



Australian Government
Department of Health

SECRETARY

Senator Rachel Siewert
Chair of the Senate Community Affairs References Committee
c/o Committee Secretary
Senate Standing Committees on Community Affairs
PO Box 6100
Parliament House
Canberra ACT 2600

Dear Senator

Please find attached the Department of Health's submission to the inquiry into the availability of new, innovative and specialist cancer drugs in Australia. I offer the Department's apologies for the delay in providing the submission.

I hope the information provided will assist the Committee in its deliberations.

Yours sincerely

Authorised for electronic submission

Andrew Stuart
Deputy Secretary

17 March 2015

**SENATE COMMUNITY AFFAIRS REFERENCES
COMMITTEE**

**INQUIRY INTO THE AVAILABILITY OF NEW,
INNOVATIVE AND SPECIALIST CANCER DRUGS IN
AUSTRALIA**

SUBMISSION

**AUSTRALIAN GOVERNMENT
DEPARTMENT OF HEALTH**

MARCH 2015

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- Cancer Australia;
- The Australian Institute of Health and Welfare; and
- Therapeutic Goods Administration.

Information drawn from specific sources is referenced in the footnotes.

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1. EXECUTIVE SUMMARY

Despite having very high rates of cancer, Australia's cancer survival outcomes are equivalent to the best in the world. Australia's one year survival rate for all cancers combined is 81%, and overall five year relative cancer survival rates are now more than 66%.

This success is not due to one sole aspect of Australia's world class health system, but to the system working effectively across the continuum of cancer care – from excellent screening programmes, to affordable access to the medical specialists and high quality care that all cancer patients require to have the best chance of good outcomes.

Access to effective cancer medicines is an important component of that system insofar as it *further* improves health outcomes for cancer patients. Australia has a very good record on providing subsidised access to cancer medicines. There are over 100 medicines for the treatment of cancer on the Pharmaceutical Benefits Scheme (PBS). Expenditure for currently-listed medicines was close to \$1.5 billion in 2013-14; that is one in every six dollars expended through the PBS. This is up from one in eight dollars in 2012-13 and this proportion is likely to increase. At their March 2015 meeting alone, the Pharmaceutical Benefits Advisory Committee (PBAC) will be considering 11 major submissions for cancer medicines, with a potential total cost of \$589 million if they are recommended for PBS listing.

Access to medicines ultimately depends on their affordability for patients. The PBS ensures that although the cost of most new cancer therapies can run to many thousands of dollars, Australian patients pay no more than the co-payment. On average over the last five financial years, the patient co-payment funded between 2-3% of the total cost of cancer medicines, compared to 15% for non-cancer medicines. The taxpayer funds the remainder.

PBAC processes have been evolving over the years to include changes such as the Managed Entry Scheme and "pay for performance" pricing arrangements. These changes are slowly being taken up by companies as their value is recognised. Notwithstanding Australia's successes, there is always room for improvement and changes to PBAC processes can be considered, to ensure they continue to provide the optimal circumstances for all cost-effective new medicines to make successful submissions. Community interests will also continue to be served. For example, improving transparency by making the majority of the documents publically available and allowing an effective discussion in the community of the real benefits, harms and cost of the products, as well as reducing the number of re-submissions, is in everyone's interest.

In line with the National Medicines Policy, industry must also play its part in any PBS reform. The availability of new medicines is dependent on the timing of submissions to the PBAC, which is in the hands of pharmaceutical companies. The pricing of new cancer therapies should also be more closely aligned to their patient outcomes. There have been few 'transformative' cancer medicines in recent years and there is a risk to innovation if business models continue to focus on the financial rewards associated with 'me-too' medicines, and not significant innovation.

Australia's challenges with access to expensive new medicines, including cancer medicines, are not an isolated experience. Expenditure on cancer medicines has increased worldwide (up to an estimated \$91 billion in 2013) and the pipeline for new medicines is strong. Almost 1,000 anti-cancer medicines are currently in various phases of pre-approval testing; more than the number for heart disease, stroke, and mental illness combined.¹ There are real challenges in establishing the evidence to support the high costs for many of these medicines, especially when benefits are incremental. Many clinicians, as well as third party payers, have expressed serious concern for future health expenditure if systems don't evolve to meet these challenges.

¹ IMS Institute for Healthcare Informatics. 2014. "Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report"

Moreover, there are opportunity costs to patients of resourcing cancer medicines at the expense of other aspects of the cancer care continuum. A focus on cancer medicines can also affect access to new medicines for patients with other diseases, such as hepatitis C or cardiovascular disease. It is important that all partners in the operation of the PBS take responsibility for achieving timely access to medicines and value for money, and to ensure that cost-effectiveness is not lost to the expectation of quicker access to medicines of marginal or unproven benefit.

2. THE AUSTRALIAN EXPERIENCE OF CANCER

Key findings

Cancer is a leading cause of illness and death. At the same time, mortality rates are decreasing and Australia has the best survival rates in the world.

The upwards trend in cancer incidence is likely to continue, due to the ageing population, as well as improved diagnostic techniques.

Approximately one third of total funding for cancer is spent on medicines.

The availability of all new and innovative measures, including medicines, must be considered with regard to their relative health gains – both across the cancer continuum and across all health priority areas.

Impact of cancer in Australia

Cancer is the leading cause of the burden of disease in Australia. One in two Australians will be diagnosed with cancer in their lifetime and one in five will die from cancer before the age of 85.²

The estimated five most commonly diagnosed cancers in 2014 were prostate (17,050), bowel (16,640), breast (15,410), melanoma of the skin (12,640) and lung (11,580) and, combined, they were estimated to account for about 60% of all cancers diagnosed that year.³ Over the same period, it was estimated that a total of 42,000 people would be diagnosed with a form of rare or less common cancer.

Indigenous Australians and people living in remote areas experience slightly lower cancer incidence but higher mortality rates compared with other Australians. Australian men have a higher rate of cancer diagnosis (55%) compared to women and they account for more than half (57%) of all deaths from cancer.⁴

The incidence of cancer is strongly associated with age. Based on 2014 estimates, one in three males and one in four females will be diagnosed with cancer by the age of 75. By the age of 85, the risk is estimated to increase to one in two for males and one in three for females.

Cancer outcomes in Australia

While cancer is a major cause of death, estimated to account for about three out of every ten deaths in 2014, the outcomes for Australians following diagnosis and treatment are the best in the world.⁵ Over the period 2007-2011, people diagnosed with cancer had a 67% chance of surviving for at least 5 years.⁶ This has improved significantly and is up from 47% over the period 1982-1987.

Australia's cancer future

Cancer prevalence is trending upwards, both in Australia and globally. The health and economic impacts on individuals, communities and the health system as a result of cancer are expected to continue to increase. Contributing factors include: improved detection; an ageing population; and improved cancer management and treatment (leading to improved survival).

² Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. 2012. Cancer in Australia: an overview, 2012.

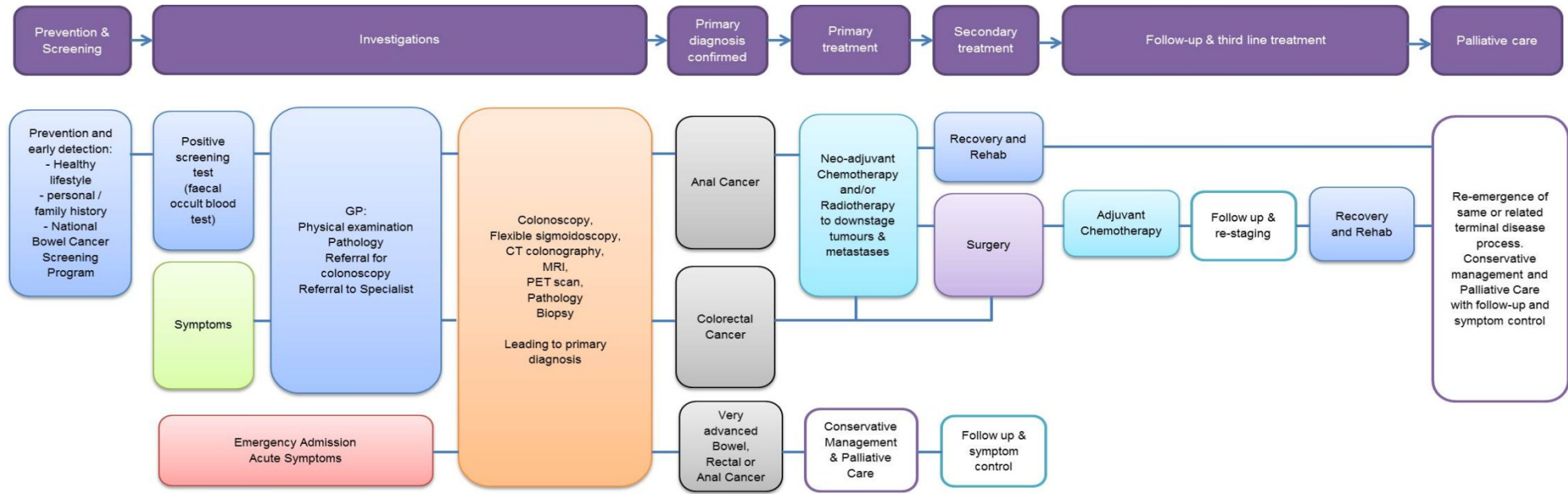
³ AIHW: *Cancer in Australia 2014 – An overview*

⁴ AIHW: *Cancer in Australia 2014 – An overview*

⁵ AIHW: *Cancer in Australia 2014 – An overview*

⁶ AIHW: *Cancer in Australia 2014 – An overview*

Patient Journey for Bowel Cancer (adapted from Bowel Cancer Australia)



Incidence data and examples of costs that maybe incurred during treatment

<p>Bowel Cancer Screening Participation – 33%</p> <p>Screening kits available on line from Bowel Screen Australia for \$45.95</p> <p>FBT Fee: \$8.90 75% - \$6.70 85% - \$7.60</p>	<p>Examples of investigation services required:</p> <p>GP consult – Level B attendance – 23 Fee: \$37.05 75% - 27.79 85% - \$31.49</p> <p>Colonoscopy – 32084 Fee: \$111.35 75% - \$83.55 85% - \$94.65</p> <p>CT scan of chest abdomen and pelvis – 56807 Fee: \$560.00 75% - 420.00 85% - \$481.60</p> <p>Liver function test- 66650 Fee: \$24.35 75% - \$18.30 85% - \$20.70</p> <p>Specialist referred consultationn – 104 Fee: \$85.55 75% - 64.20 85% - \$72.75</p>	<p>Anal Cancer 2011 Incidence* 369 persons 1.5/100,000</p> <p>Colorectal Cancer 2011 Incidence* 15,151 persons 61.5/100,000</p> <p>*age standardised rate</p>	<p>Example of Ex-man price associated with Drugs used:</p> <p>Fluorouracil – 1000mg in 20mL - \$24.15</p> <p>Capecitabine – tab 500mg - \$517.39</p> <p>Irinotecan - IV inj 500mg in 25mL - \$69.52</p> <p>Oxaliplatin – IV inf 200mg in 40mL - \$37.34</p> <p>Bevacizumab –IV inf 400mg in 16mL - \$1,720</p> <p>Cetuximab – IV inf 500mg in 100mL - \$1,705</p> <p>Panitumumab – IV inf 400mg in 200mL - \$2,912</p> <p>Raltitrexed –2mg - \$320.97</p>	<p>Potential cost of Treatments to patient*</p> <p>Drugs: \$37.70 co-payment per prescription for a general patient</p> <p>Surgery: 32030 - Rectosigmoidectomy – Fee: \$1,031.35 75% - \$773.55</p> <p>Radiation Oncology treatment - 15254 (repeated 25 times) Fee: \$1,491.25 75% - \$1,118.75 85% - \$1,268.75</p> <p>Cytotoxic Chemotherapy (x6) – 13918 Fee: \$587.70 75% - \$441.00 85% - \$499.80</p> <p>Patient outcomes (AIHW)</p> <table border="1"> <tr> <td>Anal cancer – 1 year survival</td> <td>88.3%</td> </tr> <tr> <td>5 year condition survival*</td> <td>86.5%</td> </tr> <tr> <td>Colorectal cancer- 1 year survival</td> <td>85.0%</td> </tr> <tr> <td>5 year condition survival*</td> <td>91.3%</td> </tr> </table> <p>*for those already survived 5 years after diagnosis</p>	Anal cancer – 1 year survival	88.3%	5 year condition survival*	86.5%	Colorectal cancer- 1 year survival	85.0%	5 year condition survival*	91.3%	<p>Palliative Care Costs and patient numbers (source: AIHW hospital reports)</p> <p>2011-12 9.4% of all hospital separations for bowel cancer were palliative care related</p> <p>Anal Cancer 2011 Mortality 71 persons 0.3/100,000</p> <p>Colorectal Cancer 2011 Mortality 3980 persons 15.4/100,000</p>
Anal cancer – 1 year survival	88.3%												
5 year condition survival*	86.5%												
Colorectal cancer- 1 year survival	85.0%												
5 year condition survival*	91.3%												

* Additional detail on the cost to patient is at Appendix 1

Cancer as a national health priority

Cancer is one of nine National Health Priority Areas (NHPAs) along with asthma, cardiovascular health, diabetes, injury prevention and control, mental health, arthritis, musculoskeletal conditions and dementia. The NHPA initiative recognises that the strategies for reducing the burden of illness should be pluralistic, encompassing the continuum of care from prevention through to treatment and maintenance, and be based on appropriate evidence.

The establishment of Cancer Australia in 2006, as the lead national cancer control agency, also reflects the priority status afforded to cancer care.

The continuum of care

Various sources place the annual cost of cancer to governments in Australia between \$4 billion and \$5 billion per annum.⁷ This funding supports a range of measures including research, as well as prevention programmes targeting issues such as sun exposure, alcohol and tobacco control. Hospitalisation is a major cost for state governments. Australian Government funding also delivers national screening programmes and supports timely access to cost-effective, clinically indicated treatments through the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Scheme (PBS). Funding is also provided to support high quality palliative care services. The mix of funding between different components of the continuum of care needs to be effectively balanced to ensure that it achieves the best health outcomes for the most cancer patients.

