ANZCA
FPM

30 March 2021

Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Email: Medicines.Review@health.gov.au

Attn: Medicines review section

Repurposing of Prescription Medicines

Thank you for the opportunity to provide feedback on the Therapeutic Goods Administration's (TGA's) consultation regarding repurposing of prescription medicines.

The Australian and New Zealand College of Anaesthetists (ANZCA), including the Faculty of Pain Medicine, is committed to setting the highest standards of clinical practice in the fields of anaesthesia, perioperative medicine and pain medicine. As one of the largest medical colleges in Australia, ANZCA is responsible for the postgraduate training programs of anaesthetists and specialist pain medicine physicians, in addition to promoting best practice and ongoing continuous improvement that contributes to a high quality health system.

Specific feedback in relation to the consultation questions is attached. Please keep us informed on the progress of developments in this area. In particular, we are concerned that consideration be given to any potential unintended consequences of changes affecting off-label use of prescription medicines, including patients not receiving evidence-based therapeutic interventions. It is important that clinical input is sought from specialist groups such as ours in relation to any proposed mechanisms that may impact on off-label prescribing.

We are currently looking into the extent of off-label prescribing in anaesthesia and pain medicine to establish how any proposed changes might affect our areas of practice, patient experience, and outcomes. We propose to provide feedback to TGA on completion of this process.

Thank you again for the opportunity to comment on the repurposing of prescription medicines. Should you require any further information, please do not hesitate to contact the ANZCA safety and quality policy staff in the first instance at sq@anzca.edu.au

Yours sincerely

Professor David Story
Chair, Safety and Quality Committee

Known challenges	
What are the critical concerns and challenges/barriers to repurposing medicines in Australia?	The **Known Challenges** section captures the main themes. The document seems to focus on conditions as indications and repurposing drugs for different conditions. However, labelled indications in Australia are also often limited by lower age boundary: • Adding discussion of repurposing for ages not previously approved would greatly benefit the paediatric sector and Australian children's medication safety. • In addition, the other age extreme needs to be considered. Currently most adult dosages do not have an upper age limit but we are now dosing people over 100 years of age and just assume we should "start low, go slow but don't stay low" which is just a pharmacokinetic consideration assuming that the drug's targets have not changed, which is not the case. Greater development and recognition of geriatric indications and therapy is required. Indications also stipulate route of administration and medicines are used off label via other routes. For example: Clonidine, which is indicated via IV and PO routes for hypertension, is often used in anaesthesia and pain medicine for paediatric sedation (off-label age and condition) and as an adjuvant to neuraxial local anaesthetics via the intrathecal route (off-label route). These uses of alpha 2 agonists are examples of where off label use warrants careful evaluation, and represent one of a number of drugs/classes being considered internally by ANZCA in its review of off-label prescribing of medicines in anaesthesia, perioperative and pain medicine. The issue of emerging indications, and emerging adverse effects, highlights the need for the rigor built into medicines regulation. Much is made of "repurposing older medicines" based on the unfounded assumption that their safety profile has been established. However, these older medicines did not go through the rigorous preclinical and clinical studies now required for a new medicine. For example, Proton pump inhibitors (PPIs) are potent choline acetyltransferase inhibitors and have been implicated as a dementia risk factor; methadone blocks the hERG channel and can cause arrhythmias; azithromycin has non-antimicrobial immunomodulatory effects; tamoxifen (the example on p 4) is a prodrug requiring CYP2D6 metabolism for efficacy.

