including:

- Stakeholder consultation to facilitate access and engagement of specialist clinicians, patient networks, research bodies, registries and international contacts to enable contribution of rare disease expertise.
- Inputs to submissions through written submissions, consumer hearings, stakeholder meetings, patient/family interviews and organisational surveys, for consideration by the committee.

The Department is also continuing to explore the use of digital health care and improving integration to enable person and family-centred care delivery. This work is supported by the HTA Consumer Consultative Committee and the HTA Consumer Evidence and Engagement Unit.

The HTA Consumer Consultative Committee was established on 1 March 2017 to provide strategic advice and support to the principal HTA committees and the Department to ensure optimal consumer engagement and participation in HTA processes. Members of the Committee are consumer representatives from the following principal committees and their related sub-committees: PBAC, MSAC and PLAC. In March 2019, consumer representatives from the TGA Advisory Committee on Medicines and the TGA Advisory Committee on Medical Devices also joined as members. The Committee has progressed several initiatives to support increased involvement and engagement of consumers, including:

- Promoting greater public understanding of HTA decision-making processes, through workshop presentations for consumer members and various consumer forums
- Contributing expertise to the development of the Medicines Status Website, and updates to MSAC public summary documents to promote accessibility of information

- Developing a mentoring pilot program for HTA consumer committee representatives across the Office of Health Technology Assessment to support effective participation in HTA activities.

To assist the work of the Committee, in 2019, a designated HTA Consumer Evidence and Engagement Unit was established within the Department of Health's Technology Assessment and Access Division to allow the development of structured projects of engagement with consumer and patient groups.

The Department has actively supported rare disease organisations to engage in the submission processes, including those put forward by pharmaceutical companies, or in collaboration with clinical specialists. This has been demonstrated through the successful listing of vorinostat (Zolinza®) for relapsed or refractory cutaneous T-cell Lymphoma (CTCL) on the PBS as a result of submission by Rare Cancers Australia in 2016.

In 2011, the manufacturer had submitted an application to PBAC for vorinostat, which was rejected based on unacceptably high and uncertain cost-effectiveness ratios and an incorrect comparator. In 2016, Rare Cancers Australia sponsored a revised application, which was supported in principle by the manufacturer. A major submission was considered by PBAC at the November 2016 meeting, and the Committee deferred the recommendation to liaise directly with the manufacturer to clarify financial impact issues, including patient numbers and agreement on details for the risk share agreement. In March 2017, vorinostat was recommended for listing by the PBAC and was listed on the PBS on 1 July 2017.

The success of this submission, demonstrates the flexibility and responsive of Australia's HTA processes. The collaboration across parties was a key factor in securing the positive outcome.

The Medicines Status Website was launched in February 2020 and enables consumers to search and monitor the status of medicines as they progress through the PBS listing process. The Medicines Status Website was developed for consumers, in collaboration with consumers and the pharmaceutical industry, to improve the transparency of PBS listing processes. It also enables consumers to better understand how they can contribute to PBAC decision making and the steps that must be completed to list a medicine on the PBS.

Conclusion

In summary, Australia has strong regulatory and HTA performance capabilities and overall, they compare favourably against major international regulatory and HTA agencies. The current processes have demonstrated capacity to enable efficient assessments of new technologies and therapies, to support timely, affordable and equitable access to cutting-edge treatments for all Australians, especially in areas of high unmet clinical need.

As with all established systems, regular reviews and reform has delivered incremental and sustained improvements at both technical assessment and process levels. The Department will continue to progress reforms to improve assessment and listing processes, involve increased transparency and consumer engagement, deliver efficiencies in the regulatory and reimbursement assessment of clinical data for medicines, harness digital solutions for joint process improvements and put greater emphasis on post-market monitoring for both medicines and medical devices.