Medicines as a component of cancer care

As the diagram on page 3 shows, medicines are one component of the cancer treatment journey and are often used in patients with end-stage disease, providing a small health gain. It also demonstrates the potential opportunity costs associated with favouring one component of care over another. Notwithstanding the separate budgets each area of expenditure represents, total available funding for healthcare is not limitless and choices need to be made to ensure that cancer care is both clinically optimal and cost effective. In 2013-14, public funds of just under \$1.5 billion were used to subsidise the cost of PBS-listed cancer medicines. An additional \$53.3 million was spent on the Herceptin Programme. With total cancer expenditure estimated to be around \$4-5 billion, this means one third of current funding is used for medicines. Any additional focus on medicines must continue to be weighed against other components of the continuum of care, as well as against other health priority areas.

Innovative approaches in Australia

Australia has delivered cutting edge measures to tackle tobacco, the world's leading cause of cancer morbidity and mortality. Smoking rates in Australia have declined significantly over the past twenty years, with the number of daily smokers decreasing from 24.3% in 1991 to 12.8% in 2013.⁸ Tobacco excise increases and anti-smoking campaigns have contributed to this decline and the recent, world first, introduction of plain packaging is expected to contribute even further toward cancer prevention.

Australia has also been a world leader in its development and introduction of the Human Papilloma Virus (HPV) vaccine, which aims to prevent up to 99% of cervical cancers. A recent review identified a significant reduction in the rate of abnormalities which is expected to lead to a reduction in burden of illness and death due to cervical cancer over time.

⁷ Deloitte Access Economics, July 2013: *Access to cancer medicines in Australia* & AIHW, 2013: *Health system expenditure on cancer and other neoplasms in Australia, 2008-09*

⁸ AIHW, 2014: *National Drug Strategy Household Survey*

These investments, whilst not for medicines, highlight that innovation continues to play a key role in addressing cancer in Australia. Further, Australians can expect an even greater 'return' from prevention strategies that target lifestyle factors (tobacco, alcohol, diet and exercise) because they improve health outcomes not only for cancer, but also for other leading causes of disease, including diabetes and cardiovascular health.

3. CANCER MEDICINES AND THE PHARMACEUTICAL BENEFITS SCHEME

Key findings

Over 100 medicines used to treat cancer are already available through the PBS. Cancer medicines are amongst the most expensive medicines subsidised through the PBS. One in every six PBS dollars is spent on cancer, which is up from one in eight. The PBAC has one of the fastest evaluation processes in the world, with a 17 week timeframe from submission to recommendation.

The Pharmaceutical Benefits Scheme (PBS)

Under the PBS, the Government subsidises the cost of medicines, with patients paying a contribution depending on their status as a general or concessional patient. The PBS also provides safety nets to protect high medicine users from excessive medicine costs. As at December 2014, the PBS subsidises over 780 medicines, in more than 2,000 forms and strengths, available in over 5,100 brands.

The National Medicines Policy provides the overarching framework for the operation of the PBS. It provides for, among other things, timely access to medicines Australians need at a cost individuals and the community can afford, and the maintenance of a responsible and viable medicines industry.

The Pharmaceutical Benefits Advisory Committee (PBAC)

Since 1953 Government has relied on independent advice from the PBAC to decide which medicines will be subsidised through the PBS. PBAC brings together the highest levels of clinical, health economic and pharmacological expertise and includes an oncologist, a haematologist and a paediatrician who are experts in the treatment of cancer, as well as a consumer representative.

The PBAC uses a rigorous Health Technology Assessment (HTA) methodology to evaluate applications. The PBAC essentially asks the question 'Is it worth spending an additional \$x to achieve the additional benefit offered by the new drug compared to existing therapy?'. In answering this question, the PBAC takes into account a range of factors including the availability and cost of alternative treatments and the total cost and probable demand for the proposed medicine.

PBAC also welcomes comments from patients, carers, members of the public, health professionals or members of consumer interest groups on submissions they will be considering. Generally, there is a 5 to 6 week period in which to provide comments before each meeting. The PBAC agenda for each medicine submission includes time to consider public comments, including patient stories and experiences. This means recommendations take into account Australian patient experiences when assessing the clinical need.

It is generally acknowledged that Australia has led the world in the use of economic evaluation as a prerequisite for listing. This includes the use of a quality adjusted life year (QALY) as an assessment tool. A QALY is a value used to measure changes in life expectancy and changes in quality of life from health interventions such as medicines. A QALY of 1 is a year of perfect health, whereas death is considered to be zero. This measure is used because it can give some comparability between varying health conditions, such as those that cause death very quickly to those that cause significant disability but do not shorten lifespan.

Cancer medicines currently available through the PBS

The availability of new and established cancer medicines is important insofar as it *further* improves health outcomes for cancer patients.

As at 1 February 2015, there are over 100 medicines available through the PBS for the treatment and management of cancer. These include medicines for common cancers, such as prostate and breast cancer, as well as less common cancers like anal cancer and soft tissue sarcoma.

Most PBS medicines used in the treatment of cancer are subsidised under section 100 of the *National Health Act 1953* (NH Act) through the Revised Arrangements for the Efficient Funding of Chemotherapy Initiative and the Highly Specialised Drugs Program.

A large number of cancer medicines are also available under the General Schedule (section 85 of the NH Act). These include medicines that directly treat cancer, as well as 'support' medicines to manage the associated side effects such as nausea and pain.

Efficient Funding of Chemotherapy

These arrangements provide a subsidy for chemotherapy medicines that are injected or infused, as well as related pharmaceutical benefits, such as anti-nausea medicines. These medicines are also available to patients in private hospitals under the General Schedule (see Appendix 1). Under EFC patients pay only one co-payment for each original prescription. Repeats are dispensed free of any PBS co-payment.

Highly Specialised Drugs (HSD) Program

Some cancer medicines are provided through the HSD Program because of their clinical use or other special features. They are supplied through public and private hospitals with appropriate specialist facilities. For example, the oral cancer medicine lenalidomide has potentially serious side effects and patients receiving it through the HSD Program must be registered in a risk management program.

Herceptin Program

Since 2001 the Government has also funded the Late Stage Metastatic Breast Cancer Program outside the PBS to provide trastuzumab (Herceptin[®]) for eligible patients whose breast cancer has spread (metastasised).

Supporting the affordability of PBS cancer medicines for individuals and the community

In 2013-14, public funds of just under \$1.5 billion were used to subsidise the cost of PBS-listed cancer medicines. This represents approximately one sixth (16%) of the total PBS expenditure of \$9.2 billion for that year (not including \$53.3 million for the Herceptin Program). The patient contribution (co-payment) of \$31.8 million in that year represents 2% of the total expenditure, with taxpayers paying the remaining 98%.

Cancer medicines are amongst the most expensive medicines on the PBS

Despite reaching one sixth of total expenditure, cancer-related scripts (2.6 million) supplied in 2013-14 represent only around 1% of all PBS scripts (213.7 million). The funding benefited approximately 3% (over 337,250 patients) of the total 9.8 million patients supported through the PBS in that year.

Reducing the financial impact for individuals

The PBS co-payment arrangements and safety net provisions help ensure the costs of medicines are affordable for Australians. Approximately 80% of the PBS benefits are provided to concession cardholders, who pay the concessional rate (currently \$6.10) for their medicine.

The subsidy removes financial barriers for access to medicines such as Abraxane[®] (nab-paclitaxel), which was listed on 1 November 2014 for the treatment of advanced pancreatic

cancer. The government approved \$92 million over the Forward Estimates to list this medicine, without which patients would face an average cost of \$16,000 for a course of treatment.

Financial value provided by the PBAC process

The NH Act prohibits the PBAC from recommending medicines that are “substantially more costly than an alternative therapy or alternative therapies” unless “the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy”.

The comparative cost-effectiveness method used by the PBAC achieves better prices by referencing the prices of new medicines against existing treatments. Medicines which offer the same health benefits and have the same safety profiles will generally attract similar prices. As a result of this approach, the expected costs for eight cancer medicines listed in 2013 or 2014 are 16% lower than the costs proposed in the submissions which avoided over \$60 million in costs over four years (net of confidential rebates from pharmaceutical companies).

Managing ongoing PBS costs

The cost of PBS medicines is continually reviewed to ensure ongoing cost-effectiveness. One such mechanism is price disclosure, which monitors the discounting behaviour by pharmaceutical companies for medicines subject to competition. The disclosed price is used to ensure any discounts being offered in the private market are reflected in the price paid by government.

A number of cancer medicines have taken significant price disclosure reductions. For example, the ex-manufacturer price of an 80 mg vial of docetaxel was \$1,420 when it was first subsidised in August 1996. As a result of competition, the price is estimated to be reduced to \$17.43 following the next round of price disclosure, scheduled for 1 April 2015. This achieves a better price for the government and therefore for taxpayers.

Price reductions can also directly benefit patients. For example, the price of ondansetron 8mg tablets (used to treat nausea from cancer treatment) has decreased from \$57.50 to \$22.70. For general patients, this means they now pay \$22.70 per script, rather than the co-payment of \$37.70.

Providing timely access to cancer medicines

Timely access to medicines is achieved through co-operation of key stakeholders, including pharmaceutical companies, government bodies and prescribers. The PBAC is involved in recommendations for access to subsidised medicines, but not all medicines.

Pharmaceutical companies

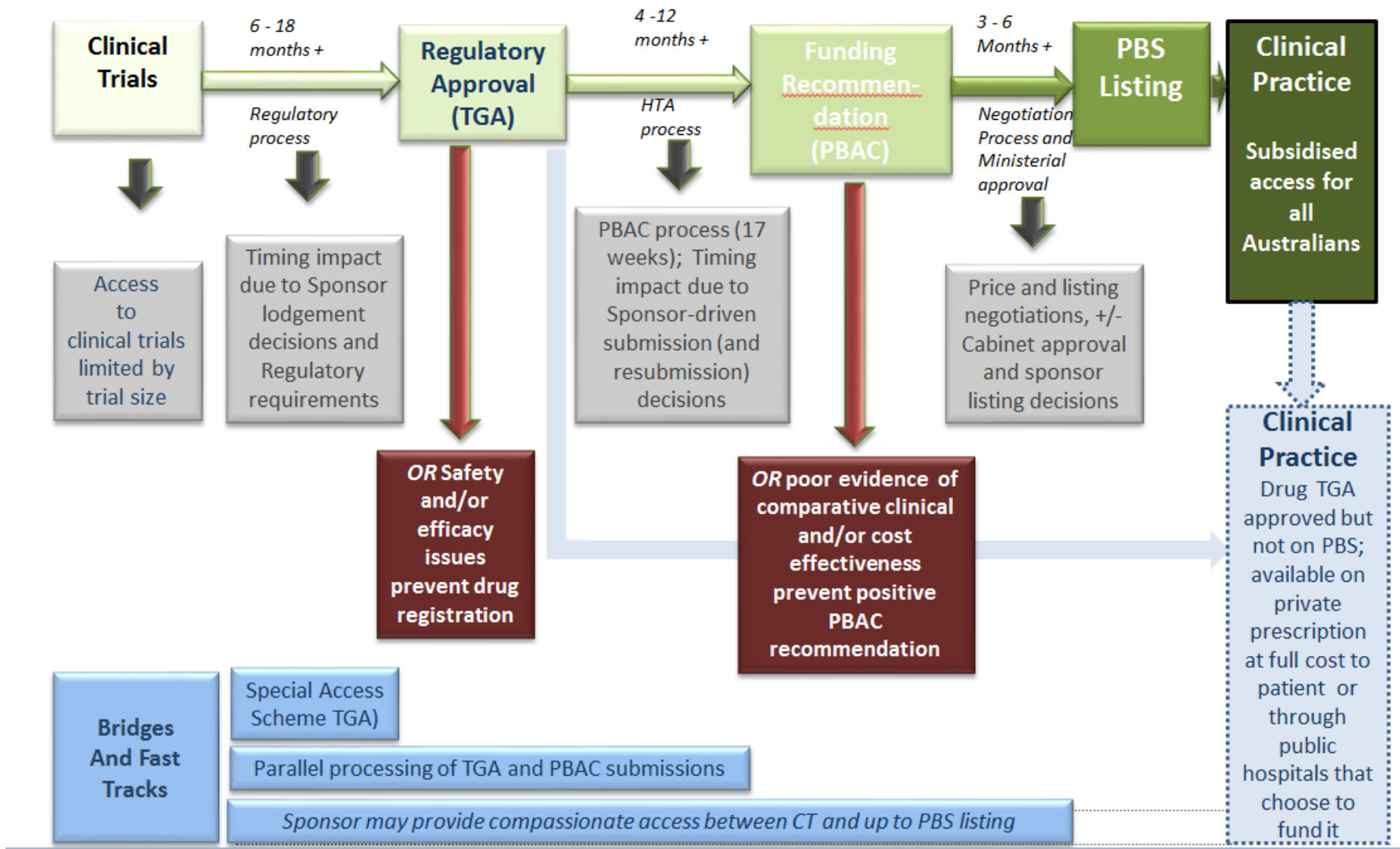
The first step in providing access to medicines in Australia is an application to the TGA to have the medicine or new treatment approved for use in Australia. This is done at the discretion of the sponsor; usually a pharmaceutical company.

Therapeutic Goods Administration

The TGA carries out a range of evaluations to ensure medicines meet acceptable standards for quality, safety and efficacy. The registration process consists of eight phases, with established timeframes that are specified under the *Therapeutic Goods Act 1989* (TG Act).

A Category 1 application includes applications for new chemical and biological entities, new generic medicines, or new uses or variations for registered prescription products. Those applications are allowed a statutory 255 TGA working days for evaluation and finalisation of the decision. TGA has the discretion to accelerate the process. In 2013, the average time for TGA to process new cancer medicine (new chemical entities) from the start of evaluation to making a decision was 236.6 days.

Pathway for Access to New Medicines in Australia



Alternate access options

The current legislation in Australia provides some options to accommodate the provision of medicines not on the ARTG, such as oncology medicines, for urgent public health needs. Australian patients are also able to access unapproved medicines through clinical trials. Some public hospitals will also fund non-PBS medicines for their patients (see diagram on page 8).

