Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Provisional Approval pathway for prescription medicines

Proposed registration process and post-market requirements

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TGA Health Safety Regulation

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1. Introduction

Purpose and scope

The purpose of this consultation paper is to:

- outline the objectives of the Provisional Approval pathway for prescription medicines being developed by the Therapeutic Goods Administration (TGA)
- seek feedback from consumers, health professionals and industry on the proposed pre-market registration process; post-market requirements specific to provisionally registered medicines; and lapsing or transition to full registration.

This paper focuses on aspects of the Provisional Approval pathway that will inform the necessary legislation and regulation amendments for implementation. It will also inform further development of TGA business processes and guidance documents for sponsors, which will be finalised following targeted consultation with industry later in 2017.

Background

The Review of Medicines and Medical Devices Regulation (MMDR review) was undertaken by an Expert Panel in 2015.[1] In response, the Australian Government agreed to implement expedited pathways for the registration of new medicines in certain circumstances, noting that legislative amendments would be required for implementation.[2]

Two separate expedited pathways are currently being developed by the TGA. The ***Provisional Approval*** pathway will allow sponsors to seek a time-limited provisional registration of certain prescription medicines that do not meet our full clinical data requirements, where the potential benefit of earlier availability of the medicine outweighs the risk that additional data are still required. The ***Priority Review*** pathway will involve faster assessment of certain prescription medicines that meet our full data requirements, with a target timeframe of 150 working days for a decision to be made regarding registration of the medicine.

In October 2016, we released a public consultation paper, *Consultation: Expedited pathways for prescription medicines*, on the proposed eligibility criteria and designation process for both of the expedited pathways. An overview of the outcomes of this consultation process is available at: <https://www.tga.gov.au/submissions-received-expedited-pathways-prescription-medicines>.

Implementation of the Provisional Approval pathway will be supported by broader MMDR reforms to develop a more comprehensive post-market monitoring scheme for medicines and medical devices. The TGA has released a separate consultation paper, *Strengthening safety monitoring for medicines in Australia,* seeking comments on the implementation of a range of enhancements to our Medicines Vigilance Framework (see:

[1] Expert Panel, Review of Medicines and Medical Devices Regulation: Report to the Minister for Health on the Regulatory Framework for Medicines and Medical Devices (31 March 2015), Recommendations 3, 8 & 10, p. ix-xiv, available at: <http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation>

[2] Commonwealth of Australia (Department of Health), Australian Government Response to the Review of Medicines and Medical Devices Regulation (September 2016) available at: <https://www.tga.gov.au/mmdr#austgovt>

<https://www.tga.gov.au/consultation/consultation-strengthening-monitoring-medicines-australia>).

Given that provisional registration will be based on early clinical data, these medicines may potentially be of higher risk and will be prioritised within the TGA's enhanced post-market monitoring and compliance activities.

2. Overview of the Provisional Approval pathway

Context for change

Many international regulators have the capacity to expedite the assessment of prescription medicines in certain circumstances. For example, the European Medicines Agency (EMA),[3] US Food and Drug Administration (FDA)[4] and Health Canada[5] have programs that allow certain prescription medicines to be assessed for market authorisation on the basis of less, or different, clinical data than would normally be required for a standard assessment.

While the TGA does not currently have a formal program for the early registration of promising new medicines, we have previously registered medicines on the basis of early clinical evidence of efficacy and safety in exceptional circumstances where there was potential for significant benefit to patients with unmet clinical needs, noting that more evidence was needed to verify clinical benefit. The TGA has worked with the sponsors to facilitate the registration of these medicines and ensure that risk management strategies are in place to help maintain our high standards for quality, safety and efficacy. Introduction of the Provisional Approval pathway will provide sponsors and TGA decision makers (delegates) with a formal and transparent process for registration of certain promising new medicines on the basis of early clinical data.

Objective of Provisional Approval

The objective of the Provisional Approval pathway is to allow certain promising new medicines to reach patients with unmet clinical needs earlier than might otherwise be the case, while ensuring appropriate measures are in place to manage the risks inherent in the fact that additional data are still required. The pathway could allow medicines to reach Australian patients up to two years earlier than under the current framework.

