MTPConnect
MedTech and Pharma Growth Centre

DRUG REPURPOSING: BUILDING THE PATH TO AUSTRALIAN SUCCESS

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Contributors

MTPConnect thanks the following for their contributions to this report:

- **Stakeholders** from across the medical technology, biotechnology and pharmaceutical sector who provided their valuable input
- **Michelle Burke** at Indigo Advisory for her authorial assistance
- **Professor Beth Webster**, director of Swinburne University of Technology's Centre for Transformative Innovation, for her review of this report's economic analysis.

About MTPConnect

MTPConnect is Australia's Medical Technology, Biotechnology and Pharmaceutical (MTP) Industry Growth Centre. We are an independent, not-for-profit organisation that champions a sector-led approach to accelerating the growth of Australia's MTP sector. As an independent body, MTPConnect is attuned to the needs of all participants in the sector. We drive connectivity, innovation, productivity and competitiveness in Australia's MTP sector. We foster collaboration, address workforce challenges, open up international markets and optimise regulatory and policy frameworks. By doing so, we help maximise opportunities for Australian scientific and technological breakthroughs to be translated and commercialised, improving health outcomes and driving economic growth.

Further information is on the MTPConnect website at: https://mtpconnect.org.au

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Contents

RECOMMENDATIONS FOR ACTION

RECOMMENDATION 1

Adopt a broad definition of repurposing

Repurposing's aim should be to identify and develop a new use of an existing drug with the goal of making that product available to patients for that use.

Pathways to drug repurposing should focus on new indications for existing drugs but continue to have a broad scope.

RECOMMENDATION 2

Pursue four goals for Australian repurposing

Pursue policies that promote:

- an open prioritisation process in which key stakeholders can participate
- independent assessment and prioritisation of candidates
- a structure for collaboration and access, including appropriate incentives designed to increase repurposing effort
- a sustainable funding base.

RECOMMENDATION 3

Consider creating an Australian Repurposed Development Program

Examine a repurposed drugs program which could:

- oversee funding
- prioritise drugs for study
- coordinate clinical trials
- organise development and initial manufacture of innovative treatments, where required
- where necessary, purchase adequate supplies for treatment.

Consider using MTPConnect to run this program, as recommended by the Australian Medical Research Advisory Board.

EXECUTIVE SUMMARY

Drug repurposing provides Australian patients greater access to medicines that have already been proven to be safe and cost-effective for other conditions. It is also an opportunity for Australian industry to grow new consumer markets.

Repurposing gives existing drugs important new uses

Drug repurposing has scored a number of prominent victories for global health. Among them are:

- remdesivir, first researched as a potential treatment for the Ebola virus and now being used against COVID-19
- acetylsalicylic acid, the active ingredient in aspirin, now reducing risks for people with several cardiovascular conditions
- thalidomide, an infamous disaster as a morning sickness treatment but now an important drug for use in the treatment of myeloma, a type of blood cancer.

We can safely say that there are drugs already in existence that have the potential to treat a number of today's diseases. Consequently, there is a significant opportunity to identify and develop these drugs.

Interest in repurposing is surging

Interest in drug repurposing has been rising for several years. It can be faster and more cost-effective to repurpose an existing drug relative to traditional drug development processes. It starts with an existing base of safety knowledge.

Bringing a new medicine or vaccine to market may now cost as much as US$2.8 billion on average and require between 10 and 15 years' work. This is a problem for both the industry, which requires an adequate return on investment, and for patients, particularly those with less common conditions, who may be left with fewer treatment options. It is fuelling the growing interest in repurposing.

And the COVID-19 pandemic has further underlined repurposing's importance. Repurposed drugs are among the biggest hopes for better COVID-19 treatments.

Repurposing faces an information paradox

Repurposing is designed to create new ideas and evidence about use – in this case, the use of drugs.

Yet repurposing faces a known economic paradox: on their own, markets will underproduce new ideas and facts. This is because people will not pay for ideas *before* their content is disclosed, but have no need to pay for them *after* their content is disclosed. Further, even if some people pay for knowledge or information, it is often difficult to prevent them from freely passing this content to other people, who then in turn have no need to pay.

Patents are designed to prevent this sharing of content. They provide incentives for patent holders to find new uses and markets for their existing drugs as well as providing the fundamental protections to discover new medicines and treatments. But for-profit companies sometimes have fewer incentives to continue researching drugs *after* they receive approval for their initially proven uses. This is particularly the case for less common conditions, and in markets that have weaker intellectual property protections than those in the US, EU and UK, including for regulatory data protection. And companies have less incentive to conduct research and trials on drugs once their patents expire, because they cannot prevent competitors from free-riding on their findings.

The end result is that market drivers and the current intellectual property system in Australia are insufficient to realise the significant opportunity that drug repurposing presents.

There are challenges too for developing new uses for patented drugs, where system barriers (such as for regulatory and reimbursement approvals) impose high costs and create disincentives.

A related challenge is that successful drug repurposing requires many stakeholders to coordinate with each other – but most countries lack an obvious lead body or focal point.

These widely acknowledged global problems are essentially what economists call a 'market failure'. It is known in the global pharmaceutical sector as 'the problem of new uses'.

Countries such as the US, the UK and Canada are improving their repurposing systems to solve these and other repurposing challenges. So should Australia.

Australia has a viable repurposing solution

One solution to Australia's drug repurposing problem stands out: a public-private partnership program to coordinate the key stakeholders. It would effectively act as an 'air traffic controller' to help overcome barriers to repurposing.

This program would use a mix of incentives to foster collaboration between researchers, industry, investors, regulators and other stakeholders. A lead body would:

- provide incentives for groups interested in researching, developing, testing and financing repurposed drugs
- where appropriate, fund information-gathering and screening of preclinical research for the most promising Australian repurposing candidates
- assemble medical, scientific, legal and economic experts to decide the national priorities for drug repurposing
- ensure participants do not get in each other's way
- coordinate financing of projects to research drug repurposing candidates
- coordinate Australian stakeholders' cooperation with our international counterparts
- if necessary and appropriate, oversee government investment in projects
- bring together the most appropriate public- and private-sector partners in the value chain to repurpose projects
- facilitate coordination of clinical trials to reduce duplication and maximise impact
- oversee the progress of repurposing projects until they deliver drugs to consumers.

Australia need not reinvent the wheel. The challenges are significant; from costly and uncertain regulatory and reimbursement processes to weak intellectual property protections and lack of incentives for repurposing. But by participating in a global repurposing program, we can obtain information on research and trials undertaken by other countries and bring health and economic benefits for Australians by driving better repurposing outcomes.

Australia can also focus its repurposing research activity in areas of existing strengths and capabilities, such as clinical trials and associated high-value manufacturing. This will help the federal government achieve its employment and export targets.

We can make repurposing happen in Australia

Improved repurposing systems have already been proposed for the US. In Australia, a 2017 Australian Senate committee suggested some elements of such a solution. And in 2018, drug repurposing was made a research priority for the Medical Research Future Fund (MRFF), the Australian Government's $20 billion long-term investment fund for Australian health and medical research. Its importance has since been reaffirmed in the third set of MRFF research priorities, covering the period 2020 to 2022, which calls for industry partnerships to identify drugs with repurposed therapeutic potential.

Industry stakeholders are asking for leadership. As Australia's Industry Growth Centre for the Medical Technology, Biotechnology and Pharmaceutical (MTP) sector, MTPConnect has the reach, profile and expertise to make such a repurposing program a success. Now we have set out a way to make it happen.

INTRODUCTION: RESPONDING TO THE RISE OF REPURPOSING

Repurposing puts existing drugs to new uses

When we repurpose a drug, we:

- *identify and develop*
- a valid *new use*
- of an *existing* drug
- with the goal of *making it available to patients* for that new use.[1]

This concept of *drug repurposing*[2] springs from a simple but powerful insight: some therapeutics originally used to treat one condition are later found to successfully treat others.[3]

Repurposing has been explored for conditions ranging from breathlessness to ageing, and from smoking addiction to breast cancer (see Table 1, p.7).

Among the most prominent examples:

- Thalidomide, developed to treat pregnant women's morning sickness, proved disastrous for their babies. It damaged lives and, as a by-product, changed the way drugs are regulated. Yet today, with appropriate cautions,[4] the same drug's anti-inflammatory properties make it an important treatment for leprosy. And it can also help treat the very different condition of multiple myeloma, a type of blood cancer. It blocks the blood supply to cancerous cells, and stimulates the body's immune system to attack myeloma cells (Hussein, 2005).
- Acetylsalicylic acid, the active ingredient in aspirin, has been used for millennia to relieve pain and fevers. But low-dose aspirin is now prescribed for many people with a high risk of cardiovascular events, to prevent blood clots from forming. It is also used among older adults to reduce the risk of colorectal cancer, and was recently being assessed as a treatment for bipolar disorder (Talevi, 2018).
- Sildenafil was developed to treat angina. It gained far greater success as an erectile dysfunction treatment called Viagra, and has since been repurposed again to combat pulmonary arterial hypertension (Ghofrani et al., 2006).
- Fexinidazole was abandoned by a pharmaceutical firm at an early stage. But the Drugs for Neglected Diseases initiative, a Swiss not-for-profit research group, supported further research when the drug was found to show anti-parasitic qualities. After years of work, it was approved for the treatment of sleeping sickness in the Democratic Republic of the Congo. It is the first oral medicine created to treat the disease, and works for all stages of it (Neau et al., 2020).
- Remdesivir, a broad-spectrum antiviral drug, was first noted in 2016 as a potential treatment for Ebola virus. In 2017 it showed activity against the coronavirus family of viruses. In 2020 it was urgently investigated as a potential treatment for COVID-19. It was granted conditional approvals for use in the US, Japan and Europe between April and June of 2020 (Saint-Raymond et al., 2020) and provisional approval by Australia's Therapeutic Goods Administration (TGA) in July 2020. In late October 2020 it became the first treatment for COVID-19 to be fully approved for adult use by the US FDA (US Food and Drug Administration, 2020).