PBAC and access to subsidised medicines

As with the TGA, sponsors can apply, at their discretion, to the PBAC to list new medicines on the PBS or to make a significant change to an existing PBS-listed medicine. The submission needs to be received four months prior to the relevant PBAC meeting. During this time, the submission is evaluated by expert evaluators and by the PBAC's sub-committees, where necessary.

While timeframes are not readily comparable across countries that use different approaches, there is general acceptance that the PBAC standard of 17 weeks from submission to recommendation is one of the fastest reimbursement systems in the world. For instance, the United Kingdom (UK) chooses what drugs they will evaluate, rather than accepting submissions. It can take up to 54 weeks for a 'multiple technology appraisal' in the UK; less time is needed for single technology appraisals.

Timely decisions by the PBAC for cancer medicines

Cancer medicines accounted for 19% of all submissions (major and minor) considered by the PBAC between 2010-2014 inclusive, accounting for 22% of major submissions and 15% of minor submissions. During this period, there were 30 new cancer medicines considered by the PBAC and 37 distinct requests to add or change a cancer indication.

There is a trend towards an increasing number of cancer submissions. The PBAC considered 30 cancer-related submissions in 2010 and 40 cancer submissions in 2014. The growth in major submissions (mostly new medicines) has outpaced minor submissions, from 14 submissions in 2010 to 40 submissions in 2014; a 186% increase.

Between 2010-2014, 54% of cancer-related submissions to the PBAC received a positive recommendation. This is comparable to the overall proportion (64%) of recommended submissions. 32% of cancer submissions were recommended after initial consideration, climbing to 50% after two submissions (see diagram on page 11).

Stakeholders have raised multiple submissions (initial submission and re-submission) as an issue affecting the timeliness of listing new medicines. Multiple submissions also present an administrative burden for the PBAC and lead to over-crowding of meeting agendas. Addressing this issue is a common goal. This may be a productive area for further industry consultation, given that, currently, the number and timing of re-submissions is a decision made by sponsors.

Improving timely decisions with comprehensive evidence

The intent of access to new cancer medicines is to further improve health outcomes for patients in terms of Overall Survival and Quality of Life. This is reflected in the tools used by the PBAC to assess cancer medicines, such as the Quality of Life Year (QALY) gained.

One of the main difficulties in assessing cancer medicines is that survival improvements are difficult to determine, as they are generally not the main outcome measured in cancer trials. Many trials use response rates or Progression Free Survival as the main outcome measure. PFS refers to the length of time, from either the date of diagnosis or the start of treatment, that patients diagnosed with the disease survive without their disease advancing.

While this is considered an improvement in the quality of a cancer patient's life, many new cancer medicines improve Progression Free Survival but do not lengthen the patient's life. Further, Progression Free Survival outcomes do not readily translate to improvements in Overall Survival or Quality of Life, but sponsors often use Progression Free Survival clinical trial data to make assumptions about Overall Survival. This can make Overall Survival estimates overly optimistic. However, even with optimistic estimates, the Overall Survival benefits for cancer medicines submitted to PBAC are generally quite low. Combined with high medicine costs, these small improvements means some cancer medicines are found not to be cost-effective.

It is clear from representations made to Government and the Department that cancer patients want access to 'life-saving' therapies, and there is a perception that the PBAC's evaluation methodologies are limiting access to life-saving new therapies. In response, some patients and stakeholders have suggested that PBAC rely more on PFS as a valid endpoint in itself.

It should be noted that the PBAC does give weight to Progression Free Survival, especially where Quality of Life improvements can be demonstrated. Medicines that offer Progression Free Survival benefits but not Overall Survival benefits may be able to be valued as 'life-enhancing', but the evidence does not support them as being 'life-saving'. This distinction is often not reflected in the prices requested by sponsors.

Additionally, due to ethical concerns, patients in the control arm of randomised trials are often given the trial drug once disease progresses, which can limit the available evidence.

A key factor influencing the timing of decisions is the quality of evidence provided to support the application. The rigour of the PBAC process does not advantage applications that are not adequately supported by evidence of both clinical and cost-effectiveness. It is accepted that this high standard may sometimes present a barrier and could limit the capacity for certain medicines (eg for rare cancers) to meet the evidentiary requirements. The 'evidence dilemma' is especially challenging for rare diseases. For example, it can be difficult to establish a clinical trial from the limited patient population and the resulting aggregated data may not provide sufficiently detailed evidence. It is accepted that there may need to be another assessment pathway for certain, unique medicines. Improving the use of 'managed access' (linking progressive payments to emerging evidence) is currently being explored through the Access to Medicines Working Group and may offer a solution for these issues.

Options for improving timelines with parallel processing

In an effort to improve access to new medicines, since January 2011, sponsors have been able to use 'parallel processing' to progress items through the TGA and PBAC simultaneously. Submissions may be made to the PBAC at any time after lodgement with the TGA. The PBAC requires a positive TGA delegate's overview in order to make a recommendation and medicines need to be registered on the ARTG before any listing on the PBS is able to be finalised.

A recent example of the parallel process is dabrafenib, used for the treatment of malignant melanoma. Dabrafenib was approved by both the TGA and the PBAC in July 2013; the associated genetic test was approved by MSAC in August 2013; and it was listed on the PBS on 1 December 2013. That is only five months from registration for use in Australia, to subsidised access for patients.

It is up to the sponsor to decide whether or not to apply under parallel processing. To date, only 20% of major submissions for cancer have used this option.

Timing for implementation following a PBAC recommendation

Following a positive recommendation, sponsors are required to negotiate final arrangements, such as pricing and any applicable prescribing restrictions, with the Department of Health. The recommendation must then be approved by Government. Depending on the total cost, the approval can be granted by the Minister for Health. Medicines that cost more than \$20 million in any one year of the Forward Estimates must be put to Cabinet for approval.

Following approval by Government, six weeks are required to finalise the legal requirements and risk sharing arrangements, update information systems and implement any data requirements.

The average time to listing following a positive PBAC recommendation for cancer medicines is 6.1 months. Recommendations for cancer medicines that involved major submissions to the PBAC take an average 7.3 months to list, whereas minor submissions take 4.9 months.

Under new Cabinet thresholds 12 cancer medicines, treating 15 types of cancer, that would have required Cabinet approval have instead been approved by the Minister, thereby speeding access to subsidy for patients.

Cancer medicines under current consideration for the PBS

At its November 2014 meeting, the PBAC recommended 12 submissions for cancer medicines. The majority are now listed or approved for future listing. The PBAC also supported ceasing the standalone Herceptin Program and aligning similar medicines under the Highly Specialised Drugs Programme. The medicines yet to be listed are still under negotiation with the sponsor(s), or will need to be implemented at the same time as changes to the Herceptin Program, if approved.

A further 11 major submissions for cancer medicines are scheduled to be considered at the forthcoming March 2015 meeting, with a potential cost of \$589 million over the Forward Estimates. These represent 23% of the total number of submissions (60) to be considered at that meeting.

The role of pharmaceutical companies and the PBAC in achieving a timely decision for cancer medicines

			Green		Yellow		Red		Grey		Green		Yellow		Red		Grey	
			First Recommendation		Deferred		Not recommended		Non appearance									
3 Years	51 weeks	12																
	34 weeks	11																
	17 weeks	10																
2 Years	51 weeks	9																
	34 weeks	8																
	17 weeks	7																
1 Year	51 weeks	6																
	34 weeks	5																
	17 weeks	4																
0 Year	51 weeks	3																
	34 weeks	2																
	17 weeks	1																
			Jul-14	Jul-14	Jul-13	Jul-11	Mar-14	Nov-13	Mar-14	Nov-13	Nov-13	Jul-11	Jul-13	Nov-14	Nov-14	Nov-12	Jul-12	Nov-12
			Mar-14	Jul-14	Mar-13	Mar-11	Nov-13	Mar-14	Nov-13	Nov-13	Jul-11	Jul-13	Nov-14	Nov-14	Nov-12	Jul-12	Mar-12	Jul-11
			Mar-14	Jul-14	Mar-13	Mar-11	Nov-13	Mar-14	Nov-13	Nov-13	Jul-11	Jul-13	Nov-14	Nov-14	Nov-12	Jul-12	Mar-12	Jul-11
			Brentuximab	Enzalutamide	Dabrafenib	Lenalidomide	Bevacizumab	Paclitaxel (nab)	Everolimus	Denosumab	Sunitinib	Trastuzumab emtansine	Crizotinib	Axitinib	Abiraterone	Ipilimumab		
			Lymphoma	Prostate cancer	Melanoma	Myelodysplastic syndrome	Ovarian cancer	Pancreatic cancer	Breast cancer	Bone tumour (giant cell)	Pancreatic NET	Breast cancer	Lung cancer	Kidney cancer	Prostate cancer	Melanoma		

The above table shows the timelines for some cancer medicines considered by the PBAC over the period 2009-2014. As it can be seen, a significant number of cancer medicines are recommended after the initial consideration by the PBAC. In many cases, the medicines that have taken a longer time to achieve a positive recommendation have done so because the company has chosen not to make resubmissions for a period of time. In some cases, the companies make subsequent submissions after receiving a positive recommendation. This is often to try to achieve a higher price or more favourable listing conditions.

4. INTERNATIONAL COMPARISONS

Key findings

Australia compares very well internationally on cancer outcomes.

There is growing global concern about the high costs of cancer medicines, which often provide minimal health benefit. Funding expensive new cancer medicines is a common policy issue in developed countries.

Similar to Australia, many countries use 'value for money' assessments to decide which medicines to fund, and containment pricing strategies to manage ongoing costs.

Australia is the lucky country – comparison of cancer outcomes

Although cross-country comparisons of cancer outcomes are not straightforward, recent evidence suggests that cancer outcomes in Australia are the best in the world. This is despite Australia's cancer incidence being one of the highest in the world.

Australia's 5-year relative survival outcomes compare very well to other countries. A European study published in 2014⁹ showed that 5-year relative survival generally increased steadily over time for all European regions (see Appendix 3). However, even allowing for a five year time lag in data and some methodological differences, Australia's 5-year relative survival outcomes were significantly better than Europe's and England's for the same cancer types.

The mortality-to-incidence ratio (MIR) is used as a proxy measure of survival in the international context, with a low value MIR indicating longer survival. AIHW notes that the MIR for Australia was 0.3. By comparison, the MIR for the world was 0.6, indicating that Australia has higher survival from cancer than the world combined.¹⁰

The same European study noted the low survival of English and Danish cancer patients has attracted significant interest and analysis. The main cause seems to be delayed diagnosis. Underuse of potentially successful treatments (possibly related to the advanced stage of disease at the time of presentation) and poor or unequal access to treatment also seem to play a part. This reflects positively on Australia's investment in screening programmes, access to specialists and universal access to medicines.

International concerns about the price of cancer medicines

Funding expensive new cancer medicines is a policy issue in all developed countries and Australia is one of many countries grappling with rising costs. Most are facing increased budgetary constraints due to lower economic growth, at the same time as increased pressures on the health budget as cancer incidence grows due to ageing populations. The IMS Institute for Healthcare Informatics (IMS) reports that "the average cost per month of branded oncology drug treatment in the U.S. is now about \$10,000, up from an average of \$5,000 a decade ago".

The IMS also reported that the global market for cancer medicines reached \$91 billion in 2013, up from \$71 billion in 2008, representing a compound annual growth rate of 5.4%.¹¹ They observe that the modest rate reflects a lack of breakthrough therapies for very large patient populations, patent expiries, reductions in the use of supportive care medicines and stronger payer management. This rate of growth is significantly lower than seen during the 2003-2008 period when growth each year exceeded 15%, driven by a small number of breakthrough therapies". It is noteworthy that for cancer medicines approved by the US FDA between 2002 and 2014, the average improvement in survival was only 2.1 months.

⁹ Lancet Oncol 2014; 15: *Cancer survival in Europe 1999 – 2007 by country and age: results of EURO-CARE-5*.

¹⁰ AIHW 2014: *Cancer in Australia: an overview*.

¹¹ IMS, 2014: *Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report*

These findings reflect a broad international concern that many new cancer medicines offer only a small incremental survival benefit to patients, at times with significant toxicity, but with a cost substantially higher than older medicines. Costs are also substantially higher than other new, non-cancer medicines.

Globally, many cancer specialists are expressing concern about the high costs and the often minimal benefit obtained from that expenditure. In October 2012, a group of doctors at the Memorial Sloan-Kettering Cancer Center in the US published an op-ed piece in the New York Times explaining that the hospital decided not to buy a new treatment (Zaltrap®, ziv-aflibercept) for colorectal cancer because “the drug has proved to be no better than a similar medicine we already have for advanced colorectal cancer, while its price — at (USD)\$11,063 on average for a month of treatment — is more than twice as high”.¹²

A later article outlined changes in health outcomes and costs over time. The article noted that in 1994, the median survival rate for someone with advanced colon cancer was eleven months and the lifetime costs of the drugs used to treat the average patient would be about (USD)\$500 at today’s prices. By 2004, the median survival rate had increased twofold but the drug costs had increased by many hundreds for that extra eleven months. “Whereas we had hoped that small, incremental gains would be a springboard to something bigger and more productive, I fear those small, incremental gains have become a business model. Right now, it is safer for a pharmaceutical company to strategize for large-scale clinical trials that look for small, incremental gains that will get a drug to market, than to swing for the fences and try for the big advance.”¹³

Even where the health benefits may be considered large, the prohibitive cost can act to restrict access, even after the reasonable timeframe to recoup development costs. For instance, in 2013, a group of experts in Chronic Myeloid Leukaemia (CML) described how the price of imatinib has actually increased in the US from \$US30,000 per year to \$92,000 per year.¹⁴

Recently, the World Innovation Summit for Health (WISH) released a report from their Delivering Affordable Care Forum¹⁵. They note “affordability is inextricably linked to value, but also tied to issues of quality, efficiency, equity and accessibility,” and their report began:

“We must confront a stark reality: cancer care is not affordable for most patients, many payers, and nearly all governments. This is a real and immediate issue across the world. In resource constrained countries the costs for best-practice cancer care are not affordable at all. In high-income countries different challenges related to affordability and sustainability of cancer care have emerged. The expectation is that these challenges will only intensify”.