The MMDR review recommended that the registration of medicines on the basis of early clinical data should be:

[3] European Medicines Agency (EMA), Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (February 2016), available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf>

[4] U.S Department of Health and Human Services, Food and Drug Administration, Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics (May 2014), p. 15-24, available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

[5] Health Products and Food Branch, Health Canada, Guidance Document: Notice of Compliance with Conditions (revised September 2016), available at: <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/noccg_accd-eng.pdf>

- available only to certain medicines that meet the transparent eligibility criteria
- provisional and time-limited, with a requirement for the sponsor to collect and submit further clinical data to demonstrate efficacy and safety in order for the product to be granted full registration
- subject to any conditions imposed by the TGA (which may be consistent with those imposed by an overseas regulator if relevant and applicable to the Australian context)
- subject to the provision of clear advice to consumers and health practitioners that the medicine has been granted provisional registration.[6]

One of our principles is that health professional and consumer confidence in TGA regulation of the safety, efficacy and quality of therapeutic goods must be maintained. In line with this principle, the Provisional Approval pathway will be restricted only to those medicines where there is promising evidence that earlier availability has the potential to provide a significant benefit to patients with inadequate treatment options for serious and life-threatening conditions. It is not intended to provide a second-tier regulatory pathway for any medicine with insufficient evidence.

In implementing this pathway, we will ensure that the objectives, benefits and risks of the Provisional Approval pathway are clearly communicated with industry, health professionals and consumers. Sponsors will be provided with clear guidance to help them determine the most suitable regulatory pathway for their medicine before making an application to the TGA. This will help ensure that the Provisional Approval pathway is appropriately utilised by sponsors to facilitate earlier access to certain promising medicines for patients.

Phases in the Provisional Approval pathway

The Provisional Approval pathway involves four phases:

1. **Designation process:** sponsors will be strongly encouraged to request a pre-designation meeting approximately six to seven months prior to dossier submission. Sponsors will then be required to submit a designation application for the Provisional Approval pathway to determine whether the medicine meets the eligibility criteria. Eligible medicines will be designated as suitable for a Provisional Approval application for a six month period (with the possibility of a six-month extension to the validity of the designation if agreed by the TGA).

   For further information on the designation process, please refer to *Consultation: Expedited pathways for prescription medicines* (released in October 2016) and the summary of consultation outcomes available at: <https://www.tga.gov.au/submissions-received-expedited-pathways-prescription-medicines>.

2. **Pre-market registration process:** where successfully designated, sponsors will submit a Provisional Approval registration application and supporting dossier for assessment by the TGA. A decision will be made within legislated timeframes by the TGA delegate as to whether the medicine will be granted a time-limited provisional registration on the Australian Register of Therapeutic Goods (ARTG).

3. **Post market requirements in the provisional registration period:** sponsors of provisionally registered medicines will be required to fulfil any conditions of registration imposed by the TGA. This will include requirements to collect and submit post-market

[6] Recommendation 8 and 10, Expert Panel, p. 74.

clinical data on safety and efficacy for evaluation by the TGA to substantiate continuing provisional registration and, ultimately, for the product to be granted full registration.

4. **Lapsing or transition to full registration:** Provisional registration will automatically lapse after a two year period, unless the sponsor has applied for full registration of the medicine or the TGA has granted an extension to the provisional registration period. The TGA will conduct an assessment of the additional clinical data on efficacy and safety and a decision will be made by the TGA delegate about whether the medicine will be granted continued provisional registration or full registration on the ARTG.

Further details on the proposed registration process and post-market requirements are provided in the subsequent sections of this consultation paper.

Consultation with external experts

Given that the Provisional Approval pathway will require TGA delegates to consider a higher level of uncertainty about the efficacy and safety of medicines, it may be necessary to draw on advice from external experts to inform decision making throughout each of the phases outlined above.

The Advisory Committee for Medicines (ACM) provides an advisory role to TGA delegates on both pre-market and post-market aspects of the regulation of prescription medicines. The Advisory Committee for Vaccines (ACV) provides advice on pre-market and post-market aspects of the regulation of vaccines. Ad hoc expert advice is also available to TGA delegates via a specialist advisory panel. Expert advice may be sought from other experts, including international regulators, experts in the therapeutic area and/or researchers involved in ongoing clinical trials. Potential conflicts of interest will need to be managed to ensure this process is robust and transparent.