Box 1 The mission behind this report

MTPConnect commissioned this report as part of its mission to drive connectivity, innovation, productivity and competitiveness in Australia's MTP sector.

For this discussion paper, we partnered with Michelle Burke at Indigo Advisory. We surveyed more than 30 Australian-based stakeholders; from consumer and patient organisations to researchers, major pharmaceutical companies and commercialisation experts. We also examined more than 40 reports in the medical, research and economic literature.

1 We explore the definition of repurposing more deeply in a latter sub-section,'Stakeholder beliefs about repurposing'.
2 The repurposing concept is also sometimes called 'drug repositioning'.
3 In this report, the term 'drug repurposing' is used to cover research and deployment efforts on both approved and unapproved drugs. Some commentators argue that the latter category is better described as 'rescued'.
4 In the US, for instance, thalidomide dispensing is regulated by a program called Thalidomide REMS (formerly known as the System for Thalidomide Education and Prescribing Safety, or S.T.E.P.S.).

Not only can drugs be repurposed, but they can also be used to develop ***analogues***. These work like the drug itself, but with variations, such as fewer side effects. As an example, an analogue of thalidomide known as lenalidomide is more easily absorbed by the body.

While repurposed drugs to date have mostly been those that are either close to, or already off-patent, potential also exists for repurposing on-patent drugs, particularly for less common conditions where there is significant unmet need. In this context we must recognise that different research and development (R&D), regulatory and reimbursement pathways may need to be developed to better incentivise repurposing. Stakeholders have made it clear that these pathways should not disrupt the existing business models of research-based pharmaceutical companies.

Stakeholders in our survey pointed out that while access for patients was the goal of any repurposing pathway, the starting point for the process varied. They range from those at the target identification stage through to those where evidence is already available. The pathway elements may be summarised as:

- research, development, evidence generation or collation
- system navigation to ensure patient access, including the TGA and Pharmaceutical Benefits Scheme (PBS).

Box 2 Common terms in drug repurposing

Repurposing: The process of identifying and developing a valid new use of an existing drug with the goal of making it available to patients for that new use.

Indication: A valid reason for using a particular test, medication or procedure. One medication, for instance, can have several indications.

Off-label: A term denoting the use of a drug for a purpose (or occasionally at a dose) outside of the approved indications, i.e. what it has regulatory approval to treat. When it has been approved for that use, it is called on-label. Evidence for a drug's effectiveness is often available years before it is approved for such a use. But doctors are known to prescribe drugs off-label only when no suitable on-label drugs are available.

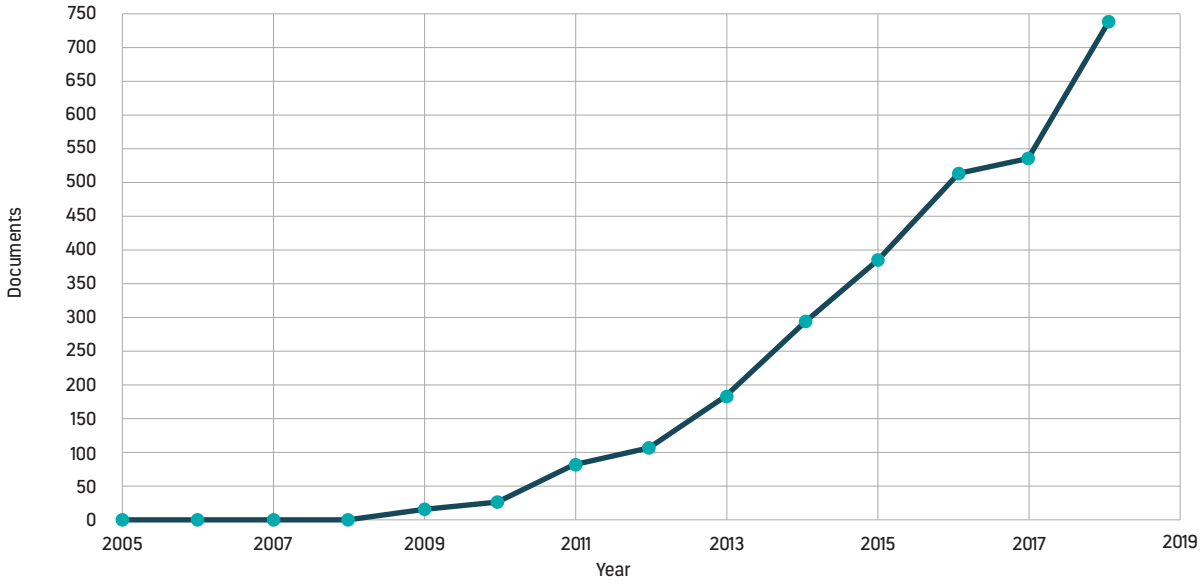
INTRODUCTION:
RESPONDING TO THE RISE OF REPURPOSING

Interest in repurposing is rising fast

The figure below shows the increase in global interest in repurposing within the field.

Figure 1: The explosion in repurposing publications

Number of publications indexed by the Scopus citation database containing the terms 'drug' and 'repurposing' or 'drug' and 'repositioning' in their title, abstract or keywords, by publication year.



Source: Talevi and Bellera (Talevi & Bellera, 2019)

The table below shows the range of repurposing attempts made to date. Note that:

- some have successfully reached patients
- some are in progress
- some have failed or stalled
- some were never launched for the original use but were resurrected for a repurposed use.

Table 1: Repurposing efforts are now widespread

Some well-known repurposed pharmaceuticals grouped by distinguishing feature.

Pharmaceutical group	Existing use	Repurposed use
bisphosphonates	Decrease risk of fractures	Breast cancer
rituximab	Non-Hodgkin B-cell lymphoma	Myasthenia gravis CD+ lymphoid cancers
tamoxifen	Breast cancer	Prevention of breast cancer
raloxifene	Osteoporosis	Breast cancer
metformin	Diabetes	Cancer, ageing
thalidomide	Morning sickness, nausea	Leprosy, multiple myeloma
morphine	Pain	Breathlessness, COPD
ivermectin	Parasitic worms	Scabies
zoledronic acid	Reduce risk of fractures	Hypercalcaemia in cancers affecting bones
fulvestrant + CDK inhibitor		Combine in breast cancer
antihypertensives		Poly-pill; combine in low doses
A2RA antagonists	Hypertension	Neuropathic pain
Bexsero vaccine	Meningococcal B	Gonorrhoea
sildenafil	Angina	Erectile dysfunction
bupropion	Depression	Smoking cessation
ropinirole	Hypertension	Parkinson's disease
zidovudine	Cancer	HIV/AIDS
various antivirals		Coronavirus

Source: Various studies

INTRODUCTION:
RESPONDING TO THE RISE OF REPURPOSING

With this report, we aim to show how Australia can participate more vigorously in this evolving activity. We have consulted with a wide range of stakeholders (Box 3) as well as surveying the literature.

Box 3 MTPConnect has consulted the full range of stakeholders

The stakeholders consulted for this report are listed in Appendix 2. They include:

- consumer and patient organisations
- researchers, including clinical researchers and academic researchers and representative institutions
- representatives of clinical advisory groups such as the Medical Oncology Group of Australia and the Cancer Council
- the Pharmaceutical Benefits Advisory Committee (PBAC) chair and deputy chair
- Federal Department of Health officials, including officials in:
  - the Health Products Regulation Group (including the TGA)
  - the Health and Medical Research Office (which oversees the MRFF)
  - the Health Technology Assessment division (which oversees the PBS)
- industry associations AusBiotech, Medicines Australia and the Generic and Biosimilar Medicines Association
- selected large pharmaceutical companies based on experiences and/or case studies to date
- representatives of the Office of the Minister for Health and Aged Care
- investors and commercialisation experts
- drug development experts
- commercial organisations providing services to the medicines sector.

Discussions focused on experiences to date, the pathways used and the challenges of Australia's current approach.

The stakeholders expressed strong interest in improving Australia's repurposing effort. Based on the number of both successful and failed case studies, Australia has a tangible opportunity in the field. It possesses both the capabilities and the capacity to improve the number and reach of repurposed medicines.

