Prescription Medicines MMDR Reforms
Overview and Designation Process:
Expedited Pathways for Prescription Medicines

Adrian Bootes
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14 October 2016
Review of Medicines and Medical Devices Regulation (MMDR review)

- The review was conducted by an expert panel, comprising Emeritus Professor Lloyd Sansom AO, Mr Will Delaat AM and Professor John Horvath AO.

- The expert panel reported in two stages:
  - Stage One Report – provided to Government in March 2015
    Regulatory Framework for Medicines and Medical Devices
  - Stage Two Report – provided to Government in July 2015
    Regulatory Frameworks for Complementary Medicines and Advertising of Therapeutic Goods

- The MMDR review made 58 recommendations relating to the regulation of medicines, medical devices, post-market monitoring, complementary medicines and advertising of therapeutic goods.
Government response

• On 15 September 2016, the Australian Government released its response to the MMDR review.

• The Government accepted the majority of the review’s recommendations in full or in-principle and announced a program of reform to facilitate their implementation.

• We will be implementing these reforms in a staged approach over the next 12 to 24 months.

• The Government response identified the need for consultation with stakeholders in progressing the reforms.
Expedited pathways for prescription medicines

• The MMDR review recommended that we implement “expedited pathways for promising new medicines in certain circumstances”.

• Two new ‘expedited’ pathways are being developed:
  – **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances
  – **Provisional Approval** on the basis of early data on safety and efficacy, where the immediate availability of the medicine outweighs risk that additional data is still required.

• The key objective of the expedited pathways is to facilitate earlier access to medicines that address unmet clinical needs for Australian consumers, without compromising our standards for safety, quality and efficacy.
Proposed eligibility criteria for expedited pathways

All three proposed criteria must be satisfied for entry into the expedited pathways:

- **Serious condition** – the medicine is indicated for the treatment, prevention or diagnosis of a life threatening or seriously debilitating disease or condition; AND

- **Unmet clinical need** – the medicine addresses an unmet clinical need in Australian patients; AND

- **Major Therapeutic Advantage** –
  
  For Priority Review: there is *substantial* evidence *demonstrating* that the medicine provides a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia.

  For Provisional Approval: there is *promising* evidence from *early data* indicating that the medicine is likely to provide a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia.
Proposed designation process for expedited pathways

Please note: this is a draft process only and will be finalised by the TGA following consultation.
Proposed designation process: key details

Duration of designation
• Sponsors should know whether a medicine is eligible for designation 6-8 weeks prior to submission.
• It is proposed that designations for the expedited pathways will lapse if a full submission for registration is not provided within three months of a designation being granted.

Appeals
• Sponsors will be able to seek internal review of the designation decision.

Publication
• It is important that there is transparency of designation decisions for the expedited pathways.
• We will seek your feedback on the options for publication of designation decisions as part of the upcoming public consultation.

We welcome your feedback on the proposed designation process in the upcoming public consultation
Priority Review

• Priority Review is currently scheduled to be implemented in the next 12 months, subject to consultation feedback, and will involve:
  – New and flexible business processes to reduce the timeframe for assessing certain medicines with a full data dossier
    ▪ Decision regarding registration in the ARTG to be made more quickly
    ▪ Target of 150 working days recommended by the expert panel, consistent with benchmarks set by the FDA and EMA
  – More flexible and timely arrangements for seeking external expert advice in order to facilitate the shorter timeframe
  – Exit pathways if the sponsor does not meet requirements for Priority Review
  – Full registration in the ARTG
Provisional Approval

• Provisional Approval is currently scheduled to be implemented in the next 18 months, subject to consultation feedback, and will involve:
  – Allowing the TGA to provide provisional registration on the ARTG in the absence of full Phase III trial safety and efficacy data
  – Full non-clinical modules would still be required
  – Provisional registration granted for a specified period of time (currently proposed 2-3 years)
  – Sponsors will be required to collect and submit post-market safety and efficacy data
  – Enhanced post-market monitoring and surveillance by both the medicine sponsor and TGA
  – Medicines may be able to obtain full registration when enough data is provided to confirm adequate safety and efficacy standards