The report makes a number of recommendations, including pursuing performance-linked reimbursement schemes for new medicines, noting however that such a scheme requires accurate data capture systems. They suggest that health systems, particularly cancer care services, should “adopt the principles behind a “continuous learning healthcare system” which “incorporates data collection and dissemination as an essential component of their cancer strategy”, citing Qatar’s National Cancer Program. In Australia, the increasing use of e-health records may assist in the data collection required to implement these kinds of pricing and monitoring policies whose ultimate aim would be to improve the effectiveness and quality of cancer care.

¹² http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html?_r=0

¹³ <http://nymag.com/news/features/cancer-drugs-2013-10/>

¹⁴ Price of drugs for chronic myeloid leukemia (CML), reflection of the unsustainable cancer drug prices: perspective of CML Experts. Blood doi:10.1182/blood-2013-03-490003

¹⁵ “Delivering Affordable Cancer Care: A Value Challenge to Health Systems.” Report of the World Innovation Summit for Health (WISH) Delivering Affordable Cancer Care Forum 2015

International pricing and evaluation of new cancer medicines

Most developed countries have either public or private health insurance arrangements that provide subsidised patient access to medicines. Most countries adopt various cost containment policies, such as reference pricing or price/volume agreements, and many use some form of health technology assessment prior to subsidy, with some using cost-effectiveness frameworks as well. It has been estimated, for instance, that European countries who negotiate prices pay 20%-40% lower prices than in the US, where Medicare is legally prohibited from price bargaining¹⁶.

Cost-effectiveness assessment has been seen by some as limiting access to new drugs, especially cancer drugs where evidence of comparative cost-effectiveness can be weak.¹⁷ England's National Institute for Health and Clinical Effectiveness (NICE), for instance, has been criticised for not approving a number of expensive new cancer medicines, primarily because of cost.

Moreover, different countries may come to different funding decisions based on similar evidence of cost-effectiveness: "... it is noteworthy that even with the same clinical evidence for anti-cancer drugs, reimbursement policies vary among countries because the criteria of cost-effectiveness and additional costs are country-specific and difficult to standardize."¹⁸

Variations in cost effectiveness are also influenced by the price offered by drug companies for the same medicine, which can vary from country to country. However the use of "published versus effective" prices to protect commercial sensitivities makes the amount of variation difficult to quantify because, as a result, international prices are not transparent.

United Kingdom – Cancer Drug Fund

In response to criticism over access to new cancer medicines, the British government took the unique step of establishing a temporary Cancer Drugs Fund (CDF) in 2010 to meet the costs of some cancer drugs either rejected by NICE or not yet evaluated by them. The CDF funding was originally capped at £200 million per year, but in 2013-14 was overspent by £30.5 million.

The UK Government announced both that it would increase the CDF budget to £280 million in 2014-15 (and to £340 million in 2015-16), and that the list of drugs on the CDF would be reviewed, with a focus on 'value for money'. NHS England was to negotiate CDF drug prices with companies and to "look at ways to create better alignment between the CDF and the NICE assessment process". This followed concern about inconsistency of new drug funding decisions across the NHS, and the CDF remains contentious for "the resource implications and impact on overall outcomes of assigning specific funds to a selected disease area versus other conditions".¹⁹

In January 2015 the outcome of the CDF review was announced and, reflecting this, the most recent CDF list (version 3.0) indicates that there are 35 drugs for 62 indications that have ongoing funding, but a further 25 indications that will only be funded until 12 March 2015 and removed from the CDF thereafter.

Over the last two years, some consumer and industry stakeholders have called for Australia to have a cancer drugs fund with dedicated funding and low access thresholds, similar to the CDF.

¹⁶ IMS Institute for Healthcare Informatics. 2014. "Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report"

¹⁷ Cheema PK, Gavura S, Migus M, Godman B, Yeung L, and Trudeau ME. International variability in the reimbursement of cancer drugs by publically funded drug programs. *Current Oncology* Vol 19, No 3, June 2012

¹⁸ Lim et al. *BMC Health Services Research* 2014, 14:595

¹⁹ Ellen Nolte, Jennie Corbett : International variation in drug usage : An exploratory analysis of the "causes" of variation. RAND corporation 2014 www.rand.org/t/rr899

However, analysis shows that 48% of the requests for CDF new patient applications in 2013-14 were for medicines and indications already funded on the PBS, or medicines that have since been recommended for PBS funding. 38% of the requests were for medicines not seen by PBAC, and only 9% were requests for medicines rejected by PBAC (see Appendix 4). In light of this, it appears difficult to sustain the argument that an English-style CDF would significantly improve access to new cancer drugs for Australians.

Access to new cancer medicines – international comparisons

Cancer medicine pricing is an international issue, for an international industry, but access and subsidy responses are necessarily national. Funding decisions will be based on a range of local factors – clinical need, fiscal constraints, and opportunity costs to fund other forms of cancer care and prevention, as well as other diseases. Public funders look to maximise societal benefit, and thus must use different criteria to individuals making personal treatment choices that address their own needs and preferences.

It is therefore difficult to compare access to new cancer medicines across countries, especially as access is not simply about their availability in a particular country, but their affordability for the patients who will be using them.

For instance, a recent study²⁰ comparing the US and Australia focused on cancer drugs approved between 2000 and 2009. While finding that at that time fewer cancer drugs were subsidised in Australia than available in America, they observed that out-of-pocket payments for US Medicare patients were considerably higher. They highlighted that the approach used in Australia had contributed to lower prices and so enhanced affordability for both taxpayers and patients for the drugs considered.

Recently, there have been several drug utilisation comparisons between countries. However, these often can contain methodological flaws and are a poor proxy for cancer related health outcomes. For instance, a common methodology used to determine utilisation has been total milligrams of a drug sold in a country divided by total country population. This is uninformative if, among other things, no consideration is given to age differences in populations, utilisation of substitute treatments, differing national guidelines, stage of cancer, breakdown by indication, or incidence/prevalence of those cancers for which the medicines are used in each country.

Moreover, as noted by one of the drafting assistants on the UK's Richard's Report, "prescribing levels are the ultimate process measure – at best they represent an input rather than an outcome ... levels of utilisation cannot necessarily be used to draw conclusions about service quality. Information on drug usage simply tells you how much drug has been used and little more".²¹

The ability to deliver timely access to medicines is also affected by the timing of the applications which, in Australia, is at the discretion of pharmaceutical companies. It is acknowledged that these companies operate in a global industry and this can affect their decisions. Sponsors often choose to apply first in the US or Europe, delaying consideration of the medicine in Australia.

For cancer medicines (new chemical entities) submitted to the TGA between 2009-2014, TGA submissions were made an average of 38 weeks after FDA submission (USA) and 29 weeks after EMA submission (EU). This kind of business approach seeks to establish, as early as possible, a positive response in the regions offering the most potential for profit, due to their large population size. This avoids the situation where a deferral or rejection from a country with a small population, like Australia, could influence other authorities, thereby jeopardising the profit margins that could be achieved in larger countries/regions.

²⁰ Wilson A, Cohen J. Patient access to new cancer drugs in the United States and Australia. *Value Health* 2011;14:944–52

²¹ <http://www.mhpc.com/health/international-variations-in-health-do-they-matter-and-should-we-care/>

5. A HEALTHY FUTURE FOR CANCER MEDICINES - CHALLENGES AND OPPORTUNITIES

Existing arrangements work well, but will need to continue to adapt

Australia's achievement of having the best cancer survival rates in the world is a clear sign that the current system is not broken. The significant investment in cancer medicines will be ongoing, supporting both health outcomes and the sustainability of the pharmaceutical industry.

The development of new technologies and changing community expectations are all factors that will influence the way the PBS and the PBAC operate in the future. Improving existing processes and introducing new methods offer the best means of maintaining Australia's record of supporting timely access to cost-effective cancer medicines that deliver proven health gains.

The future holds both expected and unknown challenges. The following paragraphs outline issues and suggestions that provide scope for further consideration, in conjunction with stakeholders.

Supporting timely access to cancer medicines in Australia

Notwithstanding that access to cancer medicines can be gained early through clinical trials, the majority of Australians have expectations of subsidised access to medicines once they are registered. The rigorous assessment process of both the TGA and PBAC and the knowledge that the medicine may already be registered in other countries can result in frustration and the perception of delay for Australians. This is especially important for expensive cancer medicines, often used in late stages of the disease where time may be counted in months.

Governments work to established timeframes; timing for sponsors is discretionary

The listing times for medicines on the PBS vary and are largely driven by when pharmaceutical companies make a submission to the TGA and the PBAC. For example, bevacizumab for ovarian cancer was approved by the TGA in early 2012, but was only submitted to the PBAC for the November 2013 meeting. Pharmaceutical companies are also able to decide whether (and when) to re-submit following a rejection by PBAC, as demonstrated in the diagram on page 12.

The Department is currently working with Medicines Australia, the peak body for the discovery driven pharmaceutical industry in Australia, to review options for increasing transparency of the PBAC processes. This would increase awareness for consumers and assist them to understand the multiple factors affecting timing of decisions. It would also allow for patients and prescribers to make informed decisions about treatment options, based on the most up-to-date information. In the past, some pharmaceutical companies have been hesitant to increase transparency which can be viewed as a risk to their commercial interests.

Best practice in regulation and health technology assessment

Although timelines for the TGA and PBAC compare well with other countries, both agencies are continually seeking ways to expedite processes. For example, a current review, *Expert review of Medicines and Medical Devices Regulation*, is exploring options to enhance current TGA processes and remove unnecessary duplication.²²

In addition, there is increasing pressure for the PBAC, which is being asked to consider more submissions than ever before. As technology advances, the PBAC can expect to consider increasingly complex, personalised medicines, including cancer medicines. The existing processes, which were established to evaluate medicines with less complex molecular structures, need review from time to time to ensure they remain fit for purpose.

²² Expert Review of medicines and medical devices regulation.

Evidentiary requirements and the changing nature of medicines

The Health Technology Assessment methodologies used by the PBAC have evolved and will need to continue to evolve. New assessment pathways, that do not undermine the overarching principles of proven clinical effectiveness, safety and cost-effectiveness, will provide the best means of assessing the increasingly complex array of medicines currently under development.

The PBS has adopted innovative pricing models to provide access to new drugs whilst also supporting the development of a stronger evidence base. For example, the existing 'managed access' approach is being reinvigorated to provide options for medicines that are used to treat rare cancers, by allowing a phased evaluation and listing, linked to progressive payments. Earlier access than would otherwise be obtained could be granted, where safe to do so, for use in those patients who have no other treatment options. The health outcomes would be tracked and reviewed, with approval for broader use only once sufficient evidence of effectiveness becomes available. This is currently being explored through the Access to Medicines Working Group.

Early access is not without risks

Although access to medicines through clinical trials can be an option, the trials cannot always identify patients who will benefit from treatment, nor the risks of the medicine. Similarly, any 'early' access through the PBS must pay appropriate respects to safety. This is especially important for many cancer medicines, which are known to be toxic.

An important example of this is cetuximab, a medicine used to treat colorectal cancer. It has taken over 10 years to identify the correct group of patients who benefit from treatment with cetuximab by gradually excluding those that did not respond and/or only experienced the adverse events associated with cetuximab. Ponatinib, used to treat leukaemia, is another example. The medicine was given accelerated regulatory approval in the USA. It was subsequently found to cause adverse events, such as heart attacks and deep vein thrombosis, in 27% of patients. Without this information up-front, prescribers and patients took on unknown risks. Refer to Appendix 2 for more detail.

Affordability for all – getting the balance right

The current fiscal circumstances in Australia are well-documented. Governments have finite budgets and choices have to be made on where to allocate resources, not just across the health sector, but the full government sector.

Cancer funding remains a sensitive issue. Making judgments about the level of support for rare cancer patients is especially difficult, noting that it involves spending significant amounts of taxpayer dollars on a very small, but very sick, sub-group. The trend in increasingly expensive, personalised medicines will continue to place pressure on both the family and national budgets.

Rising cost of cancer medicines

Compared to the costs of cancer medicines listed on the PBS prior to Jul 2009, the cost of more recent cancer medicines is significantly higher and has grown at a rate of 33% per year (see Appendix 1). Total benefits paid grew from \$954 million in the 2009-10 financial year to \$1.486 billion in 2013-14; a growth rate of over 10% each year.

There is limited transparency and therefore limited understanding regarding the key cost drivers that influence medicine pricing. Some Australian experts note: "It's more likely to be dependent on the price the company believes individuals and healthcare systems are willing to pay".²³

Some argue that high drug development costs are driving the higher prices and are the price of innovation.²⁴ Others claim that most drug development costs are associated with marketing

²³ Emeritus Professor Lloyd Sansom & Dr Michael Sorich, 2014: The Cost of cancer medicines. Who pays? Who should pay?

²⁴ http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

rather than research and development²⁵, which is often undertaken by publicly funded institutions²⁶, lessening the cost to industry. Further they argue that tax concessions, such as the Orphan Drug Tax Credit, are not offset against the estimated costs.²⁷

There is some evidence that drug companies may have significant economic motivation “towards safer but less transformative therapeutics”²⁸, at an opportunity cost of directing research and development to more innovative (and financially risky) areas.

Incremental gain is good; improving life expectancy would be better

The ‘incremental gain’ approach offers a more certain profit and an earlier return on investments for pharmaceutical companies. This may have the unintended consequence of encouraging short-term research that focuses on augmenting existing benefits quickly, rather than longitudinal research into transformative and possibly curative areas.

In addition, the increasingly expensive price tag for these medicines represents marginal value and, it is difficult to justify continuing acceptance of high costs for treatments that offer very small benefit. It is vital that PBS pricing policies continue to put pressure on medicine pricing and further consideration of ‘pay for performance’ (ensuring that the price reflects available evidence of the health benefit) is also warranted.

Community expectations and funding priorities

There is widespread support for the PBS as a means of reducing (or eliminating) financial barriers for individuals, by sharing the cost of medicines across the community. It is becoming increasingly clear that the PBS cannot be all things to all people. There will need to be ongoing discussions about the balance between the social and economic value.