REPURPOSING PROMISES RESULTS AND RETURNS

Repurposing offers faster delivery and lower cost

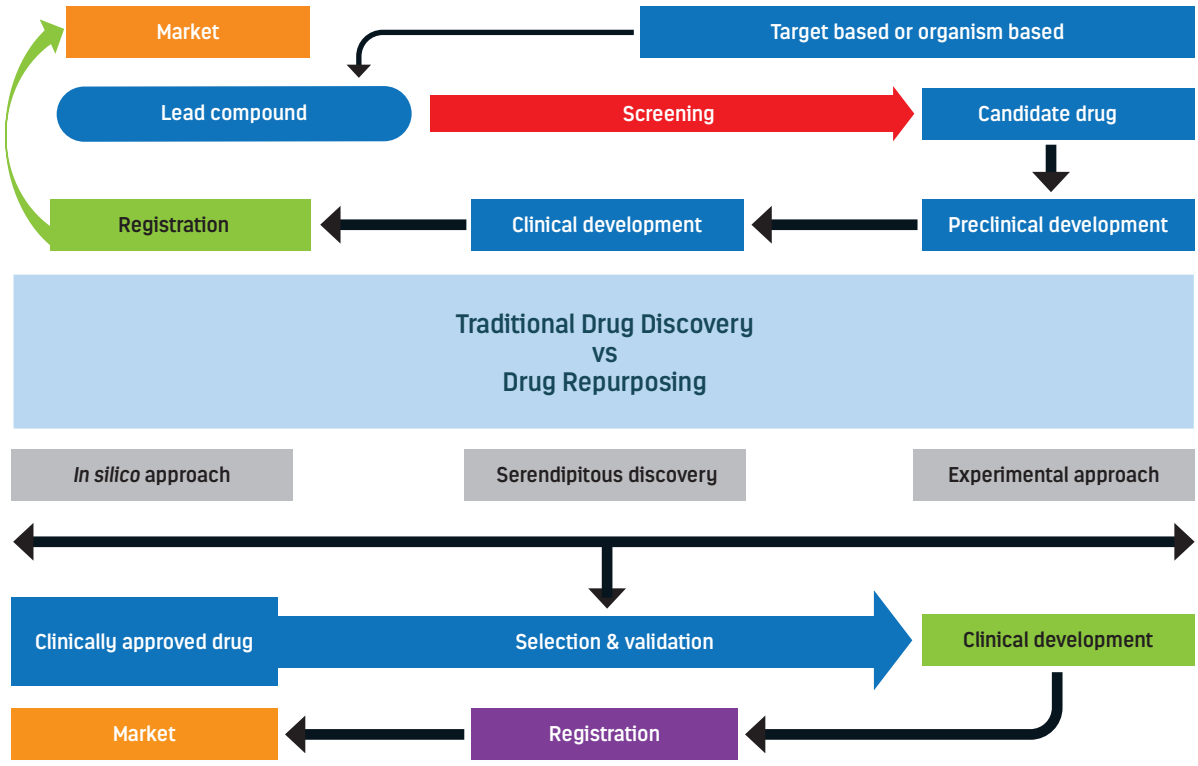
For the past 75 years, the pharmaceutical industry has generally used variations on the following broad model for drug development (Figure 2):

- use scientists to research, develop and test new compounds
- screen to find the most effective candidate
- develop that candidate
- then seek regulatory approval and potential reimbursement through PBS listing.

Such an approach is a high-cost undertaking. It can take decades and cost in the billions of dollars.

- Traditional drug development is often said to require 12 to 15 years on average (Hughes et al., 2011).
- One recent estimate puts the *average* cost of bringing a new drug to market at US$2.8 billion in 2018 US dollars (Wouters et al., 2020).

Figure 2: Traditional drug discovery vs drug repurposing



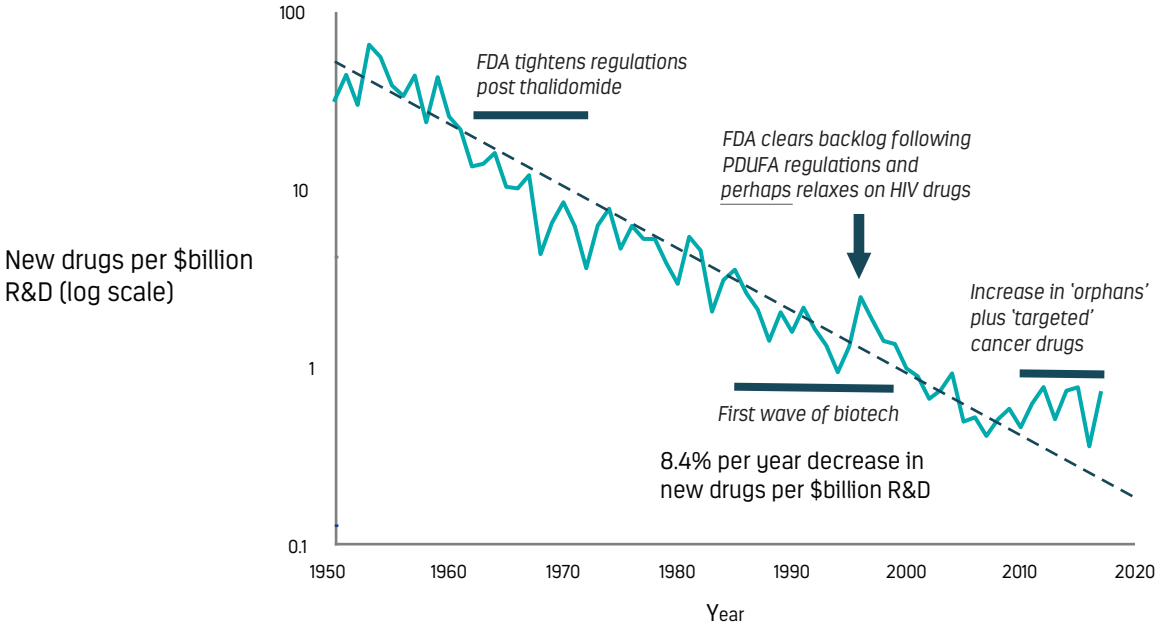
Source: Rudrapal et al., 2020

Yet such spending does not always generate returns. Over recent decades, the industry has had to contend with deploying more and more researchers for longer and longer periods yet finding fewer new therapeutics (Halabi, 2018).

Figure 3 depicts this decline in drug R&D productivity.

Figure 3: Pharmaceutical R&D productivity has fallen

Number of new molecules approved by US FDA (pharma and biotech) per global US$billion invested in research and development.



Source: Jones and Wilsdon (Jones & Wilsdon, 2018)

This R&D productivity problem besets many industries (Bloom et al., 2020). But it has become famously severe in the pharmaceutical sector.[5] One group of authors has suggested that the sector suffers from the opposite of the famous 'Moore's Law', which describes rising productivity in the semiconductor industry. At one point, analysts were predicting that pharmaceutical R&D returns would go negative by 2020 or soon after. Although that hasn't happened, on some measures global returns are at historically low levels (Steedman & Taylor, 2019). In 2019, on one estimate, global R&D returns for pharmaceutical companies fell to 1.8 percent, from 10.1 percent in 2010 (Steedman & Taylor, 2019). Developments such as 'personalised medicine', once expected to reverse this trend, have not yet revived returns (Martin & Bowden, 2019).

By 2004, researchers began to explore a new strategy for checking the fall in drug R&D returns (Ashburn & Thor, 2004). They suggested taking a drug that had already been developed to fight one disease and exploring whether it might be effective against another target. This is the technique known as *repurposing*.

5 Among the explanations is Pammolli et al's suggestion that "the simplest problems have already been solved, and researchers are left with more difficult challenges" (Pammolli et al., 2010).

Repurposing appeals to pharmaceutical researchers, the industry and government because it offers the simultaneous promise of:

- greater speed[6]
- lower cost[7]
- reduced risk that the drugs involved will fail safety hurdles.

In the past 15 years, the global pharmaceutical industry has embraced repurposing. While the precise extent is not clear, some analysts claim about a quarter of new US market entrants are repurposed.[8]

There is evidence of considerable interest in, and use of repurposed drugs. However, most of this use occurs informally through the physicians, rather than through the formal regulatory pathway.

This informal use is called off-label consumption (Soares, 2005) and it is widespread. For instance, the US National Comprehensive Cancer Network estimated that in US cancer treatment in 2005, 50 to 75 percent of drug or biologic therapy use occurred off-label. Physicians make their recommendations based on their own clinical observation, academic research and collegiate information exchange. Nonetheless, formal testing for repurposing will ensure less ad hoc, safer and more certain patient benefits. It could also lead to wider use, as it will provide access to publicly available and approved scientific evidence supporting the use of the repurposed medicine.

Repurposing offers a particularly attractive path to treating:

- emerging infectious diseases, such as COVID-19
- difficult-to-treat and neglected diseases, which are less appealing as subjects of traditional drug discovery.

Several pathways lead to repurposing

Repurposing candidates arise in several ways, as our stakeholders noted and as researchers have described (Martin & Bowden, 2019; Talevi, 2018). The main ones are:

- **Serendipitous discovery:** In many cases, a new potential use comes to light when researchers note unexpected effects (such as limiting inflammation) from existing use. So far, these instances have mostly involved relatively obvious effects. Thalidomide was one of the world's most investigated drugs when its anti-cancer effects were spotted. Aspirin was already one of the most used drugs in the world. The relevant side effects of minoxidil and sildenafil became obvious without any detailed investigation.
- **Rational discovery:** In some cases, a new use occurs to researchers or, often, practising clinicians, as they come to better understand how a drug works. For instance, imatinib began as a treatment for chronic myeloid leukaemia. But over time researchers came to better understand the operation of tyrosine kinase inhibitors, of which imatinib is just one. The drug is now used to treat at least five other conditions, including gastrointestinal tumours.
- **Systematic discovery:** New computational tools[9] allow researchers to search through and analyse the contents of large data sources such as public drug libraries. By doing so, the researchers aim to identify uses for previously developed or partly developed drugs. They base their analysis on known interactions between drug molecules and various protein targets. Most large pharmaceutical companies now use these techniques for repurposing (Akhoon et al., 2019). Some institutions are reported to have created databases containing tens of thousands of drug samples and corresponding patient data (Chilukuri et al., 2017).

