



**Submission to
the Senate Inquiry into
the availability of new, innovative and
specialist cancer drugs in Australia**

February 27, 2015

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EXECUTIVE SUMMARY	

Patients with cancer do not have the time to wait to get access to new medicines.

Yet for Australian patients, the evidence shows that it takes longer for them to gain subsidised access to cancer medicines compared to their counterparts in the UK, Canada, France and Germany.¹ This delay has a detrimental impact on health outcomes for the individual cancer patient, their carers and society.

Delays in access are of particular concern because Australia is the official *cancer capital of the world*, with the highest age-standardised incidence of cancer on a global level.² Half of all Australians will develop cancer in their lifetime and one in five Australians will die from it.³

Treatments for cancer include medicines, surgery, and radiotherapy. Whilst significant advances have been made in all these areas of treatment during the last three decades, the biggest advance has been in the field of medicines used to treat cancer. For example, some innovative medicines have increased survival by as much as 40 per cent for some cancer patients.⁴ Cumulative innovations in medicines for other cancers have contributed to a 10 per cent drop in mortality and an increase in overall survival up to two and a half years for some patients⁵ (from as little as six months).

The Australian system for determining value for money of medicines is called Health Technology Assessment (HTA). HTA was first implemented in Australia 20 years ago and has not evolved adequately to the changes in the development of medicines and diagnostic technologies that have occurred in that time. Whilst all new medicines are impacted, this inquiry provides the opportunity to examine how the growing system deficiencies particularly impact specialised cancer medicines.

Many cancer stakeholders^{6,7} have expressed their views that access to cancer medicines in Australia is frequently suboptimal and unsustainable. There is a significant time lag between the TGA's approval to market the medicine and the PBS listing processes. There is also an absence of any meaningful debate about what the Australian community considers the 'value' of a cancer drug, or what the acceptable level of funding for caring for patients nearing the end of their life should be.

Action is needed now to improve both the registration and the reimbursement pathways for cancer medicines. The limitations of Australia's reimbursement approach, based on antiquated cost-effectiveness methodologies, needs to be reviewed. This inquiry provides an opportunity for Australia to learn from the experiments of other countries and to develop world leading innovative access approaches so that Australian patients can get timely, subsidised access to the latest cancer treatments. Dialogue with industry is critical to achieving workable solutions and approaches.

¹ Wonder Drug Consulting, February 3, 2014, "Reimbursement success rates and timelines for new medicines for cancer: an international comparison", accessed at: <http://medicinesaustralia.com.au/issues-information/oncology-industry-taskforce/>

² AIHW, 2014, "Cancer in Australia: an overview 2014". Cancer series no. 90. Cat. no. CAN 88. Canberra: AIHW, pp.78

³ AIHW, 2015, "Australian Cancer Incidence and Mortality (ACIM) Books: All Cancers combined. Canberra: AIHW. <http://www.aihw.gov.au/acim-books>.

⁴ European Society Medical Oncology Meeting, 26-30 September 2014, Madrid, program available at <https://www.webges.com/cslide/library/esmo/browse/search/E1>

⁵ Richard M. Goldberg, 2013, "Cancers of the Colon and Rectum: A Decade in Review" presented at The Gastrointestinal Cancers Symposium, 2013, available at <http://meetinglibrary.asco.org/content/76484>

⁶ Deloitte Access Economics, July 2013, "Access to cancer medicines in Australia", accessed at: <http://medicinesaustralia.com.au/issues-information/oncology-industry-taskforce/>

⁷ Cancer Drugs Alliance (CDA) Forum, March 2014, press release accessed at: <http://www.cancerdrugsalliance.org.au/news/24/cancer-groups-unite-to-place-patients-front-and-centre-in-funding-of-new-medicines>

Improving timely and equitable access to cancer medicines may also generate broader system improvements that create timely and equitable access for all medicines, benefitting all patients. Timely access to innovations must be ensured.

This submission will provide an overview of the contribution of medicines to the treatment of cancer and the health and wealth of Australia. It will highlight deficiencies in the system that denies timely access. Ultimately, it will reinforce the need for improvements to the system for cancer medicines that could also be applied to improve the system for all medicines access.

Medicines Australia has already identified the following options to improve the system through a number of recent submissions to a variety of reviews⁸. The recommendations that are equally relevant to this review and can be summarised as follows:

1. Government to work with industry to develop **innovative access models** that will:
 - acknowledge the complexity of cancer and the limitations of current regulatory and reimbursement systems.
 - deliver more flexible evidentiary requirements which deal with issues such as crossover in clinical trials (rather than denying access on the basis of uncertainty).
 - properly reflect the value to patients, carers and the community from cancer medicines.
2. Implementation of **system efficiencies/ changes to deliver faster access times** for patients:
 - Fast track registration options for the TGA.
 - Improved parallel TGA/PBAC processes.
 - Ways to reduce PBAC submission “churn” so that first time submissions succeed, (e.g. a partnership approach).
 - Allocation of resources based on complexity of submission, to enable the PBAC to spend more time on the more complex listing applications, particularly new cancer medicines.
 - Streamlined PBAC/MSAC processes where co-dependent technology exists.
3. Commit to **expert oncology and consumer input** as central to the decision making process:
 - Inclusion of oncology relevant expertise is particularly needed given the many different types of cancer that exist, and the speed with which treatment regimens are evolving.
 - Consumers should have a stronger voice in deciding what the system of universal access should fund, as well as providing input to the decision makers about the reimbursement of individual cancer medicines. Such input might help address the issues of comprehensive inclusion of benefit, its valuation (and help address uncertainty).

Recommendations to the Senate Inquiry Committee

Medicines Australia appeals to the Committee to note the very significant impact which groundbreaking, new cancer medicines have on the lives of Australian patients suffering cancer, and the need for Government to continue to list these medicines on the Pharmaceutical Benefits Scheme in a timely manner.

Medicines Australia also seeks endorsement of the improvements proposed (above) to make Australia’s registration and reimbursement processes world leading, to ensure fast and efficient access to cancer medicines.

⁸ For more information please review the following Medicines Australia submissions to Government:

- 2015-16 Federal Budget Submission ([February 2015](#))
- Submission to the Expert Review of Medicines and Medical Devices Regulation ([January 2015](#))
- Senate Economics References Committee’s inquiry into the Australian Innovation System ([July 2014](#))
- Submission to the Post-Market Review Of The Life Saving Drugs Programme ([November 2014](#))

PART 1

Submission to the Senate Inquiry into the availability of new, innovative and specialised cancer drugs

Medicines Australia welcomes the opportunity to provide a submission to the Senate Inquiry into the availability of new, innovative and specialist cancer drugs in Australia.

Medicines Australia represents the research-based pharmaceutical industry in Australia, which brings new medicines, vaccines and health services to the Australian market. Medicines Australia's members are responsible for the discovery, research, development and commercialisation of up to 86 per cent of medicines currently available on the Pharmaceutical Benefits Scheme (PBS) by value. Last year, this industry generated over \$3.4 billion in exports, and invested over \$1 billion in research and development (R&D).

Access to new and innovative cancer medicines and improving the conditions to facilitate this access are a priority for patients, clinicians and the pharmaceutical industry. Medicines Australia was concerned by the evident delays in reimbursed access to new cancer drugs for Australian patients and established an Oncology Industry Taskforce (OIT) in 2012 to examine the problems in more detail and to understand the compelling case for change.⁹

This submission is focussed on access to cancer medicines and the deficiencies in the system that denies timely access. However, improvements to the system for cancer medicines must be viewed in the context of improving the system for all medicines access.

Burden of disease

Australia has the highest age standardised *incidence* of cancer in the world¹⁰ and has been referred to as the cancer capital of world. The number of new cancer cases diagnosed in Australia more than doubled between 1982 and 2014 (from 47,417 to 123,920 cases), and cancer is now the most common cause of death.^{11,12} It has been postulated that the world is approaching an era where cancer will become the dominant cause of mortality in the developed world.¹³ Data for 2014 estimates that; 1 in 3 males and 1 in 4 females in Australia will be diagnosed with cancer by the age of 75, with the risk increasing to 1 in 2 for males and 1 in 3 for females by the age of 85.¹⁴

⁹ The Medicines Australia OIT has commissioned several independent research projects:

- Deloitte Access Economics Report: "Access to cancer medicines in Australia", released in July 2013
- Wonder M. February 3, 2014: "Reimbursement success rates and timelines for new medicines for cancer: an international comparison"

For more information on the reports and findings, including 27 submissions from various stakeholders in response to the Deloitte Access Economics Report, please visit <http://medicinesaustralia.com.au/issues-information/oncology-industry-taskforce/>

¹⁰ AIHW 2014. Cancer in Australia: an overview 2014. pp. 78

¹¹ These numbers exclude basal and squamous cell carcinoma of the skin, as these cancers are not notifiable diseases in Australia.

¹² AIHW 2015. Australian Burden of Disease Study: fatal burden of disease 2010. Australian Burden of Disease Study series no. 1. Cat. no. BOD 1. Canberra: AIHW. pp xi

¹³ Cancer is also the leading cause of death in the USA for those under 85 years with cancer overtaking circulatory diseases as the predominant cause of mortality. Jemal et al, Cancer Statistics, 2010, pp 291

¹⁴ Data from the AIHW calculated that between 1982 and 2014 new cases (incidence) of prostate cancer, bowel cancer, breast cancer and lung cancer significantly increased. More than half (55 per cent) of the cancer cases diagnosed in 2014 are expected to be in men. The most commonly reported cancers in 2014 are expected to be prostate cancer, followed by colorectal (bowel) cancer, breast cancer in females, melanoma of the skin, and lung cancer. AIHW 2014. Cancer in Australia: an overview 2014. pp. 18

Growth in cancer incidence can be attributed, in part to: the growth in, and ageing of, the population; widespread health screening programs leading to higher rates of diagnoses and; improvements in technologies and techniques for identifying and diagnosing cancer. Consequently, now more than ever, Australian patients need timely and affordable access to medicines to treat these life-threatening diseases. Currently, Australians are missing out on vital new treatment options.

Evidence shows that it takes longer for Australian patients to gain subsidised access to cancer medicines compared to their counterparts in the UK, Canada, France and Germany.¹⁵ These delays have a real impact on health outcomes for the individual cancer patient, their carers and society in general.

Cancer accounts for about 30 per cent of deaths in Australia¹⁶. Cancer treatments, such as innovative medicines, can demonstrate a contribution to improved survival from cancer over time. Five-year survival rates from all cancers rose from 46 per cent in the period 1982-1986 to 67 per cent in 2007-2011¹⁷. For all cancers, the age-standardised mortality *rate* is estimated to have decreased by 20 per cent.¹⁸ Australians with cancer generally have better survival prospects compared with people living in other countries. However, these improvements are not consistent across all cancers and differ across population groups¹⁹.

Development of new, innovative and specialised medicines is a key driver of increases in survival rates from cancer and other diseases.