3. Pre-market registration process

Data requirements for the registration application

The Provisional Approval pathway will allow certain medicines to be provisionally registered in the ARTG on the basis of early clinical data on efficacy and safety. For example, early clinical data may be based on fully validated surrogate endpoints or other early data relevant to the medicine's safety and efficacy, rather than comprehensive data from Phase III clinical trials.

Provisional Approval registration applications must include comprehensive quality and non-clinical safety modules that fulfil the TGA's mandatory data requirements[7] and scientific guidelines for the specific application type adopted by the TGA from the European Union and the International Conference on Harmonisation. In line with existing TGA guidance, where the sponsor chooses not to provide data according to a particular guideline or aspect of a guideline, a scientifically robust justification must be provided to explain why the guideline is not applicable and why the proposed alternative is valid.

For standard registration applications, there is an expectation that all information and data that the sponsor wishes to be taken into account by the TGA will be presented at dossier submission.

[7] TGA, Mandatory requirements for an effective application (updated July 2015). Available at: <https://www.tga.gov.au/publication/mandatory-requirements-effective-application>

For Provisional Approval, it is likely that pivotal or supporting clinical trials will be ongoing during the pre-market registration period.

On a case-by-case basis, the TGA may agree upfront for the sponsor to make a rolling submission of clinical or other relevant data during the assessment period, where this information might have a material impact on the registration decision. However, this approach could lead to inefficiencies and potential delays if aspects of the evaluation needed to be revised to account for the additional data. In order to facilitate evaluation planning and TGA resourcing, sponsors will need to prospectively discuss any additional data that will be generated after submission of the dossier and the proposed timeframe for submission. Additional data may only be accepted up to a certain point in the registration process and may require a 'stop-clock' in the statutory timeframe for completion of the registration process.

It is proposed that a rolling submission of clinical data may not be accepted unless there has been an upfront agreement between the sponsor and the TGA prior to dossier submission, and where timeframe and resourcing implications have been taken into account. Additional data that does not affect efficacy and safety considerations should be submitted as a separate application after the medicine has been provisionally registered in the ARTG.

Data requirements for the registration application

Q1. Do you envisage any difficulties with the proposed clinical, non-clinical and quality data requirements or Provisional Approval registration applications?

Q2. Do you envisage any difficulties in providing prospective advice on timelines for submission of clinical data?

Timeframe for the pre-market registration process

It is proposed that the pre-market registration process for Provisional Approval will follow a similar internal evaluation process to the standard Prescription medicines registration process and be completed within current legislated timeframes. However, in line with the objective of the Provisional Approval pathway to facilitate earlier access to vital medicines, the TGA will prioritise the assessment of Provisional Approval registration applications.

Given that Provisional Approval applications will be based on early clinical data, there is likely to be increased uncertainty about the efficacy and safety. These applications may require a higher level of scrutiny and deliberation in order to understand these uncertainties and weigh up the benefits and risks of earlier availability of these medicines. Closer coordination between clinical, non-clinical, quality and Risk Management Plan (RMP) evaluation areas will ensure that any emerging safety signals are identified and managed. As noted above, the TGA delegate may seek external expert advice on issues concerning the application earlier in the pre-market registration process. The application may also be referred to a scheduled meeting of the ACM or ACV for advice at the request of the TGA delegate during the evaluation process. Timeframes for the pre-market registration process will need to accommodate these activities. As discussed above, consideration is also being given to the impact of rolling submissions of clinical data on the legislative timeframe for the Provisional Approval pathway.

Factors influencing our decision making

Accepting the application for evaluation

When a Provisional Approval registration application is received, it is proposed that the TGA will consider whether:

- the product has designation to seek provisional registration
- data in the dossier supports the evidence and/or undertakings that were presented in the designation application to justify that the eligibility criteria have been fulfilled
- the sponsor has fulfilled our data requirements for Provisional Approval applications or has reached agreement with the TGA about a rolling submission of clinical data during the assessment period
- the sponsor has provided sufficient information for the TGA to determine whether the necessary confirmatory data to achieve full registration can be completed in the provisional registration period.

