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Abstract

The Commonwealth Government of Australia has subsidised access to drugs since 1948 via the Pharmaceutical Benefits Scheme (PBS). Through the PBS, the Commonwealth Government aims to provide affordable, timely and equitable access to necessary medicines at an affordable cost to the Government. The PBS is one of the three pillars of government funding of the Australian health system. The other two pillars are free treatment in public hospitals, funded jointly by the Commonwealth Government and State and Territory governments, and the Medicare Benefits Scheme (MBS) where the Commonwealth Government subsidises consultations with clinicians occurring out of hospital.

Pharmaceutical policy today in Australia is complex as a result of multiple reforms implemented over a number of years. These reforms introduced or changed pre-existing mechanisms with the aim to control prices and manage demand, and thus control expenditure, while maintaining equitable access. However some policies conflict and some result in unintentional, and sometimes detrimental, incentives.

Section 1 provides some historical background to the PBS and explains the avenues through which patients can access PBS-subsidised drugs. Section 2 discusses PBS expenditure in the context of total expenditure on drugs in Australia, the high rate of growth in PBS expenditure over time, and the key drivers of the high rate of growth. Section 3 describes the role of the Pharmaceutical Benefits Advisory Committee, focussing on the process used to evaluate the drug, the drivers of PBAC decisions, and issues faced when reviewing currently listed drugs. Section 4 lists several mechanisms that can be used to minimise uncertainty and reduce the risk of making an incorrect decision. Finally Section 5 describes the methods used by the Australian Department of Health and Ageing (DoHA) to manage the costs and demand for, and thus affect uptake of, drugs once listed on the PBS.

1. Introduction to the Pharmaceutical Benefits Scheme

Prior to the introduction of the PBS, drug costs were largely funded by the individual patients. Free or affordable access was also possible through public and charitable hospitals in some states, or though Friendly Society Dispensaries; but by and large access was restricted to those who could afford to pay[1].

The RPBS was established in 1919 and was the first scheme that provided free access drugs, but these benefits were restricted only to ex-service personnel. Early legislative attempts which aimed to provide access to drugs to the general population included the *Pharmaceutical Benefits Act 1944*[2] and the *Pharmaceutical Benefits Act 1947*[3], however both were challenged in the high court by the Australian Branch of the British Medical Association and ruled unconstitutional[4]. Despite the challenges, the Commonwealth Government provided free immunisation against diphtheria and whooping cough in 1947. In 1950, following an election in which the Menzies Liberal-Country Party coalition government came to power and the 1951 double dissolution election which gave the party control of the senate, a broader scheme was introduced which provided free access to 139 "life saving and disease preventing drugs" to the general population. The scheme was voluntary and participation by doctors was limited[4]. The National Health (Medicines for Pensioners) Regulations, under the *National Health Service Acts 1948 and 1949*[1], came into effect in 1951 which provided free access to Australian pensioners to drugs listed in the British Pharmacopoeia, a broader list of drugs with some exceptions/additions specified in the regulations[4]. Finally the *National Health Act 1953* was passed and it became commonplace for clinicians to prescribe drugs on the PBS schedule to the general population using Commonwealth Government-issued prescribing pads. Eventually the *National Health*

[1] The legislation was passed by the previous Chifley Australian Labour Party government but never implemented for constitutional reasons.

Act No. 72 1959 combined the existing pensioner and general population schemes, expanded the list of drugs available, and introduced patient co-payments[4].

The key legislation relating to the PBS is Part VII of the *National Health Act 1953*[4, 5]. In general, the PBS covers the cost of drugs prescribed by clinicians out of hospital and dispensed at community pharmacies. Following a consultation with a patient, a clinician writes a prescription for a drug which the patient takes to a pharmacy. The pharmacy dispenses the appropriate drug to the patient and, if listed on the PBS schedule, charges the patient a co-payment with the remainder of the cost covered by the Commonwealth Government. If the drug is not listed on the PBS then the entire cost is incurred by the patient, but may be partially reimbursed by private health insurance. Drugs prescribed to inpatients in public hospitals are covered, with a few exceptions, by the hospital budget and thus provided free to the patient. Drugs prescribed to inpatients in private hospitals are treated similarly to those prescribed by clinicians out of hospital: funded though the PBS, out-of-pocket or private health insurance.

2. PBS Expenditure

In 2008-09, the PBS subsidised more than 700 drugs available in more than 1,800 forms and marketed as more than 3,400 brands[6]. In 2008-09 the PBS and the Repatriation Pharmaceutical Benefits Scheme (RPBS) covered 59% ($8.9 billion) of total expenditure on drugs in Australia ($15.2 billion)[2][7]. Drugs not subsidised via the PBS/RPBS include drugs which cost less than the co-payment (17.4%), private prescriptions for non-PBS-listed drugs (9.1%), over-the-counter medications[3] (67%) and other[4] (6.6%)[7]. The PBS/RPBS covered

[2] Excluding drugs prescribed to inpatients in public hospitals which are covered by the hospital budget.

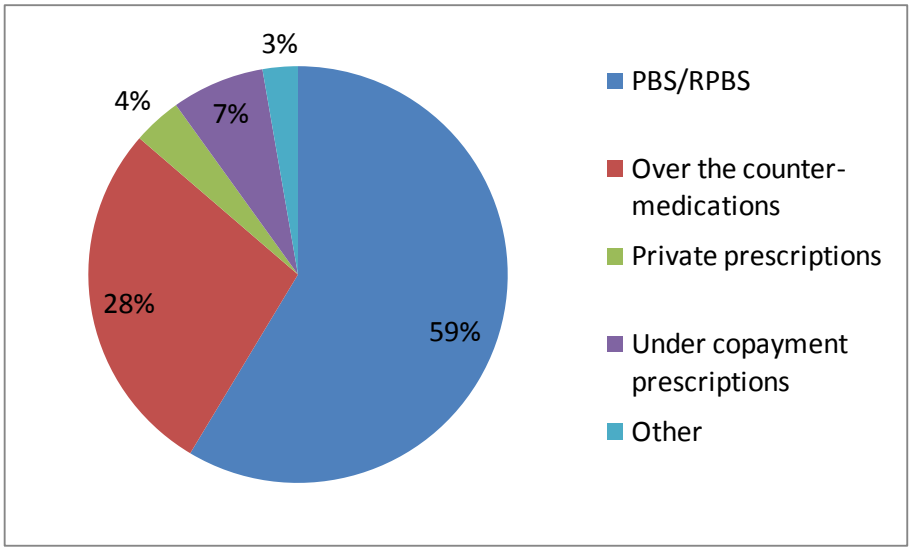
[3] Includes pharmacy-only medicines, aspirin, cough and cold medicines, vitamins and minerals, herbal and other complementary medicines, and a range of medical non-durables, such as bandages, bandaids and condoms.

[4] Injury compensation insurance payments and some DoHA expense items.

71% of expenditure on prescribed drugs[5] ($10.6 billion) in 2008-09. The average total expenditure on drugs per person was $702 in 2008-09[8].

In 2008-09 the Commonwealth Government contributed 49.1% ($7.5 billion) of total expenditure on drugs in Australia ($15.2 billion) through the PBS/RPBS, up from 47% in 1998-99[7]. The average benefit paid per person was $345 in 2008-09[8]. The Commonwealth Government also covered a further 2.4% ($360 million) of the costs of other drugs not listed on the PBS/RPBS. The cost of the remaining total expenditure on drugs was largely covered by individuals[6] (48.2% or $7.3billion) with private health insurance covering 0.3% ($49 million)[7][7]. If the cost of over-the-counter medications is excluded, then the Commonwealth Government contributed 71% and individuals 28% of expenditure on drugs.

Figure 1: Total Drug Expenditure by Type of Drug



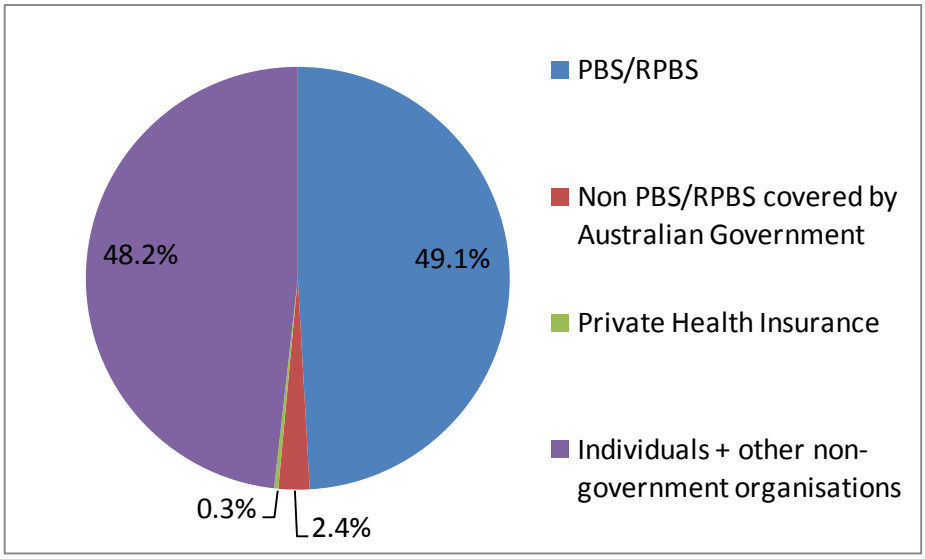
Source: [7]

[5] PBS, under copayment, and private prescriptions of non-PBS-listed drugs

[6] Including PBS co-payments

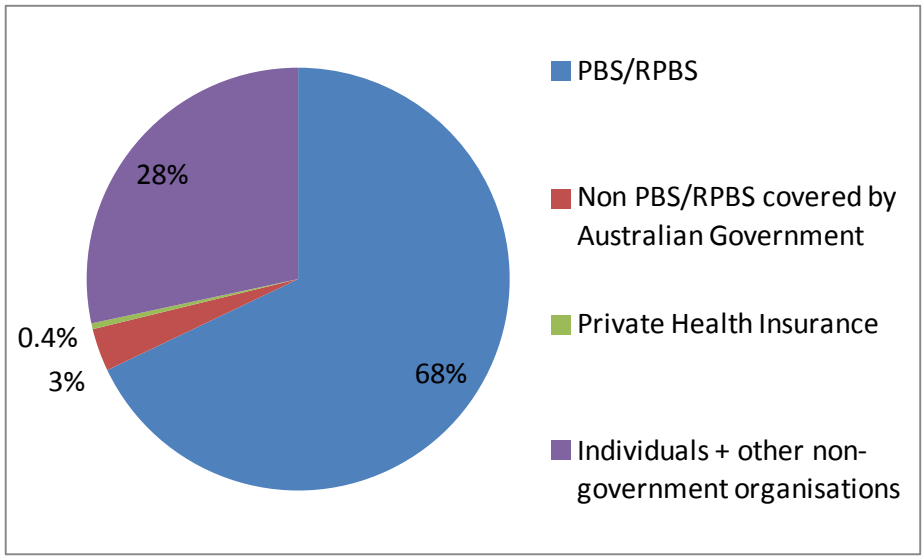
[7] Data on drug expenditure in public and private hospitals covered by State and Territory governments was not available.

Figure 2: Total Drug Expenditure by who pays, including over-the-counter medicines



Source: [7]

Figure 3: Total Drug Expenditure by who pays, excluding over-the-counter medicines



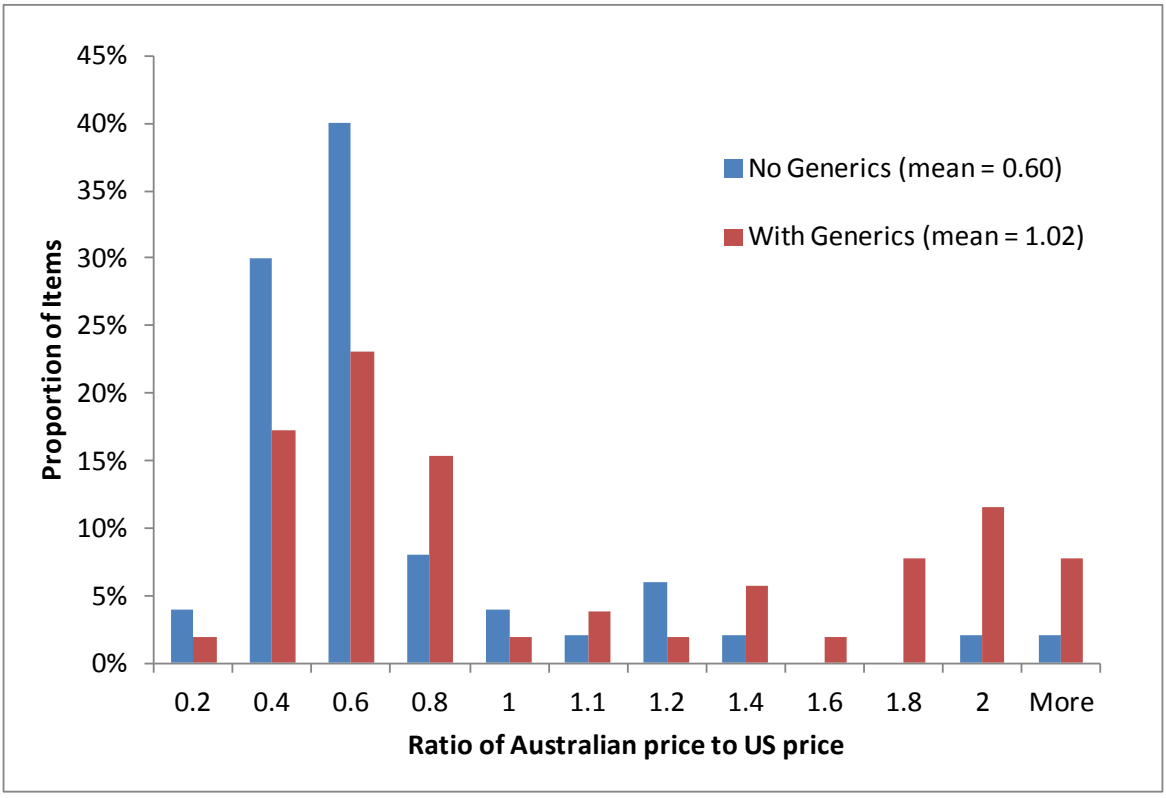
Source: [7]

Total expenditure by the Commonwealth Government on the PBS/RPBS (excluding co-payments) has increased substantially from $3.1 billion in 1998-99 to $7.5 billion in 2008-09 (in 2008-09 prices)[7]. As a proportion of the entire expenditure on health by the Commonwealth Government, expenditure on the PBS/RPBS has increased from 10.9% in 1998-99 to 15.3% in 2008-09 (in 2008-09 prices)[7].