In serendipitous discovery, evidence can sometimes appear partly through clinical use. As our stakeholders pointed out, access to the drug for that use may remain limited – and yet the drug may come to be prescribed commonly off-label.

In some cases, such as thalidomide, the new use of the drug differs greatly from the original. In other cases, such as imatinib, the new use is related to the old.[10]

6 It is often claimed in academic articles that repurposing may require three to 12 years compared to traditional drug development's 12 to 15 years. Note that while these figures are commonly used, their precise origins are unclear.
7 One analysis has suggested repurposing costs no more than 60 percent of the cost of developing a new drug (Rudrapal et al., 2020).
8 As early as 2011, one drug repurposing firm claimed that repurposed drugs made up "more than 30% of new market entrants" to the US pharmaceutical market (Persidis, 2011). A more recent commercial study claims that "of 28 drugs (including both novel and repurposed) approved by the US FDA in the first quarter of 2020, 12 were repurposed", and that "around 25%-40% of annual pharmaceutical revenues are generated from the sales of repurposed drugs" (*Drug Repurposing Service Providers Market, 2020-2030*, 2020). It is important to note that the reliability of the methodologies used in these commercial claims is not clear.
9 These are sometimes called informatics tools.
10 This is also referred to as an 'adjacent' indication.

In either case, repurposed drugs hold advantages for their developers:

- Repurposed drugs have generally been tested. So drug developers understand more about how they affect the body than they do about new drugs. They may, for example, better understand their safety at particular dosages, and how they interact with other drugs and with particular foods.
- This knowledge reduces the risks in developing the drug for its new use and researchers may be able to safely bypass certain steps in development.

Box 4 COVID-19 pushes repurposing into the limelight

The fight against the COVID-19 pandemic has moved drug repurposing squarely into the spotlight. Existing antivirals, antimalarials and antirheumatics are all being explored for potential effects on COVID-19.

It was inevitable that repurposing would make up a substantial part of the effort to identify a potential therapeutic or preventative treatment for COVID-19. The global challenge of this disease has demanded the rapid development of remedies – much faster than the normal drug discovery process can give us. As pharmacologist Steve Alexander and co-authors noted in an April 2020 paper (Alexander et al., 2020):

"Clearly initial drug discovery should focus on repurposing licensed drugs, as dosage and safety information are largely to hand … As a 'second wave', *de novo* discovery focusing on novel agents may allow future refinement and capacity to treat patients who are unable to be treated by, or are unresponsive to, the repurposed agents, but it would be very unlikely to have these new drugs available to treat the current crisis."

The result was a surge in repurposing efforts. By May 2020, the COVID-19 database at www.redo-project.org/covid19db/ listed 918 drug-based interventional trials. Of these, 633 included at least one repurposed drug (Mucke, 2020).

One example is remdesivir, a drug originally designed to treat Ebola and Marburg virus infections, which has been shown to have some effect against COVID-19 (J.H. Beigel et al., 2020) and has been approved for use against it. Other drugs are also being explored for their ability to influence the disease. Indeed, the repurposing of drugs to fight COVID-19 is now one of several innovation episodes depicted as examples of "ultrafast innovation" (von Krogh et al., 2020).

Stakeholder beliefs about repurposing

When stakeholders talked with us about the scope of repurposing, we found almost all favour a broad definition. Drug repurposing is taken to encompass both drugs in use and those yet to reach the market. And it encompasses a diverse range of situations.

Expect continuing variety

Stakeholders believe that repurposing proposals have been and will continue to be highly variable. They will have different needs, show different gaps in understanding, and need different elements to assure access for patients. The breadth of case studies in Table 1 also underscores this need for variety.

- Repurposing candidates are identified by various methodological approaches. These include clinical experience, mining of prospects, and network analyses.
- Candidates show up different gaps in our understanding and require resolution of different issues before patient access is secured. Some require basic, or translational research. Others are more developed, with existing research, so that they only require consideration by regulators.
- Stakeholders noted that evidence for a repurposed drug often evolves over time and through clinical use.

All this underscores the importance of ensuring broad criteria for candidates and the pathways they take to success.

Avoid disrupting models where repurposing works

Stakeholders recognise that industry already develops new uses or indications for existing drugs as part of normal business practice. This might be called 'repurposing'. But stakeholders do not support changing this normal business model *where it is already effective*. In some cases, the market may fail to provide pathways for industry to support this type of repurposing. Where the normal pathway *is not effective*, and action is required, such candidates should be included in the scope. In the words of one stakeholder: "Anything that is not accessible or not likely to be accessible without intervention."

Other stakeholder beliefs

The stakeholder group also generally believes that:

- Repurposing can be based on a body of evidence from multiple studies or from a single study.
- Repurposing can apply to an expansion of use either over time or from a series of studies.
- Repurposing should encompass medicines where different lines of therapy (primary or upon failure) are proposed.
- Repurposed medicines may need new registration and reimbursement pathways that account for new collaborative R&D approaches.
- Repurposing should include referring to prevention versus treatment being the same strict purpose but different use.
- Repurposing should encompass rarer conditions where the 'use' may not be different (for example targeting a particular biomarker) but the *indication* – that is, the targeting of a specific disease – *is* different.
- Repurposing should encompass new combinations of drugs, given that for some intractable conditions, a combination of existing drugs may be the only option available.

Stakeholders did *not* suggest a priority list or therapeutic area upon which to focus. In fact, stakeholders strongly recommend any pathway be agnostic to therapy area or stage.

While stakeholders do not want to exclude on-patent drugs[11] from repurposing, they noted that such cases might require different paths, different expertise, and different approaches to partnerships. This is notwithstanding that repurposed off-patent drugs may also require new or different pathways.

Stakeholders differ on the extent to which repurposing should cover 'new formulations' and 'new populations'. For example, one stakeholder said a new paediatric use would require a reformulation or new dose-defining studies.

RECOMMENDATION 1

Adopt a broad definition of repurposing

Repurposing's aim should be to identify and develop a new use of an existing drug with the goal of making that product available to patients for that use.

Pathways to drug repurposing should focus on new indications for existing drugs but continue to have a broad scope.

11 On-patent drugs are produced and marketed exclusively by their owner, typically a pharmaceutical company that discovered or bought the rights to them.

MARKET FAILURES THREATEN DRUG REPURPOSING

Stakeholders report, and the literature suggests, that drug repurposing is subject to market failure in several ways.

The economics of insufficient drug repurposing

Repurposing is essentially about creating new ideas and evidence about use. So it quickly comes up against two well-known problems in the economics of ideas.[12]

- The first problem is known as the Arrow information paradox (Arrow, 1962). People will not pay for new ideas and facts unless they understand their content. But once the content is disclosed, people know them – and so have no more need to pay for them.

  And even if some people pay for the knowledge or information, it is often difficult to prevent them from passing this content to others. These other people then have no need to pay for that content.

  A great deal of information has the economic characteristics of a fireworks display: you can't charge people for it.[13]

  The result of the Arrow information paradox is that markets alone can produce too few new ideas and facts.

- Arrow himself also points to a second information economics problem that bedevils drug repurposing. Unlike most goods and services, information that has been produced can then be used by any number of people without diminishing its value. This suggests that for information to be optimally used, its marginal cost should be zero. Yet to reward an information producer for the cost and risk of producing valuable information, market prices for that information must be positive.

  And so in this second way, too, markets alone can produce too few new ideas and facts.

These two issues matter particularly in the economics of innovation. We run heightened risks when we use research to produce information and knowledge. These risks arise because we cannot predict output with any certainty from a given set of workers, materials and equipment, the way we can when we use machines to make goods.

On top of all that sits one more problem: the negative economic effects of under-producing information and knowledge compound. A major part of their value is that they let us develop further information and knowledge.

For these reasons, even very market-orientated economies give considerable public support to the production and free distribution of research and other knowledge and information producing activities. This support is most prominent as:

- public research grants for universities
- government research institutes
- private sector research and development subsidies
- the maintenance of an intellectual property system.

Drug repurposing creates knowledge and information. Existing forms of support are geared towards ameliorating market failure in the discovery and commercialisation of new drugs. But they provide insufficient incentive for the repurposing of existing drugs.

Intellectual property laws do not adequately support repurposing

In trying to resolve the Arrow innovation paradox described above, our system of biopharmaceutical innovation relies heavily on a 'market exclusivity period' for new drugs. This exclusivity period is the span of time when the drug is 'on-patent'. During this time, the innovator can market it without competition from generic versions of that drug. For pharmaceuticals in Australia, this exclusivity period can last for up to 25 years from the date of filing a patent application. However, the time-consuming nature of pharmaceutical R&D and the fact that patentees are usually unable to market their inventions until their product has received regulatory approval means the period of market exclusivity is often far shorter.