The process for Provisional Approval and associated enhanced post-market surveillance is currently being developed. Public consultation on Provisional Approval will occur in 2017.
MMDR Update: Enhanced Post-Market Monitoring
Prescription Medicines MMDR Reforms

Dr Claire Larter
Risk Management Plan Evaluation Section
Pharmacovigilance and Special Access Branch

14 October 2016
Background/Scope

• TGA intends consulting on a number of enhancements to our Medicines Vigilance Framework in response to MMDR.
• This includes the introduction of a number of new vigilance tools.
• Like our existing vigilance tools, they will be applied on a risk management basis.
• We continue to see post-market monitoring as a collaborative activity TGA shares with sponsors, health professionals and consumers.
Areas for consideration

• RMP Compliance Monitoring Program

• Black Triangle Scheme ▼

• Pharmacovigilance Inspections Program
RMP Compliance Monitoring Program-Proposal

• TGA to follow up with sponsors where RMP activities have not been completed within the timeframes given in the RMP

• Will operate within TGA’s existing Regulatory Compliance Framework, where we will seek to work with the sponsor in the first instance to achieve compliance.

• Risk based prioritisation
  ▪ Provisionally registered products
  ▪ First in pharmacological class
  ▪ Identified safety concern of special interest that require additional monitoring/ mitigation
Black Triangle Scheme -Proposal

• To alert health professionals and consumers that the medicine is subject to intensive monitoring by TGA
• Encourage health professionals and consumers to report adverse events for medicines in the scheme
• Targeted use to maintain potency of the symbol
  – first in pharmacological class NCEs
  – new medicines with safety concerns
• Will require the assistance of sponsors, health professional and consumer groups to implement the communication strategy to support the Scheme.
Pharmacovigilance Inspections Program

• Full implementation following the PV Inspection Pilot
• Program will apply to Sponsors of:
  – prescription medicines
  – over-the-counter medicines
  – listed and registered complementary medicines.
• Risk-based prioritisation of sponsors for inspection, considering:
  – the risk that non-compliance is occurring, and
  – the potential consequences of this.
• Again, TGA will take a cooperative compliance approach to work with sponsors in the first instance where there are non-compliance findings.
What Else?

• A new Adverse Events Management System
  – This will cover both medicine and medical device adverse events.
  – Will enable system to system exchange of adverse event reports using standardised international message formats such as ICH E2B R2 and R3. This functionality will make it easier for sponsors to send and receive adverse event information to/from the TGA.
  – Will assist the TGA in enhancing its signal management capabilities through more advanced signal detection and data analysis processes.
Medicine Regulation Stream

Scientific Evaluation Branch - 3 of 5 projects

• Work-sharing with comparable overseas regulators (CORs)
  – Simultaneous submissions to multiple agencies
  – Independent decision making

• Use of COR assessment reports
  – Submitted by the applicant in Australia
  – Complete reports, unredacted

• Variations to registered medicines
  – Risk based approach
Use of overseas reports and work-sharing

• Rely on identification of ‘Comparable Overseas Regulators’
  – Consultation on criteria to identify COR

• Build on existing cooperation initiatives, e.g.
  – Australia-Canada Regulatory Cooperation Initiative
  – International Generic Drug Regulators Programme

• Benefits
  – Remove ‘submission lag’
  – Reduce evaluation times
  – Better alignment of regulatory requirements between regulators
Variations to registered medicines

• Creation of new ‘notification’ rather than ‘request for variation’
  – Review of existing change codes
  – Amendment to the Act
  – New fees/charges

• Applies to all registered medicines
  – New e-form for Rx meds
  – Enhancements to existing portal for non-Rx meds
Public Consultation
2016 Orphan Drug Program proposal

Adrian Bootes
Assistant Secretary
Prescription Medicine Authorisation Branch

14 October 2016
Intent of the TGA orphan drug program

The original intention, as set out in the Explanatory Memorandum at the time of the amendment to the Therapeutic Goods Regulations in 1997, states:

‘The Regulations... provide for an orphan drugs program by waiving fees in relation to the designation, evaluation and registration of orphan drugs, orphan drugs are drugs used in the treatment, prevention or diagnosis of rare diseases, and are often not commercially viable because of their small market potential. The amendments provide an opportunity for sponsors to market orphan drugs in Australia at a reduced cost through the waiving of application and evaluation fees...’
TGA orphan drug program - figures

• **Types of registration applications** received (2011 - 2015):
  – ~51% new chemical entities/ combinations
  – 41% extension of indication
  – 3% generics
  – 6% major variations

• 52% of approved designations were for haematological drugs and antineoplastic disorders (2011 - 2015).

• The ratio of orphan to non-orphan submissions was ~1:3 in 2015 (extensions of indications and new chemical entities)

• **$4 million** in fees **waived** for orphan drugs per annum currently
Developments in the orphan field

• Global growth in orphan drug development linked to a move of pharmaceutical development towards more targeted therapies

• **78% increase in orphan designations in Australia** from an average of 14 (program start) to a current average of 25 designations per annum

• A shift in indications has been observed over time:
  – from broader indications and ‘whole’ diseases.
  – to narrow indications (e.g. molecularly-defined subset of a disease, or limited to very specific stages of a disease)

• Given TGA operates on a full cost recovery basis, such an increase is a risk to the viability of the program.

**Reforms are required to create a fair Australian orphan drug program which is fit-for-purpose and sustainable into the future**
Subsequent revenues

- Between 2015 and 2020 the market for orphan drugs is estimated to grow by 11.7% per year to $178 billion

- It is predicted that orphan drugs to account for 20% of global non-orphan prescription sales by 2020
Outcomes 2015 public consultation

- The consultation considered 4 potential reform packages based on:
  - orphan drug definition,
  - the patient threshold and the
  - charging model

- None of the proposed reform packages received majority support.

- The majority of respondents supported a change to the orphan disease threshold that could allow more diseases to qualify as orphan

- The 100% fee waiver received more support than other charging models.
## Plans I: Proposed rare disease threshold

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<tr>
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<th>‘Rare disease’ threshold</th>
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<tbody>
<tr>
<td></td>
<td>Individuals</td>
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<tr>
<td>Current</td>
<td>2000</td>
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<tr>
<td>Proposed (EMA criteria)</td>
<td>~12,000</td>
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* Intent at program start (1997)
Balancing the changing system

• **Adoption of a 5/10,000 rare disease threshold in isolation was predicted to increase** the number of orphan new entity submissions **1.7-fold**.
Plans II: Proposed orphan drug criteria

- Rare disease + ‘Serious condition’ OR Lack of financial viability + ‘Serious condition’
- Alternative methods of diagnosis, prevention or treatment
- Medical plausibility of the orphan indication
- Medical plausibility of subgroups
Predicted impact of adopting EMA criteria

- More candidates could be eligible for orphan status (threshold), however;
- Some currently eligible candidates will be excluded based on
  - a lack of ‘seriousness’ of the condition (life threatening, chronically debilitating / life threatening, seriously debilitating or serious and chronic)
  - existing availability of treatments for the condition,
  - lack of significant benefit over existing treatment (c.f. AU standard of care)
  - lack of medical plausibility of the indication and exclusion of not appropriate subgroups (e.g. based on disease stage or patient population)
- Model predicts no major impact on the number of orphan registration applications when all 4 criteria are applied to past applications
Benefits of adopting EMA criteria

- Alignment with an international regulator
- Less restrictive disease prevalence threshold
- Does not increase financial burden on other sponsors
- Predicted to be financially viable for TGA
- Creates a fair program, the program incentive (fee waiver) is targeted towards conditions where there is no existing treatment or significant benefit over existing treatment
- Only ‘serious’ conditions will be eligible
- Medical plausibility of orphan indication (generally no subgrouping unless unsafe or not effective in the remaining population)
- Retains the option to apply for orphan status based on lack of financial viability rather than the disease prevalence
Proposed designation process

