Australian Government
Department of Health
Therapeutic Goods Administration

Repurposing of Prescription Medicines

URL: https://consultations.health.gov.au/tga/repurposing-of-prescription-medicines

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TGA Health Safety Regulation

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Consultation overview

Repurposing is the process of identifying new uses (or 'indications') for medicines. In some cases, prescription medicines may have been used 'off-label' for many years to treat conditions that they do not have formal regulatory approval (i.e. are not registered) for. Whilst this may be accepted clinical practice, obtaining formal regulatory approval for the repurposed indication can lead to wider and safer use as it means that the evidence base for such clinical use has been independently reviewed and found sufficient, and that the benefits of such use outweigh the risks. Regulatory approval of the indication would also address the medico-legal concerns that can arise form off label use, increase patient and healthcare practitioner confidence and enable the possibility of reimbursement for the indication through listing on the Pharmaceutical Benefits Scheme (PBS).

Repurposing older medicines is generally considered by industry to be a lower risk and cost activity compared to the development of new medicines. In order to register a new indication on the Australian Register of Therapeutic Goods (ARTG) for an existing medicine, a sponsor is required to make an application to the Therapeutic Goods Administration (TGA) with scientific data to support the new indication. As preclinical development will have already been completed there is likely to be an established record of safety for the medicine which can be generalised where the dose and patient populations are similar for the new and existing indications.

Recently, repurposing older medicines has been a prominent area of research for potential COVID-19 treatments. Repurposing has also been recognised as a key topic in public submissions for the ongoing inquiry into approval processes for new drugs and novel medical technologies in Australia by the House of Representatives Standing Committee on Health, Aged Care and Sport.

In recent years, the TGA, often in cooperation with the relevant clinical colleges has promoted repurposing directly with sponsors, with mixed success. Some examples are listed below:

Tamoxifen

Tamoxifen has been in clinical use for the treatment of breast cancer since the 1970s and is registered and reimbursed for this indication in Australia. Tamoxifen was also approved by the United States Food and Drug Administration (US FDA) in 1998 for the reduction in breast cancer incidence in high risk women, but was not approved in Australia or reimbursed for this indication despite wide 'off-label' use for this purpose supported by recommendations in Australian and international guidelines.

To facilitate registration of the 'off-label' indication, the TGA worked with the innovator sponsor of tamoxifen to develop a literature based submission. This approach streamlined the application process with a focus on safety and efficacy without the requirement for quality or nonclinical information (as this was already established). Despite tamoxifen being off-patent at the time, none of the generic manufacturers took an interest in applying to extend indications because, as stated at the time, this was not part of their usual business model.

Rifampicin

Rifampicin was as an important 'off-label' treatment option for Buruli ulcer, a skin/soft tissue infection due to a mycobacterium, of growing concern in coastal parts of Victoria.

Although the market for this indication is quite small, a regulatory application was received and was approved by the TGA in October 2020 (in combination with another antibiotic). Rifampicin was subsequently listed on the PBS.

Dacarbazine

At the request of clinical groups, the TGA investigated the potential for repurposing dacarbazine for early stage Hodgkin's Lymphoma. Despite repeated approaches to sponsors, no submissions were received. The TGA cannot compel a sponsor to make a submission.

These examples demonstrate that while some successes have been had, barriers remain to the repurposing of medicines.

Why are we consulting?

This consultation seeks to understand potential obstacles and/or incentives to repurposing that may influence a sponsor's decision to extend an indication for an existing medicine – in particular for those indications that are:

- already approved overseas
- for a less common disease
- already accepted clinical practice albeit 'off-label'
- likely to be less commercially profitable.

Consultation outcomes may be used to shape regulatory and reimbursement reforms and policy options, as well as input into the review of the National Medicine Policy. It is likely that there will be further consultation as the Department considers feedback and formulates options. Implementation of some options would require government approval (regulatory change) and/or parliamentary approval (legislative change).