There is a wide variety of reasons for increasing demand for drugs, including: increasing income and willingness to spend more on health; population growth and ageing, and consequently increasing number of people with chronic diseases; conversion of some diseases from acute to chronic diseases (e.g. heart failure and cancer); availability of preventative treatments and treatments for previously untreated diseases (e.g. new lines of chemotherapies); changing expectations and awareness regarding what diseases or symptoms can be treated (e.g. gastro-oesophageal reflux disorder); improved screening rates and diagnostics (e.g. diabetes and cancer); lifestyle/behavioural changes (e.g. obesity levels); and shifting of drug costs previously borne by hospitals, and thus State and Territory Governments, to the PBS (e.g. through Section 100 and a limited amount of drugs being provided upon discharge)[9, 10]. Promotional marketing by pharmaceutical companies and inappropriate prescribing or leakage has also been blamed for higher than expected expenditure on some drugs, such as celecoxib[10].

Increasing price pressures also play a part in expenditure pressures. Firstly the average costs of new drugs are generally higher than older drugs[11]. Secondly while on-patent drugs generally cost less in Australia compared to other developed countries, off-patent drugs cost relatively more in Australia. Bulfone (2009) found that 88% of the 100 most prescribed items in terms of cost or volume for which there was no generic available (largely on-patent drugs) were of similar cost (within 10%) or cost less than in the US in 2008, compared to 63% of the 100 most prescribed items for which there was a generic available (see Figure 4). Bulfone (2009) also found that, on average, costs were 40% lower for items where no generics were available, compared with 2% higher when generic were available[12].

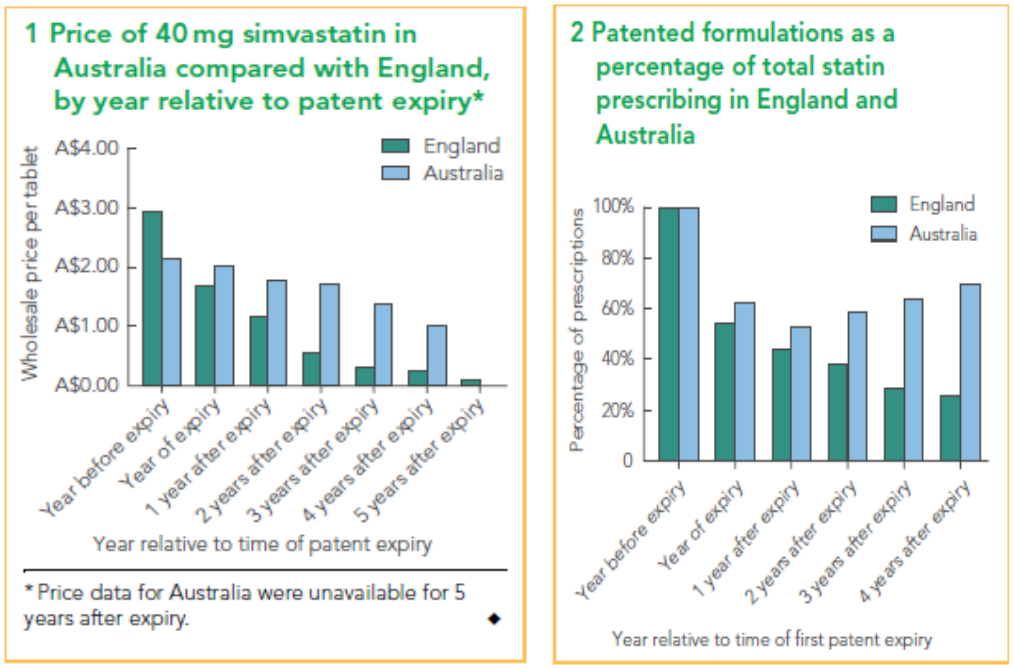
Figure 4: Ratio of the Australian price to US price for most prescribed PBS items in Australia



Source: [12]

A similar analysis by Clark (2010), who focused on statins, found that the price of simvastatin 40mg was lower in Australia compared to England prior to patent expiry. Following the loss of patent protection the price in both countries fell but more substantially in England, such that within the first year the price in England fell below that in Australia. Further analysis found that the demand for generics was lower in Australia compared to England in the first year following loss of patent protection, and that over time the demand for generics increased in England while the demand in Australia declined over time (see Figure 5).

Figure 5: The Market for statins in Australia versus England



Source: [13]

The two key reasons for the relatively higher prices of off-patent drugs and low levels of demand for generics are: the incentive to choose generics is weak as doctors do not directly face the cost of the drugs, although they may consider the financial impact on the patient, and co-payments shield patients from any price differentials above the cap (see Section 5.1); and that the reference pricing system reduces the incentive to manufacturers to offer price discounts to the Commonwealth Government (see Section 5.4).

The recent trends in PBS/RBPS expenditure, and the potential for the high growth rates to continue into the future, has caused concerns regarding its long-term sustainability of the PBS[14]. Although, the increased use of drugs may result in cost-savings in other parts of the health system.

3. The Role of the PBAC

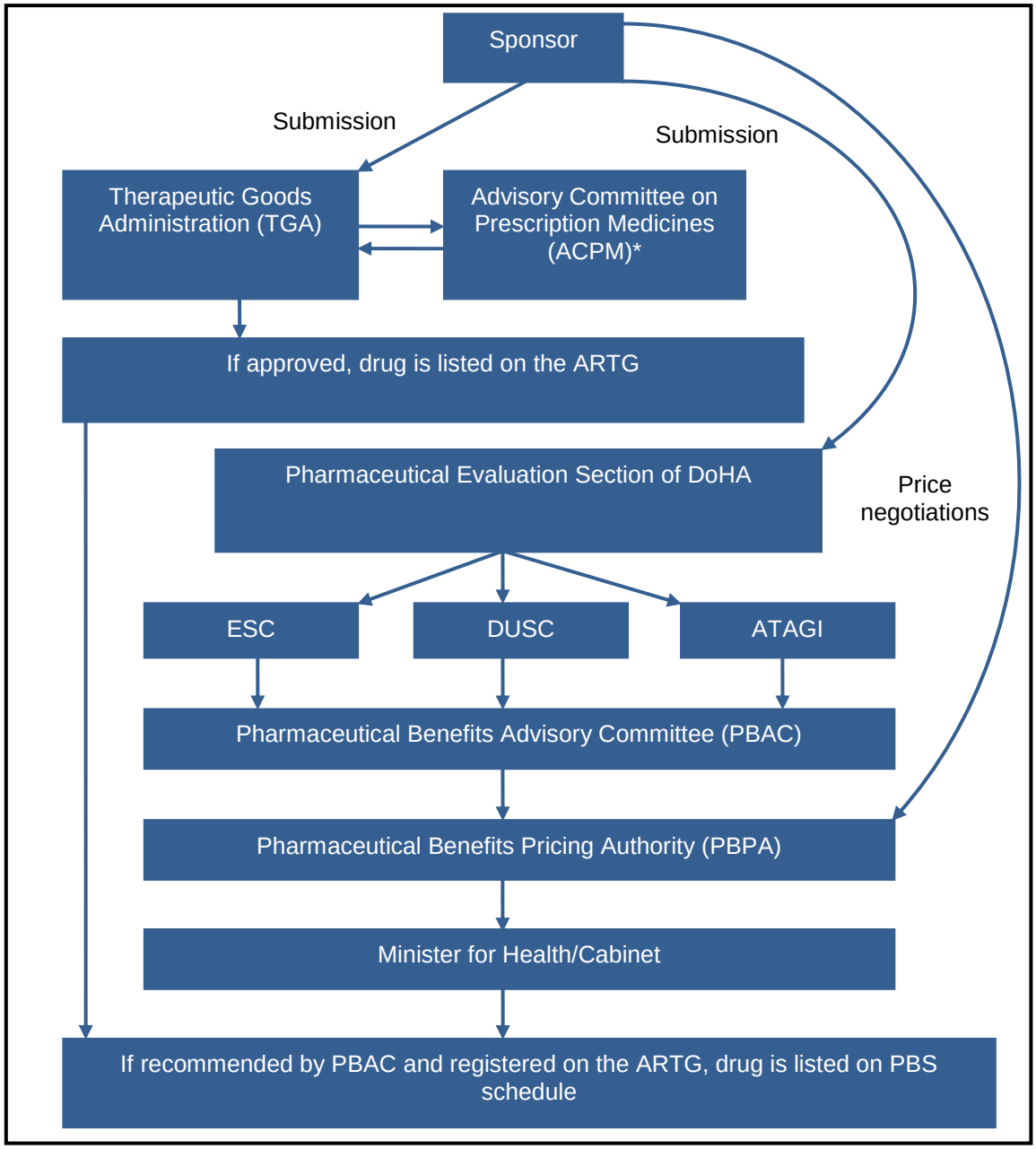
3.1. The Listing Process

A Formulary Committee was established in 1944 with the role of advising the Minister on the composition of the original formulary under the *Pharmaceutical Benefits Act 1944*. This committee later became known as the Pharmaceutical Benefits Advisory Committee (PBAC), and became an independent statutory body under Section 101 of the *National Health Act 1953*[4, 5]. Today PBAC considers which drugs should be listed on the PBS schedule and which vaccines should be listed on the National Immunisation Programme (NIP) schedule[15]. PBAC is required to consider[5, 16]:

> *"the [clinical] effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations."*

A diagram describing the listing process is provided in Figure 6.

Figure 6: Process of listing on PBS schedule



ARTG: Australian Register of Therapeutic Goods, DoHA: Australian Department of Health and Ageing, ESC: Economics sub-committee, DUSC: Drug Utilisation Sub-Committee, ATAGI: Australian Technical Advisory Group on Immunisation. *Formerly the Australian Drug Evaluation Committee

A sponsor submits a drug for consideration by PBAC after the Therapeutic Goods Administration (TGA) has licensed a good for marketing in Australia[8]. The sponsor is usually the manufacturer; but non-profit organisations or clinicians may also act as a sponsor. PBAC can also request a review of drugs already listed on the PBS[17].

[8] This has recently changed with the introduction of the parallel process (discussed below).

The committee includes clinicians, pharmacists, epidemiologists, health economists, and a health consumer advocate. Decisions are made by majority vote. PBAC also has several sub-committees which help synthesise information and identify key issues prior to PBAC meetings: the economic sub-committee which focuses on analysis of the clinical and economic data; the drug utilisation sub-committee (DUSC) which focuses on issues which may cause the budget impact to deviate away from that estimated; and the Australian Technical Advisory Group on Immunisation which provides vaccine-specific advice[18][9]. The multi-stage process of evaluation and the different points of view sought ensures that all potential aspects are considered, and thus the most important issues with reimbursing the drug identified.

Drugs considered for listing by PBAC are generally those under patent protection. However drug patents are time limited and when they expire other manufacturers are able to apply to the TGA for a license for a bio-equivalent drug (referred to as a "generic") and apply for listing on the PBS. Listing of a drug bio-equivalent drug (or new brand) to another drug already listed on the PBS is not required to be considered by PBAC or the PBPA, but a submission to the PBAC Secretary for consideration by DoHA is required[18].

Prior to 2010, the cost of PBAC submissions was borne by the Commonwealth Government. Cost recovery measures were introduced under *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009*[19]. These measures were introduced to cover the costs of the evaluation process conducted by PBAC and the sub-committees. From 1 January 2010 up to $119,500 (indexed annually using the consumer price index) is charged

[9] For some drugs, efficacy may be determined by the results of diagnostic test, such as a genetic DNA biomarker test, henceforth referred to as co-dependent technologies. In the past the drug and the test would be considered separately by PBAC for listing on the PBS, and the Medical Services Advisory Committee (MSAC) for listing on the MBS. However more recently a more integrated approach to considering co-dependent technologies has been introduced

for each major submission[10], while lower fees are charged for minor submissions[11]. A review of the cost-recovery measures was conducted in 2011; however at the time it was found that there was insufficient data to ascertain the impact on the PBS[20].