	All these newer effects were studied post marketing. Hence if applications are made for repurposing of older medicines, contemporary preclinical pharmacological studies need to be conducted.
Are there additional challenges/barriers to repurposing that need consideration?	Whilst high quality evidence may demonstrate benefit, it is rarely enough to quantify uncommon adverse events (AEs) and serious adverse events (SAEs) or comparative harms. Therefore, unprofitable repurposing/relabeling (as for children or rare disease or the older person) is compounded by potential liability for future harms claims/costs. Any repurposing and changes to indications need to be accompanied by rigorous post-market surveillance of use specifically in the context of the new indication.
Option 1. Reduce regulatory burden for repurposing medicines	
What would be the functional impact of these options in incentivising medicines repurposing?	Cost-shifting due to TGA support and fees relief would be an incentive for sponsors in so far as current costs are a disincentive. However, the substantial financial cost of development of evidence on safety and efficacy, and potential legal responsibilities still mean market forces will determine where commercial entities place their priorities. Support for well-designed non-commercial trials may be appropriate for those areas of clinical priority which are commercially unattractive, especially if designed in consultation with TGA (in a manner not dissimilar to that used by FDA for commercial development). However, these changes are unlikely to encourage non-commercial entities as the potential legal responsibility/liability remains so costly. It should be explicitly stated that "There are provisions under section 26BJ of the Therapeutic Goods Act 1989 that allow for any person (industry, healthcare professional, member of a scientific society etc.) to apply for a new indication to be added to the Determination" and that professional societies/colleges in particular should be encouraged and supported (for example via the Medical Research Future Fund - MRFF) to apply for a new indication. Allowing Pharmaceutical Benefits Advisory Committee (PBAC) consideration before TGA approval would be an incentive to continue with the TGA repurposing submission. Providing exclusivity periods for new indications of repurposed off-patent medicines is likely to be effective.

Are there additional options for the Department to consider to reduce the regulatory or cost burden for repurposing of medicines?	Perhaps idealistic – for non-commercial entities willing to submit application to repurpose a drug with high public health merit, TGA could advocate/facilitate research funding to support the logistics of clinician-/sector-investigator led efficacy and pharmacovigilance studies.
Option 2. Further support the development of repurposed drugs through enhancing information access	
Would access to data on real world use data lead to more repurposing of medicines? What sources exist and would be useful?	Yes but reliability is an issue. As stated, hospitals, Special Access Scheme (SAS), research and pharmacovigilance collections will be the main sources because off-label use will not be on Pharmaceutical Benefits Scheme (PBS) and the current adverse drug reactions reporting system is not functioning as it should with a worrying reduction in the number of reports submitted. The role of registers, or equivalent observational tools, to better examine post-market performance and safety is an option which warrants consideration in re-purposing. It may facilitate collection of high quality data to support re-purposing.
Are there other non-commercial datasets that could be obtained that would assist in facilitating repurposing?	Hospital e-prescribing data e.g. Medchart where the indication for use is indicated during prescribing. Pharmacovigilance studies such as RAPID, monitoring outcomes and AEs of medicines use in palliative care and soon in paediatric chronic pain. Given the very recent Australian Covid-19 vaccine adverse effects App, consideration could be given to developing similar Apps for all routine off-label uses and new indications (repurposing) of registered medicines
Option 3. Actively pursue registration and potential PBAC review of additional indications for medicines	
What are the main barriers that would lead to sponsor refusal to apply to register a new indication?	Risk/liability for unknown and future harms outweighing market size and remuneration. The other main barrier is the perceived “them and us” notion; TGA should encourage greater co-operation and collaboration between pharma industry and professional societies/colleges.
Would there be interest from non-commercial groups to become sponsors to enable registration and reimbursement of repurposed medicines?	Yes, but consideration of legal indemnity may be needed given that costs could be great if unforeseen harms emerge. Infrastructure and funding for pharmacovigilance and efficacy studies may be needed. Conflict of interest issues would emerge just as for TGA as a sponsor-supporter.

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?	It is difficult to see how TGA could legally or ethically compel an application. It would be hard to legislate that sponsors can be forced to shoulder additional legal responsibility and financial risk for repurposed medicine harms. Moreover, if off-label use is forbidden (compelling the application) then this would lead to interrupted supply to patients, delays in essential care, and potentially harms. Deeming a new indication based on high quality evidence seems ethical and most likely to increase prescriber and consumer confidence and safety. However, without a sponsor, TGA may have to hold the legal responsibility for surveillance and harm.

End of feedback