Australian Government
Department of Health

Repurposing of medicines

Follow up consultation

March 2022

Background

Prescription medicines have been used ‘off-label’ for a given indication for many years to treat conditions or uses that have not been registered in Australia. Whilst this is often aligned with accepted clinical practice, it can lead to patient inequity as it is applied in an ad hoc manner at the discretion of individual doctors. It also can involve significant medicolegal risk in cases where the particular off-label use is not generally accepted in clinical practice. New uses are not always supported by evidence and the off-label use may not be reimbursed meaning the off-label use may be uneven.

Obtaining regulatory approval and registration on the Australian Register of Therapeutic Goods (ARTG), addresses medico-legal concerns and increases patient and medical confidence which will lead to wider and safer use, and improve the equity of access to medicines. To seek reimbursement through the Pharmaceutical Benefits Scheme (PBS) listing also requires formal registration of the indication on the ARTG. Repurposing medicines has the potential to remove some of these barries and improve the access of patients to the medicines they need.

For a sponsor to market a new therapeutic use for an existing medicine in Australia, they need to seek regulatory approval for an ‘extension of indication’. It is common to extend an indication to other populations such as from adults only to paediatric or adolescent patients. Extending indications is a relatively common and successful paradigm in expanding access to patients and the commercial value of new drugs.

In general terms, there are two types of indication expansion:

‘Cascading’ extension of indications:
- Changes to population (e.g., expansion to include adolescents).
- Use of a medicine for a closely related condition (e.g., use of an oncology medicine for a related tumour type or for the same tumour type in a different organ.)

Novel clinical use
- May involve a different body system.
- May be pharmacodynamically different.

An extension of indication typically involves a high administrative burden and significant costs for the sponsor. Therefore, most regulatory and reimbursement applications for extension of indications occur whilst the medicine remains on-patent and the original developer or licensor of a medicine can benefit from their intellectual property. The obstacles of seeking the extension of indications are countered by the potential revenue. After patent and/or data protection ceases sponsors are less likely to seek the extension as price reductions reduce the incentive for an initiating sponsor. The return-on-investment is expected to be low or even absent for medicines that are out of basic patent and regulatory protection.

The process of extending indications is also known as ‘repurposing’. For this consultation the focus is the process of marketing authorisation for novel clinical uses of existing medicines registered on the ARTG, rather than the commonly used practice with certain on-patent medicines of extension of indications to related populations. The intent of consultation is to establish options to reduce barriers and identify incentives for medicines to be repurposed for novel clinical uses. There is a particular focus on off-patent medicines, although opportunities for repurposing on-patented medicines also exist.

Targeted medicines

The Department is aiming to improve the environment to encourage the repurposing of medicines, with a primary focus on **novel clinical uses** of proven safe medicines.

To be considered for repurposing the medicine must:

- Have a history of safe usage within Australia;
- Be a prescription medicine that is registered on the ARTG or has formerly been registered on the ARTG (but not cancelled through safety concerns);
- Have limited commercial viability – not part of a commercial planned extension of indications program.

It is recognised that different approaches for identification of candidates for repurposing may be required for on-patent (innovator) and off-patent (generic) medicine.

It will also be important that any process developed to support the repurposing of medicines for a novel indication does not disrupt the existing, active process of extension of indications (particularly of on-patent medicines). Since 2015, over 230 medicines have had their indications extended on the ARTG.

How to respond?

The Department welcomes feedback on the options presented in this paper and encourages alternative suggestions that may assist. The consultation hub poses questions to encourage feedback within the tool. Stakeholders are also welcomed to provide more specific responses and attach a separate response document if required by uploading a response document (if required) on the final page.

https://consultations.tga.gov.au/tga/2022repurposingmedicines/

The information presented in this survey is identical to this document.

Consultation overview

In 2021 the Department conducted the following consultations on understanding barriers to repurposing medicines in Australia:

- Public consultation February 2021
- Stakeholder meeting May 2021
- Three roundtable discussions July 2021

The previous consultations focused on identifying potential incentives to overcome barriers of repurposing of medicines.