But the patent system does not provide many incentives for either the patent owner or other firms who may want to find a new use for an already-patented drug. This problem has a formal name in economics – 'the problem of new uses' (Eisenberg, 2005).

The patent owner may not want to conduct formal trials for new uses, as these trials may reveal unanticipated side effects which will damage the market for the original use (Eisenberg, 2005). By the time the drug is repurposed for its new use, its remaining market exclusivity period may be just a few years, if anything (Smith, 2011).

Other firms have limited incentives to invest in the research and formal trials for new uses while the original patent is in place. Not only would they need licensing permission from the patent owner – which may not be granted – but the patent owner could free-ride on the other firms' trial data.

12 In technical economic terms, the first problem results from information's non-excludability, the second from its non-rivalry.
13 This quality (in economic terms, non-excludability) is why fireworks displays are usually put on by local or state governments, not private businesses.

Off-patent drugs lack repurposing incentives

Because of the disincentives to repurpose drugs which are on-patent, the vast majority of drugs ever repurposed are no longer under patent – that is, they are 'off-patent'.

Off-patent status means the drug can be produced as a 'generic', without the originator's permission and without royalties. So drug prices fall significantly after patents expire.

Once a drug is off-patent, a firm investing in further research and clinical development has very few ways to recoup their investment and once production begins, they may be undercut by lower-cost generic producers. Getting a strong composition patent[14] will not be possible if the molecules are the same as the original patent. Even if the discovered new use is novel enough to be filed as a new-use patent,[15] it is well accepted that these are hard to enforce as competitors can legally manufacture the compound and sell off-label.

Studies confirm these mechanisms are indeed forestalling exploration of repurposing. After listing potential extensions to patent privileges for anti-cancer drugs, Verbaanderd and colleagues note the persistence of difficulties in getting regulatory approval for new anti-cancer uses of an existing drug (Verbaanderd et al., 2020). These difficulties combined with weaker patent protection mean that "[p]harmaceutical companies often choose not to invest in new therapeutic indications after expiry of basic patent and regulatory protection periods of their approved products".

The problem is more severe because even for such drugs, the cost of development for new uses can be substantial in typical developed economies. Verbaanderd and colleagues argue that regulatory permission to market such drugs "entails a high administrative burden and significant costs" (Verbaanderd et al., 2020). They find the return on investment in such drugs is typically expected to be low.

In sum, repurposing for some drugs is rarely funded wholly by the private sector.

System and regulatory impediments drive up costs

Stakeholders were clear that any effort to improve repurposing outcomes needs to result in consumer access to new medicines.

However, the pathway to delivering on this was far less clear. Particular challenges exist when moving from the point of evidence availability through the regulatory and reimbursement pathway. This is an inflection point past which many candidates do not progress.

A key issue relates to who can put forward a TGA application. Currently, only those entities willing to take on the enduring liabilities and responsibilities, including supply, are able to make applications to the TGA. Supply will generally be viable only where a sponsor already supplies for existing uses (either generic or originator companies). Existing sponsors also have access to worldwide safety databases to inform the regulatory review. In addition, the application for reimbursement process is also lengthy, expensive and uncertain. In practical terms, this limits applications to company sponsors.

So it is sponsors that bear the cost of navigating the resource-intensive and complex application process. And for many companies, the cost of compliance is a barrier to participation and an impediment to securing approval for consumer access to repurposed medicines. This barrier will be lower if sponsors' costs are minimised, with a 'no loss' approach limiting negative cost consequences even if no commercial return is realised.

Regulatory expertise is lacking

Further adding to the problem, researchers working on repurposing typically lack the expertise or resources to navigate regulatory and reimbursement hurdles. Respondents in our survey specifically cited the need to increase knowledge of the role of intellectual property in drug repurposing. In short, repurposing requires not just specialist pharmaceutical expertise but specialist regulatory and reimbursement expertise.

Off-label drugs do not maximise consumer reach

When an existing drug is used off-label, it is essentially informally repurposed. As described earlier, this occurs when evidence gathered from academic research, physician observation or collegiate information exchange suggests that an existing regulated drug can treat a disease other than for which it had been formally tested and approved by the regulator. However, the use of drugs off-label carries risks. These drugs have, almost by definition, not been fully tested for contraindications and side effects in the new patient population, and/or not reviewed and approved by the relevant regulator.

Critically, to the extent a drug is a suitable candidate for a new use, a lack of reimbursement and information available to patients and physicians means it is not reaching all consumers who would benefit.

14 A composition patent is based on the molecules patented, regardless of use.
15 A new-use patent is based on a new indication or new user population.

As Verbaanderd and colleagues note, other "substantial ethical and legal challenges" also exist for this option (Verbaanderd et al., 2020, p.7). Patients are often confronted by some combination of:

- a lack of strong scientific information to support off-label use
- a lack of information about the specific use for which the drug is being prescribed off-label
- a risk of unknown adverse events
- lack of government reimbursement for use.

In short, regulatory approval provides benefits for both consumers and sponsors in the market.

Investors lack sufficient mechanisms for collaboration

A consistent theme of discussions with stakeholders was that successful repurposing requires collaboration, particularly with industry (more in Appendix 3). There was broad agreement that the requisite research and development capabilities exist within Australia's research community. But there was also agreement that stakeholders are not uniformly well-integrated or networked around repurposing projects. There is not always critical engagement with consumers, sponsors, companies or drug development experts.

The economic literature also reflects this issue. Scott et al. note with respect to Alzheimer's research that the economic literature "highlights the potential for collaboration among public- and private-sector stakeholders" (Scott et al., 2014, p.18). But the barriers to successful collaboration, together with other problems, loom large enough for them to comment that in the case of Alzheimer's disease, no single company will be able to overcome them. "Even the largest companies are limited in their ability to develop treatments," they argue.

Existing government interventions in the market (such as research grants and the intellectual property system) by themselves are not sufficient to overcome the market failures in repurposing.

Current law discourages repurposing

The end result of these problems is that current intellectual property laws effectively discourage formal repurposing of many drugs, in Australia as elsewhere.

Canadian health law expert Sam Halabi has described "broad agreement that there is insufficient repurposing activity because of numerous intellectual property protection and market failures" (Halabi, 2018).

Some analysts of the problem have concluded that the key to overcoming these problems is further extension of the market exclusivity period. (Other legal solutions have also been proposed but have not yet been accepted.[16])

US intellectual property analyst Richard Smith puts it simply: "Commercial success of a repositioned drug will depend on achieving effective market exclusivity through a combination of intellectual property and regulatory exclusivity" (Smith, 2011).

However, as even many supporters of a longer exclusivity period accept, these incentives do not always provide a practical solution. Smith notes that this "problem of new uses … has vexed firms, legislators and regulators for most of the last decade".

Box 5 COVID-19 shows repurposing's problems

COVID-19 may illustrate critical market failures in drug repurposing. Susan Athey and her colleagues (Athey et al., 2020) argue that COVID-19 offers the same problem as many other conditions. There are "generic drugs that might hold clinical promise but remain unexplored because innovators view the revenue potential as small compared to the development costs and the risks".

Academic researchers might be expected to simply choose the more promising drugs, new or repurposed. But in practice there is pressure even on them to discover drugs that will create funding streams for their institutions.

Athey and her colleagues also note that for any drug to be repurposed and used against COVID-19, it must find patients who can complete clinical trials. By June 2020 there were already reports of such shortages, they write. And new drugs tend to be given priority access to this "limited patient pool".

16 See for example Benjamin Roin's suggestion for an infrastructure to monitor new uses (Roin, 2014).

CURRENT POLICY APPROACHES TO REPURPOSING

Global approaches vary

Internationally, approaches to repurposing and its problems differ. Some countries apply existing funding pathways to support the identification and development of repurposing candidates by explicit *inclusion* to the program outline.

- The UK's Biomedical Catalyst: Developmental Pathway Funding Scheme funds repurposing efforts as part of its new drug development and testing work.
- The US is among the countries to provide specific incentives for repurposing drugs.
  - It provides regulatory pathways for repurposed drugs to gain approval based partly on information in approvals already given to other parties.[17]
  - The Orphan Product Extensions Now (OPEN) Accelerating Cures and Treatments Act of 2017 sought to provide an extra six months of exclusivity for patent holders who repurpose drugs to address rare diseases.[18]
- The Canadian Institutes of Health Research has partnered with Muscular Dystrophy Canada to develop two specific grants to support drug repurposing programs (Hernandez et al., 2017).
- The European Commission aims to create a framework for many drug repurposing projects with a not-for-profit or academic stakeholder. Termed a 'champion', this stakeholder would assemble the rationale for a new drug indication with the aim of bringing it on-label (European Commission STAMP expert group, 2019).

Australia has not focused on repurposing

Until the 2021 Department of Health consultation on repurposing of prescription medicines, Australia had not sought to take action akin to the US, UK, Europe or Canada.