The existing Health Technology Assessment techniques used by the PBAC protect the PBS from unnecessary expenditure, by assessing value for money in comparison to existing treatment options. It is vital that the PBAC continues to use and evolve HTA to ensure the available funding is directed to proven, cost-effective measures. This may include ‘managed exit’ processes, to routinely de-list medicines that cannot provide up-to-date evidence of their effectiveness and need.

Increasing the transparency of PBAC decision-making would support greater understanding across the community. This paves the way for Australian taxpayers to make an informed contribution to the discussion.

All stakeholders must contribute to a sustainable future for cancer medicines

As outlined in Australia’s successful National Medicines Policy, access to cost-effective medicines is a matter of ‘shared responsibilities’. It is important that partners in the operation of the PBS take responsibility for achieving value for money, and that a fair distribution of costs and savings between the partners continues to be achieved. The same levels of co-operation must apply to timeliness, both in submitting applications and working together to achieve decisions that support industry and consumers alike.

²⁵ Donald Light and Hagop Kantarjian, *Cancer Drugs' Rising Costs: The \$100,000 Myth Claims justifying the high price of new cancer treatments don't add up*

²⁶ Aaron S. Kesselheim, Yongtian Tina Tan and Jerry Avorn. The Roles Of Academia, Rare Diseases, And Repurposing In The Development Of The Most Transformative Drugs. *Health Affairs*, 34, no.2 (2015):286-293.

²⁷ <http://www.ip-watch.org/2015/02/03/questions-about-funding-text-of-tufts-study-on-drug-costs/>

²⁸ Fojo T, Mailankody S, Lo A. Unintended Consequences of Expensive Cancer Therapeutics-The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity. The John Conley Lecture. *JAMA Otolaryngology-Head & Neck Surgery* December 2014 Volume140. Number 12

APPENDIX 1: PBS cancer medicines - utilisation and expenditure

Expenditure on cancer medicines

Of the estimated \$4-5 billion spent annually on cancer, close to one third (\$1.5 billion) supports access to medicines through the PBS. Around one sixth of all PBS expenditure supports access to cancer medicines. An additional \$50 million is used to fund the Herceptin Program each year.

Figure 1.1: Cost of PBS cancer medicines

PBS expenditure for cancer medicines	Benefits paid (\$ billions)				
	2009-10	2010-11	2011-12	2012-13	2013-14
PBS and RPBS benefits paid - cancer	\$0.994	\$1.087	\$1.135	\$1.230	\$1.486
Total PBS benefits paid – all medicines	\$8.392	\$8.873	\$9.194	\$8.996	\$9.149

Figure 1.2: Cost of Herceptin Program

Expenditure for Herceptin Program (non-PBS)	Benefits paid (\$ millions)				
	2009-10	2010-11	2011-12	2012-13	2013-14
Total benefits paid	\$48.9	\$53.3	\$54.1	\$57.2	\$53.3

Cancer medicines are amongst the most expensive

Cancer medicines are, generally, more expensive than non-cancer medicines.

New cancer medicines are making up an increasing proportion of total PBS spending on cancer medicines. PBS benefits paid for newer cancer medicines increased at a rate of 33% per year over the last five financial years, compared to a growth rate of only 5% per year in benefits paid for established cancer medicines.

Figure 1.3: Top 10 most expensive cancer PBS medicine by benefit, 2013-14

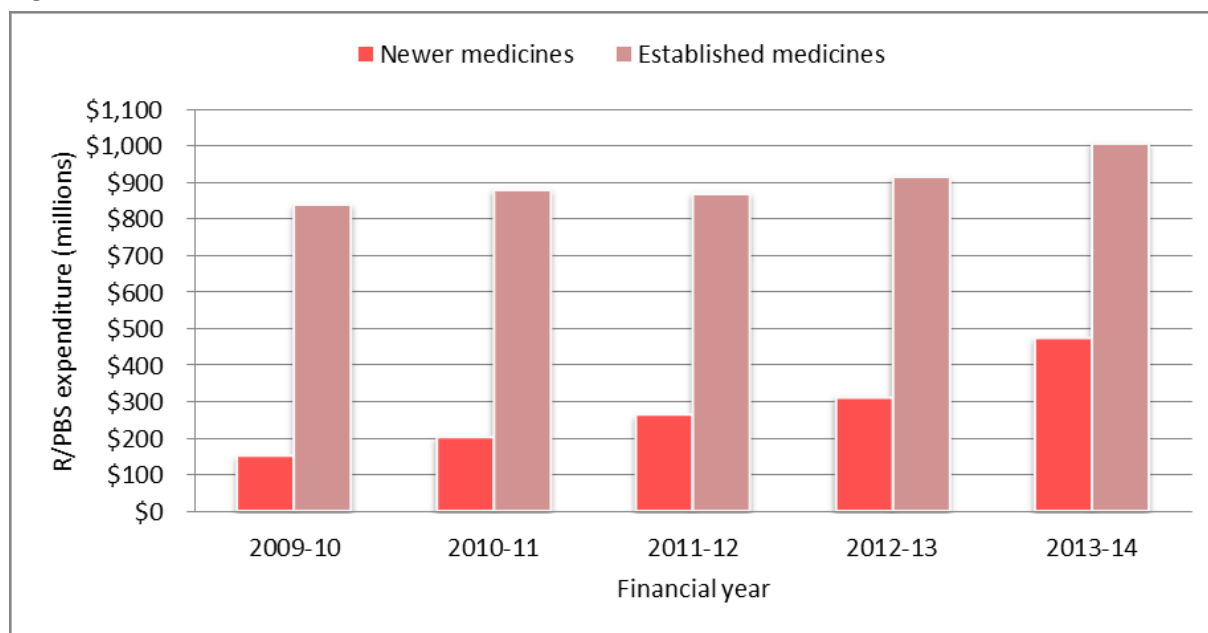
Rank	Drug Name	Patient Count	Scripts	Benefit	Patient Co-payment Contribution	Benefit per Patient
1	RITUXIMAB	9,077	42,686	\$147,878,837	\$218,016	\$16,292
2	IMATINIB	2,526	24,879	\$96,289,418	\$465,571	\$38,119
3	TRASTUZUMAB	3,466	30,549	\$94,510,793	\$244,556	\$27,268
4	PEGFILGRASTIM	12,692	45,376	\$87,624,811	\$1,063,348	\$6,904
5	BEVACIZUMAB	3,845	32,728	\$74,995,025	\$113,275	\$19,505
6	IPIILIMUMAB	807	2,346	\$73,852,789	\$18,546	\$91,515
7	LENALIDOMIDE	1,481	9,897	\$63,450,651	\$122,591	\$42,843
8	GOSERELIN	20,651	68,556	\$59,775,807	\$914,810	\$2,895
9	BORTEZOMIB	2,142	30,810	\$52,612,479	\$35,231	\$24,562
10	LEUPRORELIN	13,182	34,427	\$42,357,849	\$309,871	\$3,213

Figure 1.4: Patient number and expenditure for cancer medicine versus non-cancer medicine

Financial Year	Cancer Medicine			
	Patient Count	Scripts	Benefit	Patient co-payment contribution as percentage of total cost
2009-10	270,510	1,957,274	\$993,745,236	3%
2010-11	287,127	2,066,655	\$1,086,669,622	3%
2011-12	295,470	2,234,906	\$1,135,299,000	3%
2012-13	314,056	2,434,837	\$1,230,201,528	2%
2013-14	337,289	2,607,167	\$1,485,961,705	2%

Financial Year	Non Cancer Medicine			
	Patient Count	Scripts	Benefit	Patient co-payment contribution as percentage of total cost
2009-10	9,323,301	196,783,171	\$6,998,721,883	17%
2010-11	9,493,086	202,950,640	\$7,359,173,190	17%
2011-12	9,521,127	207,170,478	\$7,646,269,254	17%
2012-13	9,450,295	208,178,027	\$7,562,826,568	17%
2013-14	9,437,378	211,113,143	\$7,709,455,066	16%

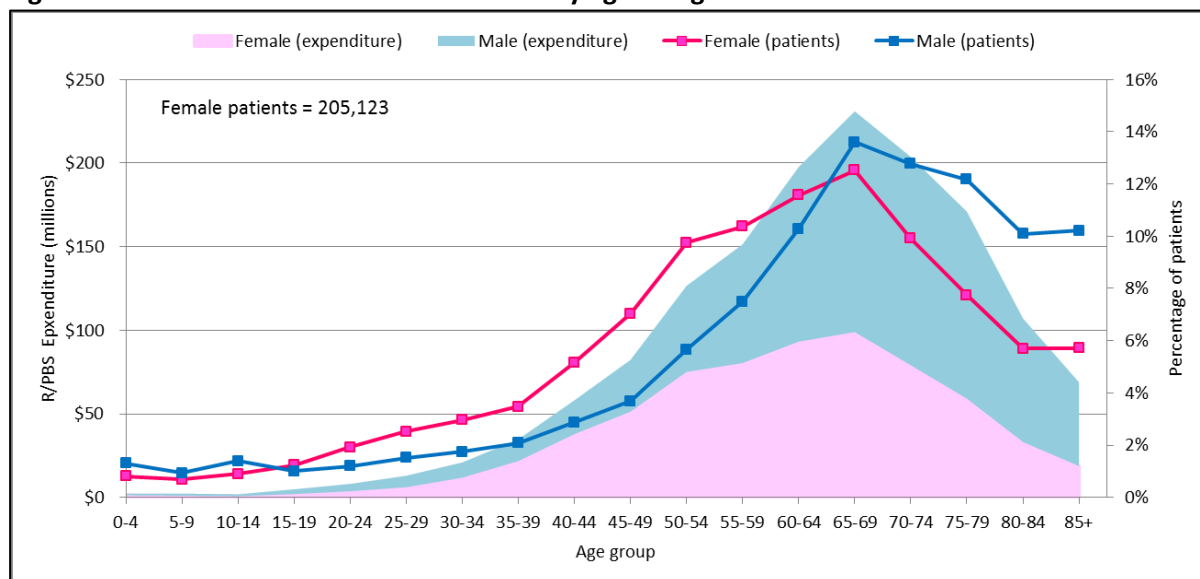
Figure 1.5: Cost of established versus newer PBS cancer medicines



The impact of subsidies on the cost to individuals

The majority of incidence of disease is in those aged 65 and over. This is reflected in the PBS usage data.

Figure 1.6: Use of PBS cancer medicines by age and gender



Access in public and private hospitals

The cost of chemotherapy medicine treatment is funded by the PBS for patients in community pharmacies, private hospitals and public hospitals participating in Public Hospital Pharmaceutical Reforms (the Reforms) only. Under the Reforms, eligible hospitals can receive access to PBS funding for day-admitted or non-admitted chemotherapy patients only. Of all states and territories, only NSW and ACT have declined to participate in the Reforms. Chemotherapy services in non-participating public hospitals are funded by states/territories. As such, public hospitals in NSW and the ACT are not eligible to claim for chemotherapy medicines under the PBS.

Figure 1.7 provides information on separations for chemotherapy for same-day acute separations (public hospitals and private hospitals) and outpatient care individual occasions of service (by outpatient clinic type) in selected public hospitals.

Figure 1.7: Hospital separations (public and private hospitals) by states and territories 2011-12

	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Total
Public	2,943	83,239	23,040	29,378	77	2,091	657	451	141,876
Private	41,862	58,860	68,569	31,045	21,044	n.p.	n.p.	n.p.	226,933
Outpatients	85,268	1,394	9,718	640	26,653	1,029	0	3,975	128,677
Total	130,073	143,493	101,327	61,063	47,774	3,120	657	4,426	497,486

Financial support across the care continuum

Government funding supports access to a range of treatment options, including benefits for medical services. The following table outlines typical costs and benefits for a patient with bowel cancer, who has an ‘uncomplicated’ patient journey.

Figure 1.8: Bowel Cancer patient journey - examples of the costs of medical services

Service type	MBS #	Item description	Fee	85%	75%	MBS Benefit
Initial Investigations		Total	\$925.15	\$792.03	\$694.04	\$797.60
GP Consult	23	GP Consult - Level B attendance	\$37.05	\$31.49	\$27.79	\$37.05
Pathology	66650	CEA - blood test for monitoring malignancy or monitoring of hepatic tumours, gestational trophoblastic disease or germ cell tumour	\$24.35	\$20.70	\$18.30	\$20.70
Pathology	66500	Liver function test	\$9.70	\$8.25	\$7.30	\$8.25
Therapeutic Procedure	32084	FLEXIBLE FIBROPTIC SIGMOIDOSCOPY or FIBROPTIC COLONOSCOPY up to the hepatic flexure, WITH or WITHOUT BIOPSY	\$111.35	\$94.65	\$83.55	\$94.65
Pathology	72823	Examination of complexity level 4 biopsy material with 1 or more tissue blocks	\$97.15	\$82.60	\$72.90	\$82.60
Specialist (surgeon)	104	Specialist, referred consultation	\$85.55	\$72.75	\$64.20	\$72.75
Computed Tomography	56807	COMPUTED TOMOGRAPHY - scan of chest, abdomen and pelvis	\$560.00	\$481.60	\$420.00	\$481.60
1st Phase of Treatment		Total	\$6,095.40	\$5,222.00	\$4,600.70	\$5,222.00
Specialist (Radiation Oncologist)	104	Specialist, referred consultation	\$85.55	\$72.75	\$64.20	\$72.75
Therapeutic procedure	15254	Radiation Oncology Treatment (repeated 25 times)	\$1,491.25	\$1,268.75	\$1,118.75	\$1,268.75
Therapeutic procedure	15269	Radiation Oncology Treatment (repeated 25 times*3 fields)	\$1,605.10	\$1,382.60	\$1,232.60	\$1,382.60
Therapeutic procedure	15521, 15559 or 15562	Radiation dosimetry	\$339.90	\$288.95	\$254.95	\$288.95
Therapeutic procedure	15550	Simulation for three dimensional confirmal radiotherapy	\$658.60	\$580.20	\$493.95	\$580.20
Therapeutic procedure	15705	Radiation oncology treatment verification (x25)	\$1,915.00	\$1,628.75	\$1,436.25	\$1,628.75
2nd Phase of Treatment		Total	\$2,105.19	\$912.85	\$1,578.95	\$1,670.55
Specialist	105	Subsequent specialist appointment	\$43.00	\$36.55	\$32.25	\$36.55
Therapeutic procedure	32030	Rectosigmoidectomy (one potential surgery option)	\$1,031.35		\$773.55	\$773.55
Therapeutic Procedure	17610	Anaesthetist, pre-anaesthesia consult	\$43.00	\$36.55	\$32.25	\$36.55
Therapeutic procedure	20790	Initiation of management of anaesthesia	\$158.40	\$134.65	\$118.80	\$118.80
Pathology	73338	A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV).	\$362.59	\$308.25	\$271.95	\$308.25
Pathology	72838	Example of complexity level 7 biopsy material with multiple tissue blocks	\$466.85	\$396.85	\$350.15	\$396.85

