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Australian Guidelines for Cost-Effectiveness Studies of Pharmaceuticals :

The thin end of the boomerang ?

by

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by

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Abstract

In the Summer of 1990, the Australian government took a major step by requiring evidence of cost-effectiveness of new medicines prior to reimbursement by the public health care system. This paper assesses whether the methodological principles behind the guidelines are sound and whether they raise important new logistical and policy implications. It is concluded that, whilst the guidelines may represent the 'thin end of the wedge' for the pharmaceutical industry, in that other countries may follow the Australian lead, they also may represent the 'thin end of the boomerang' for government. Namely, the development of explicit guidelines for public funding decisions concerning new health technologies, places as many demands on funders (the government) as it does on the suppliers (the industry).

1. INTRODUCTION

Australia has long been regarded by the pharmaceutical industry as a difficult country in which to market its products (Chew *et al.*, 1985). Having only a small domestic industry, Australia acts as a 'price taker', securing prices far below the world average for the relevant medicines. The main reimbursement control mechanism is the Pharmaceutical Benefits Scheme (PBS), which is operated by the Commonwealth (Federal) Government. In order for a medicine to be reimbursed for use in primary care it has to be listed under the PBS. Listing is obtained by making a submission to the Pharmaceutical Benefits Advisory Committee (PBAC). An amendment to the 1953 National Health Act in August 1987 required the PBAC to consider effectiveness and cost when recommending to the Minister the listing of items on the PBS. The intention of this amendment was to encourage the PBAC to consider the full economic impact of each drug, and to select drugs that are cost-effective. Once listing is obtained, price negotiations take place with the Pharmaceutical Benefits Pricing Authority. Pricing decisions are based on a number of factors, including advice from the PBAC, but in the main a 'cost-plus' approach has predominated to date.

In the Summer of 1990, the Commonwealth Government issued new draft guidelines for the pharmaceutical industry on preparation of submissions to the PBAC (Commonwealth of Australia, 1990). The main change was that the submissions would now include economic analyses, first on a voluntary basis and then on a mandatory basis by January 1993. In addition, the PBAC might request an economic appraisal in the interim where a given medicine could lead to significantly higher expenditure under the PBS. The new draft guidelines are designed to provide a format for all PBAC applications (excluding generic listings) whether or not economic data are included with the application. Early sections of

the guidelines set standards for submitting data on effectiveness, adverse effects and likely usage levels of the medicine concerned. Later sections lay down standards for the submission of economic data, including the choice of comparator therapy and the costs and consequences to be measured.

Australia is therefore the first country to propose mandatory guidelines for economic analysis prior to reimbursement of medicines. The pharmaceutical industry has already undertaken economic analysis in support of its products in a number of countries. These have been used in price setting, price defence and the promotion of pharmaceuticals (Drummond, 1989/90). In some countries, studies have been used in price negotiations; in some others with free pricing the industry has been encouraged to undertake cost-effectiveness and cost-benefit studies (DH, 1990). However, this is different from a formal requirement and the pharmaceutical industry is concerned that the Australian government's action represents the 'thin end of the wedge'. Namely, if this approach to the granting of reimbursement status proves workable, it could be applied by other countries having concerns over cost-effectiveness. More widely, the Australian cost-effectiveness guidelines represent an example of the use of economic appraisal to encourage a rational diffusion and use of health technology (Drummond, 1987) and, as such, require closer examination.

Therefore, this paper provides a commentary on the proposed guidelines. In the next section the content of the guidelines is outlined and comments are made on the methodological principles embodied within them. Then, in Section 3, the implications of the guidelines are discussed, considering both the logistical issues (e.g. in assembling good quality data within an acceptable timeframe), and the policy issues (e.g. in making decisions about the price and availability of new medicines). Finally, in Section 4, a few tentative conclusions are drawn and some

suggestions made for monitoring the introduction of the guidelines.