If PBAC decides to recommend a drug for listing on the PBS schedule, price negotiations are entered into with the manufacturer by the Pharmaceutical Benefits Pricing Authority (PBPA), who makes recommendations about the listing price. In contrast to the PBAC, which is an independent statutory committee, the PBPA is a regulatory authority. The PBPA consists of representatives from DoHA, industry, consumer representatives and the Department of Industry. According to their policy manual, factors considered by the PBPA when considering pricing include: clinical and cost-effectiveness; prices of alternative brands (especially if approved on the basis of a cost-minimisation analysis or if a combination drug), comparative prices of items containing drugs in the same Anatomical Therapeutic Chemical groups, and/or prices of items containing the drug in reasonably comparable overseas countries; cost information; prescription volumes, economies of scale, special storage requirements, product stability, special arrangements; and other factors the applicant may wish the PBPA to consider and/or any directions of the Minister[12][21]. The PBPA also applies cost-recovery measures under *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009*[19], in addition to the cost-recovery measures applied for PBAC submissions. The price category applied depends on the complexity of the pricing

[10] Request to list a new drug or for a currently listed drug, substantially change the restriction (including new indication or de-restriction), enable review of the comparative cost-effectiveness to inform the PBPA on its therapeutic relativity or price advantage, or list a new form (or strength) for which a price advantage is requested.

[11] For a currently listed drug, request to list a new form or strength of a currently listed drug for which a price advantage is not requested, change the maximum quantity per prescription or the number of repeats per prescription, or clarify the wording of a restriction.

[12] Level of activity being undertaken by the company in Australia, including new investment, production, research and development is not currently taken into consideration.

submission, with higher prices ($25,000) applied to drugs that involve more detailed negotiations such as those involving risk-share schemes.

Finally, following successful price negotiations with the PBPA, the Minister for Health, and subsequently cabinet, must approve all drugs prior to listing on the PBS schedule. On the other hand, if PBAC rejects a drug then it cannot be listed on the PBS schedule, although PBAC can advise the Health minister whether a drug meets the criteria for the Life Saving Drugs Program, which lies outside the PBS[13][22].

When a drug is listed on the PBS schedule, pharmacists agree to dispense PBS listed medicines at an agreed dispensed price, with the patient paying a set co-payment (see Section 5.1 for details) and the Commonwealth Government paying the difference. An example of a PBS listing is provided in Table 1. The agreed dispensed price includes allowances for the ex-manufacturer price, a wholesaler margin, a pharmacy mark-up and a dispensing fee. However the pharmacists may negotiate with wholesalers and manufacturers on the price paid, resulting in a potentially larger mark-up for the pharmacist[14].

Table 1: Example of PBS listing

Item Code	Name, manner of administration and form & strength	Brand name & manufacturer	Max quantity , No. of repeats*	Pack Size	Dispensed price for max quantity	Price to consumer **	Cost to Government ***	Example profit to pharmacy#
8481J	RISEDRONATE SODIUM, Tablet 5mg	Actonel, Sanofi-Aventis	28, 5	28	$46.55	$35.40	$11.15	$9.31

*28 tablets x 6 prescriptions (1 original prescriptions and 5 repeats) = 168 days of treatment.**General co-payment ***Dispensed price for maximum quantity minus price to consumer # Assuming ex-manufacturer price is 80% of dispensed price for maximum quantity. Source: [23]

[13] Following the rejection of a drug for listing on the PBS due to unacceptable cost-effectiveness, PBAC can advise the Health minister whether a drug meets the criteria for the Life Saving Drugs Program, which lies outside the PBS. These drugs are typically expensive, are used to treat rare diseases, and are considered by PBAC as clinically necessary and effective. The program currently covers treatments for Gaucher disease, Fabry disease, mucopolysaccharidosis type I, II and VI, infantile-onset Pompe disease and paroxysmal nocturnal haemoglobinuria. In 2009-10 it was estimated 163 patients were assisted by this program at a total cost of $76.152m (excluding program support), suggesting that the average cost per treatment was $467,190 per annum

The average time from Advisory Committee on Prescription Medicines (ACPM)[14] recommendation to PBS listing has increased from 13.6 months in 2000 to 34.2 months in 2009[24]. This may be due to a variety of reasons.

Firstly, the increase in the average time may be due to delays in the submission to PBAC by a sponsor. Pearce (2012) followed 63 products/indications recommended by ACPM in 2004. By August 2010 63% of products/indications were submitted to PBAC, and the average time from ACPM recommendation to submission to the first PBAC review was estimated to be 17 months (median = 9 months)[25].

The time from submission to consideration by PBAC cannot be a driver of the increase as it is fixed at 17 weeks. However the number of times a submission is rejected and subsequently re-submitted may be a driver of the increase in the average time. Pearce (2012) found that 55% products/indications were recommended at the first submission and products/indications were submitted to PBAC an average of 2.8 times[15][25].

Thirdly, the time between re-submissions may also be a driver. Of the products which were recommended by PBAC, the average time from first submission to recommendation was 29.4 months[16]. For these products, the evaluation time was 6.9 months[17]. Thus the total time taken by the sponsor to revise the submission was 22.5 months

Finally, the increase also may be due to delays and deferrals in cabinet approval, and thus PBS listing, following a PBAC recommendation, which has increased from 4.6 months in

[14] Formerly the Australian Drug Evaluation Committee (ADEC)

[15] Times submitted to PBAC = 2.8 times = 113 submissions/40 products/indications.

[16] Average time from first submission to recommendation = 29.4 months = (22 submitted once *(575 days+17 weeks*7)+13 submitted >1 time*(575 days+17 weeks*7+538 days))/35 approvals/365*12

[17] Number of submissions per approved product = 1.77 = (22 submitted once + 13 submitted >1 times + 27 negative decisions for those submitted >1 times)/35 approvals; total time being evaluated = 1.77*17 weeks*7/365*12 = 6.9 months

2005 to 5.3 months in 2008, but then declined again to 4.1 months in 2010 (although this latter data is yet to fully mature)[26].

Given the relative consistency in the time from PBAC recommendation to time to PBS listing, the delays from ACPM recommendation to PBS listing must be due to either and increasing time from ACPM recommendation to PBS submission, the number of re-submissions required, or delays in the time taken by the sponsor to revise a submission. Currently it is unknown which is the key driver.

Li (2011) analysed PBAC submissions between July 2005 and July 2009 where one of the outcomes measured was Quality Adjusted Life Years (QALYs) (n=162), and thus cost-utility analyses[27]. Li (2011) found that the time to listing increased with clinical or economic uncertainty, the presence of competitors, external pressure, the incremental cost-effectiveness ratio (ICER), and if the disease is life threatening.

In order to reduce the time from TGA approval to PBS listing, the requirement that registration on the Australian Register of Therapeutic Goods occur before submission to PBAC for consideration was recently removed, thus allowing submissions to the TGA and PBAC to be considered in parallel (referred to as "parallel processing")[28]. However this change to the process is likely to increase uncertainty, due to: the potential for a mismatch between the final TGA-approved indication and any PBS restriction, particularly if the TGA has safety concerns arising from their in-depth analysis of the data; (potentially) non-identification of key issues by PBAC, such as the risk of adverse events or actions required to mitigate risks (e.g. diagnostic tests); and the possibility of an unsuccessful or withdrawn TGA submission, meaning that PBAC wasted effort evaluating the submission.

3.2. PBAC Guidelines

Randomised clinical trials (RCTs) are considered the "gold standard" approach to measuring efficacy[29]; although RCTs often do not collect all the evidence required for an economic evaluation due to ethical, financial or practical reasons. Thus economic evaluations generally involve translating the RCT data to increase the external validity and synthesise evidence into a form suitable for decision makers. A variety of methods may be used to extrapolate RCT data, including econometric analysis, economic modelling or indirect comparisons. A variety of data sources may also be used, including observational data, quality of life surveys, administrative cost data and expert opinion. When the evidence available is not comprehensive, assumptions may also be required. Thus it is possible to use different approaches to translate the same RCT data and arrive at different conclusions regarding cost-effectiveness. Thus the process of translating the RCT data introduces uncertainty, and sometimes alters the economic evaluation results in favour of the drug.

In addition to an conducting an economic evaluation, PBAC also requires forecasts of the financial implications of listing a new drug on the PBS to ensure that resources are available to fund the new drug and that the impact on health budgets will not be onerous[18].

In January 1993 it became mandatory for sponsors making major submissions to follow the PBAC guidelines, effectively ensuring that an economic evaluation forms part of the evidence submitted for new drugs for which listing on the PBS is being sought[18]. The PBAC guidelines are summarised in Table 2. The guidelines aim to reduce the risk of the economic evaluation results overly favouring the drug by specifying the preferred methods of data collection, data synthesis, and reporting of results. The basis of the guidelines is standard practice in health economics. The guidelines are voluntary and deviations may be appropriate, however they should be clearly justified. The existence of the guidelines ensures

that inappropriate deviations from standard practice are easily identified and the key drivers of the results are understood.

Table 2: Summary of PBAC Guidelines

Element	Details	Section in Guidelines
Clinical Efficacy		
Defining the decision problem	The scope (treatment regimen, indication and any patient restrictions) is determined by the sponsor, but in general within the TGA license.	Section 1.3.1, p5.
Comparator	The treatment most likely to be displaced by the listing of the new drug. This is most likely to be another drug already listed on the PBS for the same, or similar indication, or another form of standard medical care when there is no listed alternative (e.g. a non-listed drug, a surgical procedure, or conservative treatment). More than one comparator may be appropriate. A placebo would only be accepted as a comparator when there is no alternative treatment available, or when the drug is additional to current treatment.	Section 1.3.3, p5 and Section A.4, p54-56.
Synthesis of evidence on outcomes	Based on a systematic review. Preference for direct RCTs. In the absence of an appropriate RCT, in order of priority: - an indirect comparison between RCTs with a common comparator may be conducted when the comparator in the RCT does not match that used in Australia; or - non-randomised studies may be used, including comparing single arms of RCTs. Mixed treatment comparisons should only be presented as a supplementary analysis. Comparison of both efficacy and safety (i.e. adverse events) for both treatment and comparator should be presented. Extended analysis of safety through post-marketing data also valuable.	Section B, p61 [30]
Analysis of quality of evidence	In order to assess the quality of the evidence, information should be provided on: - Selection criteria of participants. - Blinding and methods of randomisation. - Number of participants who did not receive treatment, discontinued treatment, or lost to follow-up. - Patient characteristics. - Treatment protocol, including dose, timing, duration, and concomitant therapies. - If non-inferior: definition of clinical relevant difference and whether trials were adequately powered - Definition of outcomes and when measured	Section B, p70-78

Economic Evaluations		
Type of economic evaluation	If the drug is considered non-inferior in terms of efficacy to the comparator: cost-minimisation analysis If the drug is considered superior in terms of efficacy to the comparator: - Cost-utility analysis (preferred) - Cost-effectiveness analysis - Cost-benefit analysis (as a supplementary analysis) - Cost-consequence analysis (if disaggregation of outcomes useful)	Section D.1, p118-119.
Patient population	Similar to the patients and circumstances of use in Australia. If the RCT participants and circumstances of use are not directly comparable to the Australian situation, adjustment of the clinical efficacy for application in the economic evaluation may be required.	Section 4.2, p24.
Length of follow-up	Cover the period of relevant incremental costs and benefits. If the length of follow-up in the RCT does not cover this period of time, extrapolation of effectiveness, using appropriate methods, may be required. Methods include econometric analysis (such as fitting Weibull curves to Kaplan Meier plots) or economic modelling (such as Markov or microsimulation models). A systematic literature review for studies measuring long-term outcomes using observational data may also be required.	Section 4.1, p23 and 4.2, p24.
Measure of health effects	When cost-minimisation analysis is presented: any. When a drug is considered superior: patient-relevant final outcomes, especially QALYs. Quality of life preferably measured by surveying patients within a trial using a Multi-Attribute Utility Instrument (MAUI). No preference for specific MAUI. If MAUI not available, would consider other approaches such as standard gamble or time trade-off surveys administered within trial or post-trial using scenarios. MAUI states preferably valued (thus transformed into utility weights) using a representative sample of the general population, preferably Australian. If not available, would consider valuations from patients, or carers if required. If utility weights not directly collected in the RCT, transformation of efficacy into utility weights may be required. Methods include mapping other quality of life measures to utility, or conducting a systematic literature review to identify surveys that measure utility in relevant health states.	Section C p91, and Section C.1, p97, Section 4.2, p24, Appendix 6
Perspective on costs	Health system costs. Costs should be reported by PBS, MBS and other health system costs. PBAC may also consider costs and cost offsets of non-health care resources. Data sources are preferably published, administrative or observational data. But surveys are valuable if relevant data not available.	Section 1.3, p4.
Perspective on outcomes	PBAC focuses on health outcomes however may, although rarely in practice, also consider non-health outcomes such as convenience and productivity gains.	Section 1.3, p4. Section 4.1, p23.
Discount rate	An annual rate of 5% on both costs and health outcomes.	Section D.4, p127