We are now seeking input to inform the Department's advice to Government on how it might:

- address commercial and intellectual property issues;
- identify the best candidates for repurposing;
- shortlist candidates; and
- approach and incentivise the market for repurposing a medicine.

The intention of this consultation is to develop options for Government consideration, noting that that some options may have legislative, regulatory change or financial implications that will require further assessment.

What have we understood so far?

In the 2021 consultations, stakeholders expressed broad support for repurposing of medicines whilst also identifying several issues and potential obstacles. The key themes of feedback included:

- Reducing regulatory burden, such as support to provide required data for regulatory and PBAC submissions and facilitating simultaneous regulatory and reimbursement evaluations.
- Incentives for sponsors, including application fee reductions and potential exclusivity periods for the new indication, to reduce commercial and (lack of) intellectual property barriers.
- Support by the Department for collation of published and unpublished data on the use of the medicine for the repurposed indication and sourcing of regulatory and health economic evidence internationally to facilitate the case for change.
- The need for more real-world evidence to be part of regulatory submissions and for clear regulator guidance and transparency around its usage and evaluation. Recognising that large, randomised trials for rare diseases are unlikely to be feasible and may not be ethical in cases where sufficient observational evidence suggests effectiveness.
- Socialised benefits whereby other companies benefit from the actions of the initiator company repurposing an off-patent medicine.
- Changing market forces as there is a risk of influencing a commercial marketplace through providing incentives, subsidies, and additional services. This could inadvertently impact the viability of future regulatory and reimbursement submissions for the same indication as the proposed repurposing.

Details of the consultation submissions received and a summary of our findings to date can be found on the TGA website: https://www.tga.gov.au/consultation/consultation-repurposing-medicines

Stakeholder discussions and analysis of the consultation submissions has demonstrated:

- Where an indication has a marginal commercial viability, regulatory requirements may reduce the likelihood of a sponsor making an application for registration and reimbursement through the traditional extension of indication process.
- There is disparity between recognised Standards of Care involving some older medicines and the ease of access to these medicines through the current regulation/reimbursement model.
- Off-label usage of prescription medicines and the associated real-world data is not captured in a way that enables future registration or reimbursement of these treatment options.
- Repurposing could be facilitated in cases where there is a formal evidence base – such as extensive medical literature on a potential repurposing application or a regulatory approval by a comparable overseas regulator for the indication.

Two benefits can be achieved by addressing these problems:

- Access to potentially effective treatment options will become more equitable for patients by registration and reimbursement for the repurposed indication.
- More repurposed treatments can be identified and targeted for registration/reimbursement if the capture and access to real-world data sets by researchers, clinicians and patient groups is improved, or if assistance is provided to the applicant to compile available evidence.

As previously stated, it will also be critical to ensure the existing, active process of extension of indications (particularly of on-patent medicine) continues unaffected.

What might a repurposed medicine process look like?

1. Potential candidates are identified through a combination of:

Department undertakes gap analysis of registered prescription medicines on the ARTG compared to international registrations

Department undertakes analysis of Standards of Care and similar documents to find unregistered usages with Australia

Interested parties (patient advocacy groups, clinical support and/or colleges) could provide potential candidates that meet critical criteria for the Department to shortlist

Medical Professionals could provide interest in a medicine/indication based treatment and associate extra information

2. Candidates are prioritised

An independent reference group select the top candidates based on their expertise, with a primary focus on unmet need in Australia as identified in the system.