Between 1982-1987 and 2007-2011 the AIHW reported the greatest survival gains in prostate cancer, kidney cancer and non-Hodgkin's lymphoma.²⁰ Additionally, the Department of Health's own Drug Utilisation SubCommittee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) has recently released a report showing that mortality in Chronic Myeloid Leukaemia (CML) has declined in the period 2001-2013. The report demonstrates that increased survival from CML is directly attributable to the utilisation of the Tyrosine Kinase Inhibitor (TKI) treatments²¹.

Nevertheless, there are some cancers that continue to have low survival rates, such as cancers of other digestive organs (from 10 to 12 per cent), pancreatic cancer (from 3.5 to 6.1 per cent) and some forms of lung cancer (from 9 to 14 per cent).²²

Evidence from a recent Rare Cancers Australia report shows the value of research for rare cancers, as a proportion of their burden of disease and mortality, is lower than the cancers where gains in survival have increased, see Figure 1. Rarer, less common cancers are more

¹⁵ Wonder Drug Consulting, February 3, 2014, "Reimbursement success rates and timelines for new medicines for cancer: an international comparison". pp. 50

¹⁶ over 45,000 cancer deaths in 2014
AIHW, 2014, Cancer in Australia: an overview, pp.1

¹⁷ A 5 year survival rate of 67 per cent means that people diagnosed with cancer had a 67 per cent chance of surviving for at least 5 years compared with their counterparts in the general population.

¹⁸ From 209 per 100,000 in 1982 to 168 per 100,000 in 2014, AIHW, 2014, Cancer in Australia: an overview, pp.51

¹⁹ Notably, the AIHW finds cancer outcomes differ across population groups, with the data showing that in 2008–2012, for all cancers combined, Indigenous Australians experienced higher mortality rates than non-Indigenous Australians.

²⁰ AIHW, 2014, Cancer in Australia: an overview , pp.38

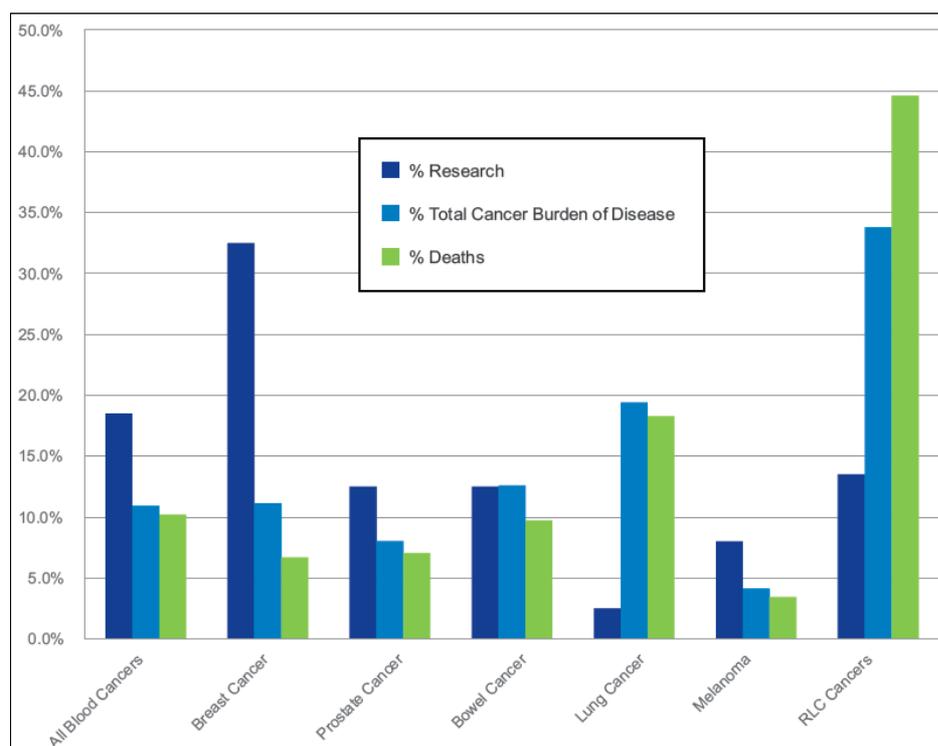
²¹ Drug utilisation sub-committee (DUSC), February 2014, "Tyrosine kinase inhibitors for the treatment of Chronic Myeloid Leukaemia", Available online at: <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/tyrosine-kinase-inhibitors-2014>

²² AIHW, 2014, Cancer in Australia: an overview , pp.38

difficult to investigate by their very nature of being rare, and thus rare cancers commonly demonstrate poorer outcomes.²³

Additionally, even where research has uncovered effective medicines for these cancers, they have poor success rates when attempting to get positive recommendations from the PBAC for listing on the PBS. This is principally due to the difficulty in generating required amounts of research data when cancers are rare and patient numbers are small.

Figure 1: value of research for rare cancers, as a proportion of their burden of disease and mortality



Source: Rare Cancers Australia, 2014, "Just a little more time: rare cancers baseline report" pp.19,

A recent research study has shown that while 10 of the 26 medicines for rare cancers seeking PBS listing through the PBAC were eventually listed, another 16 have not been listed; 12 of them due to negative or deferred decisions by the PBAC.²⁴ Moreover, even when the sponsor has secured a positive recommendation, listing has not eventuated due to a number of hurdles faced in the 'post-PBAC' phase of the process. This may include the sponsor's inability to accept the price requested by the PBAC or the proposed terms of a risk share arrangement.

How medicines have contributed to improved survival

As formerly stated, treatments for cancer include medicines, surgery, and radiotherapy. Significant advances have been made in all these areas, however, developments in cancer medicines have provided some of the most significant gains.

For example, many newer cancer medicines are developed to target and interrupt specific molecules involved in the growth of cancer cells. These include hormone therapies for hormone sensitive tumours; treatments that block the growth of blood vessels supplying a tumour (angiogenesis), treatments that cause cancer cells to self-destruct (apoptosis); and

²³ Rare Cancers Australia, 2014, Just a little more time: rare cancers baseline report, pp.9-11

²⁴ Wonder Drug Consulting, 2014, pp. 22-24

immunotherapies that stimulate the body's own immune system to destroy cancer cells. The addition of these innovative approaches and advanced targeted medicines to the therapeutic armamentarium has revolutionised cancer treatment in the last 15 years.

Advances in cancer medicines commonly deliver modest incremental benefits, such as extensions to life, measured in weeks or months. The Pharmaceutical Research and Manufacturers of America (PhRMA) explains progress does not happen with one breakthrough but rather incremental stepping stones.

“Each new cancer medicine whether it extends a life by 6 months or 3 years, reflects the cumulative nature of medical discovery.”²⁵

PhRMA goes on to explain, ‘In addition, as each new medicine is used in the real world; earlier in the disease stage and in combination with other medicines; its value is more fully realised. This step by step transformation has led to increased survival, improved patient outcomes and enhanced quality of life for many cancer patients’.

PhRMA has collated a range of quantifiable gains in survival for cancer patients over time:²⁶

- Between 1988 and 2000, improvements in cancer survival created 23 million additional life years.
- Treatment advances for Chronic Myeloid Leukaemia (CML) have increased the 10 year survival rate for CML patients from less than 20 per cent to more than 80 per cent.
- Childhood cancer survival rate is 83 per cent today, compared to 58 per cent in 1970.

Nevertheless, the existing HTA process has become ill-equipped to recognise and adequately value the ongoing incremental benefits and limitations facing researchers gathering data on cancer medicines. This has led to frequent and repeated denial of reimbursement. This step-wise progress is therefore hampered, as patients are unable to gain early access to each new development and medical professionals are unable to gain experience with them.

²⁵ PhRMA, 2013, “ Cancer medicines are worth it”, April 25 , 2013, available at www.phrma.org/response-to-blood-editorial-price-of-drugs

²⁶ PhRMA, 2013, “Innovative Oncology Medicines Have Led to Impressive Gains in Patient Survivorship”, 31 May 2013, available at <http://www.phrma.org/innovative-oncology-medicines-have-led-to-impressive-gains-in-survivorship>

Case Studies: Providing access to new medicines improves patient survival

Breast and colorectal cancers are examples of where a series of relatively modest gains have resulted in significant cumulative improvements over a 10-15 year period. Evolutions in chemotherapy regimens, hormone treatments, biomarkers and bone modifying medicines are leading to success in treating cancer.

1. In the early 2000s, a new medicine added to traditional chemotherapy for metastatic breast cancer (mBC) increased the time to disease progression by **six months**. This was seen as a significant gain for patients. Other new medicines have since been made available, **slowing disease progression by 12 months** and subsequently up to **19 months**, as well as increasing **survival by up to 16 months^a**.
2. Australia has one of the highest incidence rates in the world for metastatic colorectal cancer (mCRC). With the advent of targeted therapies, overall survival for incurable colorectal cancer has increased from a median of six months with best supportive care (palliation of symptoms and improving quality of life without treating the disease itself) to nearly **30 months^b**. Improvements in overall survival are associated with new, innovative and specialised medicines for mCRC (Figure 2).

Figure 2: Improvements in overall survival due to targeted mCRC drugs 1980-2015

Source: Richard M. Goldberg, 2013

^a S.M. Swain et. al., 2015, "Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer", N ENGL J MED 372:8.

^b R.M. Goldberg, 2013, "Cancers of the Colon and Rectum: A Decade in Review" presented at The Gastrointestinal Cancers Symposium

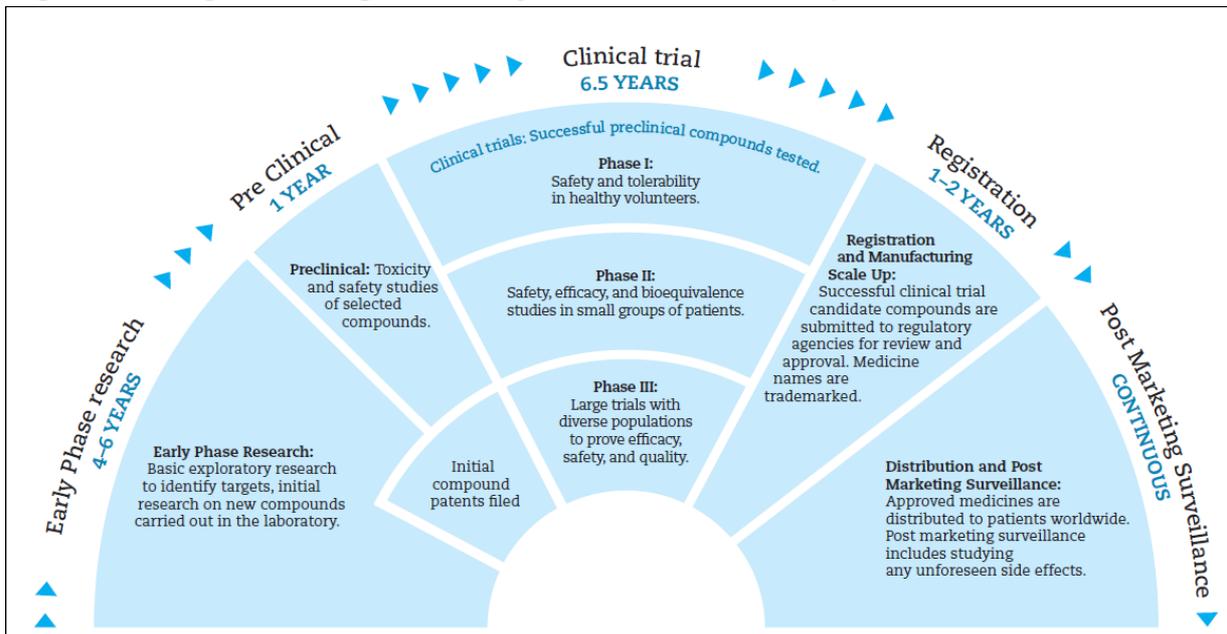
Cost of cancer medicines

Drug development is a costly and risky process. It takes about 10-15 years to develop one new medicine from the time it is discovered to when it is available to treat patients.²⁷ This is due to the lengthy stages of medicine discovery and development (see Figure 3). Ultimately, around one medicine receives marketing approval for every ten thousand compounds that enter the research and development (R&D) pipeline. This does not include the additional time to apply and list a medicine in the various registration or reimbursed / subsidised insurance schemes.