Consultation scope

Scope:

- Incentives and barriers to repurposing of medicines currently or previously on the ARTG, including both genericised medicines and innovator medicines under legal protection (e.g. under patent or exclusivity).

Out of scope:

- Medicines not yet (or previously) registered in the ARTG for any indication including new and novel medicines that may be still in the clinical development phase.
- Extensions of indications to closely related conditions – e.g. use of an oncology medicine for a related tumour type or for the same tumour type in a different organ. "Cascading" extension of indications has become a very common approach to oncology drug development e.g. for PD-1 and PDL-1 checkpoint inhibitor antibodies.

How to respond

The Department welcomes all feedback, including feasible approaches that may minimise barriers to repurposing of medicines.

This consultation poses questions to encourage feedback, however you are also welcome to provide more specific responses and attach a separate response document if you wish.

Submit your views by clicking the link below – this will step you through questions seeking specific feedback.

Alternatively, the full consultation paper can be downloaded and you can upload a response document on the final page.

Known challenges

Although there are existing mechanisms to enable the registration and reimbursement of repurposed indications for older medicines, it is recognised that industry concerns and challenges still exist, including:

- **Off-label use:** Many inexpensive medicines may be already used to a significant extent 'off label' and if supported by clinical guidelines, or used in hospital situations (where there may be formal approval of its off-label use by the hospital medicine and therapeutic committee) there may not be sufficient incentive to seek TGA registration and PBS reimbursement (if applicable) for the particular indication.
- **Evidence gaps:** While the TGA will accept literature-based submissions and high-quality observational studies in regulatory submissions, there may still be significant challenges in assembling 'regulatory quality' data to support an application to register a new indication. There may be an actual evidence gap or an over-reliance on case reports and lower quality evidence that are unable to meet the required efficacy and safety standards. It is recognised that there are challenges to gathering evidence and conducting research when off-label use of medicines has become standard practice in the absence of formal regulatory approval.
- **Socialised benefits:** In cases where the medicine's patent has expired and it is now available with innovator and multiple generic sponsors, it can be difficult to encourage a company to make a regulatory submission for a new indication because in such cases, if one company gets TGA approval for an extension of an indication other companies may similarly benefit (except in the rare case where a company had a prior 'method of use patent' for that indication).
- **Outside of therapeutic area:** Many Innovator sponsors tend to focus their business on particular therapeutic areas. If the repurposed use is for a substantially different therapeutic area this may be unattractive for a sponsor, even if they hold exclusivity for the molecule, due to logistics and costs.
- **No innovator:** In many cases, the repurposed medicine is an older medicine which has many generics and the innovator sponsor may no longer supply the medicine in Australia. In these situations, the generic sponsors may be unwilling to extend the indications *de novo* given other sponsors can similarly benefit.

- **Lack of regulatory experience**: To extend an indication requires significant understanding of regulatory processes. Some generic sponsors may be unfamiliar with the process to extend an indication *de novo,* notwithstanding existing TGA guidance.

In considering the potential options presented in this consultation, The Department also recognises the following operational challenges and risks:

- **Allocation of resources toward repurposing medicines:** Departmental efforts involved in implementing potential options will need to be adequately and appropriately resourced, especially in the setting of fee reductions, acknowledging that the medicines regulation by the TGA and PBAC submissions are cost recovered.
- **Determining the trigger for action:** Initiation of any of the potential options will likely need to be supported by a prioritisation mechanism to ensure efforts are appropriately targeted, especially under options where either investment of public funds is supporting repurposing or fee waivers have been provided. This could potentially be through assessing the public health-benefit criteria of the potential repurposing.
- **Changing market forces:** 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.
- **Conflict of interest:** Where the Department is providing additional support above and beyond what it ordinarily provides for registration or reimbursement it could be seen to create a conflict. Policy design will need to ensure this can be managed.

Question: What are the critical concerns and challenges/barriers to repurposing medicines in Australia?

