Australia's pharmaceutical benefits system: flawed but improving, and better than anywhere else

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The composition and role of the Pharmaceutical Benefits Advisory Committee (PBAC) has been the subject of acrimonious debate through the media in recent months, with accusations of government subjugation to strong industry lobby groups at the future expense of the Australian taxpayer. An understanding of the issues at this more political level is helped by appreciation of the rationale for the current process of listing drugs for reimbursement on the Pharmaceutical Benefits Scheme (PBS). I will try to give the non-economist reader an overview of the system and share some perceptions of the strengths and weaknesses of what is fundamentally a good system.

Overview of the system of reimbursement

Prescription drugs in Australia are declared on the PBS by the Federal Minister for Health, based upon a sequence of recommendations of different institutions and committees. In short, in order to be able to market a new pharmaceutical entity, a company must first have received approval through the Therapeutic Goods Administration (TGA) which reviews the safety, efficacy and quality of the medication.

Patients taking such medications will pay the full cost of the drug unless it has been further listed on the Pharmaceutical Benefits Schedule (PBS), whereupon they will only have to pay a standard of copayment of no more than approximately $20, with the Government subsidising the difference between the copayment and the manufacturer's price. Pre-conditions for listing of a drug on the PBS include approval of the Therapeutic Goods Administration (TGA) for the indication for which the drug is proposed for listing on the PBS, demonstration of acceptable cost-effectiveness (that is, acceptable value-for money) and final agreement on the listed price. Recommendations for listing on the PBS based upon a drug's cost-effectiveness are made by the PBAC followed by price negotiation between the manufacturer and the Pharmaceutical Benefits Pricing Authority (PBPA). However, the PBPA position on pricing is heavily influenced by the PBAC's view of the drug's cost-effectiveness.

The decision-framework for PBS listing

The rationale and methods of the PBAC's evaluation of medications are based upon sound economic principles, including that of 'allocative efficiency'. For this concept to be understood, it should be recognised that economics is not just about reducing costs. Economics in the health sector is concerned with identifying the 'value-for-money' of one therapy compared with another. Expressed alternatively, it is used to compare alternative therapies in order to identify which of them generates the greater health outcomes from the last dollar spent.

The decision framework for an economic evaluation of a pharmaceutical, or any other therapy or health care activity, is outlined in Table 1. It shows alternative combinations of cost and health outcomes that might arise from a new drug compared to an existing drug, and the decision that logically follows. Scenarios 1 and 2 are straightforward. If the patient is better off at no extra cost, or if savings can be made without compromising patient welfare, the drug warrants funding support. Scenario 3 is usually associated with support, particularly if some patients have difficulty tolerating the existing medications. Also straightforward is scenario 4 where costs are increased without identifiable benefit and the drug should be rejected for funding.

Table 1: Decision Framework

Scenario	Impact upon Cost of Treatment	Impact upon Patients	Decision
1	Costs decrease	Gain in health and/or quality of life	Support
2	Costs decrease	No change	Support
3	No change	No change	Support
4	Costs increase	No change	Reject
5	Costs increase	Gain in health and/or quality of life	?

Less straightforward is scenario 5 where additional benefits are gained, but only at increased cost. (A further possibility not addressed in this paper is a reduction in both costs and health outcomes, but the underlying logic is much the same). Economics resolves this issue by a process of comparing the ratio of additional costs to benefits of the pharmaceutical to that of alternative pharmaceuticals listed for the same indication. By re-allocating resources to those therapies generating greater health outcomes per dollar, and away from those with the lesser health gains per dollar, the same health care expenditure must necessarily increase health gains for the community without increasing the overall budget.

Allocative efficiency occurs when the ratios are equalised. Theoretically, once allocative efficiency is achieved, the purchasing mix of the PBS budget cannot be further improved as the ratio of costs and health gains would be equalised across all drugs that Australia can afford to list given the PBS budget. Were they not equalised, some health gains would then be forgone as the opportunity would exist to reduce funding of less cost-effective drugs in order to provide greater funding to more cost-effective drugs. This is exactly the focus of the PBAC when reviewing pharmaceuticals for listing on the PBS. In essence, the PBAC is endeavouring to adopt the perspective of a well-informed consumer participating in a market for prescription medications.

This is also why the PBAC Guidelines for the preparation of economic evaluations of drugs proposed for listing specify a societal perspective be adopted, rather than that of the health system funder. In the latter case, patients' costs would not be considered and, under the Australian health financing system, a greater interest in cost shifting to State governments.