It is proposed that if a Provisional Approval registration application does not meet all of the above criteria, the TGA may not accept the registration application for evaluation.

Registration decision

During the decision phase of the standard process, the TGA delegate will determine whether the application is to be approved (possibly after being modified or varied) or rejected. In order to approve the product, the delegate must be satisfied that the benefits sufficiently outweigh the risks. There may be special conditions of registration associated with the approval; these may include the conduct of post-market activities by the applicant, or a revision of existing documentation. Overall, the delegate must be satisfied that the quality, safety and efficacy of the medicine have been satisfactorily established for its intended use.

Given the decision to grant provisional registration will be on the basis of early clinical data on efficacy and safety, a number of additional factors may influence the registration decision about whether the benefits outweigh the risks of the product. It is proposed that these factors will include whether:

- there is sufficient evidence that the benefit-risk balance of the medicine is positive
- there is promising evidence that early availability of the medicine will provide a significant benefit to Australian patients with unmet clinical needs
- the sponsor has a demonstrated capacity to generate and submit comprehensive clinical data on the efficacy and safety of the medicine within the timeframe for provisional registration so as to achieve full registration
- the sponsor has a demonstrated capacity to comply with any other conditions of registration that are imposed by the TGA.

We propose that failure to meet these factors during the registration process will provide the TGA with a reason to consider rejection of the application for Provisional Approval. In line with the standard process, the sponsor will be provided with an opportunity to respond to any concerns before a final decision is made.

Factors influencing our decision-making

Q3. Are there other factors that should be taken into account during the dossier submission and evaluation phase for Provisional Approval applications?

Q4. Are there other factors that should be taken into account to inform the registration decision for Provisional Approval?

4. Post-market requirements in the provisional registration period

Conditions of provisional registration

Requirement to collect confirmatory data on efficacy and safety

A medicine will only be granted provisional registration on the condition that the sponsor can demonstrate their ability to collect and submit the efficacy and safety data that would normally be required for full registration during the provisional registration period. In order to ensure our standards for evidence are maintained, it is expected that the sponsor will conduct appropriate clinical trials to generate the confirmatory data.

In order to demonstrate their capacity to fulfil this condition of registration, the sponsor should be able to provide evidence that planned clinical trials will be completed within the provisional registration period, taking into account the possibility of future extensions. For example, the sponsor may provide evidence that the trial is fully or almost fully recruited prior to registration, or the data can be obtained through another mechanism that is deemed suitable by the TGA (such as the same treatment regime in a similar population group).

In exceptional circumstances, the sponsor may propose to demonstrate that sufficient confirmatory data will be generated through 'real world' observational data from a patient registry. The TGA would need to prospectively approve any deviation from the normal standards of evidence based on a suitable scientific and clinical justification provided by the sponsor.

The conduct and completion of confirmatory studies and/or patient registries will be a requirement of the sponsor's Risk Management Plan (RMP), which will be imposed by the TGA as a condition of provisional registration. Sponsors will be required to comply with any other conditions of provisional registration imposed by the TGA, as outlined below. It is anticipated that the provisional registration conditions will generally be consistent with those imposed by comparable overseas regulators if relevant and applicable to the Australian context. Consideration will be given to whether any Australian-specific activities may be required to monitor or mitigate safety concerns that are unique to the Australian population.

Other conditions of provisional registration

The requirement for sponsors to generate confirmatory efficacy data to assess the efficacy and safety of provisionally registered medicines is in addition to existing pharmacovigilance requirements. Similar to other prescription medicines, the need for pharmacovigilance activities

to be undertaken by sponsors to monitor the real-world effectiveness and safety of their product will be assessed on a case-by-case basis. Any activities that will be required to monitor and mitigate safety concerns associated with the product will be specified in the RMP which is imposed by the TGA as a condition of registration.

As part of the RMP, provisionally registered medicines will be required to regularly report on safety and efficacy information about the medicine, based on the additional data that becomes available during the reporting period. Periodic Safety Update Reports (PSURs)[8] are usually submitted annually for the first three years of registration. The TGA will determine whether a PSUR, or suitable alternative, is required more frequently for a provisionally registered medicine.