Element	Details	Section in Guidelines
Uncertainty	Uncertainty should be explored, using one-way sensitivity analysis. Multi-way probabilistic sensitivity analysis accepted but not required.	Section D.6, p141-2.
Guidelines for Financial Implications		
Type of analysis	Market approach if non-inferior/cost-minimisation analysis; otherwise, epidemiology approach.	Section E, p143.
Data sources	Preferably published, administrative or observational data. But surveys are valuable if relevant data not available. For uptake sources include: PBS/RPBS data for therapeutically equivalent drugs that are already listed and overseas data on the use, in markets similar to Australia, of a proposed drug that has no PBS-listed comparator.	Section E.1, p145-7.
Outcomes	Cost to PBS (treatment alone and including effects on other PBS drugs), MBS, total health care system estimated separately.	Section E
Time period of analysis	Financial implications each year, up to five years after listing	Section E.2, p151 and E.3, p153.
Discounting	None	Section E, p144.
Uncertainty	Uncertainty should be explored, using one-way sensitivity analysis. Possibility of 'leakage' should be considered.	Section E.6, p158-161

Source: [18]

3.3. Drivers of PBAC Decisions

As noted previously, PBAC is required to consider[5, 16]:

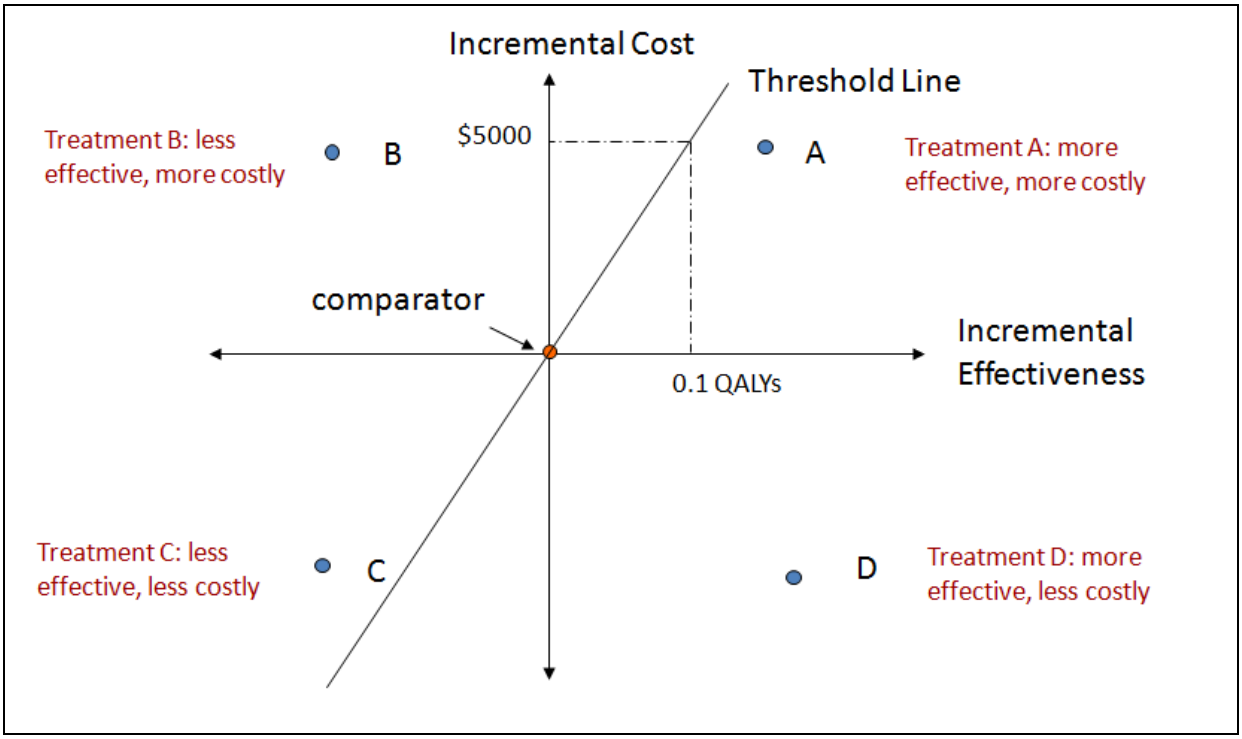
> *"the [clinical] effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations."*

If the drug is considered equally effective (i.e. non-inferior) to the comparator, then PBAC is likely to recommend the drug if it is equally or less expensive than the comparator(s). If the drug is considered to be superior in terms of efficacy and is cheaper than the comparator(s), then PBAC is likely to recommend the drug. If the drugs that are considered superior in terms of efficacy but also more expensive than the comparator, the incremental efficacy and costs are summarised using an incremental cost-effectiveness ratio (ICER). The ICER which is then used to assess whether the drug represents value for money[31].

Typically, the ICER is calculated as follows, where A and B refers to the drug and the comparator, respectively:

$$ICER = \frac{Cost_A - Cost_B}{Effectiveness_A - Effectiveness_B}$$

Figure 7: Incremental Cost-Effectiveness Plane



PBAC does not have an explicit cost-effectiveness threshold where the drug is (not) recommended if the ICER lies below (above) a specified level. Harris (2008) conducted an econometric analysis of PBAC decisions on major submissions between February 1994 and December 2004 where effectiveness was measured using either life years gained (LYG) (n=138) or QALY gained (n=116) and the ICER was greater than zero[32]. The study used an enhanced confidential administrative database held by DoHA. The study explored whether

a range of clinical[18], economic[19] and other factors[20], including the base case ICER, influenced whether PBAC recommended a drug be listed on the PBS. The study found that an increase in the ICER from $46,000/QALY (mean ICER) to $56,000/QALY reduced the probability of recommendation by 6% (95%CI: 4% to 10%) (see Table 3) the estimated marginal effects for the statistically significant variables). Confidence in the clinical significance of the difference in effect had a stronger impact on PBAC decisions, with an increase in the probability of a positive recommendation by 23% (95%CI: 14% to 44%) when the condition was not life-threatening and by 36% (95%CI: 3% to 68%) when the condition was life-threatening (see Figure 8). This is not surprising as PBAC decisions are often made first on the basis of clinical evidence/need and then on value for money – if there is significant clinical uncertainty then the ICER is also likely to be highly uncertain.

Under the *National Health Act 1953*, PBAC must also consider the total cost to the PBS to ensure that the impact on health budget will not be onerous. Confirming that the total cost is considered by PBAC, Harris (2008) found a 1% (95%CI: -1% to 0%) decrease in the probability of a positive recommendation for every $1 million increase in the budget impact.

Overall it is clear that PBAC does not base its decisions on a single ICER and a drug may still be rejected despite having a low ICER, largely due to clinical or economic uncertainty.

[18] Whether the drug had a clinically significant impact, the precision of clinical evidence (whether P>0.05); the level of evidence (head-to-head RCT, indirect comparison, non-randomized); the quality of studies (low, moderate, high); whether the comparator and population is relevant to Australian situation, whether there is no alternative acceptable therapy, whether a drug treats a life threatening disease (life expectancy <5 years).

[19] The economic model validity (reliable, flaws, critically flawed), the methodology used to translate the health outcome into QALYs (reliable, flaws, critically flawed), the methodology used to estimate costs (reliable, flaws, critically flawed), the base case ICER, the uncertainty surrounding the ICER (upper limit in sensitivity analysis), and the total cost to the Commonwealth Government ($m).

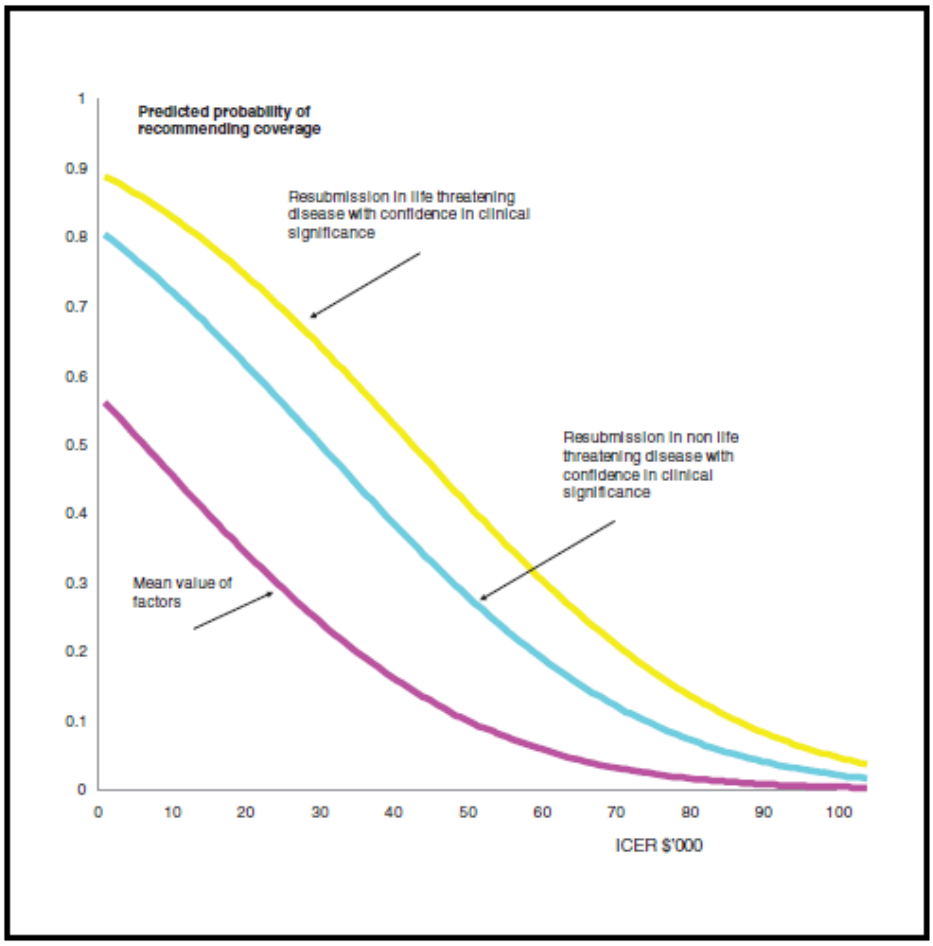
[20] Whether previously considered, and a dummy variable for 2001 when membership of PBAC significantly changed.

Table 3: Drivers of PBAC recommendations

Variable	Marginal effect on probability of positive recommendation (95%CI)	P-value
Clinical		
Impact is clinically significant (=1)	28% (9%, 47%)	<0.00
Relevant evidence for Australian situation (=1)	12% (-4%, 28%)	0.12
Life threatening disease (=1)	44% (18%, 70%)	<0.00
Life threatening * clinical significance	-23% (-38%, -8%)	<0.00
Economic		
ICER (↑ by $10,000)	-6% (-10%, -4%)	<0.00
Budget Impact (↑ by $1m)	-1% (-1%, -0%)	0.02
Highest ICER (↑ by $10,000)	0.02% (0%, 0%)	0.06
Other		
Previously considered (=1)	15% (2%, 28%)	0.02

Source: [32]

Figure 8: Predicted probability of PBAC recommendation



Source: [32]

When the estimated ICER is considered high, PBAC may also consider the "rule of rescue". All drugs, including those deemed to be orphan drugs (i.e. where the prevalence of the

condition affects ≤2000 individuals in Australia), are considered by PBAC[18]. Due to the costs of research and development spread over a small patient population, these drugs often cost more than other drugs and thus often fail to meet cost-effectiveness criteria[33]. The "rule of rescue" is based on stringent criteria, which were adopted in 2003[32]. All four factors must concurrently apply for the rule of rescue to be invoked[18]:

- No alternative, non-pharmacological or pharmacological, exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction.
- The medical condition defined by the requested restriction is severe, progressive, and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the close a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.
- The medical condition defined by the requested restriction applies to only a very small number of patients.
- The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition.