A small team within the Department prepare micro-dossiers on each of these medicines, and indications, identifying what the Australian Government knows

An internal examination of the micro-dossier to consider its probability for success:
- Historic risk profile of the medicine/indication combination
- Evidence available in the Department
- International regulatory status

A proposition is generated outlining:
- additional clinical evidence required
- the cost to the sponsor for participation
- special conditions that may be applied
- early indications of likely reimbursement opportunities
- support mechanisms offered

3. Sponsors are engaged

The proposition is sent to all sponsors with the medicine registered on the ARTG (if the medicine is under patent, only to the sponsor with the patent)

Where agreement is reached, the Department supports each of the participants as equal partners

If no sponsor wishes to participate, the department may consider opening the proposition to a tender model for non-commercial entities to act as sponsor

4. Candidates are evaluated for safety and efficacy

Participants who agree are supported to apply based on the conditions in the proposition

The TGA and PBAC evaluation processes are followed and their recommendations are given to the relevant Delegates for approval or rejection

Assuming the risk benefit assessment is favourable, the medicine/indication is included on the ARTG, and recommended for PBS listing

Challenges remaining

There are at least four core challenges to overcome in the development of a repurposing of medicine policy:

A. Overcoming commercial constraints and addressing intellectual property issues;
B. Identifying potential candidates;
C. Prioritising candidates;
D. Encouraging sponsors to apply for regulation and reimbursement by removing obstacles and/or providing incentives from the regulator or government.

Although we have provided some suggestions, we note that no Government decision on these has been made at this stage. Several options would require legislative or regulatory change, as well as funding. We welcome additional ideas or guidance that may practically assist in overcoming these challenges.

A. Commercial and intellectual property (IP) issues

Problem statement: The obstacles relating to commercial and IP issues are different between medicines that are on-patent vs off-patent.

The Department received clear feedback from stakeholders during the initial consultation that compelling sponsors to apply or deeming indications would not be supported by industry.

Two groupings of medicines must be recognised when considering commercial and intellectual property concerns: 1. those that have patent and/or data protection, and 2. those that have been genericised, normally off-patent.

The incentives and approaches suggested in this paper have potential to reduce barriers for both types *if* sponsors are willing to participate in repurposing. However, there is a clear differential required where they do not, particularly where a proposed indication may not fit within a sponsor's therapeutic focus, or their global product development strategy.

1. On-patent

The Department may be able to pursue a repurposing opportunity by facilitating access for an alternative sponsor to licence the medicine for a repurposed indication, dependent upon the interest level of the parties involved.

Question 1: What practical options may encourage an innovator to work with a third party to allow an on-patent medicine to be brought to market?

Question 2: How could product stewardship issues be managed in this circumstance?

2. Genericised (off-patent)

Where the medicine is off-patent and no sponsor expresses interest within the set time, the Department may choose to seek public expressions of interest for sponsorship of the new indications, or it may place the details on file for a future review.

Question 3: What would be the most effective method to engage with potential non-traditional sponsors (such as non-profit groups, clinical colleges etc) where no interest is displayed by current sponsors of registered medicines?

Question 4: How could product stewardship issues be managed in this circumstance?

B. Identifying potential candidates

Problem statement: There is no central information collection or collation of off-label treatment options that could be used by the Department or others to identify potential medicines for repurposing.

We have identified four general approaches for finding candidates, although responders are invited to propose alternatives.

In addition, any of these four options below could be augmented by **enabling any party to make an application around a particular candidate for repurposing**. The application could then undergo an assessment by the Department and following expert committee review if considered appropriate would move into development of a submission.

The four options below may be pursued in combination; they are not mutually exclusive:

1. **The Department could identify potential candidates through gap analysis of registered prescription medicines, comparing the indications registered in Australia to international registrations.**

Benefits

- Will highlight the disparity of indications internationally and drive greater alignment.

Challenges

- Indications used internationally may not reflect actual or anticipated usage of the medicine within Australia.
- Could require significant clinical prioritisation to select highest priority candidates.
- Although comparable overseas regulator dossiers may be available, assessment will require structured clinical review as there is currently limited international harmonisation of indication wording.