Question: Are there additional challenges/barriers to repurposing that need consideration?

Some potential options

A number of possible approaches have been identified to encourage a greater number of regulatory and reimbursement applications for repurposing older medicines. These options are not exhaustive nor mutually exclusive, however they balance facilitating repurposing pathways without compromising on the key elements of safety, quality, and efficacy. The cost effectiveness of any repurposed medicines would need to be considered separately.

These options are intended to stimulate discussion and feedback, noting that they would require additional considerations including potentially legislative amendments.

Each of these approaches relies upon an Australian sponsor taking legal responsibility for the product including pharmacovigilance requirements.

Option 1. Reduce regulatory burden for repurposing medicines

- Provide enhanced and structured regulatory support for applicants seeking to repurpose medicines:
  - Providing dedicated support for clinical trial design (where needed) and scientific advice
  - Assistance with the development of literature reviews to simplify literature based submissions
  - Increased direct support on repurposing where sponsors are non-industry based
  - Develop specific regulatory guidance documents for repurposing medicines
  - Facilitating access to comparable overseas evaluation reports through the TGA where they exist
  - Improved coordination of multi-country submissions for repurposing with other regulators.

This may alleviate some regulatory burden for potential sponsors, particularly where they may have limited regulatory experience. These measures could also encourage non-commercial entities to consider becoming a sponsor for a particular indication, although these sponsors still must take legal responsibility for the product including pharmacovigilance requirements.

In some cases there may be existing funding/support streams (e.g. through the MRFF repurposing program) that could also be used to support evidence gathering for an eventual registration and reimbursement application.

It may also be possible to explore the interest of comparable international regulators and HTA agencies in encouraging a multi-country submission.

- **Provide fees and charges relief:**
  - Providing fee relief for certain repurposing submissions for medicines that have low commercial returns but high public health gains.
  - This would be subject a TGA and PBS determination being made following application to the TGA. For medicines that have low commercial returns but high public health gains.
  - Potential for shifting a single evaluation fees to a smaller payments over a 3-5 year period or reduction in PBS reimbursement.
  - Expansion of the orphan designation periods for particular indications.
  - Potentially provide technical advisory support to non-commercial sponsors.

Currently the TGA application and evaluation fees for an extension of indication are around $148,000, along with ongoing annual fees based on medicine type.

Providing TGA and PBAC fee relief is an existing option for medicines determined to be ‘orphans’ by the TGA for rare diseases.

- **Simplify/streamline simultaneous submission for regulatory and reimbursement evaluation:**

- Supporting applicants through centralised case management for regulatory/reimbursement submissions.
- Extending the current parallel processing pathways for regulation and reimbursement of medicines.
- Allowing a PBS evaluation to be sought prior to regulatory approval to understand if reimbursement would be likely if the extension of indication were approved by TGA.

A recognised challenge to extend any indication is the twin assessment of regulation followed by reimbursement, in particular the commercial risk involved at each stage. For marginal or smaller target population indications, PBAC consideration prior to TGA may provide more certainty to a sponsor as to the likelihood of whether the new indication is likely to be reimbursed, although if the medicine were not subsequently TGA approved reimbursement of that indication could not proceed.

- **Provide exclusivity periods for new indications of repurposed off-patent medicines:**
  - Provide exclusivity to the first sponsor who seeks TGA approval for an extended indication to hold regulatory approval for the use of a particular medicine for that indication for a period of time.
  - Provide exclusivity to the first sponsor to seek PBS listing for the use of a particular medicine for an indication for a period of time.
  - This could particularly be appropriate for non-commercially viable indications that have significant public health benefits, although there would be the requirement for an agreed and codified process to determine “non commercially viable” and “significant public health benefits”.

Providing exclusivity could increase the viability for a sponsor, even in a small market – particularly for a generic medicine. It is likely that legislative changes would be required to implement these options.

Question: What would be the functional impact of these options in incentivising medicines repurposing?