Service type	MBS #	Item description	Fee	85%	75%	MBS Benefit
3rd Phase of Treatment		Total	\$2,058.85	\$1,750.90	\$1,544.80	\$1,750.90
Chemotherapeutic	13918	Cytotoxic Chemotherapy (x6)	\$587.70	\$499.80	\$441.00	\$499.80
Chemotherapeutic	13945	Long-term implanted drug delivery device for cytotoxic chemotherapy (x6)	\$315.00	\$267.90	\$236.40	\$267.90
Chemotherapeutic	13815	Central Vein Catherisation	\$85.25	\$72.50	\$63.95	\$72.50
Chemotherapeutic	13942	Ambulatory drug delivery device (x6)	\$391.50	\$333.00	\$293.70	\$333.00
Consultant Physician	110	Consultant Physician, referred consultation	\$150.90	\$128.30	\$113.20	\$128.30
Consultant Physician	116	Each attendance subsequent to the first in a single course of treatment (X7)	\$528.50	\$449.40	\$396.55	\$449.40
Tests throughout treatment		Total	\$630.30	\$541.80	\$473.70	\$541.80
Pathology	66650	CEA - blood test for monitoring malignancy or monitoring of hepatic tumours, gestational trophoblastic disease or germ cell tumour (x3)	\$73.05	\$62.10	\$54.90	\$62.10
Pathology	65070	Erythrocyte count, haematocrit, haemoglobin (x12)	\$203.40	\$173.40	\$153.00	\$173.40
Pathology	66512	5 or more tests described in item 66500 (x12)	\$212.40	\$186.00	\$159.60	\$186.00
Diagnostic Imaging	58503	Chest (lung fields) by direct radiography (x3)	\$141.45	\$120.30	\$106.20	\$120.30

Note: It is likely that this patient would reach the Medicare Safety Net threshold of \$440.80 which is calculated from the gap amount. Once this threshold is reached, 100% of the schedule fee for out of hospital services is covered.

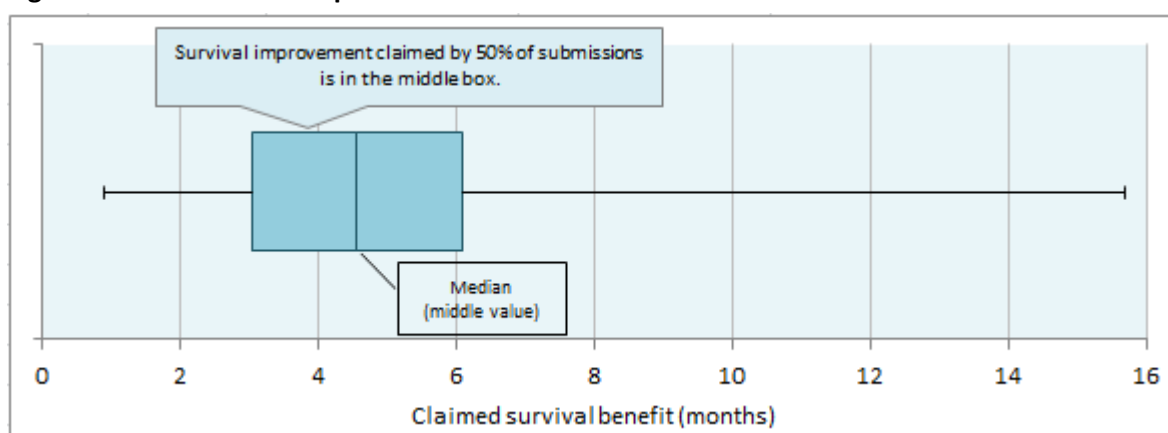
APPENDIX 2: Examples of PBAC processes for cancer medicines

Survival improvements from cancer medicines submitted to the PBAC

There have been few 'transformative' cancer medicines, leading to a perception amongst some that the PBAC is not recommending cancer treatments that offer substantial improvement. The PBAC evaluates the submissions it receives. Many of the cancer-related submissions are for medicines that provide limited benefits.

For cancer medicines approved by the US FDA between 2002 and 2014, the average improvement in survival was only 2.1 months. This is similar to the survival benefits seen by medicines submitted for PBAC consideration between 2010 and 2014. Two thirds of cancer medicines where the company claimed a survival benefit improved survival by less than 6 months. This includes extrapolated survival improvements that were not seen in clinical trials and not accepted by the PBAC.

Figure 2.1: Survival improvements claimed in cancer submissions to PBAC

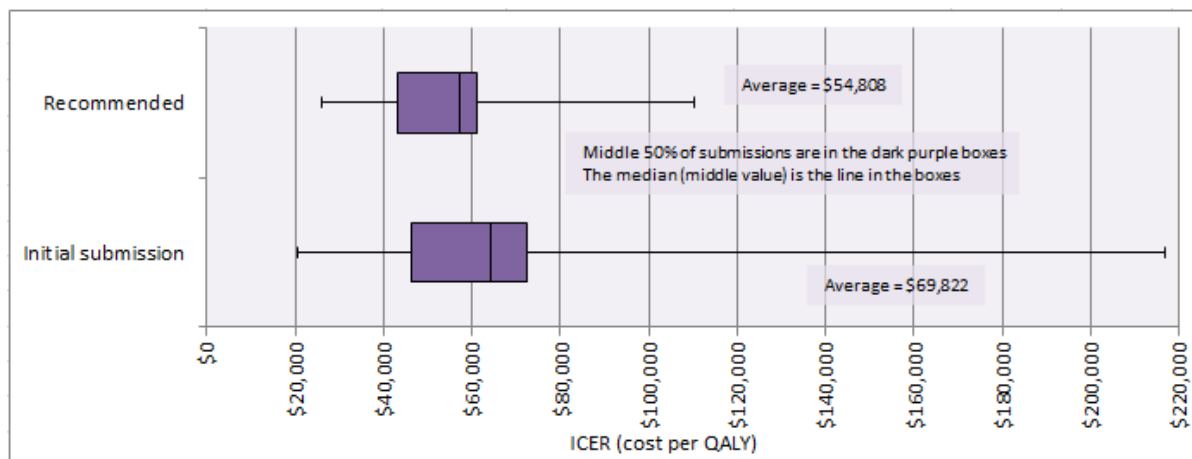


Note: N=42 submissions. Where there were re-submissions, the largest survival claim was used. Excludes submissions that did not claim to improve survival.

ICERs for cancer submissions to the PBAC

The PBAC does not use a definitive threshold when assessing cost effectiveness of medicines. Figure 2.2 presents the cost-effectiveness thresholds of initial cancer submissions to the PBAC and cancer submissions that were recommended by the PBAC.

Figure 2.2: ICERs for first cancer submissions vs. recommended cancer submissions



Note: Both groups include first time recommendations

Risks associated with early access

Initial trials of targeted therapies do not necessarily identify patients who will benefit from treatment. Cancers are often biologically complex; targeting one aspect of disease process, such as a gene mutation, may not produce much clinical benefit. The effect of cancer medicines may be inactivated for by other means.

Case study: Early access to ponatinib²⁹

Ponatinib was granted accelerated approval from the United States FDA on 14 December 2012. It was approved with a Boxed Warning alerting patients and healthcare professionals that arterial thrombosis and liver toxicity have occurred in patients treated with ponatinib.

On 31 October 2013, marketing of ponatinib was suspended after the FDA observed an increase in the number of serious vascular occlusion events identified through continued safety monitoring. This was considered to represent a significant change in the safety profile of ponatinib, as the proportion of patients on the drug experiencing vascular occlusion events such as blood clots and severe narrowing of blood vessels was significantly greater than the proportion reported at the time of its approval in December 2012. Safety precautions taken as a result of this finding included further limiting the patients to be treated with the medicine.

The November 2014 ponatinib submission to the PBAC (received by the Department in July 2014), requested PBS listing for a *larger* group of patients than what was recommended in the USA.

Case study: Early access to cetuximab

One example is cetuximab, a medicine used to treat colorectal cancer in patients. It has taken over 10 years to identify the group of patients who benefit from treatment with cetuximab. It was originally intended for patients whose cancer expressed epidermal growth factor receptor (EGFR).

Cetuximab is a monoclonal antibody medicine which would target and block EGFR. Blocking EGFR would help stop the growth and invasiveness of new cancer cells.³⁰ The PBAC considered and rejected cetuximab three times for the treatment of metastatic colorectal cancer that has tested to be EGFR positive. It was found that cancers do not necessarily test positive to EGFR in order to respond to cetuximab.³¹

Later, it was then found that patients whose cancers had Kirsten rat sarcoma viral oncogene (K-RAS) mutations had little benefit from cetuximab. The PBAC then considered and rejected a further four submissions where data from the original trials (which included patients with K-RAS mutations) re-grouping the trial patients based on whether or not their tumour had a K-RAS mutation. At its July 2010 meeting, the PBAC recommended listing of cetuximab for certain patients with K-RAS wild type metastatic colorectal cancer.

In 2013, results from a clinical trial for panitumumab, another monoclonal antibody that targets EGFR found that patients with RAS mutations (including K-RAS) had worse survival when using the panitumumab when compared to standard chemotherapy.³² *A group of patients with colorectal cancer may have had shortened lifespans due to the use of anti EGFR treatments.*

²⁹ <http://www.cancer.gov/cancertopics/druginfo/fda-ponatinibhydrochloride>

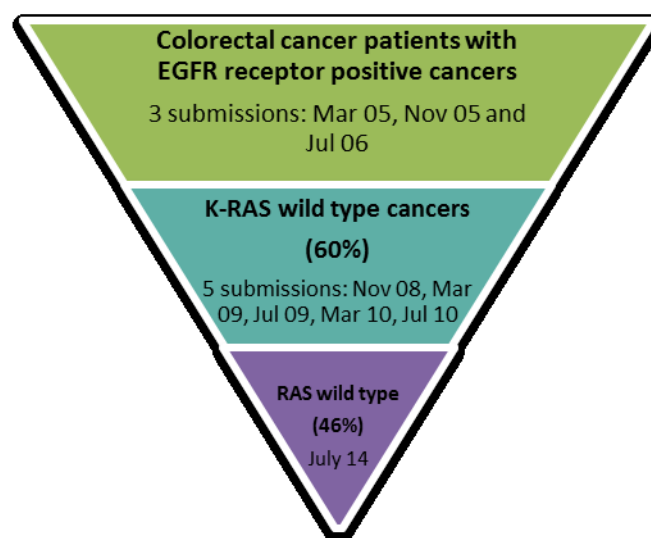
³⁰ http://dtp.nci.nih.gov/timeline/flash/success_stories/s17_Erbitux.htm

³¹ Chung KY, Shia J, Kemeny NE, Shah M, Schwartz GK, Tse A, Hamilton A, Pan D, Schrag D, Schwartz L, Klimstra DS, Fridman D, Kelsen DP, Saltz LB. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol.* 2005 Mar 20;23(9):1803-10.

³² Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wiezorek J, Sidhu R, Patterson SD. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med.* 2013 Sep 12;369(11):1023-34.

Figure 2.3: Cetuximab considerations by PBAC for colorectal cancer

Colorectal cancer patients with EGFR receptor positive cancers 3 submissions: Mar 05, Nov 05 and Jul 06
K-RAS wild type cancers (60% of metastatic colorectal cancers) 5 submissions: Nov 08, Mar 09, Jul 09, Mar 10, Jul 10
RAS wild type (46% of metastatic colorectal cancers) 1 submission: July 14



Note: Prevalance of RAS mutations taken from the MSAC public summary document from October 2014 meeting relating to RAS testing. Available from <http://msac.gov.au/internet/msac/publishing.nsf/Content/current-assessments-1>

APPENDIX 3: International overview of 5 year survival

The following table shows the reported 5 year relative survival from time of diagnosis – from EUROCARE-5³³ and AIHW³⁴

Region	Data period	Cancer type										
		Stomach	Rectal	Colon	Colorectal*	Lung	Melanoma	Breast	Ovarian	Prostate	Kidney	Non-Hodgkin's lymphoma
European mean	2000 - 2007	25.1%	57.0%	55.8%	-	13.0%	83.2 %	81.8%	37.6%	83.4%	60.6%	59.4%
England	-	17%	53.7%	51.3%	-	8.8%	85.3%	79.3%	30.6%	80.4%	51.8%	56.7%
Australia	2007 - 2011	27%	-	-	66.9%	14.3%	90.4%	89.6%	43.0%	93.2%	73.4%	72.1%

*Colon and rectal cancer data not reported separately in Australia

NOTE: there were methodological differences in estimating 5 year relative survival between the EUROCARE-5 study and AIHW

³³ *Cancer survival in Europe 1999 – 2007 by country and age: results of EUROCARE-5* Lancet Oncol 2014; 15: 23–34. Online December 5, 2013

³⁴ AIHW 2014. *Cancer in Australia: an Overview*. Cancer series No 90.

APPENDIX 4: The English Cancer Drugs Fund

The Cancer Drugs Fund (CDF) is an example of a dedicated fund source for cancer drugs.

Over the last two years, some consumer and industry stakeholders have called for Australia to have a cancer drugs fund with dedicated funding and low access thresholds, similar to the CDF managed by the National Health Service (NHS) in the United Kingdom. This appendix outlines the rationale behind the English CDF, the way it operates and associated issues, and examines the alignment between the cancer drugs currently listed on the CDF and the Pharmaceutical Benefits Scheme (PBS).