In 2017, an Australian Senate committee (Senate Select Committee into Funding for Research into Cancers with Low Survival Rates, 2017) recommended the Australian Government:

- ensures funding is available to researchers investigating whether existing drugs may be suitable for treating low survival rate cancers (recommendation 16)[19]
- works with industry to consider a mechanism to repurpose drugs (recommendation 17)[20]
- considers a mechanism to permit access to and properly supervise use of off-label drugs for low survival rate cancer patients without further treatment options, on compassionate grounds (recommendation 18)[21]
- has the Therapeutic Goods Administration and the Pharmaceutical Benefits Advisory Committee examine the appropriateness of their approval and assessment processes for existing drugs repurposed for use in low survival rate cancers (recommendation 19).[22]

Discussions with other consumer organisations confirm that as in other nations, repurposing concerns apply across the cancer field and a range of other 'neglected conditions'.

The Australian Government identified drug repurposing as a research priority in both the 2018–20 and 2020–2022 *Australian Medical Research and Innovation Priorities* reports (Australian Medical Research Advisory Board, 2018, 2020).[23] While noting that drug repurposing is "difficult", the 2020–2022 report highlighted the importance of partnering with industry to identify and research drugs with repurposing potential. The 2018–2020 report specifically nominated MTPConnect as the centre that should create a partnership investment program with industry.

Despite these moves, stakeholder reports and feedback suggest Australia has had mixed success with efforts to encourage drug repurposing.

Many stakeholders suggest that Australia's existing repurposing efforts have significant problems.

- The stakeholders' own pathways to repurposing remain highly uncertain.
- Potential repurposing candidates are identified in an *ad hoc* way.
- There is discomfort about the perceived incentives and disincentives attached to progressing candidates.

Where candidate drugs have moved down the pathway in Australia, that progress has relied on key individuals – and usually on having low resource requirements.

17 These are granted under Section 505 of the United States Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. 9).
18 Under the 2017 OPEN Act (Orphan Product Extensions Now Accelerating Cures and Treatments) legislation (H.R. 1223 — 115th Congress).
19 https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Funding_for_Research_into_Cancers/FundingResearchCancers/Report/b02
20 ibid
21 ibid
22 ibid
23 From this point onwards, this report will refer to that paper as the Priorities document.

Box 6 The Australian Government's drug repurposing priority

Extracts from *Australian Medical Research and Innovation Priorities 2020-2022* (Australian Medical Research Advisory Board, 2020):

On the type of solution needed

Foster an enduring partnership with industry to systematically identify drugs with repurposed therapeutic potential for investigative research.

On why action is needed

The application of an existing therapeutic to a new disease indication is attractive in terms of decreasing both development costs and the time to patient access. De novo drug development can take well over a decade. Currently, repurposing of drugs is difficult and achieved by access to comprehensive libraries of clinical compounds. New technologies and advances in experimental methods can accelerate the identification and access to drugs of interest.

On how the issue is best addressed

Create and invest in programs to identify and research drugs with repurposing potential, with a focus on supporting timely access for patients.

NEXT STEPS IN AUSTRALIAN REPURPOSING

Australian industry can benefit from a systematic approach to repurposing

In 2020, Australia was estimated to have 800 pharmaceutical product manufacturers employing 16,160 people (IBISWorld, 2020).

Global academic research suggests hundreds of existing drugs already on the market are promising candidates for repurposing. Indeed, a major area of current investigation is the effectiveness of computational techniques that sort through drug databases to identify the most promising repurposing candidates for specific conditions. For instance, a December 2020 paper describes an evaluation of the effects of 259 different drugs on Parkinson's disease alone (Ozery-Flato et al., 2021).

But without public coordination, regulatory approval to market these repurposed drugs or efforts to build medical products manufacturing capacity and capabilities, Australian pharmaceutical companies have limited scope or incentive to explore manufacturing any of these drugs at scale.

The consortium opportunity

As discussed above, information and knowledge are subject to market failure, both because it is hard to prevent others from consuming it, and also because interested parties are able to use it without diminishing other parties' ability to benefit from it.

One result of this economics is that it is efficient for interested countries to collaborate to share the production of drug repurposing information and knowledge.

And drug repurposing will be more efficient still if countries with shared institutions form a consortium to collaborate on which drugs to investigate and trials to conduct.

Three countries – the US, the UK and Canada – are already in discussions and may form such an international consortium.

Belonging to such an international consortium would mean that Australia:

- could collaborate in joint drug trials to ascertain the efficacy of drugs for new uses
- would have a seat at the table to decide which candidate drugs will be trialled
- would have advanced information about the pipeline of new trials
- could position Australian manufacturers to take a leading position when a repurposed drug is ready for regulatory approval.

Manufacturers around the world will benefit from more approvals for repurposed drugs as regulations permit the drug to be formally marketed to physicians and consumers as a remedy for the (new) specific diseases.

Combined with economies of scale in medical products manufacture, this approach could enable suitable Australian manufacturers to take a commanding lead in the local market and potentially in some export markets.

Stakeholders want a new approach

The record shows that Australia is capable of successfully carrying out repurposing research. But it also shows the pitfalls and challenges which can delay development or increase costs.

Our survey indicates that there is general support for a more deliberative, informed approach, with a clear and defined pathway and with scope to conduct investigative research as required.

Regardless of the type and nature of research, it is also apparent that attention must be directed to ensuring that the systems and processes allow for the most efficient and effective path to achieving access for patients in need. This implies some degree of due consideration by experts involved in the pathway to access, including such advice as to whether (and if so, exactly what) clinical or other research is required.

A key challenge is that repurposing success requires multiple stakeholders, where there is no obvious leader body or primary focal point. A key goal is improved stakeholder alignment to ensure success rates can be improved and more patients benefit from evidence-based repurposing of existing therapeutics.

Stakeholders highlight key issues

Respondents expressed strong interest in improving Australia's repurposing effort. They also highlighted a number of key gaps and issues:

- Definitions of repurposing differ among stakeholders, though all agree a repurposed drug is a new use of an existing product.
- Starting points for the repurposing pathway vary, though success is universally defined as giving patients access to the repurposed drug.
- Different cases are at different points on a spectrum of readiness. In some cases, a target drug has still to be identified, while at the other end of the spectrum, evidence of a drug's effect is already available but it is not approved for use.
- No group has a primary role to identify potential drug items for repurposing, even though some have the ability to do so, or can provide data regarding suitable candidates.
- No single body is responsible for overseeing the progress of a drug after it is identified as a repurposing candidate.
- The system lacks clear government support and incentives for drug repurposing to overcome the existing market failure. Some grants may be able to be applied to repurposing efforts, but no funding is available for important components such as applications to the TGA and PBS.
- The registration and reimbursement application process for sponsors – companies – can be convoluted, time-consuming and expensive and acts as a disincentive.

Four goals for Australian drug repurposing

To deliver more repurposed drugs in ways that improve people's health, stakeholders say Australia needs to do four things:

Goal 1: Run an open prioritisation process

Open up the repurposing prioritisation process to groups including patient advocacy groups, charities, government bodies, clinical groups, academia, medical research institutions, and industry.

Goal 2: Build prioritisation capabilities

Enable an independent assessment and prioritisation of candidates. Build capabilities that enable assessment and analytical support and that allow access to drug development efficiencies, research and development, and commercialisation.

Goal 3: Build a structure for collaboration and access

Develop a facilitation program or path for proactively building collaborations and access pathways that extend across consumer groups, clinicians, industry, academia and government. Use this to prioritise candidates, identify incentives, remove significant disincentives and encourage sponsorship and investment into repurposing.

Goal 4: Provide funding

Design a funding program (including grants) that can support additional research and access initiatives. Maximise the medium-term sustainability of this program.

Enablers of successful repurposing

Survey participants were asked about the biggest change needed to improve Australia's success with drug repurposing. They identified common themes:

- **Ensure all parts of the pathway are addressed, from research through to patient access.**
  - Cover the items needing research, as well as those just needing TGA and/or PBS approval.
  - Include all forms of investigative research, including early-stage pharmacology.
  - Ensure it will work for intractable examples such as rare conditions.
  - Link research goals with the means of getting the drug to patients.
  - Allow for prospective identification of drugs, including through review of clinical practice.
  - Fund candidates appropriately.
- **Focus on collaborations.**
  - Participate in international trials and build international links that encourage harmonisation.
  - Focus on patient involvement, including patient-reported outcomes in trials.
  - Think laterally about the roles and responsibilities of different stakeholders.
  - Consider and provide incentives for the formation of consortiums, including private/public partnerships.
- **Adopt flexibility, speed, pragmatism and seek efficiency through new methods.**
  - Ensure methods have contemporary relevance.
  - Consider new research methodologies and trials, the role of real-world evidence and collecting data arising from off-label and compassionate use.
  - Enable flexibility in funding to allow essential elements to be funded.
- **Seek clarity and up-front certainty through gap analyses and project planning.**
- **Ensure the incentives are balanced and improve access for various parties.**
  - Strive for 'no loss' to encourage sponsors (companies) to participate in expensive and time-consuming application process.
- **Ensure feasibility of patient access.**
  - Make repurposing propositions clinically and economically compelling.
  - Ensure the benefits of public investment are realised through patient access.

RECOMMENDATION 2

Pursue four goals for Australian repurposing

Pursue policies that promote:

- an open prioritisation process in which key stakeholders can participate
- independent assessment and prioritisation of candidates
- a structure for collaboration and access, including appropriate incentives designed to increase repurposing effort
- a sustainable funding base.