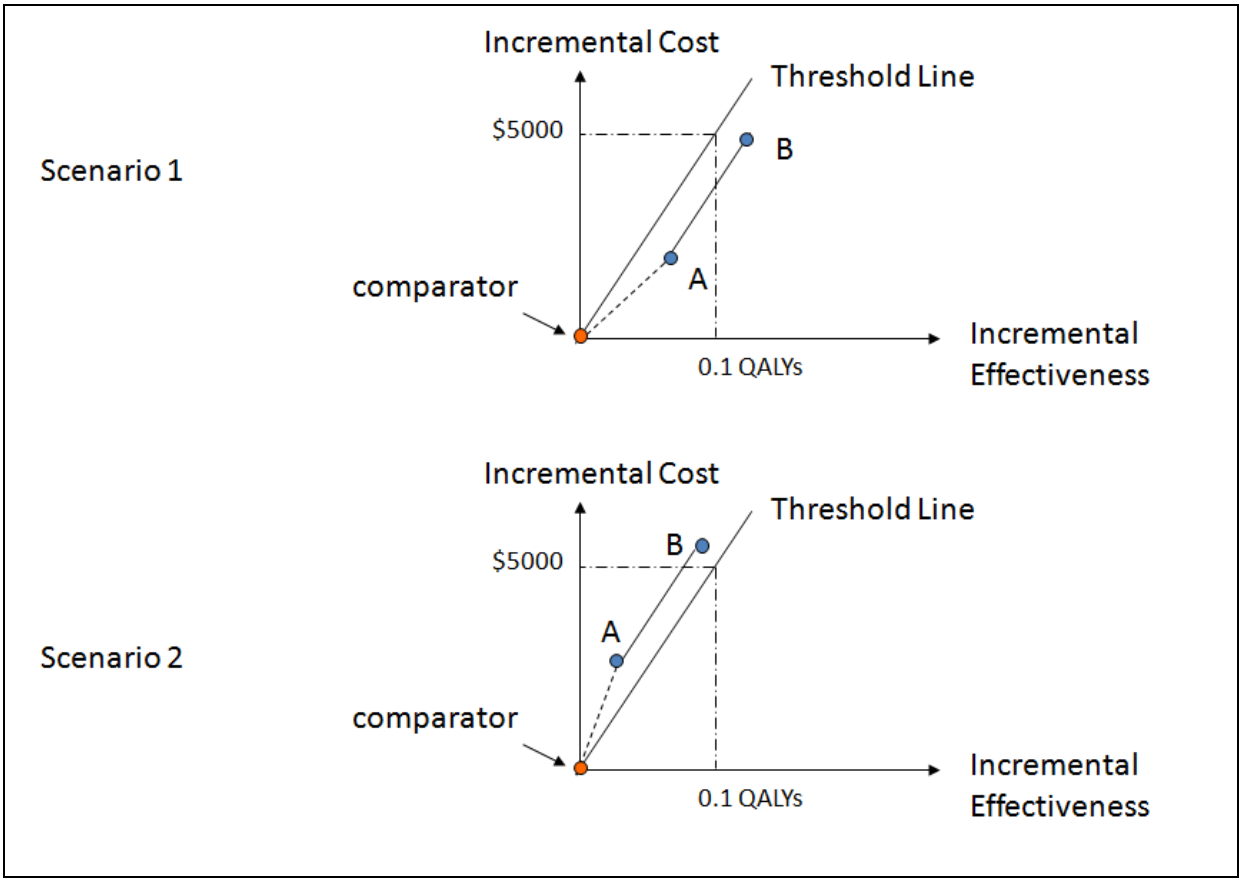
The rule of rescue supplements, rather than substitutes for, the evidence-based consideration of comparative cost-effectiveness. A decision on whether the rule of rescue is relevant is only necessary if PBAC would be inclined to reject a submission because of its consideration of comparative cost-effectiveness (and other relevant factors). PBAC also does not have an explicit cost-effectiveness threshold which determines when the "rule of rescue" is considered. The rule of rescue has only been applied four times to date: imatinib for the treatment of patients with chronic myeloid leukaemia in the accelerated and blast phases[34];

riluzole for the treatment of patients with amyotrophic lateral sclerosis aged less than 75[35] and over 75[36], and dasatinib for the treatment of acute lymphoblastic leukaemia[37].

3.4. Reviewing Currently Listed Drugs

Many drugs currently listed on the PBS were listed before 1993, and therefore have not been subject to an economic evaluation. It is possible that some of these drugs were not cost-effective compared to current clinical practice. Normally sequential consideration of drugs will mean that if a drug is considered cost-effective, then using this drug as a comparator for the evaluation of a new drug will insure that the new drug is also cost-effective compared to the original comparator (see Scenario 1 in Figure 9). However if a drug is not cost-effective, then using this drug as a comparator for the evaluation of a new drug means that there is a risk that the new drug is also not cost-effective compared to the original comparator, especially if the new drugs have a relatively higher ICER (Scenario 2 in Figure 9). This situation also applies to drugs that are considered equal (i.e. non-inferior) in effectiveness and safety against than the currently available alternatives, and thus a cost-minimisation analysis is the most appropriate form of analysis.

Figure 9: Sequential Consideration of Drugs



Even if the drug was considered cost-effective when originally considered by PBAC, this may change over time. Since listing new RCT and observational data may have become available – this new data may either confirm that the drug is cost-effective or challenge the initial PBAC decision. Similarly the cost of drugs may have decreased since listing due to patent expiry or clinical practice may have changed.

There have been calls for PBAC to review past decisions to ensure listed drugs are and continue to be value for money[9], however these reviews are rare. One of the few such reviews has been that of biological disease-modifying anti-rheumatic drugs (bDMARDs), which highlights some interesting issues with conducting reviews of past decisions[38]. Etanercept was the first bDMARD to be listed, which was subsequently used as a comparator directly or indirectly for five other bDMARDs. In clinical practice, if a patient fails therapy a

new bDMARD may be considered. Consequently the review considered several sequences of bDMARDs. In the base case all treatment sequences exceeded $100,000 per QALY, above the range normally considered cost-effective by PBAC. The ICER was considered unacceptably high even when a single bDMARD was considered. This result may have been due to the evidence presented in the original submission for the listing of etanercept, however this information is not publicly available. Delisting all bDMARDS would have caused ethical issues for PBAC, and political issues for the Commonwealth Government. Consequently a significant price reduction was negotiated and anakinra was delisted from the PBS as it was found to be inferior to the other bDMARDs. Similar ethical and political issues may be faced in future reviews of past decisions.

If reviews are to be conducted more frequently in the future, consideration must be made regarding the timing of the reviews and patent expiry, such that a particular drug is not disadvantaged as the review occurred a few months short of patent expiry.

4. Minimising Uncertainty and Reducing the Risk of an Incorrect Decision

PBAC can use a number of mechanisms to minimise uncertainty in the clinical effectiveness and cost-effectiveness, and reduce the risk of making an incorrect decision. Some of these mechanisms are used frequently, such as restrictions on the use of a drug, while others have only just become available as an option, such as Managed Entry Schemes (MES). The suitability of each mechanism is determined by the type and extent of uncertainty faced.

4.1. Restrictions

When the estimated ICER is considered high, PBAC may restrict the use of a drug to certain patients, indications, conditions or settings to minimise the risk that it is used in contexts that are less cost-effective. PBAC may also choose to restrict the use of a drug to avoid leakage to

non-TGA-approved indications or reduce the risk of costly adverse events and/or misuse, overuse or abuse, thus ensuring the Quality Use of Medicine. PBAC may recommend that a drug is listed on the PBS as[18]:

- Unrestricted benefits: clinicians may prescribe these drugs for any therapeutic uses, although uses in line with the TGA approved indication should be considered.
- Restricted benefits: clinicians may prescribe these drugs for specific therapeutic uses as determined by the PBAC.
- Authority-required benefits: clinicians are required to receive prior approval from Medicare Australia or the Department of Veterans Affairs prior to prescribing the drug.
- Streamlined authority-required: As above but prescribers must enter a four digit streamlined authority code onto the PBS prescription form rather than seek prior approval. This was introduced under the *National Health Amendment (Pharmaceutical Benefits Scheme) Act*.

A report by the Australian National Audit Office found that in 2005 59% of PBS items were restricted somehow and 27% of PBS items were subject to authority required restrictions[39]. The report found that often restrictions were considered by prescribers to be guidelines only and prescribing outside restrictions was common. Authority required restrictions were considered much more effective than general restrictions, but are more expensive to administer.

Restrictions also enable the Commonwealth Government to pay different prices for treatment of different conditions using the same drug to achieve a certain ICER. This is an optimal solution to charging a single price if the drug is not cost-effective in one or more conditions

but a lower price across all conditions is not acceptable to the sponsor. Typically such a scheme may require a potentially expensive registry, however in Australia they can be cheaply implemented using authorisation codes which differ by condition. Similarly the Commonwealth Government may wish to pay different prices for the same drug depending on the type of patient (e.g. age or sex) for the same reason. This can be implemented using aggregated PBS data on patient characteristics.

Listed drugs may also be classified as Section 100 (Highly Specialised Drugs Program) items which are drugs provided under special arrangements (e.g. public[21] and private hospitals or other approved specialist facilities) where normal supply via community medical practitioners and community pharmacy is considered less than optimum. To prescribe these drugs the clinician must be affiliated with these specialised hospital units. These drugs are typically more expensive than other PBS listed drugs and a different pricing structure, in terms of dispensing fees and mark-ups, applies to these drugs, namely to ensure the most cost-effective combination of vials is used and thus reduces uncertainty in the ICER (see Section 5.5).

4.2. Lower Price

PBAC could request a lower price from the manufacturer such that the ICER is insensitive to uncertainty in a specify parameter. The success of such an approach depends on the extent of uncertainty, and may not be effective when there is limited information or the extent of uncertainty is high. Manufacturers may be reluctant to accept a lower price if evidence could be collected which addresses the source of uncertainty and thus would achieve a higher price in the longer term.

[21] The costs of drugs dispensed to patients in public hospitals that are not listed as Section 100 items are incurred by the hospital and thus are the responsibility of State and Territory Governments.

4.3. Risk Sharing Arrangements

If the sponsor agrees, a risk sharing arrangement may be implemented to limit the uncertainty.

Schemes that focus on limiting uncertainty regarding usage (uptake, duration of treatment, and leakage) are price-volume agreements and patient access schemes[40].

Price-volume agreements involve reductions in the price per prescription paid by the Commonwealth Government when total prescriptions reach a certain level. This aim of this type of scheme is to limit leakage and penalise manufacturers for marketing outside of approved indications. More than 50 such agreements have been implemented to date[40].

Patient access schemes involve providing the drug free of charge or at a discount[40]. For example, manufacturer may reimburse the Commonwealth Government if patients require more than a set number of doses (i.e. a dose cap). Such a scheme is in place regarding ranibizumab for the treatment of age-related macular degeneration in the UK[40]. Special pricing arrangements are also in place in Australia, however details are not available[23]. This type of scheme may be considered more ethical, and thus preferable, to a dose cap where PBS subsidy of a treatment is withdrawn after a set number of doses. Such a scheme is in place regarding verteporfin for the treatment of age-related macular degeneration[23]. The former scheme can be implemented using patient-level PBS data, while the latter could be implemented through restrictions.

In comparison, pay for performance schemes aim to limit uncertainty in the clinical effectiveness of a drug. They involve reimbursing the Commonwealth Government or reducing the price when a desired level of efficacy or safety is not reached in clinical practice, thus ensuring that an agreed ICER is achieved[40]. For example, a manufacturer may reimburse the Commonwealth Government if a patient does not respond to treatment or

if an average efficacy level across a population is not achieved. These schemes are much less common, largely due to the complexity in their administration and both schemes require a potentially expensive registry that monitors clinical outcomes.

In Australia a patient registry was established to confirm the treatment effect of bosentan on overall survival in patients with idiopathic pulmonary arterial hypertension[41-43]. Only two short term RCTs (12-16 weeks) with intermediate outcomes were available for consideration by PBAC in 2004[43], which were extrapolated such that bosentan was predicted to reduce mortality from 26.6% to 5.2% per annum, thus increasing life expectancy from 2.8 to 6.7 years[42]. PBAC approved bosentan on the basis of a high ($62,267/LYG) but acceptable ICER, on the condition that mortality estimated on the basis of the registry was equal or less than 5.2%. 306 patients with idiopathic pulmonary arterial hypertension recruited between 2004 and 2007 (69% participation rate)[43]. After controlling for age and disease severity, it was estimated that the true mortality rate was 8.8%, thus the true ICER was $69,811/LYG and a 13.5% price reduction was needed[42]. Consequently between 2004 and 2007 PBAC paid around $400,000 for bosentan that could have been spent elsewhere in the health system[44]. It was also found that continuing patients (those treated with bosentan prior to PBS listing) had lower mortality rates compared to new patients[43], as they were more likely to be responders. However the data from the registry was never used because in 2008 sitaxentan was listed on the PBS for the same indication at a 15% price discount compared to bosentan, to which bosentan was price matched on the basis of similar effectiveness.

4.4. Delay Reimbursement Decision

PBAC may choose to delay making a recommendation (or reject and await re-submission) until more relevant RCT or observational data is collected that addresses the source of uncertainty; although meanwhile some patients would be unable to afford the potentially

efficacious drug and thus impacting on the achievement of equitable access to necessary drugs. This option is most likely to be considered when uncertainty in the clinical effectiveness is high.

4.5. Interim Funding

Interim funding could be recommended while the relevant evidence is collected and then the treatment is re-reviewed in light of the results at a later date. Under an interim funding approach patients would be able to afford the potentially efficacious treatment in the interim.

This was not possible until Managed Entry Schemes (MES) were introduced under a Memorandum of Understanding between the Commonwealth Government and Medicines Australia, which was signed on May 6, 2010[28]. Under a MES PBAC may recommend listing on the PBS at a price justified by the existing evidence pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price[28]. The two conditions are:

- PBAC would not otherwise recommend the listing of the drug at the proposed price because the extent or value of the clinical effect is uncertain; and
- There is a randomised clinical trial (or comparative "fit-for-purpose" evidence), due to report within a reasonable timeframe, which the PBAC is satisfied will resolve the identified area of uncertainty.

Examples of submissions that could be considered for a MES include: where the TGA has approved the drug on the basis of positive interim data, thus requiring extrapolation in the economic evaluation, but long-term follow-up of participants is planned; or where the submission is based on an indirect comparison but where a relevant head-to-head RCT is underway or is due to report results in the near future. The Memorandum of Understanding

also covers observational data to enable extrapolation to real-world practice, which is similar to Pay for Performance schemes. It is proposed that sponsors of drugs approved under a MES be required to re-submit when the new data become available. For each re-submission, cost-recovery measures would apply as per normal[45]. Despite being available as an option since 1 January 2011, PBAC has yet to recommend a MES. Many of the issues likely to be faced would be similar to that of Pay for Performance schemes.

In addition to managing uncertainty arising from limited clinical data, MESs may also help reduce processing times. That said, there is a risk that the treatment is subsequently confirmed as not cost-effective, and thus if the interim funding was allocated to other treatments overall population health would increase. Furthermore, withdrawing funding is often logistically, politically and ethically difficult[22]. Thus decision makers would wish to minimise the chance that the treatment is found to be not cost-effective and thus funding is withdrawn.