²⁷ International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Geneva, 2013, Incremental Innovation: Adapting to Patient Needs. http://www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_Incremental_Innovation_Feb_2013_Low-Res.pdf, pp.9

Many of the drugs coming to the market in 2014 were in the early stages of discovery in 1999, fifteen years ago.

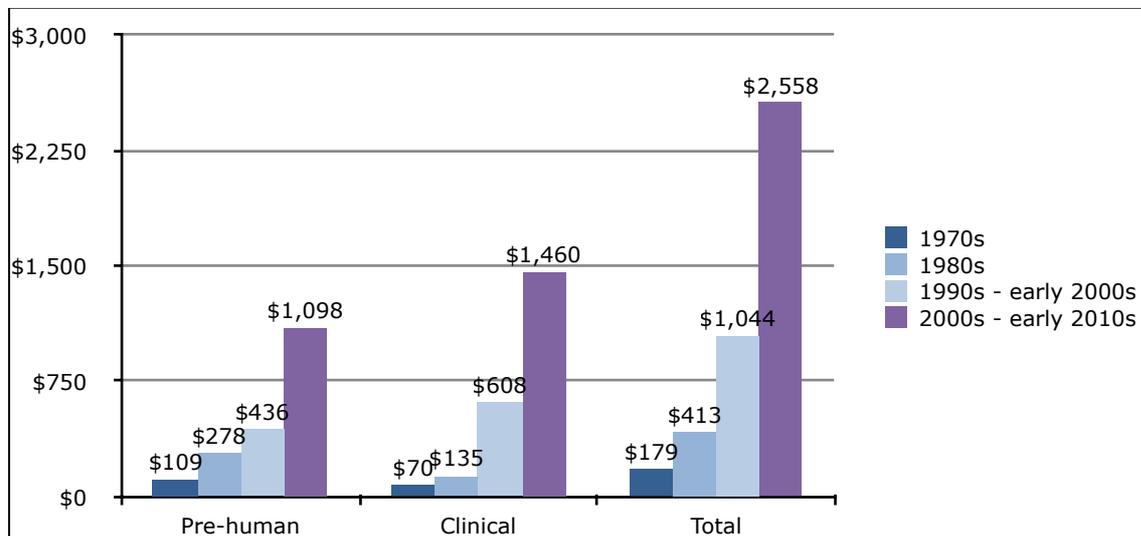
Figure 3: Stages of drug discovery and clinical development



IFPMA, 2013, Incremental Innovation: Adapting to Patient Needs.

The latest analysis from the Tufts Centre for the Study of Drug Development²⁸ estimated that the cost of development of a new prescription medicine that gains marketing approval is over \$US 2.5 billion. This includes the costs of the pre-human and clinical phases of development

(Figure 4).²⁹



Figure

4: Growth in capitalized R&D costs per approved new compound

Source: Tufts Centre for the Study of Drug Development
 Note: Y axis is expressed as millions 2013\$ US

²⁸ Tufts Centre for the Study of Drug Development, Boston, 2014, "Cost to Develop and Win Marketing Approval for a New Drug is \$2.6 Billion" available at http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study, 27/11/14

²⁹ This estimate, which updates similar Tufts CSDD analyses, was developed from information provided by 10 pharmaceutical companies on 106 randomly selected drugs that were first tested in human subjects anywhere in the world from 1995 to 2007.

While the costs of R&D apply to all medicines, not just cancer medicines, there are some particular factors, which have an added impact on the development costs for cancer medicines:

- Cancer is not one disease, but is made up of many different diseases and the specialised treatments for each disease are used in much smaller patient populations. For example, there are multiple types of lung, colorectal and breast cancer and one medicine will not work in all types. Specialised medicines are required to treat each, with the target having to be identified and the medicine developed for that target. In addition, as a diagnostic test for the target will usually have to be developed, this adds more complexity, cost and time to the R&D process.
- Clinical trials have many fixed costs, regardless of the potential patient population. Thus, if the patient numbers in the various types of cancer are relatively small, the same R&D cost will be amortised over a smaller patient group. This specialised (personalised) medicine will be used by a small number of patients, as distinct from a medicine which may be used by many millions of patients worldwide, such as a medicine for high blood pressure or to lower cholesterol.
- The duration of treatment may be much shorter than other types of medicines because it is usually initiated as an end-of-life treatment or just until a patient enters remission. A patient is not kept on a cancer medicine indefinitely. Again, this is in direct contrast to the patient who has, or is at risk of chronic diseases such as cardiovascular disease.
- Moreover, ethical responsibilities mean that patients whose cancer *progresses* in the 'control' arm of a trial investigating a new cancer medicine are allowed to 'cross-over' onto the new medicine in an attempt to get the cancer under control. However, this complicates the assessment of the survival benefit that may be attributed to the new medicine.
- Again, for ethical purposes, trials may be stopped early if significant benefit of the new medicine is seen at an interim analysis. This means that the true impact on *overall survival* can no longer be measured which adds further complexity and clinical uncertainty to the results.
- *Progression-free survival* (PFS) may be the primary endpoint of a clinical trial, with mature overall survival (OS) data not available until years after regulatory approval. This adds significant additional development costs, not often required for other types of medicines.

Why cancer patients need specialised medicines

Cancers that we may identify as a single type may present as multiple forms of the disease, and each will respond to different types of therapy with varying levels of efficacy. The number of different cancers and the nuances involved in each particular tumour site require access to a range of specific experts and efficient processes to ensure that the right treatment is applied in each case.

In global terms the Australian market is small. Industry has variable influence (generally small) over the global development of new cancer medicines. This is both in terms of clinical trial design and cost, particularly for specialised medicines targeted to treat small patient numbers. Almost all companies operating in Australia are affiliates of global companies. This often renders it difficult or impossible to meet unique requirements requested by the Australian registration and reimbursement systems.

The level of clinical trial research conducted in Australia has been in decline over recent years. Consequently, there are even fewer opportunities for the Australian industry to contribute to trial design, and less incentive for global-based companies to invest here. This reduces Australian clinicians and patients' access to, and opportunities to learn about, new medicines.

PART 2

Responses to the Terms of Reference

A): Timing and affordability of access for patients

- 竜 Australia lags behind England, Canada, France and Germany and others in delivering timely and equitable access to new cancer medicines
- 竜 This has real impact for health outcomes for the individual cancer patient, their carers and society
- 竜 Patients with cancer do not have the time to wait to get reimbursed access to new medicines on the PBS
- 竜 The timelines for patient access to cancer medicines in Australia must be reduced

A recent report from the UK shows that Australia ranks highly for the continued use of older medicines but unfortunately, ranks poorly when it comes to using newer cancer medicines (less than 5 years old) in Table 1.³⁰ Older cancer medicines are mostly off patent and are inexpensive. Some older treatments have been superseded by newer, better options. It is, therefore, disturbing that this report signals Australia's preference to rely on old, cheap options. The report is further supported by research that shows Australia lagging behind other countries in access, and backs the hypothesis that access to new, innovative treatments is getting more difficult over time.

Table 1: Countries ranked by cancer medicine use for 2012/13

Rank	New cancer medicines (<5 years)	Older cancer medicines (> 10 years)
1	Austria	Spain
2	Switzerland	Italy
3	Germany	France
4	Norway	UK
5	France	Sweden
6	Sweden	Australia
7	UK	Austria
8	USA	New Zealand
9	Canada	Germany
10	Spain	Canada
11	Italy	Switzerland
12	Australia	USA
13	New Zealand	Norway

³⁰ Office of Health Economics, 2014, "International Comparison of Medicines Usage: Quantitative Analysis", Report commissioned by the Association of the British Pharmaceutical Industry, December 2014, available at http://www.abpi.org.uk/our-work/library/industry/Documents/meds_usage.pdf, pp.11-12

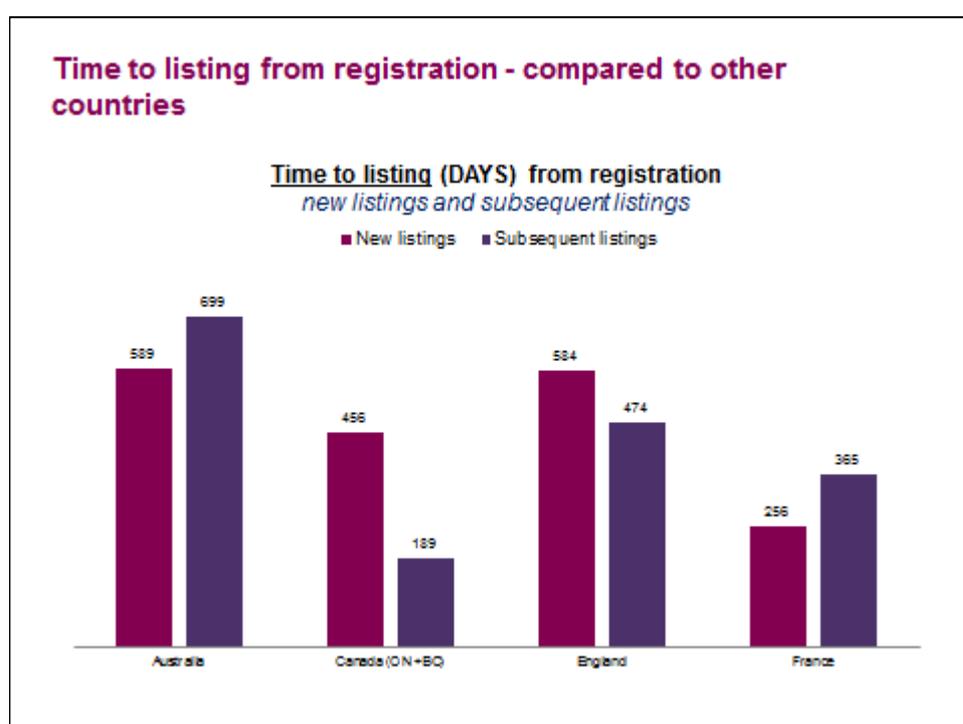
Source: compiled from Tables 3a and 3b, Office of Health Economics. "International Comparison of Medicines Usage: Quantitative Analysis", pp.11-12.