2. CONTENT OF THE GUIDELINES

The major components of economic evaluation can be characterized as: selection of alternatives for appraisal, assessment of costs and consequences, allowance for differential timing and uncertainty in costs and consequences and presentation of results (Drummond, 1981). The guidelines deal with all these aspects. They are discussed in turn below and an overall methodological assessment made.

2.1 Selection of alternatives for appraisal

The guidelines suggest that usually the comparator (to the new medicine of interest) should be the drug(s) most widely used in Australia for the relevant indication(s), and that in some cases comparisons with more than one group of drugs will be necessary. They also acknowledge that in some situations, with 'breakthrough' products, no relevant currently-listed drug comparator would exist. In this case the new medicine should be compared with no specific drug or with standard clinical management. Finally, the guidelines note that comparisons should be made using the doses recommended in the product information.

The approach suggested by the guidelines is broadly in accordance with sound principles of economic evaluation (Drummond et al., 1987), which argue that all relevant alternatives should be considered (see Appendix 1). This is to be contrasted with the alternatives compared in clinical trials, where a placebo or baseline therapy is often the comparator. (This raises logistical issues in the gathering of economic data as part of the normal clinical trials programme, which

will be discussed later.) The notion that recommended, rather than actual doses, should be used in the comparisons is slightly at odds with this practical approach. However, one defence of the use of recommended doses is that the fairest comparison between rival medicines would be one based on the manufacturers' own recommendations. The same argument would apply to the assumptions made about monitoring of therapy in estimating the costs of the associated medical care. Of course, another motivation, from the government's point of view, is that to allow the excessive prescribing of existing medicines to enter into the analysis would be 'designing in' to studies a certain amount of cost inflation. Nevertheless, it would be important to check that manufacturers' recommendations are in tune with expert clinical opinion on the use of the products concerned.

2.2 Assessment of costs and consequences

This has a number of aspects, which will be discussed in turn. First, there is the question of the range of costs and consequences that are considered. This is crucially dependent on the viewpoint for the economic study. The guidelines suggest that in considering costs, a broad viewpoint should be used, considering not only costs to the PBS, but also costs in medical services (also funded by the Commonwealth Government) and in hospitalization (which fall on the budget of the state governments and are only funded indirectly by the Commonwealth through Health Financing Grants). The guidelines also point out that occasionally, because of the condition under treatment or the age of the patients, consideration of the direct non-medical costs such as social services (home help, day care, meals on wheels, nursing and physiotherapy services) may be relevant. However, they explicitly exclude (except under special circumstances) the consideration of indirect costs and benefits (i.e. impacts on production).

This last recommendation has generated considerable debate. On the one hand it could be argued that losses in production, through patients being off work, and the corresponding gains if more effective medicines allow them to return to work earlier, represent real resource changes. The objection to the inclusion of indirect costs and benefits in the guidelines stems from the belief that there will be few actual losses in production when workers are off sick. For short term absence, production will be made up by colleagues or by the absent worker on his or her return to work; for long term absence, production will be made up by a replacement worker, who would otherwise be unemployed. The real position is likely to vary from case to case. An approach that ascribed either full production losses (valued at gross wages) or zero losses in every case is likely to be incorrect. The guidelines currently place the onus on the applicant to the PBAC to justify the inclusion of indirect benefits.

Finally, another objection to the inclusion of production gains relates to the inequalities it would introduce. Evaluations including consideration of indirect benefits would favour health care interventions for people in highly paid occupations, at the expense of the elderly or individuals who are disadvantaged with respect to employment opportunities.

Therefore, with the exception of indirect costs and benefits, the guidelines appear to encourage a broad viewpoint. Some within the pharmaceutical industry have noted that while this is within the remit of the PBAC, its power to influence resource allocation decisions outside the PBS may be limited. Therefore, undue emphasis may be placed on drug costs in the decision making of the PBAC. This point is returned to later.