Question: Are there additional options for the Department to consider to reduce the regulatory or cost burden for repurposing of medicines?

Option 2. Further support the development of repurposed drugs through enhancing information access

These concepts may support industry in identifying the potential scale of the market within Australia, or may provide insight for research organisations in gathering evidence.

- **Facilitate open-access to "real-world" Australian medicines usage data**

  Such data could come from research studies/ clinical trial outcomes databases, data gathered by clinical colleges on particular indications (e.g. to support guideline development), and hospital drugs and therapeutics committee requirements including hospital record. International data sources are more likely to be useful in cases where the indication is approved in that country.

  Because (declared) off label medicine use should be under private prescription, PBS data will not be of use although other data sources such as IQVIA and NPS Medicinewise surveys may also assist. Applications to the TGA Special Access Scheme and Authorised Prescriber Schemes will provide some information as the requested indication is provided, although such applications to TGA are often not made when it is a registered medicine being use off-label. TGA also does not record information on clinical/ patient outcomes for medicines used in the AP or SAS schemes.

- **Provide consolidated international regulatory and HTA/reimbursement information**

  Providing a simple mechanism to find related international information (both regulatory and reimbursement approval assessment reports or decision summaries for a medicine may assist patient groups and sponsors to see a medicine within a global context and identify repurposing targets without needing to track each particular country.

Question: Would access to data on real word use data lead to more repurposing of medicines? What sources exist and would be useful?

Question: Are there other non-commercial datasets that could be obtained that would assist in facilitating repurposing?

Option 3. Actively pursue registration and potential PBAC review of additional indications for medicines

Currently, if the Department was to recommend that an indication be potentially added to a medicine as a public health initiative four main outcomes are possible:

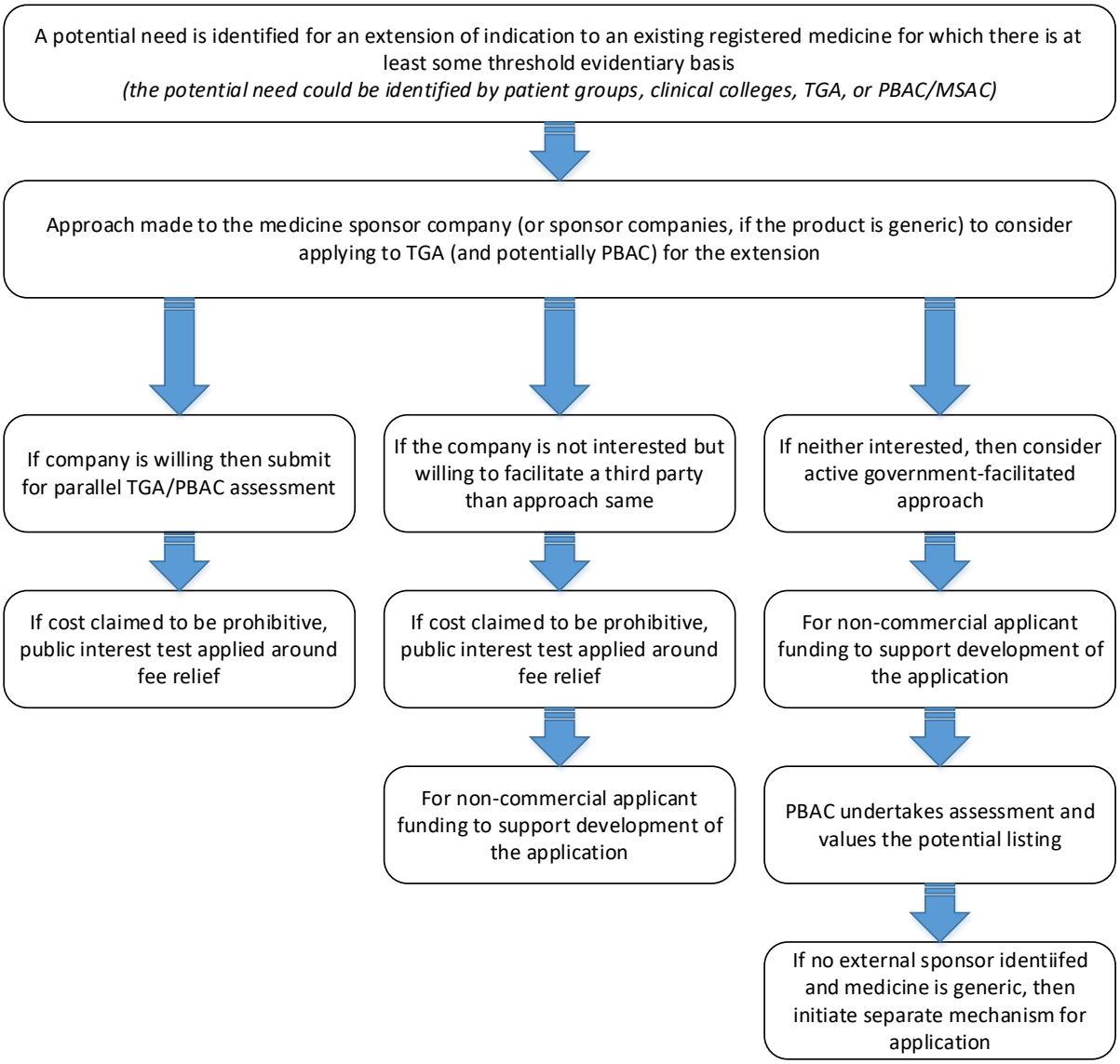
- The innovator sponsor is willing, and submits the application.
- A generic sponsor is willing, and submits the application.
- The innovator sponsor declines, but is willing to work through a third party, who may submit an application (e.g. using creative commons access).
- The innovator sponsor, generic sponsor/s and third parties are not willing to submit an application.