Access to medicines in England

Access to new cancer drugs through the NHS usually cannot occur until they have been licenced by the European Medicines Evaluation Agency. Once licenced, the National Institute for Health and Clinical Excellence (NICE), an independent organization responsible for making recommendations to the NHS on the use of new and existing medicines, procedures, and treatments, may provide guidance on its use. Not all licenced drugs are selected for evaluation by NICE; however, the criteria NICE uses for selection include impact on costs and impact on health.

Similarly to the Pharmaceutical Benefits Advisory Committee (PBAC), NICE uses quality-adjusted life years (QALYs) to measure the cost effectiveness of new drugs. Unlike the PBAC, however, NICE sets explicit QALY thresholds to determine cost effectiveness; NICE generally considers a treatment to be cost-effective if it costs less than £20,000 per QALY; treatments costing £20,000 - £30,000 are subject to debate and those costing over £30,000 are authorized only very rarely. Currently, about 40 percent of drugs new to the UK market are evaluated by NICE every year³⁵.

The NHS is legally obliged to fund drugs recommended by NICE (and must do so within three months of a positive guidance³⁶) but a lack of guidance or a negative NICE appraisal does not preclude the NHS from funding any drugs or treatments. Licensed drugs can be prescribed if the relevant local Trust is willing to pay for it, either generally or in specific cases. NICE does not negotiate drug prices; this responsibility rests with the Department of Health³⁷.

However, positive guidance does not always result in higher utilisation of medicines, and it was noted in the Richard's Report that "some categories of drug which have received a strong NICE endorsement are still used at significantly lower levels than in other countries (for example, for hepatitis C treatments or some cancer drugs)³⁸".

The Cancer Drugs Fund

The CDF was the interim solution put in place by the UK Government in 2010 following criticism of the NICE rejection rate of cancer drugs, the length of time taken by NICE to evaluate the cost effectiveness of new drugs (up to six months³⁹), and the uneven access to new cancer medicines across England.

³⁵ European Pricing Reimbursement (Baker and Mackenzie, 2011 www.bakermckenzie.com)

³⁶ <http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Gettingtreatment/Accessstotreatment/Howtreatment/saremadeavailable.aspx>

³⁷ *ibid*

³⁸ Extent and causes of international variations in drug usage. A report for the Secretary of State for Health by Professor Sir Mike Richards, CBE. July 2010

³⁹ <https://lsconnect.thomsonreuters.com/controversial-plans-extend-cancer-drugs-fund-uk-unveiled/>

Patients apply through their specialist to access drugs on the CDF and these applications are assessed by a panel of experts. Access is therefore not unconditional nor guaranteed. This is in contrast to the PBS, which provides universal access to listed cancer drugs without the need for patient applications. Cancer drugs are placed on the CDF if they prove an acceptable level of clinical effectiveness, but cost effectiveness is not one of the criteria.

The CDF was intended to be replaced in 2014 by a new drug evaluation and pricing scheme, known as value-based pricing (VBP), intended to allow the inclusion of a broader societal perspective in NICE's evaluations, but the VBP system has not eventuated⁴⁰. Nevertheless, CDF funding is not anticipated to be ongoing and has only been agreed until 2016.

The CDF funding was originally capped at £200 million per year, but in 2013-14 the CDF was overspent by £30.5 million, and in late 2014 officials announced they expected the fund to exceed its budget by £100 million by the end of the fiscal year. The overspend is attributable to more patients wanting to use the CDF and above-inflation rises in the cost of oncology drugs⁴¹. The Government announced both that it would increase the CDF budget to £280 million in 2014-15 (and to £340 million in 2015-16), and that the list of drugs would be reviewed.

In January 2015 the outcome of that review was announced, with 25 funded indications to be removed from the CDF on 12 March 2015. In announcing the decision, the CDF website stated:

"If action had not been taken to review the CDF drugs list, the Fund is projected to have grown to around £420 million next year, necessitating offsetting cuts in other aspects of cancer treatment such as radiotherapy, cancer diagnoses, cancer surgery, and other important NHS services for other patient groups."

Reaction to the delistings has been mixed, with some manufacturers whose drugs have been de-listed reportedly threatening to sue the CDF⁴². However, another commenter argued that cancer drug funding was a systemic issue and asked:

"But is continuing the CDF the right way forward, or is it papering over the cracks inherent in both the market access process in England and the misalignment between pharma's pricing and the efficacy of their medicines?"⁴³

The Chief executive of the Myeloma UK charity noted :

"Quick-fix measures such as the Cancer Drugs Fund are not effective long-term solutions to securing cancer patients access to medicines. Throwing money at fixing a complex issue does not solve the underlying reasons why these drugs are not available on the NHS in the first place ... This situation has been inevitable since the establishment of the Fund, given the finite and fixed nature of the budget and the insistence of certain pharmaceutical companies to price their treatments at a level that does not represent an appropriate level of value to the NHS⁴⁴."

Since its inception, the CDF has been subject to criticism and viewed as undermining NICE⁴⁵. Some also questioned why cancer should receive special consideration when other diseases, such as multiple sclerosis and Alzheimer's, are exempt from such funding, and noted the opportunity costs for funding more effective, non-drug cancer treatments:

"The drugs that the Cancer Drug Fund is making more available will not make a significant contribution to cancer survival. Drugs such as Sunitinib, which is used for kidney cancer, translate into an improved survival for one individual patient of about

⁴⁰ http://www.pmlive.com/pharma_news/englands_cancer_drugs_fund_fixing_a_broken_system_648945

⁴¹ *ibid*

⁴² <http://www.fiercepharma.com/story/big-pharma-threatens-sue-uk-fund-officials-nix-novartis-sanofi-and-eisai-me/>

⁴³ http://www.pmlive.com/pharma_news/englands_cancer_drugs_fund_fixing_a_broken_system_648945

⁴⁴ http://www.pmlive.com/pharma_news/englands_cancer_drugs_fund_fixing_a_broken_system_648945

⁴⁵ <http://www.theguardian.com/society/2014/nov/12/cancer-drugs-fund-drugs-reassessed-kadcyla-avastin>

three months. It is certainly a useful drug, far better than what was previously available, but it can be very toxic (some of its side-effects can be life-threatening) so, with an average 18-month course of Sunitinib costing the taxpayer £60,000, a dispassionate cost-benefit analysis could reasonably question whether that £60,000 be used better elsewhere in oncology, or even perhaps in other parts of the NHS which have not had the prominence of cancer medicine in recent years?

Both surgery and radiotherapy make a significantly greater contribution to overall cancer survival. The optimal proportion of patients with cancer that should receive radiotherapy varies by tumour type and stage, but overall it is thought to be around 52 per cent. In 2005, the radiotherapy access rate in England was only 38.2 per cent. Work is underway to increase England's radiotherapy capacity and expand the use of complex radiotherapy treatments, but there remains significant scope to improve outcomes by increasing access to radiotherapy"⁴⁶.

One of the aims of the CDF was to expedite access to new cancer drugs, but available evidence suggests that the CDF has only been used to access drugs deemed not cost effective by NICE, and has not increased access to new cost effective cancer drugs prior to NICE approval⁴⁷.

Future of the Cancer Drugs Fund

One commentator noted that the CDF was “a political intervention ... aimed at nullifying negative NICE decisions and appeasing angry newspaper editorials about 'nasty NICE' rationing cancer care⁴⁸” and that the pharmaceutical industry was also not a “major fan” of the CDF because it does not address the problems of low access, which are perceived as coming predominantly from NICE's negative decisions.

A Cancer Drug Fund Working Party was set up in January 2015 to look at better ways of getting new cancer drugs appraised and commissioned for patients⁴⁹. It consists of NHS England, the Department of Health, cancer charities, NICE, the Ethical Medicines Industry Group and the Association of the British Pharmaceutical Industry (ABPI).

In particular, they are looking at extending NHS England's “Commissioning through Evaluation” (CtE) programme⁵⁰. The CtE programme is testing an innovative approach to evaluating potentially promising specialised treatments, but for which there is currently insufficient evidence available to support routine commissioning within the NHS.

The current CtE is looking at particular cardiology services. Each scheme has been developed with the support of national clinical experts and patient representatives. The scheme enables a small number of procedures to be funded, within a limited number of selected centres, and within a limited time-frame, while evidence on the relative clinical and cost effectiveness of the procedures is gathered, compared to other treatments already available in the NHS.

Additionally, the UK Life Sciences Minister, George Freeman, indicated that during the current review of NICE (which occurs every three years) he was “not looking to reform NICE but rather have it work more closely with the UK drugs body the MHRA and pharma to use the government's new early access to medicines scheme to help speed up approval times⁵¹.”

⁴⁶ Evidence Submission (Co-authored narrative): The Cancer Drug Fund, radiotherapy and cancer survival July 4, 2011 <http://ukpolicymatters.thelancet.com/evidence-submission-co-authored-narrative-the-cancer-drug-fund-radiotherapy-and-cancer-survival/>

⁴⁷ C Chamberlain, S M Collin, P Stephens, J Donovan, A Bahl and W Hollingworth. Does the cancer drugs fund lead to faster uptake of cost-effective drugs? A time-trend analysis comparing England and Wales? *British Journal of Cancer* (2014) 111, 1693–1702. doi:10.1038/bjc.2014.86

⁴⁸ http://www.pmlive.com/pharma_news/englands_cancer_drugs_fund_fixing_a_broken_system_648945

⁴⁹ <http://www.england.nhs.uk/ourwork/pe/cdf/cdf-news/>

⁵⁰ <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/>

⁵¹ http://www.pmlive.com/pharma_news/englands_cancer_drugs_fund_fixing_a_broken_system_648945

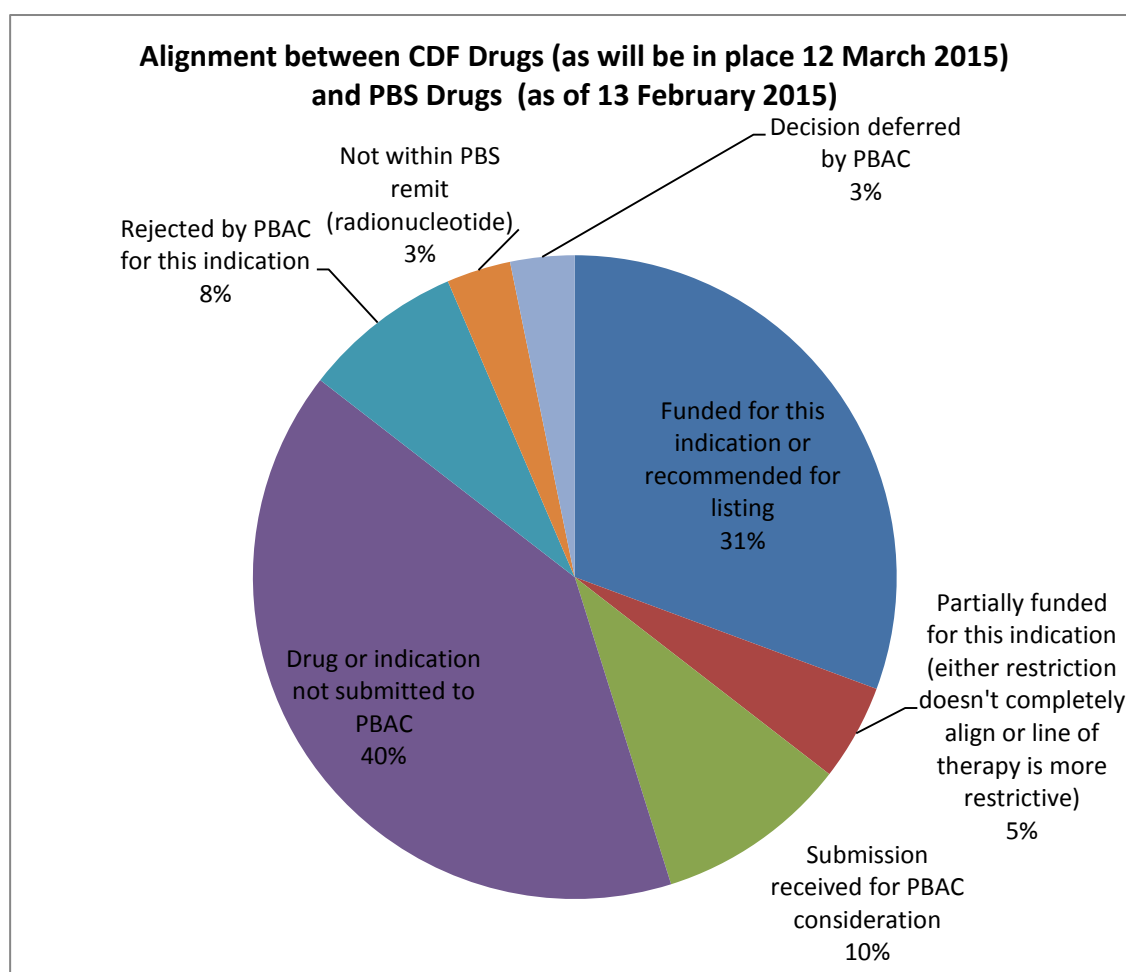
Alignment of CDF and PBS cancer drugs

The most recent CDF list (version 3.0) indicates that there are 35 drugs for 62 indications that have ongoing funding, but a further 25 indications that will only be funded until 12 March 2015.

Alignment of PBS drugs and indications with those CDF indications that will be continuing demonstrates that:

- 40% (25 indications) have not been submitted to PBAC (the PBAC cannot compel a sponsor to provide a submission)
- 36% of the drugs and indications on the CDF have either full (11 indications) or partial (3 indications) PBS funding, or have been recommended by the PBAC (7 indications);
- 10% will be considered by PBAC at their March 2015 meeting (6 indications);
- 3% have had their decision deferred by PBAC (2 indications);
- 3% are radionucleotides and are therefore not within the remit of the PBS (2 indications).

Only 8% of CDF listed drugs considered by PBAC have not been recommended for PBS funding, and of the 25 indications that will be delisted by the CDF in March 2015, 15 are either on the PBS or recommended for listing.