The PBAC provides guidelines (Commonwealth Dept of Human Services and Health, 1995) for the preparation of submissions which list important issues that need to be addressed and to encourage methodological rigour in evaluations by stating preferred approaches. These guidelines specify the structure of submissions from which further insight to the decision-making criteria of the PBAC can be derived. A submission should comprise four sections which, in simplified form, are as follows.

Section 1

What is the drug proposed for listing on the PBS? For what use is it approved by the TGA? What is the comparator - that is, which is the drug or other therapy that it would most often replace if listed? If appropriate, the comparator may be 'placebo'.

Section 2

This includes the listing of all scientific evidence of the relative efficacy and effectiveness of the drug and its comparator, culminating in selection of the most rigorous evidence available. The Guidelines specify a hierarchy of evidence with strong preference given to randomised double-blind trials directly comparing the drug to the comparator therapy.

Section 3

An economic evaluation of the likely cost-effectiveness of the drug versus the comparator therapy, when used in Australia. Such evaluations need to consider a range of issues including the long-term effectiveness and the relevance to Australia of the data reviewed in Section 2 in terms of the patient population and clinical practice. Reflecting the 'consumer' approach to purchasing decisions, the PBAC also requires outcomes to be expressed in patient-relevant terms. For example, blood pressure reductions should relate this to reductions in acute myocardial infarction and stroke and survival gains. Alternatively, Forced Expiratory Volume in one second (FEV_1) gains in respiratory medicine should be expressed perhaps in terms of reductions in exacerbations and/or hospitalisations.

Section 4

In Section 4, the analysis shifts from economic evaluation to financial analysis. Whereas Section 3 determines value-for-money, Section 4 is used to decide if the drug can be afforded by estimating the likely cost to the PBS budget following listing. In 1999, two applications were lodged with the Federal Court to review the decision processes of the PBAC.

The Pfizer (Viagra) court decision confirmed the importance of section 4 by ruling that a drug that represents acceptable cost-effectiveness could be rejected on the grounds that the total cost could not be accommodated within the health care budget (Pfizer Pty Ltd v Birkett. Federal Court of Australia, 20 March 2000. <http://www.fedcourt.gov.au/judgments/judgmts.html, accessed February 2001).

To evaluate pharmaceuticals in isolation is undesirable, just as the management of any individual component of the heath care system in isolation is potentially inefficient. The PBAC therefore explicitly examines the broader implications of submissions by taking a societal perspective in Section 3, and by taking into consideration any projected savings to other levels of government in Section 4.

Submissions need to be comprehensive and are usually detailed, comprising around 100-200 pages plus appendices. The largest part is typically Section 2, a weighting which reflects the importance the establishing clinical effectiveness as well as cost-effectiveness. As the PBAC review clinical data to estimate effectiveness in practice were the drug to be listed, the review is from a different perspective to that of the TGA.

I believe it is fair to say that the capacity to demonstrate cost-effectiveness has grown in importance to PBAC decisions to the point where it is of equal importance to that of demonstrating effectiveness. This is contentious at times as the application of economic theory to the evaluation of pharmaceuticals involves important methodological issues as well as issues related to the application and interpretation of results.

Methodological issues

Valuing health outcomes can be problematic due to the diversity of clinical settings, diseases and pharmacological and non-pharmacological therapies that can be implicated in submissions to the PBAC. For instance how does the value of a 50% improvement in moderate psoriasis for the life expectancy of the patient compare with two months of progression-free survival for a cancer patient? The objective of equalisation of cost/outcome ratios (allocative efficiency) requires that these statistics be made commensurate.

Extrapolation of surrogate outcomes such as blood pressure or FEV1, to for outcomes such as survival or reduced hospitalisations, can be difficult. Arguably, the gold standard outcome for a PBAC submission is that of quality-adjusted life-years (QALYs). A QALY is a year of life that has been multiplied by a weight reflecting the quality of life of patients suffering from the condition or disease concerned. An important attribute of QALYs is that the weightings, which should be derived in accordance with appropriate scientific principles,

reflect the strength of patient preferences between different health states. There are a number of unresolved technical issues in relation to the use of QALYs, but a common difficulty is that the weights themselves have not been well reported, and have often been derived by inappropriate methods.