In cases where there is no commercial party interested in submitting a repurposing application, subject to further exploration, the following options could be considered. It is acknowledged that legislative amendments would be required to implement these options.

- **Seek public expressions of interest for sponsorship of new indications of a medicine, potentially limited to non-commercial organisations:**
  - A non-commercial organisation (e.g. a clinical or patient group) to take the submission through the TGA and/or the PBAC.
  - The agreed 'sponsor' would be able to on-licence the medicine with the approved indication to a commercial sponsor.
  - Provide some form of exclusivity (e.g. through changes to the Therapeutic Goods Act or National Health Act) for the indication.
  - Implementation of other regulatory and reimbursement support mechanisms (as outlined above) to simplify the regulatory process.
- **Compel the sponsor of the medicine to make an application for the additional indication:**
  - The sponsor would be obliged to provide the evidence in support of the additional indication sourced through their reasonable endeavours in good faith.
  - The sponsor would commit an offence if it fails to comply with the requirement to apply for an additional indication; or if the evidence it gave is false and misleading.
  - Registration of the new indication would still be subject to TGA's evaluation and approval.
  - The sponsor would remain responsible for post-market requirements including pharmacovigilance.
- **Approve the inclusion of an additional indication for the medicine without the need for an application from the sponsor:**
  - The TGA would undertake a self-generated assessment of the safety and efficacy, and 'deem' the new indication, where approved.
  - Where the medicine is a generic, this would be extended for all relevant sponsors.

- The PBAC process would determine the reimbursement options as if the submission was through a sponsor.
- The Sponsor(s) would remain responsible for post-market requirements including pharmacovigilance.

This potential option is shown in the flow diagram below.



Question: What are the main barriers that would lead to sponsor refusal to apply to register a new indication?

Question: Would there be interest from non-commercial groups to become sponsors to enable registration and reimbursement of repurposed medicines?

Question: Would particular measures undertaken by the Department (e.g. compelling an application or deeming a new indication) be an effective and feasible mechanism to facilitate repurposing?

Version history

Version	Description of change	Author	Effective date
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