Note: higher rank denotes worse position relative to other countries (rank: 1 is highest use, 13 is lowest)

The average time from registration by the Therapeutic Goods Administration (TGA) to reimbursed access on the PBS is in excess of 18 months:³¹

- o New listings take on average 589 days (over 1 ½ years)
- o Subsequent listings take on average 700 days (nearly 2 years)
- o Disturbingly, some medicines took up to 1,600 days (4 ½ years) for a new listing and 2,400 days (more than 6 ½ years) for a subsequent listing.

Figure 5: Australia's time to reimbursed listing compared with peer countries



Source: Wonder Drug Consulting, 2014, "Reimbursement success rates and timelines for new medicines for cancer: an international comparison". Pp.5-6

Delays to listing of new, innovative and specialised cancer medicines on the PBS are influenced by decision-making processes within the PBAC. Without a positive recommendation from the PBAC, a medicine cannot be listed on the PBS and made universally available for patients in need.

³¹ Wonder Drug Consulting, pp.5-6

Timing

The two key components that enable access to new medicines in Australia are, the process for registering a product for marketing in Australia (registration); and the process to achieve government subsidy (reimbursement).

Registration:

The pharmaceutical manufacturer of a new medicine (the sponsor) applies to the TGA for registration of a medicine³². This is also referred to as market authorisation. The TGA undertakes a thorough assessment of the data collected through years of the medicine's development programme to determine its suitability (quality, safety and efficacy) for marketing in Australia. Other jurisdictions, such as the United States and Europe, have introduced 'fast track' mechanisms to further speed up the processes for registration and marketing access to innovative medicines³³, particularly where there is high clinical need.

Medicines Australia recommends introducing similar efficiencies to speed access for patients. This is highlighted in a submission to the Expert Review of Medicines and Medical Devices Regulation³⁴ and includes:

- **Optimising work sharing activities with overseas regulatory agencies** to increase efficiency. This includes the ability to adopt international decisions from trusted regulators where appropriate; and ensuring Australia upholds public health and safety through sovereign decision making; and,
- **Creating multiple approval pathways** including fasttracked, priority registrations, breakthrough medicines and re-establishing flexibility.

Prior to 2011, a sponsor could not submit an application for Government reimbursement of a new medicine until after the registration outcome was known. However, under the terms of the Memorandum of Understanding (MOU) between Medicines Australia and the Commonwealth of Australia³⁵, the sequential restriction for submission was removed.

This means that a sponsor is able to submit an application to Australia's independent reimbursement authority, the Pharmaceutical Benefits Advisory Committee (PBAC) at the same time as an application for registration through the TGA. This is known as the parallel process. The purpose of this change was to streamline the access pathways and potentially reduce delays. However, faster universal access (faster time to listing on the PBS) has not been realised as intended.

Reimbursement:

Before any patient can gain *subsidised* access to a new medicine in Australia, the medicine has to be made available (listed) on the Schedule of Pharmaceutical Benefits through the PBS. To list on the PBS requires a positive recommendation from the PBAC after it has considered an

³² <https://www.tga.gov.au/prescription-medicines>

Information on the FDA's fast track process is provided in an article in Evaluate Pharma is reproduced at Appendix A. It notes "Call 2014 the year when the FDA's breakthrough therapy designation really started to tilt the drug approval playing field. Nine NMEs with this beneficial tag zoomed through the agency's corridors last year, with an average wait of four months between application and authorisation for innovative projects like Opdivo and Harvoni³³. This focus on delivering ground-breaking agents to treat unmet medical need lowered the FDA's average approval time to 11.5 months, versus 14 in 2013."

³⁴ Medicines Australia submission to the Expert Review of Medicines and Medical Device Regulation, January 2015, accessible at www.medicinesaustralia.com.au

³⁵ Department of Health, September 2010, "Memorandum of Understanding with Medicines Australia", available at <http://www.pbs.gov.au/info/industry/useful-resources/memorandum>

application, most commonly from the sponsor. The HTA process by which a sponsor seeks reimbursement is fully described on the Department of Health's website³⁶.

PBAC cycle & engagement with decision makers

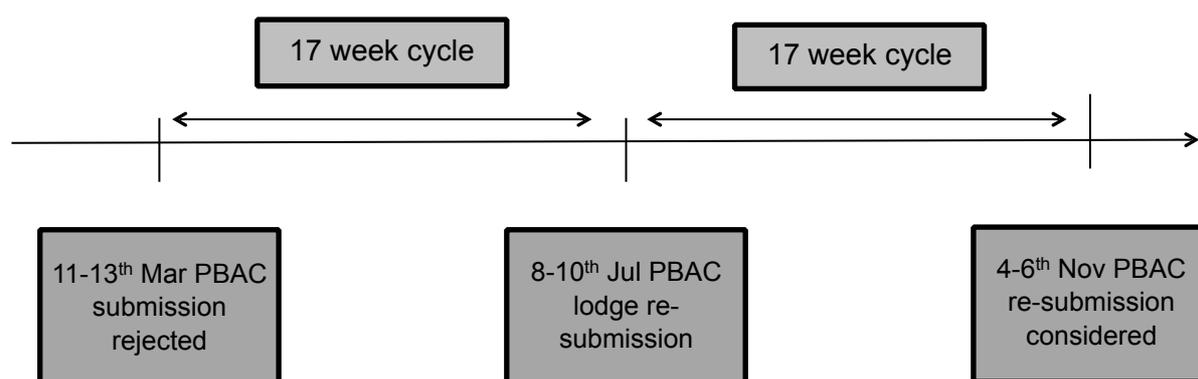
The PBAC review cycle is a fixed 17-week process; three times per year. Current and former PBAC Chairpersons have cited this as the fastest reimbursement process in the world. However, experience shows that very few medicines evaluated for cost-effectiveness receive a positive recommendation in 17 weeks; from their first submission. Most medicines and applications for new indications require more than one submission to achieve a positive PBAC recommendation and subsequent PBS listing. To prepare and resubmit, following an initial rejection, takes at least one and sometimes more cycle(s) such that it commonly takes 12-18 months for a positive decision and can take several years.

This is a key factor in the time lag from TGA approval to PBS listing. The average number of submissions required to obtain a positive recommendation from the PBAC for cancer medicines is 2.3 (approximately 3 years) for new listings and 2.5 (3.5 years) for subsequent listings. This equates to years of delay for patients³⁷.

In addition, there are significant post-PBAC processes where agreement is reached on the wording of the PBS restriction, pricing negotiations are undertaken and the Department of Finance and Cabinet review the decision. These processes can take many months further adding to access delays.³⁸

Sponsors commonly claim that they receive inconsistent advice from the Pharmaceutical Benefits Division (PBD) of the Department of Health, the independent evaluators, and the PBAC itself. This is exacerbated by the limited ability to engage with the PBAC or the evaluators. The timing of meetings (particularly following a rejection) create further delays through largely administrative and resource inefficiencies, which could be rectified through adjustments to the PBAC meeting cycle and process streamlining.

Figure 6: 2015 PBAC meeting dates & timeline for a major resubmission



By comparison the HTA system in the UK, coordinated by the National Institute for Health and Care Excellence (NICE), includes an early scoping meeting where the 'decision problem' is discussed and mutually agreed. This includes agreement on the comparator (a common reason

³⁶ PBS Listing Steps, available at <http://www.pbs.gov.au/info/industry/listing/listing-steps>

³⁷ Wonder Drug Consulting, 2014.

³⁸ For example, a targeted mCRC drug was recommended for listing by the PBAC in early July 2010, but was not actually listed on the PBS until 1 September 2011, a delay of 14 months.

for rejection in Australia), and the appropriate endpoints for determination of cost-effectiveness *prior* to the sponsor making their submission. This also informs the type of economic analysis.

Selection of economic analysis

Preparation for a major submission to the PBAC takes, on average, 4-6 months to prepare and is resource intensive, both in personnel and dollar terms. The decision to prepare for cost-effectiveness (CE) or a cost-minimisation (CM) analysis could be accurately determined through prior agreement on the 'decision problem'. However, under the current Australian HTA system, sponsors may be required to submit multiple times to address new issues that are raised during each evaluation. The need to make multiple resubmissions to address misalignment of the 'decision problem', the selection of a comparator, or to change the type of analysis is referred to as 'submission churn'. This clearly creates further delay to reimbursed access for the patient.

Co-dependent technologies

Co-dependent technologies have additional timing complexities. It is common for cancer medicines, particularly targeted medicines, to have an associated diagnostic test or treatment-associated device to ensure the medicine is used where most effective.

Submissions for targeted medicines partnered with a diagnostic test, are complex in terms of content and process. They currently require a separate recommendation from two separate committees with differing meeting schedules; The Medical Services Advisory Committee (MSAC) for the test and the PBAC for the drug. There appears inadequate interaction between the two committees, and the submission processes vary greatly between the two.

System improvements for co-dependent technologies have failed to address access delays. Drug-test pairings are being penalised by greater complexity and longer timeframes to patient access than pharmaceuticals that do not require an associated test.

Affordability

Cancer is a National Health Priority Area. This demonstrates that successive Australian Governments have made a commitment to focus attention on treating cancer patients.

Cancer was responsible for nearly one-fifth (19 per cent) of premature death and disability in Australia in 2003. However, it received only 13 per cent of total health expenditure in the subsequent year³⁹. This indicates a misalignment between Australia's burden of disease from cancer, and associated healthcare expenditure. Government subsidy of cancer medicines through reimbursement on the PBS is critical to the affordability of these medicines for patients.

Affordability is guided by a *value for money* judgment made through HTA and by the PBAC. Medicines Australia contends that there is room to broaden the basis on which *value for money* is judged. The calculation of *value for money* is based on a health economics equation; the Incremental Cost Effectiveness Ratio (ICER). The ICER is a cost/benefit ratio, quantifying the additional cost you have to pay for the additional health benefit derived, with the health benefit measured as Quality Adjusted Life Years (QALY).

The PBAC claim that they do not apply a fixed cost-effectiveness threshold or ICER in order to make a decision on *value for money*. Rather, the PBAC claim that each product is judged on its merits against the evidence provided. However, sponsors of new medicines experiences reveal that the PBAC's acceptable ICER is in the range \$45,000 - \$75,000⁴⁰. Furthermore, the implicit

³⁹ Deloitte Access Economics, pp.28

⁴⁰ G. Dranitsaris & Papadopoulos G., 2014, "Health Technology Assessment of Cancer Drugs in Canada, the United Kingdom and Australia: Should the United States Take Notice?" Applied Health Economics Health Policy, 2014, Oct 2, available at <http://www.ncbi.nlm.nih.gov/pubmed/25274258>

acceptable threshold is lowered when any form of clinical, economic and financial uncertainty exists in the economic evaluation. This contention is supported by ICER ranges captured in Public Summary Documents (PSDs) for recommended medicines.