5. Managing Costs and Demand

A variety of measures have been implemented to manage the costs and demand for a drug following listing on the PBS, particularly focusing on limiting leakage and encouraging the use of cheaper generics. The direct measures include restrictions and listing a drug as a Section 100 PBS item (as discussed in Section 4.1 and discussed further in Section 5.5), and allowing generic substitution. Other measures indirectly influence demand through the price signals faced by either patients or pharmacists, including co-payments, price premiums, reference pricing, and price disclosure.

[22] Other issues also exist with providing interim funding. Firstly RCTs may also not be possible after a drug is reimbursed and its use becomes widespread because: the incentive for companies to conduct further research is limited, especially if there is a risk of an unfavourable result; the number of patients unexposed to the treatment falls, thus limiting the comparator group; and conducting a RCT may be considered unethical, especially if the treatment is considered best-practice. Secondly, additional resources may be required to administer the drug, such as training or equipment and facilities, which are irrecoverable if interim funding is withdrawn, although this may be more likely with surgical procedures and devices compared to drugs.

As previously mentioned, the PBS is one of three pillars of the Australian health system, the other two being free treatment in public hospitals and Medicare. The different mechanisms used to fund suppliers across the health system, with differing parties contributing towards costs, can result in unintentional, and potentially detrimental, effects on the demand for certain drugs: namely the under-use of cost-effective but expensive drugs. The interaction between the PBS and other sectors of the health care system has been paid little attention in the literature.

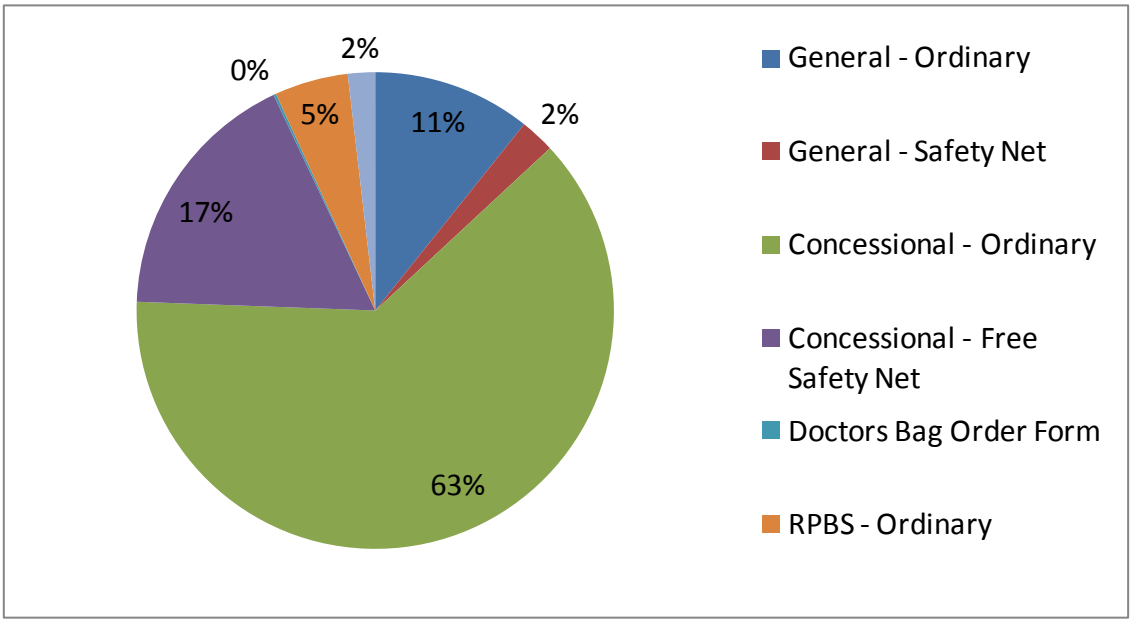
5.1. Co-payments

Co-payments were introduced on 1 March 1960 to control expenditure on the PBS and to act as a deterrent to over-use[4]. Co-payment levels have consistently risen since their introduction (see Table 5 in the Appendix). An increase in the financial burden on people on low incomes may impact on the key aim of the PBS to provide affordable, timely and equitable access to necessary medicines. Consequently the financial burden has been mitigated through: lower co-payments for concession card holders and pensioners (introduced in 1983 and 1990, respectively); a pharmaceutical allowance for pensioners equivalent to 52 weeks x co-payment (introduced in 1990); and the pharmaceutical safety net where patients face lower co-payments when their total co-payment expenditure in a calendar year reaches a pre-defined level (introduced in 1986).

In 2012 concession card holders paid $5.80 per script, falling to $0 when the pharmaceutical safety net level of $348 was reached, while the general population paid $35.40 per script, falling to $5.80 when the pharmaceutical safety net level of $1,363.30 was reached (see Table 5). In 2010 87% of all PBS prescriptions were filled by concession card holders or people eligible for the RPBS (see Figure 10). From 1995 to 2011 concessional co-payments as a proportion of the disability support pension has remained around the same level, with some

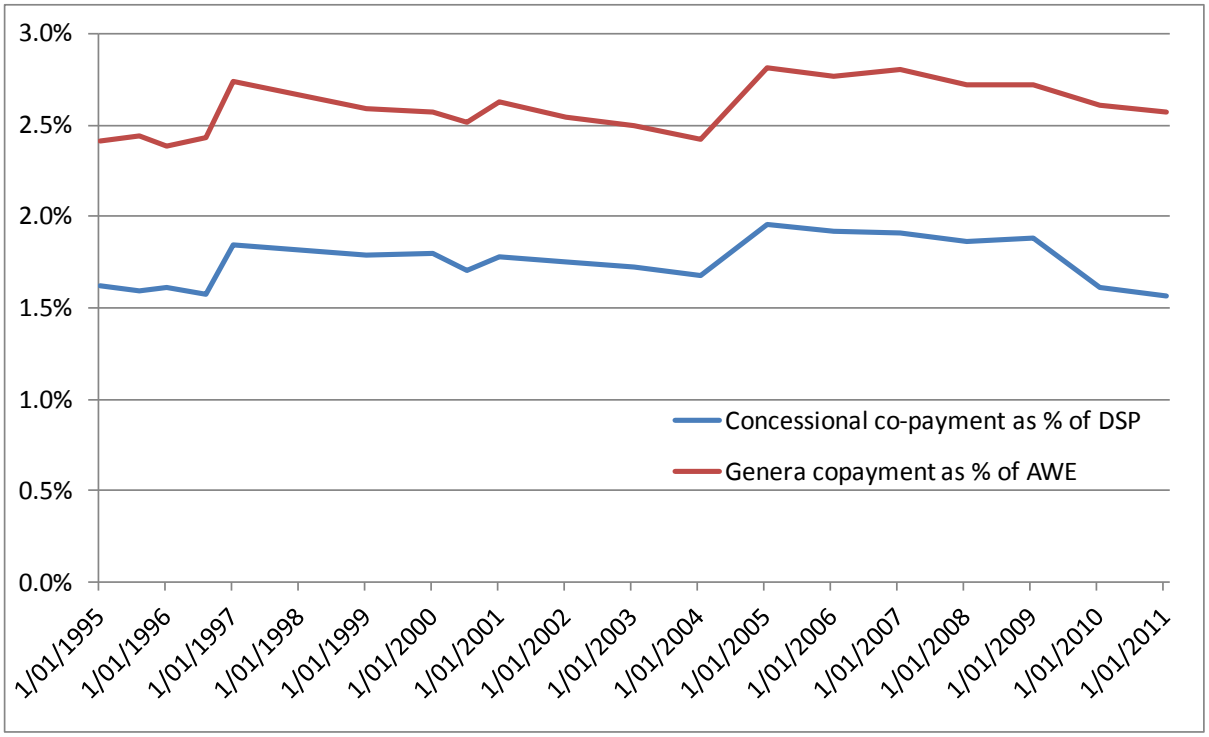
variation, while general co-payments as a proportion of average weekly earnings has gradually increased over time (see Figure 11).

Figure 10: PBS services, 2010



Source: [46]

Figure 11: Co-payments as a proportion of disability support pension (DSP) and average weekly earnings (AWE)



Source: [47-49]

Evidence suggests that co-payments have assisted in managing demand; although they may have had unintended consequences, particularly for concession card holders. Hynd (2008) found that the 21% increase in co-payments in January 2005[23] resulted in a decrease in the number of prescriptions for 12 of 17 categories of drugs, and that the average decrease in the growth in prescriptions ranged from 3.2% to 10.9% for concession card holders[50]. In particular, diseases where over-the-counter treatments were available (e.g. antacids instead of proton-pump inhibitors) and asymptomatic diseases (e.g. osteoporosis) were most affected. Hynd (2008) also found that the decrease in the growth in prescriptions was 1.8% to 9.4% higher for concession card holders compared to the general population. The reduction in prescriptions, especially for diseases such as osteoporosis, may result in increased total health care expenditure in the long run. For example, previous studies have found that emergency department attendances and hospitalisations increased following a decrease in drug utilisation due to co-payment increases[51, 52].

Thus depending on the condition being treated, co-payments may reduce the likelihood of a patient filling a prescription. However once a patient has decided to fill a prescription, co-payments shield patients from any price differentials above the co-payment across brands as patients pay the same amount regardless of the PBS listed price. Consequently, for drugs costing above the co-payment, manufacturers are unable to compete through offering lower prices to patients compared to other brands of the same drug. Drugs costing below the co-payment are not covered by the PBS.

[23] The paper suggests a 24% rise occurred, however the reported base co-payments were incorrectly reported. The paper suggests the co-payments were $3.70 and $23.10 for concession card holders and the general population, respectively. However these were the rates in 2003 – in 2004 the co-payments were increased to $3.80 and $23.70 before being increased by 21% to $4.60 and $28.60.

5.2. Brand Premiums

Brand premiums were introduced in 1990 at the request of the pharmaceutical industry to allow them to set their own prices in particular circumstances, particularly for those drugs no longer under patent protection[53]. PBS prices are set at the lowest priced bio-equivalent drug and if the manufacturer wishes to charge more the patient pays the difference in terms of a brand premium[24]. Brand premiums are paid by the patient on top of the appropriate co-payment and do not count towards the safety net. Brand premiums also encourage price awareness by patients and may result in their choosing the lowest priced bio-equivalent drug available, often the generic.

In general, the impact of brand premiums on brand choice by patients is likely to be larger for concession card holders than the general population. For example, in May 2011 the brand premium for the brands Zocor and Lipex for the drug simvastatin 40mg was $3.33, while patients filling prescriptions using generics incurred no brand premium. The brand premium represented an increase in the co-payment of 59.5% and 9.7% for concession card holders and the general population, respectively. Assuming that a 21% increase in the co-payment results in a 5% reduction in the growth in prescriptions for statins for concession card holders and a 2% reduction for the general population[50], it is estimated that the brand premium resulted in a 14.6% reduction in the growth of prescriptions for these two brands relative to generics for concession card holders and 0.9% reduction for the general population. This is however an estimation; as previously noted, the elasticity of drug utilisation to co-payments is affected by the disease being treated[50].

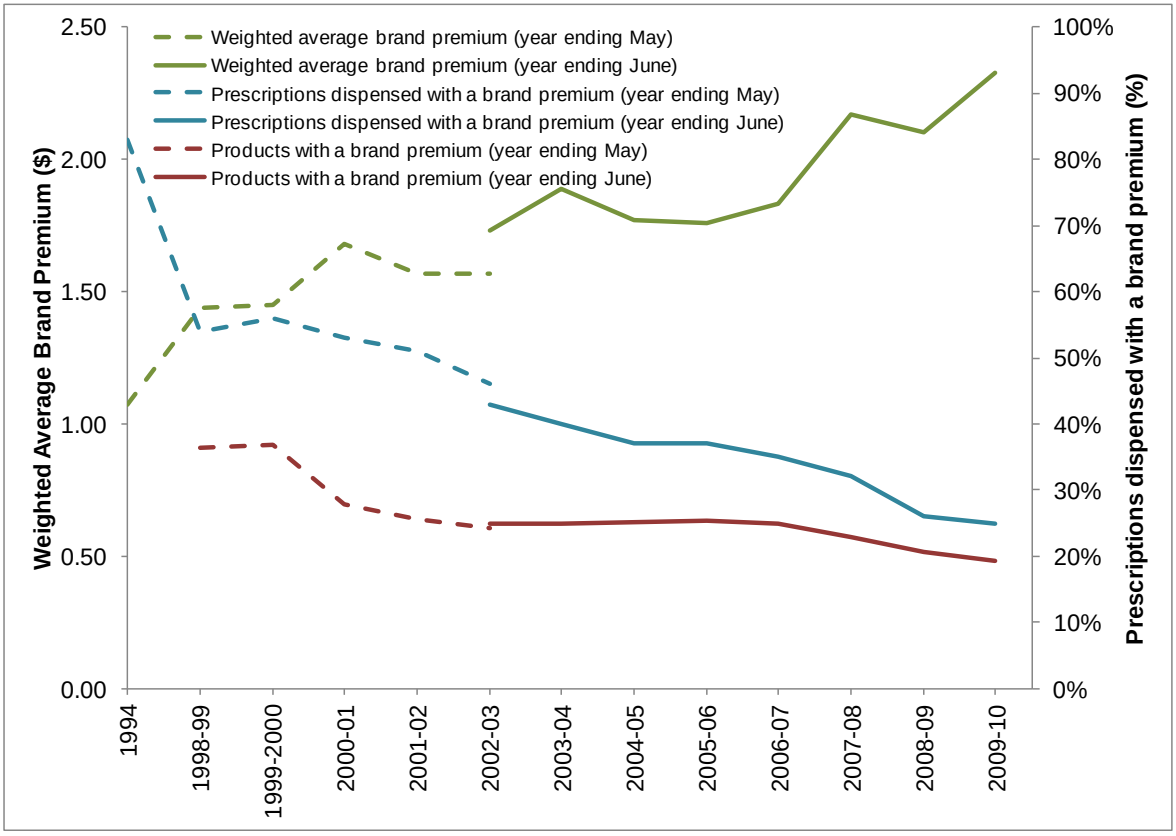
Data from the PBPA annual report shows that the prevalence of products with a brand premium has decreased over time from 36% of all drugs where generics are available in

[24] Special patient contributions are also applied to some drugs where the PBPA and manufacturer cannot agree on a price, thus ensuring continuing access by patients. In 2010 there were four drugs with a special patient contribution[53].