1. Orphan designation lodged prior to registration *(current process)*
2. Designation lapses if a registration application is not lodged within 3 – 6 months *(new process)*
3. The designation can be withdrawn or cancelled if there is evidence that any criterion for orphan designation is no longer met *(new process)*
4. No fee for designation is planned *(current process)*
5. Lodgement of subsequent registration application can occur through any of the registration pathways (including planned priority or provisional pathways depending on eligibility)

Approved Designations 86% *(n=125)*

Registration applications received 66% *(n=82)*

No Registration application 34% *(n=43)* *(1-5 year follow up)*

2016 Orphan Drug Program proposal
Call to action

• We are looking forward to your written feedback
• Public consultation opening in mid-October, closing at the end of November 2016
www.tga.gov.au
Prescription Medicines MMDR Reforms
Discussion of the proposed Priority Review process

Adrian Bootes
Assistant Secretary
Prescription Medicines Authorisation Branch

14 October 2016
TGA’s principles for expedited pathways

1. Health professional and consumer confidence in TGA regulation of the safety, efficacy and quality of therapeutic goods must be maintained.
2. TGA will provide clear guidance to enable the applicant to adhere to the designation and registration processes.
3. Applicants will be responsible for providing TGA with all information necessary to get and support continued designation.
4. Both TGA and the applicant will commit to open and timely communication to support expediting the application in the interest of public health benefit.
5. There will be transparency of the criteria, and of designation and registration decisions.
6. The designation and registration processes will be cost recovered.
7. Appeal rights regarding the designation decision will exist.
8. The designation and registration processes should not result in an unreasonable diversion of TGA resources from business as usual activities.
Priority Review: Proposed process for consultation

Exit criteria applicable throughout process to trigger transition to the standard Prescription Medicines Registration Process

Phase 2: Submission
- Data package received checked

Phase 3: First round assessment
- (Proposed 3 months)
- Dossier contents evaluated
- Approx. 90 working days

Phase 4: Section 31 response
- (Optional 30 day stopclock)
- Evaluation completed and report finalised and sent to sponsor

Phase 5: Second round assessment
- (Proposed 1 month)
- Evaluation complete and report finalised and sent to sponsor

Phase 6: Delegate Overview and Expert advisory
- (Proposed 2 months)
- Delegate Overview prepared and sent to sponsor
- External advice sought (if required)

Phase 7: Decision
- (Proposed 1 month)
- Outcomes of external expert advice sent to sponsor (if applicable)
- Delegate’s decision letter sent to the sponsor

Phase 8: Post-decision
- ATOC entry
- AusPDR drafted

- Approved
- Not approved

Appeal rights
- As per usual process

Priority Review proposed target timeframe

Discussion of the proposed Priority Review process

Please note: this is a draft process only and will be finalised by the TGA following consultation
Proposed submission and evaluation phases

Questions

1. What are your views on:
   - Rolling questions during the first round assessment
   - Sponsors not being provided with an interim evaluation report
   - TGA only sending a consolidated s31 request (with optional 30-day stop clock) if there are any unanswered questions from first round assessment?

   NB: it is proposed that sponsors will not receive an interim evaluation report

2. If we do not provide an interim evaluation report, what other information might sponsors need to respond to s31 questions?

3. Do you have any alternate suggestions for truncating evaluation/submission timeframes?
Proposed expert advisory and decision making phases

Questions

1. Are there any other factors we need to consider in taking a more flexible approach to seeking external expert advice?

2. Do you have any other suggestions for truncating the timeframe for expert advice and decision-making?
Exit criteria – transition to standard pathway

Possible exit criteria include that:
• there is evidence that the eligibility criteria are no longer met
• the medicine has been rejected for an accelerated assessment process by a comparable overseas regulator and the reasons are deemed applicable within the Australian context
• the necessary GMP clearance or certificate has not been granted
• the sponsor fails to respond within a reasonable timeframe to our requests for additional information.

Questions:
1. Are the proposed exit criteria appropriate to trigger a transition from the Priority Review pathway to the standard Prescription Medicines Registration Process?
2. What other exit criteria should be considered for the Priority Review pathway?