The World Health Organization (WHO) recommends an ICER range between 1 and 3 times gross domestic product (GDP) per capita as cost-effective.⁴¹ In 2012, the Australian GDP per capita was \$64,321 and \$44,598 adjusted for purchasing power parity. Therefore, using the criteria proposed by the WHO, The PBAC should accept ICERs in the range of \$44,598-\$133,794 as cost-effective. However, it is generally acknowledged that very few medicines with an ICER over \$75,000 are recommended by the PBAC.

The average PBS price paid for cancer medicines has declined in Australia in the last two years⁴², in comparison to an overall health inflation rate of more than four percent per annum and consumer price index of two percent⁴³. Confidential rebates (recorded as recoveries by the Government) further reduce these prices. As reported in last year's Department of Health annual report, high cost drug recoveries totalled more than half a billion dollars in revenue to Government. In 2013, this value was \$328 million.⁴⁴

IMS⁴⁵ recently compared HTA countries such as Australia (which consider how much the treatment costs per quality adjusted life year), versus countries who do not use cost effectiveness as the basis for HTA. It finds that Australia, and countries that use the cost effectiveness approach have; poorer access to new cancer drugs; reimburse fewer new cancer medicines; and take longer to provide reimbursement. This emphasises the inadequacy of the cost effectiveness approach when it comes to cancer medicines.

Conclusion:

The long timelines and complexity of processes involved in providing patient access to cancer medicines in Australia must be reduced. Improved registration and reimbursement pathways which recognise the ground breaking nature of new cancer medicines must be implemented.

⁴¹ The CHOICE (CHOosing Interventions that are Cost-Effective) project is a World Health Organization (WHO) initiative with the objective of providing policy makers with evidence for deciding on interventions and programmes which maximize health for the available resources. Following the recommendations of the Commission on Macroeconomics and Health, CHOICE uses gross domestic product (GDP) as a readily available indicator to derive the following three categories of cost-effectiveness. It deems interventions between one and three times GDP per capita as cost-effective. Available at http://www.who.int/choice/costs/CER_thresholds/en/

⁴² Calculated from PBS Expenditure Statistics for ATC group "Antineoplastic and immunomodulating agents", available at <http://www.pbs.gov.au/info/browse/statistics#Expenditure>, Accessed 16/09/14

⁴³ Australian Bureau of Statistics. 2014. "6401.0 - Consumer Price Index, Australia, Jun 2014", accessed from <http://www.abs.gov.au/ausstats/abs@.nsf/mf/6401.0>, Accessed 16/09/14

⁴⁴ \$508,646,000; Department of Health, 2014, "Annual Report 2013-14", available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/Annual+Reports-3>. Pp.301

⁴⁵ IMS Institute for Healthcare Informatics, 2014, "Impact of cost per QALY reimbursement criteria on access to cancer drugs", pp.8 available at http://www.redaccionmedica.com/contenido/images/IMS_Institute_Report_on_CPQ_Impact_on_Access_to_Cancer_Drugs.pdf

B): Operation of the PBAC and the PBS, including impact of delays in the approvals process for Australian patients;

- 竜 The Australian system for determining value for money of medicines was implemented 20 years ago and has not adapted adequately to the changes in the development of medicines and diagnostic technologies, including evidentiary requirements. This impacts all medicines as well as cancer medicines.
- 竜 There is an opportunity for Australia to learn from the experiments of other countries and develop world leading innovative access approaches so that timely subsidised access to the latest treatments are a reality for Australian patients. Dialogue with industry is critical to achieving workable solutions.
- 竜 The reimbursement system needs to operate in a way which recognises that the clinical value of cancer medicines may be modest when first approved, but grows over time.

The PBS and PBAC:

The PBS provides *reimbursed* access to medicines in Australia, underpinned by TGA registration and PBAC recommendations.

Following recommendation by the PBAC, the sponsor and the government negotiate an agreement on price and complete other necessary administrative processes. The sponsor and the government commonly enter into a *risk-share* arrangement (RSA), which is captured via a Deed of Agreement. The Deed will outline any conditions surrounding the price and volume of access to a particular medicine and will capture the point at which a sponsor is required to return additional, unanticipated expenditure back to government via a rebate. These RSAs further demonstrate the partnership between government and industry to ensure the PBS remains sustainable and manages expenditure.

The structure and function of the PBS and PBAC are underpinned by the National Health Act 1953 (*the Act*). The PBS provides a range of medicines for community-based patients, including patients with cancer. Cancer medications therefore, are accessed by patients in the community via the PBS or through participating public hospitals.

However, Australia's HTA system is twenty years old and has not kept pace with medicines development and advanced technology.

Evidentiary requirements for Cancer submissions

Evidentiary requirements for cancer do not take into account the clinical and ethical complexity when trialling cancer medicines in relation to overall survival measurements and cross-over designs. Additionally, the system is insensitive to the complexity of specialised cancer medicines which treat small patient populations, and has limited pragmatic solutions to address uncertainty.

Modest incremental improvements in survival that build upon others are undervalued and not accorded recognition or importance despite overall long term benefits to patients.

Moreover, indirect costs, including; productivity, employment costs, welfare transfer payments, amongst others are poorly valued in submission evaluations. This is in contrast to HTA systems in other jurisdictions that have attempted to take a more sophisticated approach.⁴⁶

Example of evidentiary issues under the current HTA system

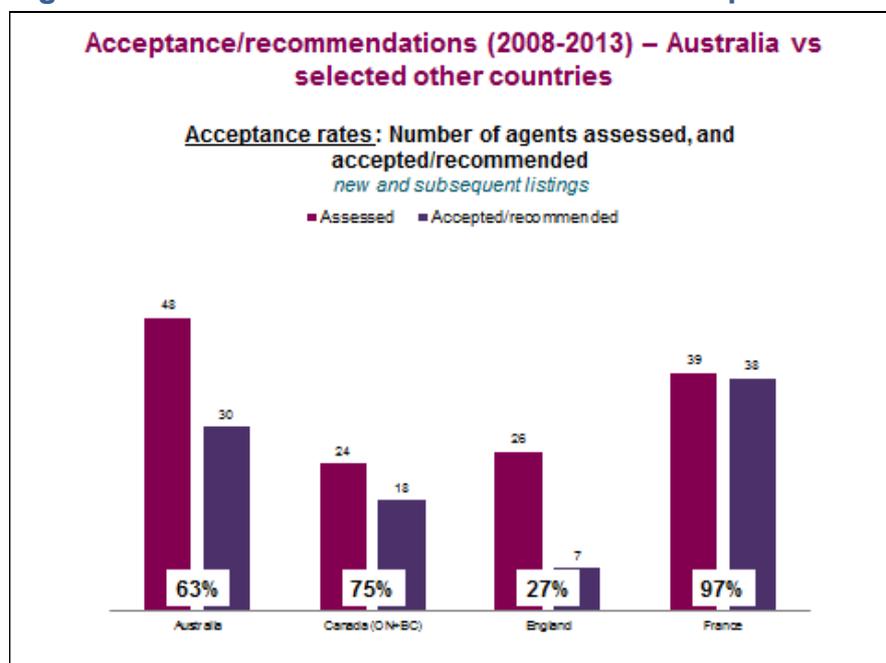
The guidelines for preparing reimbursement submissions to the PBAC state that the evidence required to show value for money should be derived from *direct randomised trials* and should include final outcomes data.

However, it is not always realistic, achievable, or even ethical to achieve these requirements particularly for cancer medicines, for example;

- Overall survival is often considered the most clinically relevant and meaningful outcome of a clinical trial. Yet, in cancer trials it is well-recognised that measurement of overall survival will prolong the duration of the trial and increase the number of patients needed to be recruited, therefore, increasing delays to reimbursement.
- Cancer patients, recruited to participate in a clinical trial of a new medicine or new indication, may be anxious that they are not receiving the 'new' medicine. Patients are commonly permitted to crossover to the trialed treatment if their disease progresses. This is widely considered ethically appropriate but further hampers the ability to measure overall survival.

Australia and others are clearly struggling with these complexities as research shows.

Figure 7: Australia's recommendation rate compared with peer countries



Source: Compiled from data in Wonder Drug Consulting, pp.5-6

Valuing health gains

Health Technology Assessment, measures outcomes by cost-effectiveness, in terms of number of Quality Adjusted Life Years (QALYs) gained relative to the cost of the medicine. HTA focuses

⁴⁶ Medicines Australia, 2015 (unpublished), "Value of Medicines Occasional Paper 1" – Please contact Medicines Australia to request a copy of this paper if required.

on increasing total utility across the population. Evidence suggests that treatments for patients with advanced cancer may have greater personal and social value than in other diseases where death is not imminent.⁴⁷

Therefore, the methods being used to assess health benefits when evaluating healthcare technologies for cancer and other end of life diseases have real limitations in terms of their ability to accurately capture the value of the health outcomes deemed important by patients.⁴⁸ For cancer patients in particular, the cost-effectiveness approach (cost per QALY) delays the scope of, and time to, access to new innovative medicines.⁴⁹

This restricted approach to valuing healthcare gains from new and innovative medicines means the indirect benefits to the community, outside the health system, are not adequately or systematically captured in PBAC evaluations. These include improved productivity from faster recovery or longer survival due to the specialised medicines; reduced carer responsibilities; easier to use and more easily tolerated treatments, among others.

Fit-for-purpose approach needed

There is a growing trend in HTA countries towards adoption of a different or more fit-for-purpose process for drugs for the treatment of cancer. In Australia to date there has been little constructive dialogue between all the relevant stakeholders about the emerging challenges in accessing new medicines, particularly cancer medicines.

The PBAC has unlimited flexibility in decision-making with respect to determining cost-effectiveness, but provides little information on how that flexibility is informed by society and taxpayers views. Medicines Australia contends that compassion for end-of-life patients should lead the PBAC to accept higher ICER and develop pragmatic approaches to uncertainty when making decisions about these treatments.

The community has little voice in the system that it relies upon to measure the value of life and the additional value new cancer medicines provide to the public.⁵⁰

More than 900 cancer medicines are currently in global development. Without much needed dialogue on the value of these treatments to patients and the community as a whole, the risk increases that many of the 900+ cancer medicines may not be available to Australian patients and/or access to them will be greatly delayed.

Lessons from other countries

The challenges faced in Australia are similar to those faced by other countries where it has been recognised that the HTA systems have not delivered cancer medicines efficiently for patients.

In the UK and Canada, the *value for money* measure of cost-effectiveness did not deliver access to cancer medicines in line with community or political expectations. Both nations rapidly introduced interim measures to improve access to cancer medicines, while continuing the search for a better system.

⁴⁷ K. Shah et al. Severity of illness and priority setting in healthcare: a review of the literature. Health Policy 2009; 93: pp.77-84.

⁴⁸ M. Garau, et al. "Using QALYs in Cancer: A review of the methodological limitations" OHE Research Paper 10/01, Oct 26, 2010

⁴⁹ IMS Institute for Healthcare Informatics, pp.8

⁵⁰ This contrasts with the UK where there was widespread debate following the approval of sunitinib in the UK in 2008/9 which resulted in NICE's review of their current process in regard to assessing the value of cancer medicines and adoption of new criteria, which included an increase in ICER threshold deemed acceptable by NICE, (Raftery, 2009). Australia has not yet had a meaningful debate about the value of life, including 'end of life care', and what the community considers acceptable.