POSSIBLE REMEDIES FOR DRUG REPURPOSING MARKET FAILURE

It should be noted that a definitive answer to the challenges of drug repurposing has not yet been accepted within the public policy community. Sam Halabi provides a useful, if US-centric, summary of the recent debate on correcting this market failure (Halabi, 2018).

It is, however, increasingly likely that in the current regulatory and industry environment, market solutions will not alone solve the problem. As one group of researchers remarks (Athey et al., 2020): "Many drugs that have a large benefit to society [but] that cannot be monetised in a way that provides high returns to investors will not be the focus of research and development by commercial drug companies." After listing some of repurposing's successes often created by extensions of patent protection or market exclusivity rights, they note:

"For each of these successes, there are many more generic drugs that might hold clinical promise but remain unexplored because innovators view the revenue potential as small compared to the development costs and the risks. It will therefore be hard to adequately monetise the benefits to justify a large new investment in trials to demonstrate the efficacy of a repurposed drug. As a result, there is too little activity in this area."

Athey et al., *Generic drug repurposing for COVID-19 and beyond*, 2020

Harmonisation of global trial regulations

With the spread of COVID-19 driving governments to fast-track prevention and treatment options, the Organisation for Economic Co-operation and Development (OECD) has suggested nations take steps to harmonise national regulations. Many trials for COVID-19 treatments and vaccines are being conducted at the national level. The current lack of harmonisation, it argues, "is slowing down the implementation of international clinical trials" (OECD, 2020). Australia has taken part in the COVID-19 ASCOT trial along with New Zealand, for instance, and is part of the 19-country REMAP-CAP trial (Australian Commission on Safety and Quality in Health Care, 2020).

International coordination would also assist in assessing many drugs not linked to COVID-19. However, the literature suggests that even COVID-19 efforts remain centred on national trials.

There are no grounds for assuming, however, that international drug development efforts will become highly coordinated over the next decade. There are similarly no grounds for assuming that such coordination would be to the advantage of the Australian pharmaceutical sector. Australia should support efforts to encourage international trials of potentially important drugs. But for the moment, Australian policy will need to proceed on the basis that global efforts will remain relatively restricted.

Public-private partnerships

The OECD has argued that in cases such as Alzheimer's research, the various distortions impeding drug discovery call for multi-stakeholder partnerships. In particular, it has argued that public-private partnerships will in many circumstances encourage open science and efficient resource sharing (OECD, 2015, p.15). It has said that:

"Public-private partnerships have the potential to reform existing drug development models through the implementation of non-linear, adaptive processes and a strengthening of collaborative approaches for the lifespan management of therapies and diagnostics: starting from basic biomedical and translational research to product registration and post-marketing surveillance. This could lead to a higher quantity and quality of potential new drugs entering clinical trials – ultimately, reducing the attrition rate during clinical trials and limiting financial loss."

OECD, *Public-private Partnerships in Biomedical Research and Health Innovation for Alzheimer's Disease and other Dementias*, 2015

Similarly, Verbaanderd et al. ultimately argue for "developing a collaborative framework between not-for-profit and academic organisations, pharmaceutical industry, health technology assessment bodies, payers, and regulators".

An 'air traffic controller'

One obvious risk in a public-private partnership is that the public sector will ultimately be required to contribute a substantial amount of the funding needed for expensive drug repurposing programs. This is not a requirement for success, and some researchers have suggested models with a more constrained role for government. In such models, government supports the establishment of a coordination body to help direct and foster collaboration between the many repurposing stakeholders.

In a recent paper, Susan Athey and her three colleagues (Athey et al., 2020, p.10) note that in US drug repurposing, the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) "plays a crucial but constrained 'air traffic control' function that the private sector is unable to provide". It funds research and development, provides technical assistance and other R&D support and creates manufacturing capacity by developing manufacturing networks.

The BARDA example holds lessons for Australia in the development of drug repurposing. The Athey paper recommends creating a "repurposed generic development program". It would be "devoted to pursuing, developing, and manufacturing promising repurposed candidates to fight infectious disease" – both COVID-19 and other pandemics.

The leadership of the program would ensure and oversee collaboration between the full range of participants. In its first phase, it would oversee funding of studies aimed at identifying promising repurposing candidates. In its second phase, it would coordinate clinical trials; among other things, it would ensure that the limited supply of trial subjects was allocated to the most important studies.

In this model, at all stages the program would look to appropriately outsource steps in repurposing projects to private-sector partners. At the manufacturing stage, the Athey paper suggests, the program would pay manufacturing costs plus a premium. The premium would be designed to ensure enough capacity to explore new uses, while not eating into the supply needed for existing uses.

ONE SOLUTION: AN AUSTRALIAN REPURPOSED DEVELOPMENT PROGRAM (ARDP)

Aims of an ARDP

Investigations such as those described above point to a possible solution to Australia's drug repurposing challenge: an Australian Repurposed Development Program (ARDP). Among other things, such a program would:

- improve coordination and collaboration between the existing Australian stakeholders
- help ensure equitable access to well-researched repurposed drugs
- provide Australia with functions European governments already provide and which are being considered in the US
- help to answer the question: 'What is being done to minimise the dangers to Australia from future pandemics?'

In the Australian context, the main aims of an ARDP would include:

- Oversee funding of the initial information-gathering and screening of preclinical research for the most promising candidates submitted to or nominated by the ARDP. This would take place with a view to further research and trials. The ARDP would contract with suitable private and public organisations for this work.[24]
- Coordinate clinical trials by a variety of organisations to test promising products. The ARDP would have a mandate to make arrangements that allow these trials to proceed at zero cost to government, including through arrangements with overseas parties. However, depending on circumstances, the ARDP might also play a part in funding trials.
- Prioritise drugs for study, as is already done in Europe.
- Where necessary, develop mechanisms to contract and pay for:
  - advanced development and manufacture of promising innovative treatments
  - scaling if and when the product shows it is effective.
- Purchase adequate supplies for treatment of the diseases being targeted.

The ARDP skillset

To reach these goals, an ARDP will need a variety of skillsets. This would include:

- Maintain relationships with a network of research organisations, from educational institutions and not-for-profits to industry, including multinational companies.
- Create a patient pool and oversee it in line with ethical standards.
- Staff itself adequately to oversee (though not itself carry out) complex assessments of prospective drugs.
- Liaise with government to ensure that the overall drug repurposing task is being carried out efficiently and effectively.
- Liaise with the TGA and Department of Health to ensure that drugs are approved and delivered to consumers in compliance with Australian requirements.
- Maintain relationships with drug sponsors to ensure that the repurposing system delivers patient access.

RECOMMENDATION 3

Consider creating an Australian Repurposed Development Program

Examine a repurposed drugs program which could:

- oversee funding
- prioritise drugs for study
- coordinate clinical trials
- organise development and initial manufacture of innovative treatments, where required
- where necessary, purchase adequate supplies for treatment.

Consider using MTPConnect to run this program, as recommended by the Australian Medical Research Advisory Board.

24 The Athey paper suggests that in some circumstances, prizes could also provide appropriate incentives, possibly at lower cost (Athey et al., 2020, p.14).

APPENDICES

APPENDIX 1: GLOSSARY OF TERMS

BARDA	Biomedical Advanced Research and Development Authority (US)
MRFF	Medical Research Future Fund
MTP	Medical Technology, Biotechnology and Pharmaceutical
NIH	National Institutes of Health (US)
OPEN Act	Orphan Product Extensions Now Act (US)
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
RGDP	Repurposed Generic Development Program
TGA	Therapeutic Goods Administration

APPENDIX 2: FULL LIST OF SURVEY PARTICIPANTS

We thank the following survey participants for their time and insights on the issues discussed in this report:

- Lorraine Chiroiu – AusBiotech
- Jennifer Herz, David Grainger, Mark Reid – Biointelect
- Chris Nave – Brandon Capital Partners
- Kirsten Pilatti – Breast Cancer Network Australia
- Dr Greg Cook, Mark Reynard, Nicole Patten – Bristol Myers Squibb
- Professor Sanchia Aranda – Cancer Council
- Professor David Currow – Cancer Institute NSW
- Leigh Farrell – Certara
- Professor David Ziegler, Dr Peter Wejbora – Children's Cancer Institute
- Simon Higgins, Maria Dionyssopoulos – Commercial Eyes Pty Ltd
- Marnie Peterson – Generic and Biosimilar Medicines Association
- Dr Paul Slade, Dr Amanda Elsome, Andrew Notley – Gilead Sciences Pty Ltd
- Dr Chris Davis – Institute for Glycomics
- Dr Deme Karikios – Medical Oncology Group of Australia Incorporated
- Elizabeth de Somer – Medicines Australia
- Nicola Richards – MSD
- Rebecca Stratford, Othon Gervasio – Novartis
- Sam Develin – Office of the Minister for Health and Aged Care
- Dr Masha Somi, Julianne Quaine – Health and Medical Research Office, Department of Health
- Professor Ricky Johnstone, Associate Professor Jayesh Desai – Peter MacCallum Cancer Centre
- Professor Kelly-Anne Philips – Peter MacCallum Cancer Centre
- Dr Mahmood Alam, Brian Hewitt – Pfizer Biopharmaceuticals Group
- Professor Andrew Wilson – Pharmaceutical Benefits Advisory Committee
- Jo Watson – Pharmaceutical Benefits Advisory Committee
- Richard Vines – Rare Cancers Australia
- Nicole Millis – Rare Voices Australia
- Carlene Todd, Josh Bowen, David Pullar – Roche Australia
- Professor Anthony Rodgers – The George Institute for Global Health
- Professor Andrew Roberts – The Walter and Eliza Hall Institute of Medical Research
- Professor Clare Scott – The Walter and Eliza Hall Institute of Medical Research
- Adriana Platona – Department of Health, Technology Assessment and Access
- Adjunct Professor John Skerritt, Professor Paul Kelly, Dr Jane Cook, Adrian Bootes – Therapeutic Goods Administration
- Dr Mark Ashton – UniQuest
- Professor Richard Head – The University of Adelaide
- Professor Jennifer Martin – The University of Newcastle
- Professor Mark Walker – The University of Queensland

APPENDIX 3: INPUTS FROM SURVEY PARTICIPANTS

Suggestions to improve Australian repurposing research

Survey participants' suggestions to improve Australia's drug repurposing research efforts are set out below:

Increase understanding of drug repurposing research and its role

- Increase awareness and understanding of drug repurposing research and its role in improving clinical practice and patient access.
- Using existing networks, increase understanding of relevant research initiatives in repurposing, including both candidates and methods.
- This may be achieved through a linkage or centralised point for listing repurposing projects, including publication of ongoing projects.