A trade-off frequently exists between choice of outcome and the scientific basis of the evaluation as the relationship of many surrogate outcomes to patient-relevant outcomes is poorly researched in the literature (for example, the prognostic significance of FEV_1 to survival in COPD patients). In the end, the choice of which endpoint to use may involve considerable judgement.

There are many other methodological issues that could themselves be the subject of a separate paper. They include the discounting of both costs and health gains. For example, both might be discounted at a rate of 5% per year to take into account a social preference for timing where distant future events (whether costs or health gains) are valued less the further into the future they are expected to occur. There is good empirical evidence confirming society has inter-temporal preferences, but the actual discount rate is subject to uncertainty and can have profound effects where the health consequences of taking a medication for a given period occur over much longer time-frame.

Statistical significance is defined, by convention, as reaching a probability (p) value of 0.05. This is a statement of the probability of a chance result based upon the data available. However, in evaluations by the PBAC, the difference between p= 0.05 and a value of p= 0.06 can appear to have an important determinant to the final decision. To be fair, it is clear that a line must be drawn at some point.

The issue is further complicated by the need to distinguish between trial centre differences (heterogeneity) and treatment (effect), and resource (cost-offset) differences. Whereas biostatisticians may argue that even higher levels of rigour should be applied to detecting treatment differences, it has also been argued that a reduced level of rigour should apply in respect of resource differences, which typically have a different distribution to those of clinical outcomes.

Finally, methodologies for determination of indirect costs (also known as the production losses as a consequence of health loss of members of the workforce) are poorly developed. For this and other reasons, they are not yet encouraged by the PBAC Guidelines.

Application issues

Prior to the requirement of demonstrating acceptable cost-effectiveness as a pre-condition for listing on the PBS, the concerns of industry in relation to the current system of economic evaluation have been reported as being that the system would (a) lower prices, (b) increase development costs and (c) further delay access to the drugs on the market (Henry, 1992). As a consequence of parallel processing by the TGA (and the Australian Drug Evaluation Committee) and the PBS evaluation process (which is restricted to 12 weeks), the available evidence suggests that the process has not unduly delayed listing.

Delays arise after the evaluation and are associated with price negotiation, Cabinet approval and gazetting on the PBS. However, these delays would exist independently of any process of economic evaluation. The more significant concern of industry that drug prices are lower in Australia is generally accepted as true, but it must be recalled that to the extent lower prices have been realised, there has been a gain to the taxpayers through reduced subsidies.

Not mentioned in the early literature are issues that have been highlighted since the implementation of the current evaluation process. I would argue that there are some apparent incompatibilities between scientific principles of evidence-based medicine and evaluation of true cost-effectiveness.

For instance, in recognition of the special problems of dependency and abuse of sedatives including the commonly prescribed benzodiazepines, the PBAC now requires that any new sedative demonstrate not only equivalent or better effectiveness but also reduced potential for dependency and abuse. The problem caused by this policy arises from the PBAC's preferred hierarchy of evidence that requires randomised-controlled trials. As no ethics committee will ever approve a trial designed to put control patients at risk of dependency and abuse

in order to 'prove' the benefits of a new alternative, it is even more difficult to list any new sedative.

The most commonly sold sedative internationally has been available overseas for over 10 years, but has since been rejected in Australia due to a lack of evidence. The issue is complicated by concern about hypnotic-sedative medications generally, with preference for non-pharmacological medications including cognitive behavioural approaches, but in short, the current system is inadvertently biased towards the continued listing of benzodiazepines in Australia.

Much of the media coverage has addressed the 'big ticket' drugs with annual sales of many millions of dollars. However, a weakness of the system to date has been the disincentive to list drugs for rare conditions or minority groups. The demands for evidence require the conduct of large multi-centred and well-monitored clinical trials. These trials are expensive and therefore not commercially viable for drugs with low sales prospects. Although orphan drugs appear to receive some favourable treatment, with some being listed in the absence of rigorous evidence, precedence exists for desirable medications failing to be submitted to the PBAC due to perceived low probability of success.

The standard approach in economic evaluations for the PBAC is to prepare computer models of costs and outcomes based upon an intention-to-treat cohort (ITT). There are good scientific reasons for requiring an ITT evaluation including avoidance of a 'healthy cohort' bias, but how many doctors would continue prescribing a medication after it has proven to be ineffective in a given patient? Although allowance can be incorporated in the economic models for patient withdrawals in trials, these are most commonly for adverse events. The economic analysis typically must assume patients tolerating the medication, but deriving no or little benefit, continue to receive the full dose for the duration of the analysis, sometimes for years. As proportions of non-responders vary between medications, the consequent evaluation distorts the relative cost-effectiveness estimates.