These mechanisms increased access; however, they also increased administrative and budgetary burdens, thus confirming them as temporary options only. Nevertheless these are good examples from which Australia can learn and seek to adopt more sustainable methods.

UK Cancer Drugs Fund

The Cancer Drugs Fund (CDF) was set up in 2011 to help patients in England access certain drugs before they received NICE approval for widespread NHS use. The scheme was due to end in 2014, but British Prime Minister David Cameron has since pledged a further £400m to keep it running throughout 2015. Its aim was to make it easier for doctors to prescribe treatments even if they had not yet been approved NICE.

As of January 2015, there were 34 drugs for 60 different cancer indications available from the CDF⁵¹ and over the last three years about 34,000 patients have received treatment that they would not have otherwise received had the fund not existed. However, the cost of the fund has led to a decision to remove 16 of the listed treatments from April 2015.

The UK has also invested heavily in processes to place the public and patients at the heart of decision-making through stakeholder involvement in order to better capture the community's experiences and needs. Members of the public now sit on the NICE Board; patient representatives are included in technology appraisal committees; patient representatives provide input to technology assessments and are involved in guideline development, in addition to the establishment of a Citizen's Council.⁵²

The pan-Canadian Oncology Drug Review

The pan-Canadian Oncology Drug Review (pCODR)⁵³ was created to assess cancer drugs and make recommendations to provincial cancer agencies/governments to guide drug funding decisions. It was established in recognition of the unique characteristics associated with cancer care in Canada. The organisation developed a specialised review process following extensive consultation of provincial drug plan experts, cancer agencies, practicing oncology clinicians, tumour-specific oncologists, patients, as well as the manufacturers of innovative medicines.

The pCODR process was considered successful, partly because of the inclusion and meaningful involvement of all stakeholders; transparency and rigour of HTA process and decision making criteria; together with incorporation of broad-based considerations of societal and patient value. The pCODR model reflected a deliberate decision to adopt a stakeholder focussed approach with cancer and to overcome challenges faced in HTA. PCODR delivered high quality, practical, scientific advice that squarely addressed the issues raised by patients, clinicians and cancer agencies unable to be addressed under conventional HTA approaches.

PCODR was integrated into the Canadian Agency for Drug Technologies and Health (CADTH) in April 2014. It is expected that the important aspects of the pCODR process: stakeholder integration and inclusion from beginning to end, will be retained.

⁵¹ National Cancer Drugs Fund list, available at <http://www.england.nhs.uk/wp-content/uploads/2015/01/ncdf-list-dec14.pdf>

⁵² The NICE Citizen Council includes 30 members of the public and provides a public perspective on overarching moral and ethical issues that NICE has to take account of when producing guidance. In addition, the initiative for patient involvement in NICE (or PIN for short) is based on a coalition of over 80 patient organisations and is committed to enabling patient groups to engage productively with NICE.

⁵³ Information regarding the pan-Canadian Oncology Drug Review Available at www.pcodr.ca

Good HTA practice

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)⁵⁴ Health Technology Assessment International (HTAi)⁵⁵ and industry associations such as the European Federation of Pharmaceutical Industries and Associations (EFPIA)⁵⁶ have identified a number of common elements for Good HTA Practice. These recommendations highlight:

- Procedural fairness in the HTA system; meaning clear processes for assessment and decision-making, plus added scope for pragmatic approaches and a merits-based appeal mechanism must be clear.
- HTA assessments of clinical effectiveness; budget impact and economic efficiency should include assessment of societal values and ethical judgments relevant to the particular patient population.
- Transparency, credibility and consistency in the methods used to assess new interventions as well as in the value criteria used to guide decisions are critical.
- Integrated stakeholder involvement (clinicians, patients, citizens, industry, academia) in the processes, with input into methodology and value criteria, as well as individual funding decisions are fundamental.

Conclusion

The Australian HTA system has not adapted adequately to the changes in the development of medicines and diagnostic technologies. This affects all medicines but has a specific impact on specialised or targeted cancer medicines.

Australia now has an opportunity to learn from the experiments (and experiences) of other countries to develop world leading innovative access approaches to ensure timely, subsidised access to the latest treatments for Australian patients. Dialogue with industry is critical to achieving workable solutions.

⁵⁴ ISPOR Good Practices for Outcomes Research, available at http://www.ispor.org/workpaper/practices_index.asp, Accessed 20 October 2014.

⁵⁵ HTAi, Publications of the Interest Sub-Groups, HTAi, Available at <http://www.htai.org/index.php?id=574> Accessed 20 October 2014.

⁵⁶ EFPIA, July 2005, "The Use of Health Technology Assessments to Evaluate Medicines: Key Principles", available at <http://www.efpia.eu/topics/industry-economy/health-technology-assessments>, accessed 20 October 2014

C): The impact on the quality of care:

- The impact of delays in treatment availability for cancer patients clearly differs from diseases where certain death is not imminent.
- There is inequity of access:
 - Some patients who can afford to pay for a new cancer treatment themselves, gain access versus patients who cannot
 - Better health outcomes are seen in urban treatment centres versus those in rural oncology settings
 - Inequity exists between private versus public access and timely treatment routes

The National Medicines Policy

The Australian Government introduced its national medicines policy in 1999.⁵⁷ The policy is intended to improve health outcomes for all Australians through a cooperative effort that ensures access and wise use of medicines. It has four central objectives:

1. Timely access to the medicines Australians need at a cost the individual and the community can afford
 - this is achieved through two principle measures; a patient co-payment and government subsidy
2. Medicines meeting appropriate standards of quality, safety and efficacy
 - this is achieved through TGA assessment
3. Quality Use of Medicines
 - ongoing activities between government, industry and health care professionals and professional associations (i.e. NPS) are aimed at achieving this objective
4. Maintaining a responsible and viable medicines industry
 - this is an acknowledgement that the industry is integral to the health of Australians and contributes significantly to the wealth and economic prosperity of Australia

For very good public health reasons the Australian Government provides a publicly funded, national insurance scheme, providing subsidised healthcare, including medicines, to the Australian population.

Unfortunately, access arrangements for cancer medicines can depend on where a patient lives; who their physician is; the availability of specialised cancer treatment in the area; and their level of private health insurance.⁵⁸ Furthermore, even with a subsidised universal health care system, a patient's ability to access an *unsubsidised*, high cost medicine will depend on their personal socio-economic status⁵⁹.

⁵⁷ Department of Health, 1999, "National Medicines Policy", available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/national-medicines-policy>

⁵⁸ Deloitte Access Economics, pp.43

⁵⁹ I. Olver, F. Marine & P. Grogan, 2011, "Disparities in Cancer Care in Australia and the Pacific", *The Oncologist* 2011;16 pp.933

A patient may be able to contribute part of the cost of a non-reimbursed drug but the amount of the contribution can vary significantly depending on their financial status or the institution. This can push patients into poverty due to ruinous health care costs and adds unacceptable psychological stress and trauma to an already potentially catastrophic life event.⁶⁰ The resultant, two-tier, health system conflicts with the core objectives of the national medicines policy.

Recent evidence from the AIHW indicates health outcomes for cancer patients differ between urban and rural regions, a concern also noted by the National Health and Rural Alliance (NHRA)⁶¹. In 2005–2009, incidence rates were highest for those living in inner regional areas of Australia; in 2008–2012, mortality rates were highest for those living in very remote areas.⁶²

There is commonly a lack of easily accessible diagnostic and treatment services in rural areas where treatment services are often rudimentary compared to large urban centres. They will also likely lack access to current research and clinical trials, which are commonly conducted in larger urban centres. These factors contribute to later diagnosis; diagnoses at more advanced stages of disease; and higher mortality rates.

The existing HTA process does not include a holistic approach to medicines subsidy. When treatment centres are remote from home there may be added costs for accommodation and other costs⁶³. Additionally, lost productivity, taxes and other revenues; welfare transfer payments; as well as the cost of a family member having to become a carer are underestimated and poorly elaborated. This exacerbates the disparity between socio-economic groups in Australia.⁶⁴

Compassionate access

Early access to unapproved medicines may be achieved through participation in clinical research trials, where possible for some patients. Other early access programmes may be initiated and funded by the company, for example: prior to a medicine being listed on the PBS (during the TGA's evaluation period or in the gap between TGA approval and reimbursement), the company may provide patients with access to the new medicine (or for a new indication of an existing medicine) through a patient access program.

Research undertaken by Deloitte found that nearly 5000 patients were provided compassionate access to non-reimbursed medicines in Australia during 2011-2012, from a sample of

⁶⁰ Rare Cancers Australia, pp.18

⁶¹ NHRA newsletter, No. 8, 2012. The NRHA Newsletter cites a 2006 study by the Clinical Oncological Society of Australia (COSA) which mapped rural and regional oncology services in Australia:

Australians in rural and remote areas have relatively poor access to cancer treatment and support:

- 38 per cent of rural hospitals administering chemotherapy had neither a resident nor visiting medical oncology service;
- only 58 per cent of rural hospitals surveyed reported that most chemotherapy orders were written by a medical oncologist;
- as the remoteness of hospitals increased, chemotherapy was increasingly administered by people other than a chemotherapy-trained nurse, such as other nurses and general practitioners;
- 7 per cent of non-metropolitan hospitals that reported administering chemotherapy had access to a radiation unit;
- many hospitals reported long waiting times for allied health and inpatient services; and
- 61 per cent of the hospitals requested urgent access to psychological services and support.

⁶² AIHW, "Cancer in Australia: an overview" pp.54

⁶³ Mark's story: "I also had nearly 8 weeks of radio-therapy, 5 days per week which I chose to have in Sydney due to the more advanced equipment. This meant that I had to be away from my family during the week but I managed to go home to Canberra on weekends." Rare Cancers Australia, pp.31.

⁶⁴ Noelle's story, as told by her husband Patrick: "At the time of diagnosis I was in full-time employment at sea and Noelle, a retired school teacher, ran a flourishing literacy consultancy. Her business stopped at once. I took all of my outstanding leave, followed by indefinite leave of absence. It soon became clear that I would need to be a full-time carer so I retired. The most immediate non-medical effect was the loss of two incomes. I had a pension but you do not lose over 60 per cent of your income overnight without noticing it." Rare Cancers Australia, pp.32.

9 pharmaceutical companies⁶⁵. This type of access is designed to be temporary, with more than two thirds of the sample used to cover the access gap between TGA registration and PBS reimbursement. Notably, the access was mostly provided free of charge. This data is presented as Table 2 below. The same research reported that approximately \$10 million of cancer medicines are provided to patients prior to PBS listing, or even experimentally prior to TGA approval, through specialist cancer centres.