1998-99 to 19% in 2009-10, however the proportion of prescriptions dispensed with a brand premium has decreased more sharply from 54% in 1998-99 to 25% in 2009-10 (see Figure 12). This suggests that the substitution of the original branded drugs for generics (generic substitution) is occurring more frequently.

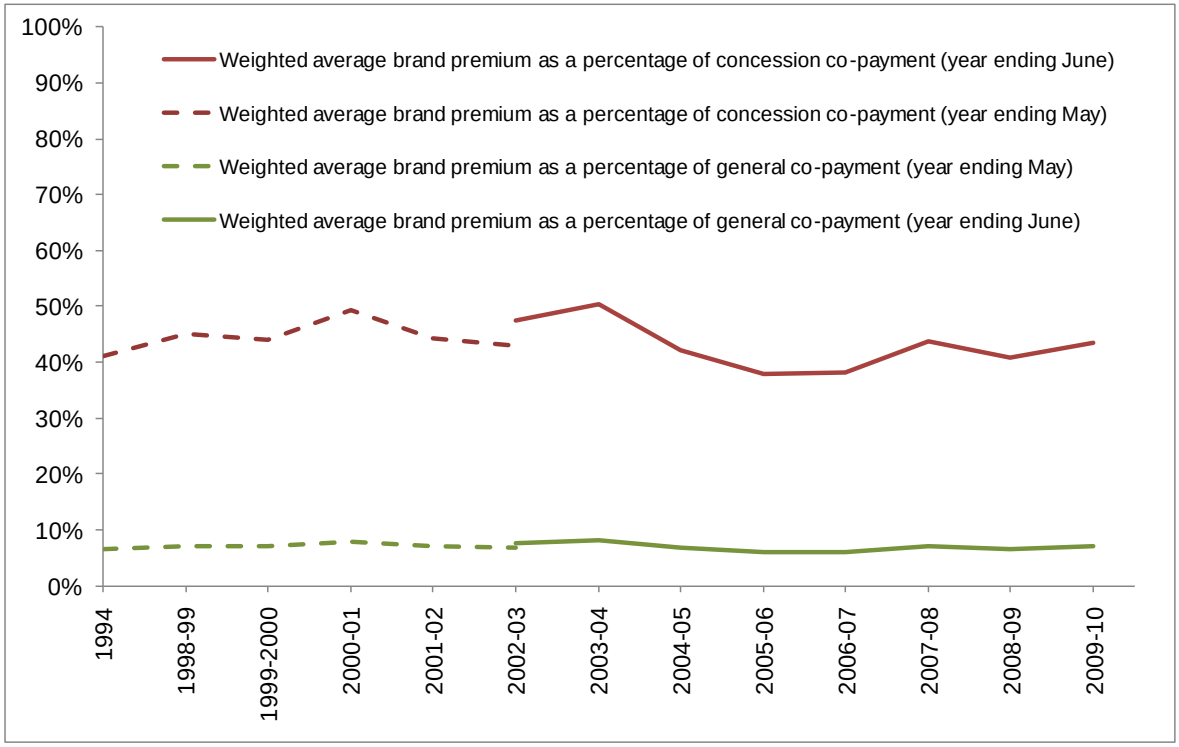
One reason for increasing generic substitution may be increasing average brand premiums (see Figure 12), however average brand premiums as a proportion of the co-payment have remained relatively stable (see Figure 13). Overall this suggests that other factors, rather than brand premiums, are driving the increase in generic substitution.

Figure 12: Brand premiums and prescriptions dispensed with a brand premium (where generics are available)



Source: [53-56]

Figure 13: Brand premiums as a % of co-payments



Source: [49, 53-56]

5.3. Generic Substitution

The impact of brand premiums on the rate of generic substitution is limited by the habits of prescribers, rules regarding generic substitution by pharmacists, and patient's knowledge of the existence of brand premiums and general acceptance of generics as bio-equivalent.

Prescriptions can be written using either a brand name (i.e. Zocor and Lipex) or the active ingredient (i.e. simvastatin 40mg). Bromley (2006) reviewed prescriptions in a single Australian hospital between December 2002 and February 2003 and found that 53% of drugs were prescribed by brand name, and that prescribing by brand name increased with the length of the generic name (measured by letters) and decreased with the number of brands on the market[57].

Since 1994, pharmacists have been allowed to substitute between drugs listed on the PBS as bioequivalent even if the prescription specifies a particular brand, unless the prescriber indicates that "brand substitution is not permitted"[58]. Examples of reasons for disallowing

brand substitution include allergies to an inactive ingredient, a lack of trust in the quality of bio-equivalent drugs[59, 60], and avoiding patient confusion, which may cause dose duplication or poor compliance[61].

Chong (2010) conducted a survey from 31 July 2008 to 31 August 2008 of the first 25 prescriptions filled on a single day at 82 Australian pharmacies (16.4% response rate) and found that pharmacists offered generic substitution for 96.4% of the drugs where generic substitution was possible[62].

Chong (2010) also found that 2.3% of prescriptions did not allow brand substitution[62]. In contrast, the Australian Medical Association (AMA) conducted a fax survey of 386 General Practitioners (GPs) (25.6% response rate) in Australia in April 2006 and found that 80% of GPs designated "brand substitution not permitted" in 0-25% of their prescriptions, while 12% of GPs designated "brand substitution not permitted" in 76-100% of their prescriptions[63]. Using a worst case scenario, the AMA estimates a higher rate of disallowing brand substitution than Chong (2010)[25]. The AMA survey found that GPs considered patient safety (e.g. errors in patient use) the key reason for disallowing brand substitution (69%), followed by patient compliance (65%), belief that the brand and generic medicines are not clinically interchangeable (61%), price (e.g. the price difference is minimal) (26%) and other reasons (15%), including patient preference, perceived tolerance to a medicine and taste. Some of these concerns may be addressed through the Practice Incentives Program Quality Prescribing Incentive requirements, where clinicians are required to participate in various activities, such as conducting a clinical audit of prescribing using materials from the National

[25] If a worst case scenario was estimated based on the AMA survey where 12% of GPs disallowed brand substitution in 76% of prescriptions, and the remainder never disallowing brand substitution the lowest possible rate of disallowing brand substitution would be 9.12%.

Prescribing Service and 'academic detailing' visits[64]. Issues regarding generic prescribing may be raised through these activities.

The decision regarding whether to substitute drugs is the patient's choice[65]. Reasons for not providing their consent include limited knowledge and distrust of generics, confusion due to changing packaging and brand names, and a lack of discussion with the prescribing doctor[65, 66]. Patients may also perceive the brand premium as a quality indicator[67]. Chong (2010) found that 78.5% of patients accepted pharmacists' recommendations to switch to a generic when made, with patients with chronic diseases significantly less likely to accept the recommendation than patients with acute conditions[62]. Several awareness programs, such as the 'Generic medicines are an equal choice' campaign funded by the National Prescribing Service, have improved patient's understanding that generics are bio-equivalent to the original branded drugs[68].

Ortiz (2010) conducted a study of PBS prescription data relating to three drug classes (statins, calcium channel blockers and selective serotonin reuptake inhibitor antidepressants) filled at least four times between from 1 August 2007 to 31 July 2008 by long-term concession card holders drawn from a 10% random sample of the Australian population[61]. The study found that more than half received only one brand of the drug (57% for statins, 60% for calcium channel blockers and 63% for selective serotonin reuptake inhibitor antidepressants), while a small proportion received three or more brands (14% for statins, 10% for calcium channel blockers and 12% for selective serotonin reuptake inhibitor antidepressants). This suggests that the potential for confusion is significant, and the authors suggest that this may be increasing over time as the number of brands available increases. Multiple switching was less common for older patients, which the authors speculate may be because they are less willing

to accept a brand switch which could be a useful protective mechanism against any potential confusion.

It has been suggested that the key driver of increasing rates of generic substitution, rather than lower prices, is due to manufacturers competing for market share by offering pharmacists discounts on the PBS listed price in order to encourage pharmacists to suggest to patients to substitute towards their brand[69].

Generic substitution by pharmacists is further encouraged by the Commonwealth Government through a premium-free dispensing incentive, introduced on 1 August 2008, whereby pharmacies are paid $1.50 (indexed annually) for each substitutable PBS drug dispensed that does not have a brand premium or other special patient contribution[14].

5.4. Reference Pricing

As previously discussed, after PBAC approves a drug the PBPA negotiates the PBS listed price and any risk sharing agreement with manufacturers. This does not mean that the price paid is not able to be re-negotiated or reduced in later years; however the benefits are largely captured by the Commonwealth Government through reduced PBS expenditure. Changes in drug prices are only felt by the patient when the price falls below the co-payment or when price premiums change.

The key driver of price changes in later years is the reference pricing system. The main form of reference pricing is the linkage of drugs approved on a cost-minimisation basis or as a combination drug[70]. If the price of a drug falls and it was used as a comparator for another drug approved on the basis of cost-minimisation, the price of the second drug must experience an equivalent fall such that cost-minimisation is maintained. In addition, if the cost of a drug falls and it is an individually listed component drug of a combination drug, the

cost of the combination drug must experience an equivalent fall such that the relative price is maintained.

Another form of reference pricing was introduced in 1998[71] where certain drugs are assigned to a Therapeutic Drug Groups where drugs are considered to be bio-similar and thus interchangeable at the individual patient level (i.e. same mode of action or similar in safety and efficacy[26])[72]. Drugs in Therapeutic Drug Groups include both on-patent and off-patent, branded and generic drugs. There are currently ten therapeutic drug groups, capturing many of the highest cost drugs in terms of expenditure for which generics are available[27].

The cost of these drugs is reviewed annually taking into account average dosage data. These data are sent to manufacturers along with an invitation to submit price proposals. If no price proposals are made, the default is the current price of the drugs (excluding any brand or therapeutic group premiums). The Weighted Average Monthly Treatment Cost (WAMTC) per patient is then calculated using the lowest proposed price for each formulation of each drug. The benchmark drug is specified based on the drug resulting in the lowest 95% upper confidence interval. The results are communicated to manufacturers to decide the price reductions required on each strength/formulation in order that, at minimum, the WAMTC is equal to that of the benchmark drug. Manufacturers may also propose an increase in the price and/or a Therapeutic Group Premium.

The aim of WAMTC is to link the price of on-patent drugs to price reductions in off-patent drugs due to price competition. The key criticism of WAMTC is that manufacturers have no incentive to reduce their price unless in response to a competitor reducing their price, as

[26] Note that these are not generics which are bioequivalent or biosimilar.

[27] Angiotensin converting enzyme inhibitors; angiotensin II receptor antagonists; calcium channel blockers; H2-receptor antagonists; HMG Coenzyme A reductase inhibitors, pravastatin and simvastatin; HMG Coenzyme A reductase inhibitors, higher potency, atorvastatin and rosuvastatin; proton pump inhibitors; venlafaxine; bisphosphonates for the treatment of osteoporosis; and bisphosphonates for the treatment of Paget disease.

competitors can price match thus conferring no competitive advantage to the initial price reduction in terms of increased volumes[12]. WAMTC may be a key driver of the relatively higher prices of generic drugs in Australia compared to overseas.

In 2007 the Commonwealth Government attempted to address the issue of high generic prices through a number of reforms to the PBS[14]. The PBS was split into two formularies: drugs listed on Formulary 1 are those where there is only one bioequivalent (i.e. no generics) or biosimilar (i.e. therapeutic groups with no generics available for any drug) brand available, while Formulary 2A drugs are those with two or more bioequivalent brands available (i.e. generics are available) and Formulary 2T drugs are those with two or more biosimilar brands available (i.e. therapeutic groups with generics available for at least one drug). In January 2011 Formulary 2A and Formulary 2T were combined into a single formulary[14]. Formulary 2A experienced an initial price reduction of 2% on 1 August 2008, 2009 and 2010 while Formulary 2T drugs experienced an initial price reduction of 25% on 1 August 2008. More importantly, on an ongoing basis the first time a bioequivalent or biosimilar brand is listed on the PBS (and thus the drug moves to Formulary 2) the drug will experience a price reduction of 12.5%[28]. A drug cannot be subject to the 12.5% price reduction more than once. Under the new system the 12.5% price reduction, which previously flowed through to all other drugs in the same reference pricing group, no longer affects drugs still listed on Formulary 1[14]. Thus this reform effectively removed much of the benefit of reference pricing between drugs still under patent protection compared to those with generics available (i.e. if a drug was listed on the basis of cost-minimisation[21]). Under the Memorandum of Understanding the 12.5% price reduction was increased to 16%[28]. Furthermore an

[28] Although this only formulised the process which has been applied administratively since 1 August 2005.

additional 2% and 5% price reduction was applied to Formulary 2A and Formulary 2T drugs on 1 February 2011, respectively.