In 2013-14, the number of indications funded on the CDF that were fully or partially funded on the PBS at the same time was 24 (this includes the indications that are to be delisted from the CDF). It is worth noting that PBS expenditure on these 24 PBS funded indications (\$A292 million) in 2013-14 was equivalent to 64% of the entire £230.5 million (\$A457 million) funding for the CDF in 2013-14.

Further, CDF data for 2013-14 indicates that 19,282 new patient applications were received over the period to access all CDF listed indications at that time (including the 25 indications that will be delisted in March 2015). Of those new applications, around 7,900 were to access the same indications also funded by the PBS in the same time period, which provided almost 14,000 Australians (both new and ongoing patients) subsidised access to those medicines.

Overall, 48% of the requests for CDF new patient applications in 2013-14 were for medicines and indications already funded on the PBS, or since recommended for PBS funding. Only 9% of the requests were for medicines and indications rejected by PBAC. 38% of requests were for medicines not seen by PBAC, with a further 3% of requests for indications that will be considered by PBAC at its March 2015 meeting.

APPENDIX 5: Therapeutic Goods Administration

Registration process for prescription medicines

Generally, a medicine must be included on the Australian Register of Therapeutic Goods (ARTG) in order to be marketed in Australia. The Therapeutic Goods Administration (TGA) administers, evaluates and makes decisions about whether data provided in support of applications for prescription medicines demonstrate that the medicine meets the required standards of quality, safety and efficacy to permit an entry on the ARTG, or support a variation to an existing entry for a medicine. The decision to approve or reject an application is made by a delegate under the *Therapeutic Goods Act 1989* (TG Act). This is different to processes such as PBS listing where there is a direct Ministerial role.

The current Streamlined Submission Process (SSP) for prescription medicine applications (including oncology medicines) was adopted in November 2010 and was designed to improve efficiency and timelines for the registration of prescription medicines without compromising the scientific rigour of the evaluation process.

The registration process consists of eight phases with eight milestones, allowing effective planning and tracking by the TGA and applicants. Each phase has established timeframes (See Figure 5.1). The TGA does have the discretion to accelerate the review process.

The data submitted in support of a new medicine should establish the quality, safety and effectiveness of the proposed product for the proposed indication. Data fall into three main categories: chemistry and manufacturing control; toxicity and pharmacology; and clinical use.

There are a number of EU guidelines which TGA has adopted in relation to oncology products. The main guideline is *Guideline on the evaluation of anticancer medicinal products in man* (EMA/CHMP/205/95/Rev.4) which came into effect in Europe in July 2013 and was adopted by TGA in April 2014. This describes the development of an anticancer product in terms of the conventional classification of Phase I, II and III trials and describes some of the issues to be explored as they apply to anticancer products.

While EU and ICH technical Guidelines adopted in Australia are generally not mandated in Australian legislation they provide guidance to sponsors to assist them to meet the legislative requirements and any deviation from a Guideline relevant to an application to register or vary the registration of a medicine must be justified. Therefore, while the TGA does endorse a number of the European guidelines for clinical development of different groups of medicines, The TGA is not prescriptive about the clinical trial design or phase. Most medicine submissions to TGA use international clinical trial data.

With regard to applications for oncology medicines, there are a number of contemporary issues that are taken into account including:

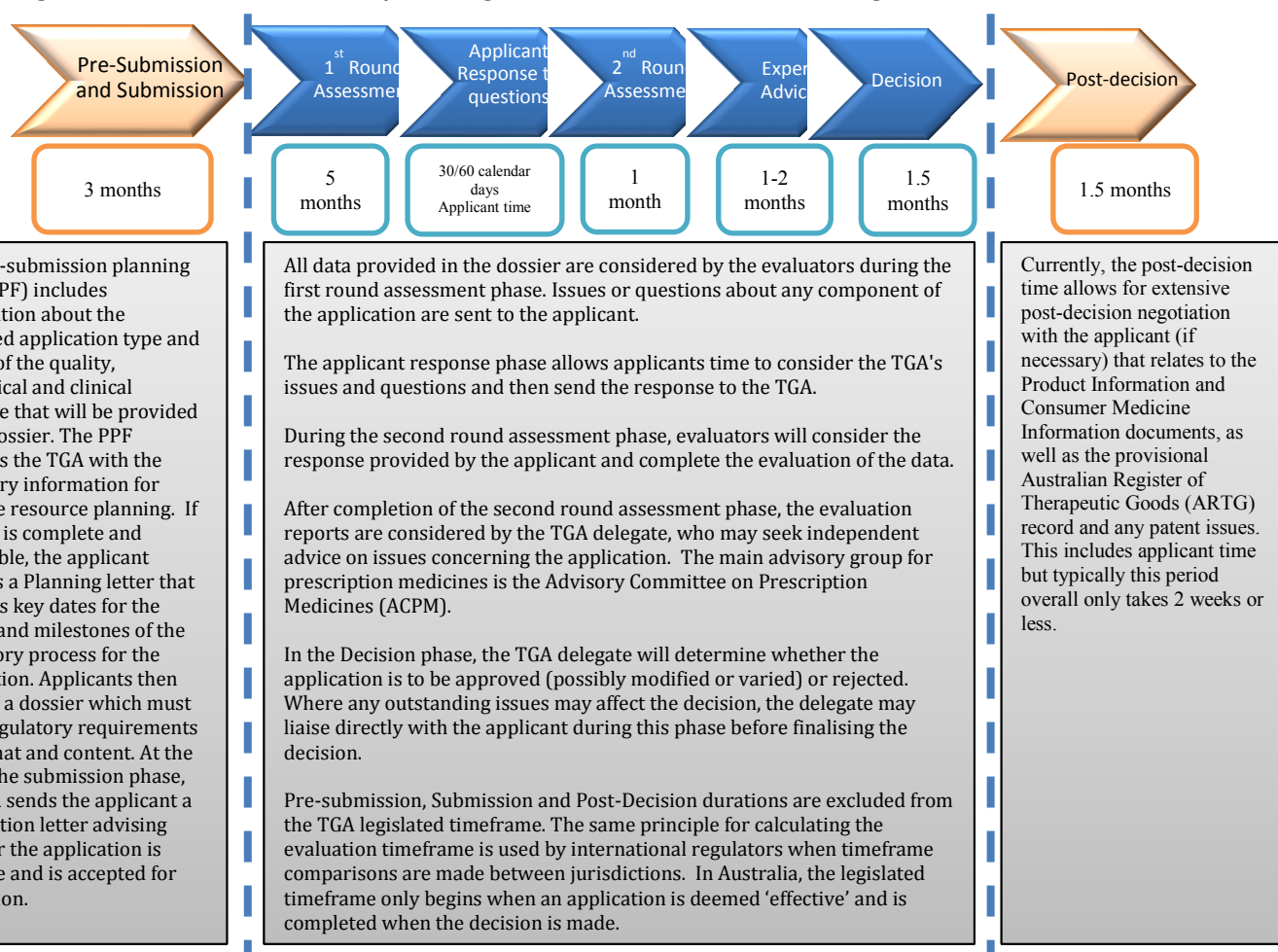
- Experience with surrogate endpoints e.g. biochemical vs clinical outcomes;
- Progression free survival not always well correlated with overall survival;
- Pressure to get better products on to the market may mean few studies of longer term outcomes available – need to monitor post introduction to the market;
- Better use of patient-defined endpoints e.g. quality of life is needed;
- Benefit/ risk tolerance differs for cancer patients than regulators;
- Personalised medicine – adequate powering with small patient groups;
- Adaptive trial designs – data gathered during trial enables treatments to be changed midway, but crossover leaves control arm of trial under-powered
 - TGA does approve medicine based on comparative trials – e.g. comparisons with standard treatments for oncology, studies of “add on” therapies;
 - Can more closely reflect likely decisions made in routine clinical practice;
 - Direct comparisons are uncommon but are more robust than meta-analyses;

- But there are challenges:
 - Often only limited differences in effectiveness between medicines in a class;
 - Individual differences in response to medicines need to be addressed;
 - How to compare medicines with greater efficacy but greater harms;
 - Choice of comparator medicine/dose can introduce biases;
 - How to deal with medicines that have a lack of superiority.

After evaluation of data and preparation of scientific reviews the delegate, usually a senior medical officer, considers the overall application and either grants approval to include the medicine on the ARTG or rejects the application. As part of the assessment process for most new medicine applications, the TGA delegate also seeks advice from an independent expert advisory committee, the Advisory Committee on Prescription Medicines.

The Act specifies the amount of time allowed to evaluate and make a decision on an application relating to a prescription medicine, depending on the type of application. A Category 1 application includes applications for new chemical and biological entities, new generic medicines, or new uses or variations for registered prescription products. These applications are allowed a statutory 255 TGA working days for evaluation and finalisation of the decision.

Fig 5.1: Current workflow for providing full market authorisation through the TGA



Priority Review

Currently, there is no formal priority evaluation system. However, if an application is considered by the TGA to be a significant therapeutic advance or of critical importance, the TGA will, wherever possible, work with the relevant applicant with a view to facilitate an early decision, provided the product meets the TGA's quality, safety, and efficacy requirements.

Australian Public Assessment Reports (AusPARs)

Since early 2010, AusPARs have been published on the TGA website for certain submissions. AusPARs provide information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine for registration in Australia.

Government review of medicines and medical devices regulation

On 24 October 2014, the Government announced an independent review of medicines and medical devices regulation. The Review will examine the regulatory framework and processes of the TGA with a view to identifying:

- areas of unnecessary, duplicative, or ineffective regulation that could be removed or streamlined without undermining the safety or quality of therapeutic goods available in Australia; and
- opportunities to enhance the regulatory framework so that Australia continues to be well positioned to respond effectively to global trends in the development, manufacture, marketing and regulation of therapeutic goods.

The Terms of Reference for the Review include benchmarking TGA regulatory arrangements against trusted international authorities, and the Government expects the outcomes of the review will identify opportunities for access to the latest treatments in a timely manner.

Supply of medicines not included in the ARTG

The current legislation in Australia does provide some options to accommodate the provision of medicines not on the ARTG, such as oncology medicines, for urgent public health needs. The Special Access Scheme (SAS) and Authorised Prescriber scheme allow doctors and patients rapid access to unregistered medicines, where such use is medically required. The SAS refers to arrangements that provide for the import and/or supply of an unapproved therapeutic good for a single patient, on a case-by-case basis. A doctor can also apply to the TGA for approval as an 'Authorised Prescriber' for the purpose of supplying medicines that have not been fully assessed by the TGA. Patients are also able to access unapproved medicines through clinical trials.

Regulation of clinical trials

Clinical trials of medicines and medical devices conducted in Australia are subject to Commonwealth Government regulation administered by the TGA.

There are two schemes under which clinical trials involving therapeutic goods may be conducted, the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial Notification (CTN) Scheme. Either notification under the CTN Scheme or application under the CTX Scheme is required for all clinical investigational use of a product, where that use involves:

- any product not entered on the ARTG, including any new formulation of an existing product or any new route of administration, or in the case of an existing medical device, new technology, new material or a new treatment modality; or
- use of a product beyond the conditions of its marketing approval, including new indications extending the use of a medicine to a new population group and the extension of doses or duration of treatments outside the approved range.

Clinical trials in which registered or listed medicines or medical devices are used within the conditions of their marketing approval are not subject to CTN or CTX requirements but still need to be approved by a Human Research Ethics Committee (HREC) before the trial may commence.

The TGA’s main focus is on access to (as yet) unapproved medicines for trials rather than end-to-end regulation of trials. Under CTN, HREC is responsible for assessing validity of the trial design, safety and efficacy of the product as well as ethical acceptability of the trial protocol. Although, TGA Clinicians can informally review protocols, particularly for first in human studies

All trials must have an Australian sponsor who initiates, organises and supports a clinical study and carries the medico-legal responsibility. If there is a major protocol change a new notification to TGA may be required. The TGA has the authority to audit clinical trials. The Sponsor is responsible for reporting adverse events during trials directly to TGA.

Approval times for New Medicines

Figure 5.2: TGA approval times for New Chemical Entities (NCEs)*

NCEs		Total of TGA and non-TGA working days					TGA working Days				
Year***	n	Median	Mean	Min	Max	Range	Median	Mean	Min	Max	Range
2011	27	284.0	301.3	207.0	527.0	320.0	235.0	229.1	160.0	255.0	95.0
2012	23	248.5	284.8	170.0	669.0	499.0	209.0	215.7	148.0	253.0	105.0
2013	38	250.0	253.2	181.0	415.0	234.0	216.0	213.2	144.0	249.0	105.0
2014 (to 1 July)	27	243.0	250.0	203.0	387.0	184.0	207.0	205.6	172.0	249.0	77.0
NCEs Stream 4 only**		Total of TGA and non-TGA working days					TGA working Days				
Year ***	n	Median	Mean	Min	Max	Range	Median	Mean	Min	Max	Range
2011	5	304.0	341.2	209.0	484.0	275.0	247.0	236.6	183.0	254.0	71.0
2012	6	248.5	298.2	170.0	669.0	499.0	186.5	192.3	148.0	247.0	99.0
2013	14	244.5	236.6	181.0	260.0	79.0	208.5	206.7	160.0	249.0	89.0
2014 (to 1 July)	9	224.0	227.4	203.0	246.0	43.0	197.0	195.2	172.0	235.0	63.0

* Times are from the date the evaluation starts to decision date, with 255 TGA days being the statutory time frame.

** Stream 4 contains both oncology and haematology products – mostly oncology.

*** Each year does include some applications that came in before the SSP and so there are some large stop times that give the big range in the ‘Total of TGA and Stop days’ data.

Figure 5.3: International comparison of total days with regulator plus days with sponsor for responses*

	All new medicines (New Chemical Entities) (2013)	Oncology medicines (2009-13)
Europe (EMA)	478	450
US (FDA)	304	240
Japan (PMDA)	342	365
Australia (TGA)	350	372** (314)***

Source: International data from Centre for International Regulatory Science, R&D Briefing 54, May 2014

* Data is total time (days) – time with sponsor typically 30-40% of total time

** Figure for 2011-2013;

*** Figure for Jan-June 2014 – 314 total days, including 197 working days with TGA