Some potentially important policy issues are also raised by the system. Logic would suggest that there might be a bias towards listing of paediatric medications. Curative medications for children have a much greater potential to generate 'life-years saved' than medications for geriatric patients, and perhaps an even greater potential for QALYs. It might therefore be expected that the proportion of paediatric medications on the PBS will grow, although a countervailing influence is the much greater incidence of diseases requiring prescription medications amongst the elderly, thus providing more incentive for pharmaceutical companies to focus upon development of drugs for the elderly population. Furthermore, medico-legal and consent issues inhibit the conduct of trials amongst children, and the convention of discounting at 5% per annum effectively eliminates much of the gains (and costs) occurring after about 20 years. If a bias still exists, either way, it may not be an issue depending upon the interpretation of community values, including the concept of the elderly having had a 'fair innings' as opposed to a life-year is of equal value no matter to whom it relates.

From a practical perspective, an issue for the PBAC is how the proposed drug will be prescribed in reality. The Drug Utilisation Sub-Committee (DUSC) provides ample evidence of drugs that are being used off-label or prescribed to a much broader population, in terms of disease severity or age, than was intended. These variations in prescribing patterns have potentially important influences upon the true cost-effectiveness of the drug once listed.

It has also been argued in industry circles that the PBAC is only interested in cost-containment. This argument fails to recognise that cost containment is inevitable as, at some price, every drug will eventually become too expensive for Australia regardless of effectiveness. Given existing budget constraints, what better system is there for allocating PBS funds than one based upon determination of 'value-for-money'? Other commonly used methods of cost containment are clearly less suitable. For example, the imposition of limits to the number of prescriptions makes patient therapy somewhat arbitrary and may not realise any cost-offsets such as reduced hospitalisations. A system of variable copayments to encourage patients to exercise increased discretion is both inefficient and contrary to Australian values of equitable access to health care.

A further criticism of the criteria for listing of pharmaceuticals for reimbursement was made in the recommendations of the Industry Assistance Commission report of 1996. The report highlighted industry perceptions of an inconsistency in government policy towards industry as evidenced by the price containment imposed by the PBS and the government's industry grant scheme designed to foster investment in pharmaceutical R&D and manufacturing growth in Australia (formerly known as the Factor f Scheme, and

currently the PIIP scheme). However, recall that the PBS process parallels the operation of a market where the PBAC exercises a countervailing market strength to that of industry. To the extent the PBAC encourages the development of an industry that responds to consumer demands by producing 'value for money' products, the policy is perfectly compatible with industry growth in a market framework. The criticism also fails to recognise the broader responsibility of Government to the Australian taxpayer.

It must also be noted that industry instigates the design, conduct and collection of trial data that form the basis of most applications to the PBAC. Relevant data may be derived from trials initiated and conducted by universities, hospitals and other health care institutions, but the pivotal evidence is usually derived from company-sponsored trials as other institutions lack the funds necessary to conduct large trials. Morgan, Barer and Evans (2000) have suggested that drug companies exercise a powerful influence over the entire process because of the financial incentives they may create for investigators, the design of trials including the choice of comparator, and the analysis of results. Whilst all behaviours described in the article have been observed by those in industry at various times, the extent to which these behaviours exist can be debated. The key point is to recognise the potentially powerful strategic position of the suppliers because they are the instigators and collectors of 'evidence-based' data.

There is also evidence internationally that companies are directing more of their research and development towards 'safe' markets, such as impotence, hair-loss, anti-inflammatories, and so on, rather than (say) malaria or drug-resistant tuberculosis. This is a reflection of shareholder commercial interests and not one that the PBAC process can readily overcome.

That industry frequently considers the PBAC decisions to be harsh has been well established. In this regard, it should be noted that a review of submissions to the PBAC from 1994 to 1997 found that 67% had 'significant problems', defined as problems which could have a bearing upon the final decision (Hill et al, 2000). Whilst the sophistication of submissions grew substantially over this period, and continues to develop further to this day, it is of interest to note the proportion of submissions with problems was relatively consistent over the period of analysis. Some introspection by industry may therefore be appropriate as well.