The second aspect of the assessment of costs and consequences relates to their measurement in physical units (e.g. hours of medical time, years of life gained, days of disability avoided). As one might expect, the guidelines for cost-effectiveness assessment stress the need to use the data generated by clinical trials, particularly with regard to clinical outcomes. In this respect the guidelines stress that the relevant outcomes are those generated by trials undertaken under realistic clinical conditions (i.e. effectiveness data rather than efficacy data) and those that are important to patients (i.e. outcomes in length and quality of life rather than changes in biomedical markers). However, the guidelines acknowledge that in some cases only data on intermediate endpoints, such as percentage reduction in blood pressure or cholesterol level, may be available. Nevertheless, there has to be a reasonable consensus that these intermediate measures relate to patient benefits in the longer term.

Fewer recommendations are made about the measurement of costs. For example, less attention is given to the fact that cost measurements made during clinical trials may be atypical of those observed in regular clinical practice, because trials may necessitate extra clinic visits, or result in patients being monitored more closely (Drummond and Davies, 1991).

The third aspect of the assessment of costs and consequences relates to their valuation. With respect to costs, the guidelines state that where actual fees are paid by the Commonwealth Government, under the PBS or Medicare schedule, these valuations should be used. However, it is not as easy to be as prescriptive for other categories of cost and the Commonwealth is planning to commission research in order to derive a series of unit prices for standardized medical procedures. With regard to the valuation of consequences, the guidelines give

cautious encouragement to the use of cost-utility analysis, where health state valuations are used to calculate quality-adjusted life-years (QALYs). However, they recognize that this approach to economic evaluation is still under development.

2.3 Allowance for differential timing and uncertainty in costs and consequences

The guidelines adopt a fairly standard approach to dealing with the differential timing of costs and consequences (i.e. now or in the future). They suggest that events in the future should be discounted to present values at an annual rate of 5% in real terms. This is in accord with the world literature on economic evaluation.

The guidelines also suggest that uncertainty in estimations should be allowed for by undertaking a sensitivity analysis, where the impact of different estimates on study results is explored. Again, this is now fairly standard practice in economic evaluations in the health care field. A particular concern, mentioned in the guidelines, is that the cost-effectiveness of a drug may diminish if it is used by patients in the community who have a disease which is less severe than those patients that participated in the clinical trials which generated the baseline effectiveness data for the economic evaluation. This is somewhat at odds with the earlier guidance on recommended doses, since a consistent approach would be to take the recommended indications, which should themselves be based on the clinical trial results. However, the indications may be broadly defined, so one approach would be to undertake sensitivity analysis of all the variables that might differ between the clinical trials and regular clinical practice. These would include dosages, compliance, patients treated and the nature of associated medical care.

The main variables affecting the cost-effectiveness of a medicine differ from study to study. However, the cost-effectiveness ratio is often sensitive to drug price, the drug's impact on health outcome, dosage in regular clinical use, the breadth of clinical indications for which it is used and patient compliance.

2.4 Presentation of results

The format of the guidelines, being set out as a series of questions, suggests an approach to the presentation of results. Certainly, applicant companies are encouraged to be transparent with respect to their sources of data and methods of estimation.

In addition, the guidelines suggest that cost-effectiveness ratios be presented (e.g. cost per cure, cost per life year, cost per QALY) and be calculated on an incremental basis. That is, compared to the alternative, what extra unit of benefit is gained relative to the extra cost?

No firm guidelines are given for interpretation of the cost-effectiveness ratios. For example, it is now common to compare the ratio obtained for a particular intervention with those for a wider range of interventions in a 'league table' or ranking (Schulman et al., 1991). Currently, such a league table does not exist for health care interventions in Australia and further work would be required to generate one. Also, no guidance is given on whether such comparisons have to be confined to drugs reimbursed by the PBS, or whether they can also embrace other health care interventions. Finally, it is not clear from the guidelines how much emphasis applicants should place on identifying financial impacts on the PBS budget as opposed to health care costs more generally. However, as stated earlier,

the guidelines suggest that a broad range of costs be considered.