2. **The Department could identify potential candidates through analysis of Standards of Care and similar documents to find unregistered usages with Australia.**

Benefits

- Provides an immediate usage pattern that is reflective of current Australian clinical practice.
- Would provide starting points for potential sponsors to find real world data through the relevant health care providers or patient groups.
- May reduce medico-legal concerns of treating health care professionals.

- May reduce medicine cost concerns of patients through potential subsidised access of current off-label prescribed medicines.

Challenges

- Quality of objective documentation on efficacy (formal evidence) may be poor or limited.
- Relies upon already established usage patterns, thus may not necessarily increase the quality or quantity of available treatment options.
- A condition may have multiple Standards of Care, potentially requiring prioritisation within a condition.

3. Interested parties (patient advocacy groups, hospital drugs and therapeutics committees and/or colleges) could provide potential candidates that meet critical criteria for the Department to shortlist.

Benefits

- Provides a “grassroots” perspective.
- Moves toward a demand driven model where group support for repurposing can be demonstrated to potential or current sponsors.
- Similar to the approach being trialled by the European Medicines Agency (EMA). The TGA can also readily access regulatory evaluations conducted by EMA and can collaborate with EMA on the regulatory evaluation if appropriate.
- Allows a range of treatments to be requested for consideration.

Challenges

- Would require additional consolidation of available documented evidence and literature as support may be based on observational experience only.
- Would require support for groups to provide potential candidates in an acceptable form.
- May require repurposing endeavours to be ‘targeted’ toward a particular condition grouping to effectively consider which medicines to support.

4. Expert clinicians and/or independent advisory committees could recommend that the Department consider additional indications for a registered medicine through a coordinated approach. Additionally, clinicians could identify the quantity and quality of clinical evidence they hold.

Benefits

- Gives voice to patients through their treating clinician.
- May allow a true demand driven model to understand the volume of patients that are likely to access the medicine if repurposed.
- May identify treatments that are not yet Standards of Care.

Challenges

- Candidates may not have documented medical literature on use and/or regulatory approvals internationally.
- Would require some investment to develop a suitable database.

- Would require additional prioritisation methods.

Question 5: Of these four options, which do you support, and why?

Question 6: Is there a combination of the above four options that would be most effective?

Question 7: Are there other practical methods possible?

C. Prioritising candidates

Problem statement: There is a need for prioritising the 'right' medicines identified as candidates for potential repurposing to support an efficient pathway through regulation and reimbursement. It is recognised that different approaches would be required for on-patent and off-patent medicines.

The Department will need a transparent process to shortlist recommended candidates, depending upon the final model for identifying candidates.

At this point, it is expected to follow at least four steps:

1. **Criteria based requests:**

These criteria, along with others identified through consultation and design, will be applied at the first round – that is when an indication is requested to be considered.

- Medicine is registered or has been registered on the ARTG (and not removed on safety grounds).
- The new indication is for a novel clinical use, rather than a cascading extension of indication.
- Medicine is used for an unregistered indication in Australia.
- Clinicians and patients support the registration for this indication, including a willingness to be involved in generation of evidence through patient reported outcomes, or potential trial approaches if necessary.

2. **An independent expert committee prioritises these requests and recommends a range of candidates for progression at recurring meetings:**

An expert committee would review the potential candidates that meet the core criteria, and prioritise based on a combination of:

- Potential improvements to patient equity of access.
- Patent status of the medicine (note: on-patent medicines would require participation and/or the expressed consent of the innovator sponsor).
- Scale of current off-label usage or potential for significant off label use.
- Availability and usage of the medicine in Australia.
- Difference between currently registered and proposed indications.

3. **A short-form assessment of existing information holdings is undertaken by the Department for the proposed candidates:**

- Scope of the level and quality of existing reference material already held by the Department (former dossiers, Drug Master Files etc).

- Scan of international regulatory and reimbursement status and history, and access to international regulatory reviews and dossiers.
- Review of the published medical literature on the potential repurposed indication. Review of known adverse events from the medicine.
- Short scan to find Standards of Care or similar recommending documents for treatments.
- Review of Pharmaceutical Benefits Scheme (PBS) for related or similar indications.
- Compile regulatory history for the medicine.