Identify drug repurposing candidates

- Explore the use of and access to drug libraries, drug screening and other tools to prospectively identify drug repurposing candidates.
- Use drug screening to identify new targets and drug libraries to 'translate' the science into repurposed candidates that may be researched.
- Consider 'goal-seeking' initiatives, particularly for less common conditions, that can identify the clinical need or molecular target and subsequently seek potential candidates addressing that need or target.
- Identification may be achieved more easily if the process of identification of candidates is eligible for support and funding.

Exploit pharmacological knowledge

- Increase the use and accessibility of specialist basic/advanced pharmacology knowledge and techniques to inform drug development and identify associated efficiencies.
- Pharmacological research may supplement existing knowledge about the candidate and how it might be expected to serve a new indication or new formulations (for example, physiologically based PK-virtual bioequivalence).
- Consider using pharmacology back-filling of regulatory approvals (older drugs used and approved based on limited knowledge), which may also be useful for comparator analysis.
- For new candidates, optimising dose and percentage target attainment through pharmacological quantitative systems approach.
- Use pharmacological profile comparisons across indications to deliver confidence in new indication, for example if the ED50[25] for the new effect is within C_{max}[26] of original indication, may have implications for regulatory review as well as future development support.
- This may be achieved by ensuring that pharmacological research and development expertise is sought for increasing number of candidates and is funded accordingly.

Exploit recent development techniques

- Build awareness and use of latest drug development options to improve efficiency of translational research in repurposing.
- Consider implementation research and/or methods to better understand the impact of real-world use in designing trials that address gaps.
- Consider applying more recent methods such as trial simulation models, which use model-based meta-analysis to normalise the responses and limit the size of trials. Tangential uses could include simulation in special populations with pharmacokinetics – for example, for renal impairment.
- Reassess subgroup analyses; redo dosing in the context of clinical need.
- This may be achieved by ensuring that drug development expertise is sought for a greater number of candidates, and is funded accordingly.

Apply rigour to drug development efforts

- Support translational research in drug repurposing, including prospective commercialisation and go-to-market strategies.
- Allow and plan for conducting a gap analysis that can inform the drug development plan.
- Increase the transparency and use of international regulatory pathways for repurposing, including the viability of applying provisions similar to the 505(b) pathway in the US.
- This may be achieved by encouraging, if not requiring, that a gap analysis and associated commercialisation plan is established prior to commencement of research.

25 ED50 is the dose that results in 50 percent of maximal bacterial killing.
26 C_{max} is the maximum serum concentration that a drug achieves in a specified area of the body after it is administered.

Encourage group approaches

- Build partnerships for drug repurposing with existing or new sponsors to share commercialisation plans and ensure enduring requirements such as supply can be met in the future.
- Provide greater access to existing safety data to allow its use in design or redesign of drug development for new uses.
- Create the material standards needed for pure or basic research.
- Understand the role of the new use in sponsor drug development plans (to ensure no duplication) and whether part of existent core data sheet and willingness to support.
- This may be achieved by direct partnership and/or contract, inclusion in consortium-type approaches to funding requests, and/or facilitation by a coordinating group.

Incorporate patient perspectives

- Ensure drug repurposing research considers and captures patient-reported outcomes.
- Make greater use of patient-reported outcomes as a requirement or way to increase the evidence base for repurposed drugs, including considering its relevance for decision-making.
- This may be achieved through inclusion of relevant partnerships with consumers in research design, with alignment of understanding about how such outcomes should be used in supporting registration and/or reimbursement in the event of research success.

Leverage developments in trial techniques

- Leverage the latest advances in trial design options and process improvements to reduce cost and complexity in drug repurposing research.
- Consider similar support to that which the US National Institutes of Health (NIH) and FDA provide in the conduct of single-arm studies agnostic to sponsors.
- Employ real-world evidence in registries and data collection in off-label use, including its use in decision-making, particularly in less common conditions.
- Leverage different types of trial designs to ensure faster decisions, with basket trials for rare tumours as used in Quebec's TRICEPS paediatric oncology research program.
- Leverage the international work in trials, including participation in international studies.
- Enhance links with required infrastructure needed for the conduct of studies, such as pathology and molecular testing, governance associated with standards, material transfer agreements, streamlined ethics and infrastructure sharing to create efficiency.
- Make greater use of (or investigate the potential to use) investigator-sponsored research models, which are supported in part or full by sponsors but are led by research investigators.
- This could be achieved by sharing of the intended project plan or research plan with other stakeholders to gain inputs to alternative research approaches.

Encourage collaboration

- Ensure collaboration, including consortiums and partnership formation, is encouraged or is a requirement for high-priority candidates.
- Make greater use of up-front decision support – including, for example, from the TGA – regarding the gaps required to be fulfilled and research plans aligned to meeting those gaps.
- Adopt a collaborative approach to best leverage skills and expertise, seek efficiencies, and recognise stakeholder rights and expertise (such as the sharing of retrospective data to design a good plan with the best knowledge available).
- This could be achieved by favouring plans that are based on a collaborative approach, through formal or informal agreements and partnerships formed prior to research initiation.

Suggestions to improve Australian repurposing pathways

The following opportunities are listed as a means to supplement the effectiveness of the pathway through the systems and processes essential to secure access for patients for evidence-based repurposed drugs:

Improve knowledge of repurposing's international regulatory pathways

- Increase transparency and knowledge of international pathways for repurposing, including the viability of the 505(b) pathway in the US.
- Optimise regulatory processes relevant for drug repurposing to provide alignment as far as possible with international processes, to increase the relevance of local research to global and local requirements.
- Strive for greater regulatory harmonisation between countries.
- Use the TGA's existing networks with other agencies to increase understanding of relevant and emergent regulatory initiatives in repurposing.
- Make greater use of up-front decision support – including, for example, from the TGA – regarding the gaps needing to be filled. This may be achieved through pre-submission engagement with the TGA in particular.

Increase flexibility in applying evidentiary requirements to candidate drugs

- Make greater use of processes designed to capture and represent the evidence-based status of a use of a drug (or group of drugs) for particular conditions. As an example, the EviQ cancer treatment database can be used to inform regulatory applications for cancer treatments.
- Make greater use of patient-reported outcomes to increase the evidence base for repurposed drugs. This may be achieved through early dialogue about ways to apply the existing evidence base.

Increase efficiencies in registration and reimbursement

- Develop a greater ability to 'piggy-back' additional indications with existing applications, so that an application for a rarer indication can be evaluated alongside a standard new indication application.
- Encourage sponsor participation in finding a pathway acceptable to all, and which maximises chances of access (including third-party contracting).
- Understand barriers and incentives to sponsor commitment to supporting or leading process.
- To increase sponsor participation, consider programs that ensure adequate funding of all system components, including those traditionally borne by sponsors and third parties such as regulatory consultants.

Reduce reliance on sponsors

- Consider the circumstances in which non-sponsor execution of the system elements of the pathway can be supported – for example, TGA submissions and PBAC applications. This will reduce reliance on the sponsor.

Increase local knowledge of intellectual property's role in drug repurposing

- Knowledge of intellectual property's role should include knowledge of data exclusivity, patent life, and method-of-use patents.
- Consider the role of measures in other jurisdictions which have incentives in patents to encourage the addition of new uses for existing drugs under certain circumstances.
- Where patents are in place, consider the viability of licensing, partnerships and other means to facilitate commercialisation.

Coordinate and communicate regulatory and reimbursement needs when ideas are generated

- Avoid investing effort into repurposing ideas that are later judged unlikely to succeed, by agreeing on an up-front plan that sets out how to meet evidentiary requirements.
- Ensure that any impact of the new purpose on existing uses – including negative impacts on existing reimbursement – is understood beforehand.
- Align the responsibilities for progressing each repurposing candidate, focusing on efficiency while ensuring decision-making remains unfettered.
- Consider ways to increase flexibility in applying the required evidence standards based on different drug development methods and/or data sources, including use of methods that leverage existing knowledge.

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