The sustainability of such programs is a significant issue for the industry, given the length of time often required for a medicine to secure a positive decision from the PBAC and get listed on the PBS. Furthermore, companies are frequently criticised by clinicians, the government and PBAC when unanticipated, lengthy delays in listing decisions mean that ongoing access cannot be commercially sustained indefinitely.

Table 2: Access to cancer medicines through compassionate use or access programs

Sponsor	Nr products	Nr patients (2011-2012)	TGA registration status		Access arrangement	
			On-label	Off-label	Fully funded	Cost-sharing
1	6	1,994	55.5%	44.5%	81.9%	19.1%
2	4	842	93%	7%	83%	27%
3	6	693	67.1%	32.9%	99.3%	0.7%
4	2	132	12.8%	87.2%	87.2%	12.8%
5	1	150	-	100%	100%	-
6	1	405	100%	-	100%	-
7	5	273	78.4%	21.6%	35.2%	64.8%
8	2	233	100%	-	100%	-
9	1	26	-	100%	100%	-
Total	28	4,748	67.9%	32.1%	85.2%	14.8%

Source: Data provided by sponsors

Source: Deloitte Access Economics, pp.51

Conclusion:

Cancer drugs are an integral part of cancer treatment services. Anything which has a deleterious impact on the composition of these services and their delivery is likely to negatively impact the quality of care received by Australian cancer patients. The current system is already associated with unacceptable delays in access to new medicines. These medicines have proven health outcomes such as improved survival and quality of life gains. Medicines Australia has repeatedly called on the Government to review the PBAC; its composition and decision making, as well as examining whether the existing approach to HTA in Australia is contemporary and fit-for-purpose. This inquiry provides an opportunity for action and a chance to change Australia's health care for the better.

⁶⁵ Deloitte Access Economics, pp.51

D): Any related matters

There are a number of related matters which Medicines Australia wishes to draw to the Committee's attention:

- The opportunity to grow and support the biopharmaceutical industry in Australia
- The need for rapid resolution of Clinical Trial reforms as repeatedly promised by successive Governments.
- The unrealised clinical value of cancer medicines
- The failure to reinvest PBS Reform savings to fund new medicines

The biopharmaceutical industry in Australia

The biopharmaceutical industry in Australia creates high-skilled, high-paying jobs in a range of fields; from fundamental (pure) research, to clinical trials, highly specialised manufacturing, regulatory and health economics as well as sales and marketing. The industry employs over 14,200 Australians and invests more than a billion dollars each year. Medicines and vaccines remain one of Australia's biggest manufactured exports at \$3.4 billion annually, although exports have declined in recent years.

Clinical trials are conducted in more than a dozen therapeutic areas. Patients involved in these trials often receive early access to innovative therapies which may be years away from being available to the general public through registration and reimbursement processes. In 2013 there were 681 new clinical trials initiated in Australia; 29 per cent were in Phase III, late stage development.⁶⁶

However, Australia is losing its clinical trial business. The global competition for clinical trials is growing rapidly. The number of new clinical trials has fallen by over 25 per cent over the last six years.⁶⁷ The fall is due to rising costs in conducting clinical trials. Australia is around 20 per cent more expensive than the US; exchange rates and the high Australian dollar have exacerbated this. The process for getting ethics committee approvals to run trials in hospitals is overly complex. This decline will be further exacerbated by the limits imposed on R&D tax credits introduced for the 2014-15 financial year.

The Government must commit to implementing long standing recommendations for improvements in the clinical trial environment. These reforms are detailed in Medicines Australia's submission to the Senate Economics References Committee's Inquiry into the Australian Innovation System.⁶⁸

Clinical value of cancer medicines

A study conducted by the Office of Health Economics⁶⁹ in the UK highlighted the dilemmas facing companies and payors in relation to cancer medicines. The study shows that for many cancer medicines, their clinical potential is undervalued and may not be evident at the time of first approval; over time and by indication. This results in pricing and reimbursement decisions that fail to adequately recognise innovation and discourages future innovation, to the detriment of society.

⁶⁶ Therapeutic Goods Administration, 2014, "Half Yearly Performance Reports, Clinical Trials (medicines)" available at <https://www.tga.gov.au/half-yearly-performance-reports-january-june-2014>

⁶⁷ Ibid.

⁶⁸ Medicines Australia's submission to the Senate Economics References Committee's Inquiry into the Australian Innovation System, available at [medicinesaustralia.com.au](https://www.medicinesaustralia.com.au)

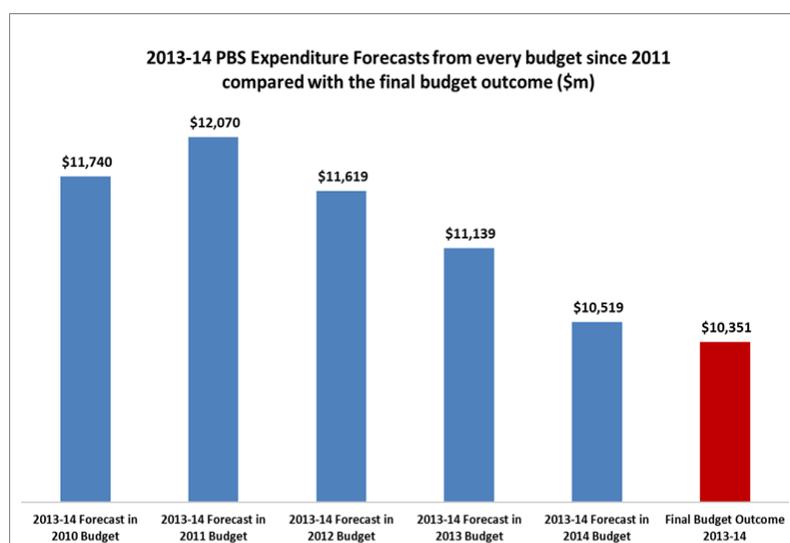
⁶⁹ Office of Health Economics, 2014, "The Expanding Value Footprint of Oncology Treatments", J.C. Rejon-Parrilla, K. Hernandez-Villafuerte, K. Shah, J. Mestre-Ferrandiz, L. Garrison, and A. Towse, May 2014, available at <https://www.ohe.org/publications/expanding-value-footprint-oncology-treatments>

The health outcome gains from new cancer drugs are often modest, particularly when reported in terms of overall survival at the time of initial regulatory approval. It can be difficult to demonstrate, during a clinical trial, that a medicine improves overall survival due to the complexity of trial design including; the number of patients required, follow-up time needed and cross-over designs followed.

Regulatory agencies frequently grant marketing authorisation to medicines based on alternative endpoints such as progression-free survival. However, the use of such surrogate indicators of overall survival is commonly considered inadequate by the PBAC. The acceptance of surrogate endpoints is one of several differences that can often arise between the requirements of regulators, whose approvals are based on absolute benefit-risk assessments, and those of payers, whose reimbursement decisions are based on comparative or relative effectiveness or cost-effectiveness assessments. In addition, there are differences in evidentiary needs across different HTA bodies. For instance, the comparator in a multi-national trial may represent standard therapy in some countries but not in others.

Reinvestment of PBS Reform savings

Significant structural reforms, developed in consultation with Medicines Australia over the last decade, have delivered a sustainable model for funding pharmaceuticals through the PBS, with enduring mechanisms to generate ongoing PBS savings. As a consequence, the 2013-14 Final Budget Outcome released in September showed, for the fifth consecutive time, a downward revision of pharmaceutical benefits and services expenditure. From a projected high for the 2013-14 year of over \$12 billion as calculated in 2011, the actual cost of the PBS for the 2013-14 year was \$1.7 billion less, at \$10.3 billion.



Source: compiled by Medicines Australia from 2010/11, 2011/12, 2012/13, 2013/14, 2014/15 Federal Budget Papers (Table 8.2) & Final Budget Outcomes 2013/14

The savings generated by these reforms should be used to fund new cost-effective medicines, so that Australian patients can continue to access the latest treatments.

Conclusion:

Decisions regarding the registration and reimbursement of new, innovative and specialised cancer medicines influence the wider Australian community and industries. Consideration should be paid to unintended consequences that may cause negative effects on society and the economy. Additionally, benefits gained through improving the availability of new, innovative and specialised cancer medicines may be transferable to improve those same conditions across the full health care system.

APPENDIX A: References and Glossary

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Glossary

Control is often used to describe the non-experimental group of patients within a trial; they usually receive a placebo, no treatment, standard treatment, or an active intervention, such as a comparator drug.

Crossover describes the movement of a patient in a clinical trial from one trial treatment to another. In many cases for cancer drug trials, a patient whose disease progresses switches to the alternative treatment.

Direct randomised trial is one that directly compares the investigational medicine to the comparator

ICER or **incremental cost-effectiveness ratio** represents the difference in cost between two medical interventions (the comparator and the new medicines) relative to the difference in outcome between the same two interventions.

Incidence describes the number of new cases per year, whereas **prevalence** is the total number of current cases.

Overall survival (OS) is defined as time from randomisation to death from any cause.

Prevalence is the total number of current cases

Progress is used to describe when a disease worsens, spreads, or returns.

Progression free survival (PFS) is often defined as the time from randomisation to disease progression (or death if the patient died before progression).

QALY (Quality Adjusted Lift Year) is a combination of the value of the health states and their duration, and every QALY is equivalent to one year of life in full health

Reimbursed medicines are those where the cost is mainly borne by the government, sometimes with the patient required to pay a small amount (a co-payment in Australia). This term is often used interchangeably with **subsidised**.

Risk share arrangements are usually negotiated between a pharmaceutical company and the Australian Government through the Department of Health. They are “designed to help maintain the appropriateness and cost-effectiveness of (PBS) listed medicines”. More information is available at http://www.pbs.gov.au/info/industry/listing/listing-steps/g-entering_agreements

Subsidise: In order to make a medicines affordable, a government may choose to subsidise a medicine by paying the cost of the medicine and passing on either no cost or a portion of the total cost to the patient. In Australia the Government subsidises the cost of medicines through the PBS, requiring patients to pay a copayment. It is often used interchangeably with **reimbursed**.

APPENDIX B: FDA fast track regulatory process

The following article was published by Evaluate Pharma on January 5, 2015. See at: <http://www.evaluategroup.com/Pharma/ViewStoryEPVantage.aspx?AlertStory=true&storyId=550480>

Breakthrough designation quickens FDA approval pace in 2014

Source **EP Vantage**

Company [Amgen](#), [AstraZeneca](#), [Bristol-Myers Squibb](#), [Eli Lilly](#), [Gilead Sciences](#), [GlaxoSmithKline](#), [Roche](#)

Tags Analysis, Free Content, Company Strategy, USA, Orphan Drug Status, Filing & Registration, Priority Review, Full Approval, Launches, Systemic Anti-Infectives, Respiratory, Oncology, Endocrine

Date January 05, 2015

Call 2014 the year when the FDA's breakthrough therapy designation really started to tilt the drug approval playing field. Nine NMEs with this beneficial tag zoomed through the agency's corridors last year, with an average wait of four months between application and authorisation for innovative projects like [Opdivo](#) and [Harvoni](#).