The TGA may require the sponsor to establish a patient registry as a condition of registration in certain circumstances, in order to collect data about the efficacy and safety of the provisionally registered medicine in Australian patients. This may include consideration of whether there is an Australian-specific safety concern that could be best addressed using a patient registry, or whether data from a comparable overseas patient registry will be generalisable to Australian patients. The latter would include consideration of whether the registered indication is comparable to that being sought in Australia.

Other post-market requirements for provisionally registered medicines will fall within the TGA's post-market monitoring and compliance framework. Enhancements to this framework are currently being developed and include an RMP Compliance Monitoring Program; a Black Triangle Scheme; and a Pharmacovigilance Inspection Program. Please refer to the separate consultation paper on the enhanced Medicines Vigilance Framework for more details Medicines (see: <https://www.tga.gov.au/consultation/consultation-strengthening-monitoring-medicines-australia>).

Conditions of provisional registration

Q5. Do you envisage any difficulties with the proposed requirement to collect and submit confirmatory data on efficacy and safety within the provisional approval period?

Q6. What factors should be taken into account when determining whether the sponsor's proposal for collecting confirmatory data is sufficient?

Q7. What other conditions or undertakings should be considered for provisionally registered medicines?

Enhanced risk minimisation and communication

Communication from sponsors

As for all medicines, the TGA will consider, on a case-by-case basis, the need for sponsors of provisionally registered medicines to undertake additional risk minimisation and communication activities. These may include patient and/or health professional education, Dear

[8] PSURs should follow the Periodic Benefit-Risk Evaluation Report (PBRER) format as set out in the ICH-E2C(R2) guideline adopted by TGA 7 June 2005, which is available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf>

Healthcare Professional letters, or limitations on which health professionals can prescribe the product (such as controlled access schemes). These commitments will be detailed in the RMP and will fall into the scope of the RMP compliance monitoring program.

It has been proposed that Product Information (PI) and Consumer Medicine Information (CMI) leaflets for provisionally registered medicines will contain a statement that the medicine, or specific indication, is provisionally registered. This will be accompanied by a short explanation using standard wording provided by the TGA to describe what provisional registration means, tailored to the target audience (i.e. health professionals or patients). This will reduce the risk of the statement being phrased in a promotional manner and may reduce the need to negotiate this wording for each product or indication.

It is also proposed that all provisionally approved medicines, including those with a combination of provisionally and fully registered indications, will be included in the Black Triangle Scheme. This scheme requires the black triangle symbol to be displayed on the PI, CMI and other advertising, promotional and educational materials produced by the sponsor. The symbol will be accompanied by an explanation that the product is subject to prioritised monitoring and a request to report suspected adverse events.

Communication from TGA

TGA has an important role in the provision of clear advice to consumers and health practitioners that a medicine has been granted provisional registration and the implications of this for the consumer.

It is proposed that the TGA website will include a dedicated webpage for the publication of provisionally registered medicines and/or indications, similar to the current webpage that publishes orphan drug designations. This webpage could include general messaging about what provisional registration is and the implications of early registration without full clinical data. It could also provide details such as why the medicine was granted provisional registration status, the clinical trials to be undertaken and other conditions of registration. We are also considering how the provisional registration status should be reflected through existing communication channels for TGA decisions, including in the ARTG published on the TGA website, Australian Public Assessment Report for prescription medicines (AusPAR), website news updates and/or media releases.

Enhanced risk communication

Q8. What information, communication and education activities should be considered to inform health professionals and consumers about provisionally registered medicines and the implications for patients?

Q9. How might the TGA and sponsors communicate to patients and health care professionals the status of a medicine with a mix of fully and provisionally registered indications?

Tracking and enforcement of registration conditions

As part of the enhanced Medicines Vigilance Framework, the TGA will implement an RMP Compliance Monitoring Program to verify compliance with activities described in the RMP. It is proposed that provisionally registered medicines will be prioritised for RMP Compliance Monitoring, providing a mechanism to proactively track whether the collection of confirmatory

data and other risk minimisation and pharmacovigilance activities are being conducted as agreed. It is proposed that the progress of RMP commitments for provisionally registered medicines, in particular the progress of confirmatory efficacy studies, be communicated through the TGA website.