4. An early assessment of probability for success will occur by the Department in conjunction with stakeholders:

- Likelihood of commercial success and likelihood of attracting a suitable sponsor (including non-commercial sponsors).
- Are there significant side effects or safety events published that would outweigh the benefits?
- Does sufficient evidence exist for a sponsor to consolidate for an application?

Question 8: What potential criteria or checks would support the intention to prioritise novel clinical uses over more traditional extension of indications?

Question 9: Would these criteria identify the most valuable candidates? Are there others that should be considered?

Question 10: In which phase should the patient perspective be a focus? What is the best process for this?

Question 11: At what stage should commercial factors be assessed? What is the best process for this?

Question 12: What type of skills/knowledge should an independent committee seek to have (noting not all areas of expertise can be available in a single committee)?

Question 13: Should the Department (in conjunction with other groups) set priority therapeutic area foci?

D. Encouraging sponsors to apply by removing obstacles and/or providing incentives

Problem statement: There are obstacles for sponsors to overcome to register a new indication for a medicine. Provision of incentives are not the only actions required.

The Department has identified the following actions it may take, based on the consultation to date and whether the product is on-patent or off-patent:

- Provide priority review to enable a repurposed off-patent indication to be registered through an abridged application and evaluation process focussing on clinical efficacy, effectiveness, and safety.
- Waive or reduce application and evaluation fees where there is limited commercial incentive to repurpose.

- Provide regulatory exclusivity for a limited period to sponsors for repurposed indications for medicines that are on-patent.
- Provide support to the development of a regulatory submission including early scientific advice and pre-submission meetings.
- Provide coordinated support from the TGA and PBAC.
- Collation of clinical evidence including real-world evidence, literature reviews, and sourcing reviews and dossiers from comparable overseas regulators and Health Technology Assessment (HTA).

Question 14: Are these actions the most important for sponsors?

Question 15: What forms of coordination support from the TGA and PBAC would be most effective for sponsors?

Question 16: Will giving an exclusivity period to a repurposed indication give incentive for sponsors to pursue a repurposing opportunity?

Question 17: How should they be funded?

Question 18: Are there other options that should be considered?

The Department could potentially use a combination of these actions to improve the viability for sponsors to apply to extend the indication. As well as these direct actions, the Department may also choose to enable sponsor(s) to extend indications within a coordinated TGA and PBAC evaluation process.

The Department would provide an offer to all sponsors holding marketing authority on the ARTG for the medicine. If a medicine is protected by patent, the Department would only engage with the sponsor holding the patent.

Feedback has shown it can be difficult to encourage a company to make a regulatory submission for a new indication where the medicine's patent has expired because in such cases, if one company gets TGA approval for an extension of an indication other companies may similarly benefit for a significantly reduced application complexity and fee. This is considered a socialised benefit.

One option may be to allow sponsors to either apply individually, or as a collective to share the fees and efforts outlined in the offer (this would require legislative change). Where exclusivity was offered, it would apply to any sponsor who responds within a set period. Again, any changes to exclusivity would require legislative change.

Question 18: Would there be interest in collaborative submissions by sponsors? Under what circumstances could this be attractive to sponsors?

Question 19: Are there other practical options to overcome the socialised benefits in order to secure at least one application?

Question 20: What time period would be considered sufficient for sponsors to consider their interests and apply?

The *Therapeutic Goods Act 1989* requires an application from a sponsor (or a collective of sponsors) to repurpose a medicine. Sponsors will retain the responsibility to provide pharmacovigilance of their medicines, including any new indications.

Next steps

The Department will consider the responses received, and will provide options to the Government, noting that changes to the *Therapeutic Goods Act 1989* and/or *National Health Act 1953* will likely be required.

Final comments

Please feel free to provide any other information or suggestions that you may have.