As previously discussed, manufacturers mainly compete for market share by offering discounts to pharmacists who can then encourage patients to substitute between generics[69]. However any cost savings made are not captured by the Commonwealth Government. The 2007 reforms also introduced price disclosure rules whereby manufacturers must provide information about the prices at which it supplies any new brand of a Formulary 2A drug (e.g. generics) across a year following first supplying the drug, excluding the first month[73]. If the weighted average disclosed price was more than 10% lower than the PBS price then the PBS price was reduced to the weighted average disclosed price. Non-price incentives such as bonus stock or in-kind payments were also covered. DoHA also invited other manufacturers to disclose their prices, however this was voluntary. Drugs subject to price disclosure were removed from the therapeutic group. Under the Memorandum of Understanding the price disclosure rules were strengthened[28, 74]. Price disclosure now applies to all Formulary 2A and 2T drugs, and other manufacturers are now required to disclose prices (voluntary disclosure removed). Cycles were set in advance, rather than being triggered by a new brand listing. In the first main cycle (1 October 2010 to 1 April 2012) if the weighted average disclosed price is less than 23% but greater than 10%, then a minimum of a 23% price discount is applied.

Initial indications suggest that these reforms have been effective in reducing the listed PBS price of drugs where generics are available. Overall 127 forms (multiple brands may be available for each form of drug) experienced a price reduction on 1 April 2012, of which 108 forms already cost below the general co-payment and a further ten forms subsequently fell

below the general co-payment[29][75]. No forms were or subsequently fell below the co-payment for concession card holders. On average, the cost savings to the Commonwealth Government were $5.50 per drug ($0.18 to $43.94). For the 108 forms that already cost below the general co-payment, the average cost saving (including brand premiums) that could be experienced by the patient was $3.85 ($0.41 to $16.35), while for the ten forms that fell below the co-payment the average cost saving was $8.36 ($0.41 to $14.64). The drug associated with the highest cost savings for patients was simvastatin. This analysis assumes that pharmacists pass on the full price reduction[30] or that patients shop around for the lowest costs available. However even when a drug costs below the co-payment, the pharmacist may continue to charge the cost of the co-payment[31] and as this is no different from previous experienced the patient may not question the price. Consequently there may be no impact on drug uptake or the duration of therapy.

5.5. Hospital Funding

In the past, drug costs for public patients were the sole responsibility of public hospitals. However due to increasing budget constraints hospital pharmacies have sought ways to minimise the costs incurred. For example, hospital pharmacies may provide only one or two days' worth of drug treatment to the patient upon discharge[76, 77]. Patients would then need to see a GP to obtain a prescription for the additional drugs needed, which was to be filled at a community pharmacy, and thus placing the cost onto the PBS. This causes significant

[29] Includes different doses of the same drug (multiple brands available for each drug)

[30] Pharmacists are free to charge whatever they want for drugs that cost below co-payment.

[31] For example, the PBS list price of Zocor (Simvastatin) 40mg x 30 was $26.10 (including $3.32 price premium) on 24 August 2012.

Online pharmacies offering Zocor to patients at co-payment include: Discount drug stores: $38.73 (including $3.33 price premium); Your Chemist Shop: $38.35 (including $2.95 price premium). Sources: http://shop.discountdrugstores.com.au, http://www.yourchemistshop.com.au

Online pharmacies offering Zocor below co-payment include: Chemist Warehouse, Epharmacy and Pharmacy direct: $20.99 (including $3.32 price premium); Pharmacy Online: $20.90 (including $2.03 price premium); Cincotta Discount Chemist: $21.99 (price premium not reported). Sources: http://www.chemistwarehouse.com.au, http://www.epharmacy.com.au, http://www.pharmacydirect.com.au, http://www.pharmacyonline.com.au, http://cincottachemist.com.au

inconvenience to the patient, particularly when they are recovering from illness or don't live close to a pharmacy. Similarly, use of a high cost drug can place a significant burden on the budget of a single hospital, creating reluctance by hospitals to use these drugs, even if highly efficacious[76]. Finally, the difference in funding structures between public and private inpatients, with effectively capped budgets for public inpatients and uncapped access to the PBS for private patients[78]. All of the above unintended consequences limit the ability for the Commonwealth Government to achieve affordable, timely and equitable access to necessary medicines.

In recent years a number of reforms have been implemented to reduce these unintended consequences and improve access to drugs. The Highly Specialised Drugs Program was introduced under Section 100 in 1990 to increase access to a limited range of high cost drugs supplied through public and private hospitals with appropriate specialist facilities for the treatment of certain chronic conditions[4]. Then in October 2001 an agreement was signed between the Victorian Department of Health Services and the DoHA to pilot changes to access of public hospitals to drugs listed on the PBS[76]. Firstly, hospital pharmacists were permitted to supply drugs under the PBS, thus enabling patients to be discharged with an adequate supply (e.g. one month) rather than being required to locate a nearby community pharmacy after discharge. Secondly, a greater selection of PBS listed chemotherapies were moved to Section 100 under the Chemotherapy Pharmaceuticals Access Program (CPAP)[79]. This program increased access to a broader range of chemotherapies for public day-admitted in-patients and out-patients[76] and shifted some of the cost burden from public hospitals (and thus State Governments) to the PBS. Since 2001 Queensland, South Australia, Western Australia, Tasmania and the Northern Territory have adopted the reforms, with 149 public hospitals (~20% of all public hospitals[80]) being covered by the agreements[81]. While public inpatients still do not have full access to the PBS, these two reforms may have

encouraged the use of certain more effective but more costly drugs, and reduced the burden on hospitals budgets, which in turn may have increased access to other drugs for inpatients. On the other hand, uptake of some Section 100 drugs is somewhat limited by the restrictions on who can prescribe these drugs.

The entitlement of patients to the entire dose of a drug received under the PBS also has had unintended consequences, particularly in the case of chemotherapy administered by intravenous infusions. For these drugs, the amount required is typically determined by the patient's weight or body surface area. Consequently, if a patient's weight is just over a certain level, then only a small proportion of one more additional vial would be needed in order to provide the patient the appropriate dose. Where drugs were paid via a public hospital budget, the remainder of the vial could be shared with another patient if they are being treated at the same time. Note that private patients would be entitled to the entire vial.

In order to reduce drug wastage, the DoHA was going to replace CPAP with the Intravenous Chemotherapy Supply Program (ICSP) where pharmacists were only reimbursed for the amount of drug used, rather than the number of vials dispensed[82]. This was met with criticism regarding the potential for under-prescribing of some high cost drugs and higher costs for the patient or the hospital[83, 84]. Consequently ICSP was not implemented and CPAP was replaced with the Efficient Funding of Chemotherapy Drugs (EFCD) initiative (Revised Arrangements). Under the initiative, pharmacists are reimbursed for the combination of vials that most cost effectively a makes up the required patient dose, with algorithms used to work out the most appropriate combination. EFCD applies to both private hospital patients (from 1 December 2011) and public hospital patients (from 1 April 2012)[85]. That said, while this approach may somewhat reduce PBS costs, the decision to share vials and thus reduce drug costs remains up to the hospital and any cost

savings falls on the hospital budget. As opposed to the proposed scheme, the impact on use of cost-effective intravenous drugs under the new scheme is likely to be minimal.

The costs associated with intravenous drug administration for public in-patients are incurred by the State Government, while MBS benefits are payable for intravenous drug administration for out-patients. Between 1995–96 and 2009–10 in-patient episodes in public hospitals for chemotherapy grew by 13% while MBS chemotherapy items charged at 85%, and thus public out-patients[32], increased by 325% (see Table 4). This may be due to changes in clinical practice, but it may be unintended due to requirements to access drugs on the PBS under CPAP/EFCD, public hospitals developing "private" out-patient chemotherapy centres in order to reduce the burden on hospital budgets or even supplement hospital budgets with MBS payments[86], or a combination of all the above. If the key reason is to supplement hospital budgets, it may also create reluctance to switch from intravenous-administered chemotherapies to oral chemotherapies. Consequently the uptake of oral chemotherapies, which may be more convenient and/or more effective for the patient, may be lower compared to what would otherwise be the case.

Table 4: Chemotherapy separations

	1995-96	2009-10	Growth
In-patients			
Public Hospitals	122,066	138,542	13%
Private Hospitals	36,312	196,952	442%
MBS statistics*			
Total	86,162	410,649	377%
Charged at 75% (thus private patients)**	34,035	188,955	455%
Charged at 85% (thus public patients)**	52,127	221,694	325%

*Based on MBS items: 13915, 13918, 13921, 13924, 13927, 13930, 13933, 13936. ** Based on calculating the MBS benefit per service, and comparing to the MBS fee for that financial year. Source: [80, 87-89]

[32] For out-patients, 85% of the MBS schedule fee is payable as benefits, while for in-patients, 75% of the MBS schedule fee is payable as benefits. Private patients are only able to claim costs from private health insurance if they are admitted (thus in-patients). Consequently if benefits paid are 75% of the fee they are likely to be private patients, and if benefits paid are 85% of the fee they are likely to be public patients.

6. Conclusion

Pharmaceutical policy today in Australia is complex as a result of multiple reforms implemented over a number of years. PBAC conducts economic evaluation to ensure the drugs listed on the PBS are value for money. The potential the economic evaluation results overly favouring the drug is minimised though using a multi-stage evaluation process with different points of view sought, and guidelines specifying the preferred methods of data collection, data synthesis, and reporting of results. However uncertainty in the economic evaluation results may still remain. PBAC can use a number of mechanisms to minimise uncertainty in clinical effectiveness and cost-effectiveness, and reduce the risk of making an incorrect decision, including: applying restrictions, requesting a lower price, entering a risk sharing arrangement, delaying the reimbursement decisions, and approving interim funding. PBAC's experience with each type of mechanism is variable and the suitability of each mechanism is determined by the type and extent of uncertainty faced. In particular, PBAC is yet to consider a MES to minimise uncertainty. There are a wide variety of policy measures used by the DoHA that influence the costs and demand for a drug, both directly and indirectly. These measures should be considered when predicting the uptake of a drug.

7. Appendix

Table 5: History of PBS Co-payments and Safety Net Thresholds

Date of Change	Concessional Beneficiaries (pensioners)		General Beneficiaries	
	Co-payment	Safety Net Threshold	Co-payment	Safety Net Threshold
1/03/1960	Pensioners none, all others paid that of the general population	None	0.5	None
1/11/1971			1	
1/09/1975			1.5	
1/03/1976			2	
1/07/1978			2.5	
1/09/1979			2.75	
1/11/1981			3.2	
1/01/1983	Pensioners paid none, all others paid $2.00		4	
1/07/1985			5	
1/11/1986	Pensioners paid none, all others paid $2.50		10	25 scripts
1/07/1988			11	25 scripts
1/11/1990	2.5[a]	130	15	25 scripts
1/01/1991	2.5	130	15	1st tier 300, 2nd tier 50
1/08/1991	2.5	130	15.7	1st tier 300, 2nd tier 50
1/10/1991	2.6	130	15.7	1st tier 300, 2nd tier 50
1/01/1992	2.6	135.2	15.7	1st tier 309.9, 2nd tier 51.6
1/08/1992	2.6	135.2	15.9	1st tier 309.9, 2nd tier 51.6
1/01/1993	2.6	135.2	15.9	1st tier 312.3, 2nd tier 52.0
1/08/1993	2.6	135.2	16	1st tier 312.3, 2nd tier 52.0
1/01/1994	2.6	135.2	16	400
1/08/1994	2.6	135.2	16.2	400
1/01/1995	2.6	135.2	16.2	407.6
1/08/1995	2.6	135.2	16.8	407.6
1/01/1996	2.7	140.4	16.8	600
1/08/1996	2.7	140.4	17.4	600
1/01/1997	3.2[b]	166.4	20	612.6
1/01/1999	3.2	166.4	20.3	620.3
1/01/2000	3.3	171.6	20.6	631.2
1/07/2000	3.3[c]	171.6	20.6	631.2
1/01/2001	3.5[d]	182	21.9	669.7
1/01/2002	3.6	187.2	22.4	686.4
1/01/2003	3.7	192.4	23.1	708.4
1/01/2004	3.8	197.6	23.7	726.8
1/01/2005	4.6	239.2	28.6	874.9
1/01/2006	4.7	253.8	29.5	960.1
1/01/2007	4.9	274.4	30.7	1,059.00
1/01/2008	5	290	31.3	1,141.80
1/01/2009	5.3	318	32.9	1,264.90
1/01/2010	5.4[e]	324	33.3	1,281.30
1/01/2011	5.6	336	34.2	1,317.20
1/01/2012	5.8[f]	348	35.4	1,363.30

a Pharmaceutical Allowance introduced equal to co-payment * 52. b Pharmaceutical Allowance maintained at $2.70 per week. c Pharmaceutical Allowance increased to $2.80 per week, d Pharmaceutical Allowance increased to $2.90 per week, e Pharmaceutical Allowance increased to $3.00 per week. f. Pharmaceutical Allowance increased to $3.10 per week. Source:[49]

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