It is proposed that existing enforcement powers under section 29 and section 30 of the Act will apply to provisionally registered medicines. Refusal or failure to comply with a condition of provisional registration may result in cancellation or suspension of registration in the ARTG. Following consultation with the sponsor, the TGA will reserve the right to revoke provisional registration if at any time an issue emerges regarding the safety and efficacy of the medicine. In this scenario, individual patients may be able to access the medicine through the appropriate schemes for access to unapproved medicines (for example, Special Access Scheme – Category B).

To maintain patient safety, the TGA will need sufficient regulatory powers to allow a provisionally registered medicine to be suspended or cancelled if there is evidence that the benefit-risk balance of the product has changed (e.g. where a confirmatory trial does not verify efficacy); or if it becomes apparent that the sponsor has no prospect of obtaining the confirmatory data to obtain full registration (e.g. a pivotal trial is cancelled). The TGA may need additional regulatory powers to restrict the approved indications for a provisionally registered medicine, in the event that an efficacy or safety concern emerges for a particular patient group.

Tracking and enforcement of registration conditions

Q10. What information should be published on the TGA website about the progress of RMP commitments, including confirmatory efficacy studies?

5. Lapsing or transition to full registration

Lapsing or extending provisional registration

It is proposed that provisional registration will be limited in duration and will automatically lapse at the end of a two year period, unless the sponsor has applied for full registration of the medicine or the TGA has granted an extension to the provisional registration period. It is proposed that an extension may be granted by the TGA delegate for a further period of one or two years, with a maximum of two extensions available to a provisionally registered medicine. This proposal will allow for regular review of the efficacy and safety data to support ongoing provisional registration, while balancing resourcing impacts for the sponsor and the TGA.

In implementing the Provisional Approval pathway, we will take into account the experiences from the EMA[9] and other international regulators, which have shown that there can be delays with sponsors fulfilling registration conditions to submit data from post-registration studies. At the time of granting provisional registration, the TGA must be satisfied that the sponsor will be able to collect the necessary confirmatory data within the provisional registration period, taking into account the possibility of future extensions. Sponsors should address potential barriers to collection of data and outline the steps they have taken to overcome them as part of their Provisional Approval application process.

[9] European Medicines Agency, Conditional marketing authorisation: Reporting on ten years of experience at the European Medicines Agency (2017). Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf>

In order for an extension to be granted, the sponsor will be required to make an application to the TGA before the provisional registration period lapses. It is proposed that the extension application will include an interim report on the clinical data that has been generated within the provisional registration period and will outline any modifications to the completion dates for ongoing clinical trials. The TGA's decision to extend the provisional registration period may include re-consideration of the proposed factors influencing the pre-market registration decision (please refer to the 'Factors influencing our decision making' section above). When the TGA is deciding whether to grant an extension, we will consider whether any of the conditions of provisional registration should be modified.

The TGA will ensure that the time-limited nature of provisional registration is communicated to industry, consumers and health professionals. If provisional registration lapses, patients may be able to continue accessing these medicines through existing avenues for unapproved therapeutic goods, such as TGA's Special Access Scheme – Category B.

Lapsing or extending provisional registration

Q11. Do you envisage any difficulties with the proposed automatic lapsing after a two year period?

Q12. In what circumstances do you envisage that an extension to the provisional registration period will be sought?

Q13. Under what circumstances should the TGA consider a modification of conditions or undertakings for provisionally registered medicines?

Transitioning to full registration

The overarching objective of the Provisional Approval pathway is to provide a mechanism for patients to access certain promising new medicines much earlier than would otherwise be the case. It is proposed that the sponsor will need to make a formal Category 1 application, or equivalent, to the TGA to seek full registration of the medicine before the provisional registration period lapses. This application may be similar to an existing Extension of Indication (EOI) application under the Prescription Medicine Registration Process, in that additional clinical data on efficacy and safety from post-registration studies will need to be evaluated. Minor variations relating to the quality of the medicine that do not affect efficacy and safety considerations should be submitted as a separate Category 3 application.

The provisional registration period will be automatically extended for the period while the TGA is considering an application to transition the medicine to full registration (and any appeal processes are being undertaken), subject to any other conditions of registration continuing to be adhered to by the sponsor.

Transitioning to full registration

Q14. Do you envisage any difficulties with the proposed process for transitioning a provisionally registered medicine to full registration?