This focus on delivering groundbreaking agents to treat unmet medical need lowered the FDA's average approval time to 11.5 months, versus 14 in 2013. There were some laggards, of course; but the three-year wait that [AstraZeneca's Farxiga](#) endured is more than offset by [Amgen's Blincyto](#), which was under review for less than three months (see table).

More break through

The breakthrough therapy designation became effective in 2012, so it is no surprise that the sector is only now starting to see its true impact. The nine breakthrough NMEs approved last year accounted for a fifth of the 43 total NMEs gaining approval through either the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER).

Taken together with the products qualifying for priority review, about half of all those approved by the FDA were subject to some type of accelerated consideration, a clear sign of how pharma has shifted into orphan diseases and unmet medical needs, particularly in oncology. Four of the nine breakthrough therapies waved through by the FDA treat cancer; other diseases that saw speedy approvals are hepatitis C, novel antibacterials and enzyme deficiency disorders.

NME approval numbers and time (months) over the past decade

Year	Priority review		Standard		Breakthrough therapy	
	Number	Avg time	Number	Avg time	Number	Avg time
2014	12	8.1	22	16.5	9	4
	43	11.5				
2013	9	6.9	24	18	2	5.4
	35	14				
2012	14	6.6	28	18	1	3.5
	42	14				
2011	16	12.5	18	19	-	-
	34	16				
2010	10	9.4	16	14.1	-	-
	26	12.3				
2009	13	9.8	21	15.3	-	-
	34	13.2				
2008	9	10.4	22	19.4	-	-
	31	16.8				
2007	13	7.6	13	15.8	-	-
	26	11.7				
2006	13	7.2	16	22.2	-	-
	29	15.2				
2005	17	8.7	11	17	-	-
	28	11.9				

At the other end of the spectrum are agents in established classes, such as the GLP-1 agonists [Trulicity](#) and [Tanzeum](#), which received standard approval in diabetes on relatively leisurely 12 and 15-month cycles respectively. The crown for long delay in the class of 2014 belongs to the diabetes drug [Farxiga](#), which got a second-pass approval after partners [AstraZeneca](#) and Bristol-Myers [Squibb](#) put to rest concerns about cancer risk.

Talking of long delays, [Roche's Esbriet](#) could be said to have been subject to a delay of nearly five years. For purposes of this analysis, however, the clock was reset by its subsequent designation as a breakthrough therapy in idiopathic pulmonary fibrosis, after which it earned approval in just five months.

FDASIA wine and roses

The data show that the message of the breakthrough designation and other reforms of the FDA Safety and Innovation Act (FDASIA), sometimes called PDUFA V, are shaking through the agency. Breakthrough approvals have pushed average waiting times down, of course, but a shortening of the time for standard review drugs has also been recorded.

More worryingly, priority review approval intervals ticked upward, but are still not at their 2011 peak. That year included outliers in the form of a 46-month approval cycle for [Firazyr](#), while the earliest NDA submission for the priority review class of 2014 was March 2013, so FDA watchers will no doubt be keeping a close eye on the progress of priority review [candidates](#) in 2015.

Meanwhile, the total number of approvals, at 43, will have many of those same FDA watchers ecstatic not only with the regulator's agreeability but also with pharma's resurgent R&D muscle; the total edges out the remarkable class of 2012.

In terms of quality, the class of 2014 had been reckoned to be more modest than that of 2013, which saw an impressive number of forecast blockbusters reach the launch pad. However, this tally shows that in terms of sheer numbers of new drugs and their speed to market 2014 will be a hard act to follow.

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APPENDIX C: PBS & PBAC Processes for Medicines

Introduction:

This document provides an overview about the Pharmaceutical Benefits Scheme (PBS), the role of the Pharmaceutical Benefits Advisory Committee (PBAC) and their requirements for the evidence for a medicine when it is being considered for reimbursement. Weblinks are provided at the end of the document at which comprehensive information can be found.

What is the PBS?

- The PBS is a national list (Medicines Formulary) of prescribed medicines, the cost of which the Australian Commonwealth Government (Govt.) has agreed to subsidise, meaning the medicines are more affordable for Australian consumers.
- Medicines available on the PBS cover a range of health conditions, or therapeutic areas.
- Approximately 10 per cent of the cost of the PBS is for specialty, high cost medicines such as medicines used to treat patients with cancer and medicines for patients with rare diseases.

How does a medicine get onto the PBS?

- Medicines must go through an evaluation process and be approved for listing by the Pharmaceutical Benefits Advisory Committee (PBAC). The process is complex and can take some time.
- The PBAC is a statutory committee that has been in place for many decades and is an independent, expert committee appointed by the Minister of Health (MoH).
 - o The MoH can only put a medicine on the PBS following a positive PBAC recommendation.
- The 'sponsor' of a submission to list a new medicine on the PBS is usually the pharmaceutical company that developed the medicine. However, doctors, specialist / patient groups can also apply to the PBAC.

What does the evaluation of a medicine involve?

- The evaluation process looks at two areas:
 - o How the medicine works (i.e., clinical benefit & safety)
 - o Economic costs associated with using the medicine.
- The clinical evaluation usually means a comparison of the medicine to another treatment (usually called the comparator). The treatment may be another medicine, or standard current medical care (no specific medicine), or another technology used to treat the condition, e.g., surgery.
- There are two economic evaluations. One identifies, measures and compares the costs (or resources consumed) involved with using the medicine. The second evaluation estimates how many patients would be likely to receive the new medicine and how much it would cost the Govt. to list it on the PBS.

Why do an evaluation?

- Australia cannot afford to spend a limitless amount on medicines
- The cost of innovative research and development (R&D) is high, so many of the new medicines are expensive, especially in oncology
- For the Govt. to decide which medicines should be subsidised, or not, the Govt. needs to know which medicine is 'good value' for money. The PBAC's evaluation provides this information.

What clinical evidence is used for an evaluation?

The highest quality information about the effect of a medicine comes from trials which are **R**andomised (*i.e., patients get assigned by chance to a treatment group, independently of the doctors doing the trial*) and **C**ontrolled (*i.e., factors which could introduce error are minimised or avoided*). These trials (which are abbreviated as RCT) are the "gold standard", and are preferred by the PBAC as the source of evidence

on which to assess the 'value' of a medicine. However, for various reasons, this type of evidence may not be available for cancer medicines, a fact the PBAC acknowledges⁷⁰.

Most RCT assess several outcomes (or endpoints), and the most relevant of these is survival, which is usually measured as overall survival (OS). Other outcomes commonly measured in oncology trials include rate of response (RR), Time to Progression (TTP), Progression Free Survival (PFS) and safety. In addition, oncology trials usually include an assessment of the quality of life (QoL) of the patient undergoing treatment. The following table lists some of the factors which affect the level of evidence in oncology, and the potential impact in terms of PBAC's consideration of the evidence.

Factor affecting evidence and explanation		Impact on PBAC consideration
Cross-over	In the terminal disease setting, a patient randomly assigned to the 'non-active / inferior' treatment is usually allowed to 'cross-over' to the 'active / superior' treatment when their cancer worsens (i.e., progresses). Not allowing cross-over is unethical.	OS reflects all the treatments the patient has had, meaning the difference in clinical effect between the treatment groups will be diluted because patients in the non-active arm has 'crossed over' to receive active treatment & so their survival will be increased.
Recruitment	Recruiting patients can be difficult because they are at the 'end stage'. Having already had many other treatments, they may be excluded from enrolment.	The trial does not provide evidence for the populations in which it may be used in the real-life Australian setting.
Evolving treatment practices	Treatment practices / drug combinations have evolved rapidly in oncology with the availability of new medicines being used in conjunction with the older chemotherapies.	The treatment regimen used in the registration trial (which supports the TGA-registered indication / combination) may be out-dated by the time reimbursement is sought.
No directly comparative (head to head) trials	Most oncology trials do not directly compare newer treatments. Rather, the new treatment is compared to the current standard of care (SOC), which is usually older chemotherapy agents, either alone or in combination.	<ul style="list-style-type: none"> - Older drugs are generic & cheap, meaning showing 'acceptable' CE is often difficult. - Comparisons across trials are problematic, and raise uncertainty about the comparative benefit.

What are the types of economic evaluations?

There are two main types:

1. Cost-Minimisation Analysis (CMA)

If the proposed medicine is no worse than (or non-inferior or equivalent to) the main comparator, there is no basis in terms of health outcomes to justify a higher price (unless there are cost offsets due to a different method of administering the proposed medicine).

2. Cost-Effectiveness Analysis (CEA) or Cost-Utility Analysis (CUA)

If the medicine is superior to the main comparator, a cost-effectiveness analysis or cost-utility analysis is appropriate to determine whether the increase in health outcomes (and any cost offsets) justifies the increase in medicine costs (and hence increased price) in terms of being acceptably cost-effective.

What is a QALY?

The QALY (quality-adjusted life-year) is a way of adjusting OS to account for the time spent in different states of health. The QALY has become widespread as a measure of health outcome in the economic evaluation of health care interventions. The key characteristics of the QALY are as follows:

- It combines life extension and Quality of Life in a single index that allows comparison across health interventions.
- The utility weight index measures strength of preference on a cardinal index anchored on a 0 to 1 interval of death to full (perfect) health, with equal intervals measured in such a way as to have equal value and an allowance for the existence of health states perceived to be worse than death (ie < 0).

⁷⁰ In regard to the clinical evidence (Section B), The Guidelines for preparing a submission to the PBAC state: "PBAC has a strong preference for clinical and economic evaluations that are based on direct randomised trials; that is, trials that directly compare the proposed medicine with the main comparator. However, PBAC recognises that direct randomised trials are not always available." (pp.74)

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- The utility weights that underpin the QALY measure are based on a sample of individual preferences. These preferences are obtained in a way that involves a tradeoff between quality and quantity of life. This provides some validity to the QALY as representing societal trade-offs and therefore social values.

The implication of using this scale is that one year of life in full health is counted as one QALY. Even though one year of life in normal health is less than one QALY, this does not necessarily mean that all incremental QALY gains are numerically smaller than incremental life-year gains. This is because incremental QALY gains can also encompass the possibility of improving quality of life, and such improvements can happen for a long period before any improvement in survival happens.

What is an ICER?

The incremental cost effectiveness ratio (ICER) indicates the 'value' of a medicine, most commonly as a cost per QALY. It is a ratio of the incremental benefits of a therapeutic intervention or treatment benefits and the change in costs associated with this new therapy or intervention. The equation for the ICER is:

$$\text{ICER} = (\text{C1} - \text{C2}) / (\text{E1} - \text{E2})$$

where C is Cost and E is Effect, 1 is the new treatment and 2 is the comparator. Costs are usually described in monetary units while benefits/effect in health status is measured in terms of (QALYs) gained or lost.

Useful weblinks about the PBS & the PBAC process follow:

PBS: <http://www.pbs.gov.au/info/about-the-pbs>

PBAC overview: <http://www.pbs.gov.au/info/industry/listing/participants/pbac>

PBAC process: <http://www.pbs.gov.au/info/industry/listing/listing-steps>

PBAC Guidelines: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-guidelines>

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