The findings of Hill et al. no doubt reflect the fact that the process of evaluation requires numerous assumptions where judgement is important. This characteristic lends itself to bias induced either overtly or subconsciously by conflict of interest. Thus the adversarial nature of the evaluation process, where industry and government evaluators may offer opposing interpretations to the PBAC, is an important element to its successful operation.

Conclusion

What has been the value of the PBAC to Australia? In relation to the aim of controlling prices, comparisons of international drug prices are difficult. Danzon (1996) reported numerous errors in studies of international pharmaceutical price differentials, highlighting the importance of different prescribing practices, manufacturer discounts, small and non-random samples, and the exclusion of generics. However, it is generally accepted that Australia's prices are substantially lower than those paid in other OECD countries. Table 2 is taken from the Industry Commission and shows Australian prices when estimated as a proportion of international prices.

Table 2: Comparisons of prices paid to pharmaceutical companies

Study Year	Benchmark Countries	Products	Australian price as % of overseas average price	
			Unweighted (%)	Products Weighted (%)
1987	11 OECD countries	top selling	55	
1990	European Union	top selling	55	
1995	OECD	top selling	71	54
1995	OECD	New	85	70
1996	United Kingdom	top selling	84	67
1996	United Kingdom	new	95	83

Adapted from: Industry Commission 1996, The Pharmaceutical Industry Inquiry Overview (www.pc.gov.au/inquiry/drugs/index.html, accessed 21 March 2001).

It is interesting to compare prices with those paid in the Philippines where purchasing has been decentralised and no effective price control exists. Per capita health expenditures in the Philippines are only about 2% of those in Australia, and yet a comparison of a small random sample of drug prices revealed that Filipinos often paid up to twice the amount as Australian consumers (Hindle, Acuin, and Valera 2001).

It is also probable that the PBS has achieved greater allocative efficiency as a consequence of economic evaluation. That the annual cost of pharmaceuticals has been increasing at a rate in excess of the overall health budget cannot be interpreted as a system failure. This simple statistic alone makes no allowance for any cost-offsets (savings) from reduced hospitalisations or other health care utilisation, nor the health gain derived from this expenditure compared to alternative uses of those funds.

It is relatively easy to criticise the PBAC and highlight the deficiencies. However, from a societal perspective, Australia's system of listing of pharmaceuticals on the national formulary for reimbursement is recognised internationally as being the best approach. It is also important to recognise that it is still a system in evolution. Issues raised above, such as the problem of minority interests, are acknowledged and are understood to be under review. The optimal use of economic evaluation is where it is not applied dogmatically. Economics cannot handle all dimensions of community values and previous PBAC decisions reveal acceptance of this by allowing listing of drugs, that might otherwise have been rejected, to be listed due to clinical need or adoption of the 'rule of rescue', reflecting a well established community value in Australia. Alternatively, listing may be rejected on the grounds of inequitable access.

However, success is constrained by the quality of the submissions, the evaluations and the data available upon which the evaluations can be based. The system will only be as good as the weakest of these elements. Hill et al (2000) note the difficulty that many companies have in finding the data necessary to prepare an economic evaluation. This is perhaps the greatest single difficulty industry and evaluators face and is a reflection of Australia's limited place in the international pharmaceutical market. The USA and Western Europe dominate this market. It is therefore not surprising that the design of trials, including the data collected and the choice of end-points, reflect the regulatory requirements of these countries.

Clinical trials of pharmaceuticals usually assess patients against clinical end-points of interest to medical doctors with resource data for health care utilisation rarely collected. Quality of life assessment is growing in importance but is usually performed using disease-specific questionnaires rather than instruments possessing the theoretical properties appropriate for estimation of the incremental QALYs (disease-specific questionnaires provide ordinal rather than cardinal rankings that reflect the strength of patient preferences between different health states).

Although Australia was the first country in the world to introduce economic evaluation as a pre-condition of listing, it is encouraging to see that this initiative has been followed by countries including Canada, New Zealand and United Kingdom (through the National Institute for Clinical Excellence). The trend is clearly towards increased evaluation of drugs. Harmonisation has occurred in regulatory approval processes and may be expected to occur to a large extent in reimbursement approval systems over time. This has the potential to help Australia substantially: the greater the number of countries requiring economic evaluation, the more likely it is that the design of clinical trials will include collection of resource data and quality of life questionnaires appropriate for an economic evaluation. Once this is achieved the debate will be less about the politics of the process, and more about the methodological issues of evaluation, which is where the debate should be.

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