6. Other considerations for implementation

Legislative and regulatory amendment

Legislative amendments to the *Therapeutic Goods Act 1989* (the Act) and the *Therapeutic Goods Regulations 1990* (the Regulations) will be necessary for implementation of the Provisional Approval pathway. For example, legislative changes may be needed to allow for a time-limited, provisional registration on the ARTG to be granted on the basis of early clinical data.

Under Section 60 of the Act, a person whose interests are affected by certain TGA decisions may make an appeal to the Minister (or TGA delegate) or to the Administrative Appeals Tribunal for review of that decision. It is proposed that decisions relating to the designation, pre-market assessment, extension of the provisional registration period and transition to full registration will be subject to appeal. The automatic lapsing of provisional registration and withdrawal from the market will not be subject to appeal. In the interests of expediting the processes for Provisional Approval applications, we are considering limiting appeal rights only to the applicant (i.e. the sponsor) of the goods in question.

It is envisaged that provisional registration and full registration on the ARTG will be similar for all other purposes under the Act.

Legislative and regulatory amendment

Q15. Do you support the proposed amendments to limit appeal rights to certain TGA decisions and to the sponsor only?

Fees and charges

Our existing processes for the registration of prescription medicines (including application and evaluation costs) are fully cost-recovered as fees from applicants, while post-market monitoring and surveillance activities are recovered in the form of annual charges. In line with the Australian Government Cost Recovery Guidelines,[10] our fees and charges may need to be increased to reflect any additional work that is associated with the Provisional Approval registration process and post-marketed requirements.

The fee implications for the Provisional Approval pathway are dependent on the outcomes of this consultation process. Further targeted consultation with industry on the business processes for the pathway will be undertaken separately.

The TGA is also considering overlaps between the Provisional Approval pathway and the TGA's Orphan Drug Program, which offers a fee waiver as an incentive for sponsors to bring eligible

[10] Department of Finance, Australian government cost recovery guidelines (Third edition, July 2014) available at: <https://www.finance.gov.au/sites/default/files/australian-government-cost-recovery-guidelines.pdf>

medicines for a small population to the Australian market.[11] It is proposed that a sponsor can make an application for both the Provisional Approval and Orphan Drug designations.

While the designation processes will be aligned where possible, eligibility for each designation will be determined separately against the specified eligibility criteria. If the TGA determines that the medicine is eligible for both designations, it is proposed that a registration application with Orphan Drug status may submitted via the Provisional Approval pathway and any associated application and evaluation fees would be waived.

Reimbursement implications

While the Provisional Approval pathway will facilitate earlier registration for certain prescription medicines on the basis of promising clinical data, subsidised access to these medicines for Australian patients would be reliant on whether the costs of these medicines would be reimbursed through the Pharmaceutical Benefits Scheme (PBS). While the MMDR review did not make recommendations about the Pharmaceutical Benefits Advisory Committee (PBAC) processes for PBS listing of medicines, the Government is working to ensure that regulatory and reimbursement processes are appropriately aligned to take advantage of the outcomes of the MMDR reforms.

Under the current PBAC framework, a PBS listing cannot occur prior to the product being listed on the ARTG.[12] It is envisaged that provisional registration on the ARTG will fulfil this requirement, noting that the key difference between full and provisional registration on the ARTG is the time-limited nature of provisional registration.

Other feedback on the Provisional Approval pathway

We welcome any additional feedback that should be taken into account in response to this consultation paper, noting that the scope of this consultation is restricted to TGA's regulatory processes in developing a Provisional Approval pathway for the registration of promising new prescription medicines.

Other feedback on the Provisional Approval pathway

Q16. Is there anything else you would like to raise that has not been covered in this consultation paper?

[11] Therapeutic Goods Administration, Consultation: Orphan drug program ¾ 2015 consultation outcomes and 2016 orphan drug program proposal (Version 1.1, October2016) available at: <https://www.tga.gov.au/consultation/consultation-orphan-drug-program>

[12] Department of Health, Pharmaceutical Benefits Scheme: Framework for the introduction of parallel TGA and PBAC processes (updated 18 February 2011) available at: <http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-parallel-TGA-and-PBAC-processes>

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 1605
https://www.tga.gov.au