2.5 Overall methodological assessment

Despite some of the minor inconsistencies identified above, the overriding conclusion is that the guidelines embody most of the principles of good economic evaluation methodology. No doubt further methodological issues could have been addressed, in particular those relating to the difficulties of conducting economic analyses alongside clinical trials (Drummond and Davies, 1991). However, the major issues raised by the guidelines are not methodological. Rather they relate to the logistical problems the guidelines pose, both for the industry and the PBAC, and the way they will be applied in determining reimbursement status for new medicines. These issues are discussed in the next section of the paper.

3. IMPLICATIONS OF THE GUIDELINES

3.1 Logistical implications

One of the major concerns of the Australian pharmaceutical industry is that the guidelines impose additional burdens in terms of the costs of research and possible delays in the introduction of new medicines. The first point to note is that the complexity of study required relates to the nature of the economic claim being made. For example, if a new medicine is considered to be of equal effectiveness to existing therapies and no premium price is likely to be requested, a simple cost-minimization analysis would suffice. On the other hand, if the product is in the 'breakthrough' category and a premium price is requested, a more sophisticated analysis would be required, relating the additional cost to the improvements in health, measured in natural units (in a cost-effectiveness analysis),

in quality-adjusted life-years (in a cost-utility analysis), or financial benefits (in a cost-benefit analysis). Therefore, it is likely that the major costs of complying with the guidelines will fall on the major, research-based companies with the breakthrough products.

Overall, a major influence on the total burden imposed by the guidelines will be the pace of their implementation. This not only relates to the timescale set by the Commonwealth government, but also to the standards of analysis it is likely to expect. Some major companies, with the available financial and human resources, may try to use the guidelines to obtain a competitive advantage, by 'upping' the standards of analysis. The logic is that the PBAC, once it has seen an excellent study, may find it harder to accept a mediocre study from a rival company. In this sense, the guidelines may offer some protection for smaller companies without the resources to commission state-of-the-art evaluations.

Another key aspect of the logistics relates to the general lack of availability of people with the necessary skills either to undertake, or to scrutinize, economic evaluations. This is likely to remain a problem in most developed countries for the foreseeable future, and is particularly acute in Australia. Therefore, the range and quality of evaluations may be self-limiting in the short term. In the medium-to-long term the guidelines imply a sizeable training need.

A welcome aspect of the guidelines is the implied link between economic evaluation and clinical trials. Although the guidelines contain rules for assessing the quality of clinical trials, the link with economics raises a number of additional logistical issues since it is clear that the clinical trials currently undertaken for registration purposes may not necessarily provide an adequate vehicle for economic evaluation. For example, they may not include the relevant end-points (e.g. impact

on quality of life), may not have long enough follow-up, may be undertaken in an 'unrealistic' setting or have insufficient sample size to detect differences in economic endpoints at the conventional levels of statistical significance. Therefore, at best existing trials may need to be adapted, at worst new trials may have to be mounted. On the other hand the inclusion of more relevant endpoints in clinical trials would be a welcome development (Buxton and Drummond, 1989).

Any additional clinical research need not necessarily be conducted in Australia in order to satisfy the criteria, although the guidelines point out that analyses need to be 'relevant to local conditions'. This means not only that local prices should be used, but that studies should take account of local clinical practices and conventions, the local organization of health care, and the epidemiologic and demographic features of the Australian population.

At present few economic evaluations of pharmaceuticals have been undertaken on the international level. However, in one case the same evaluation has been performed in four countries and the impact of local conditions explored (Drummond et al., 1991). It was found that, as long as a common methodology could be developed, it was possible to extrapolate from one setting to another. In the case of the particular medicine studied, the cost-effectiveness results were remarkably similar in Belgium, France, the UK and USA. Nevertheless, more research is required into the problems and potential of adapting the results of a study in one country to apply in another.

Another logistical issue arises from the need to make relevant comparisons. Because most clinical trials of new medicines use, as a comparator, placebo or baseline therapy, there may not be clinical trials results for the relevant 'head-to-head' comparisons. This means that, for the purposes of the economic

evaluation, such comparisons will have to be synthesized using clinical data from a number of sources. Rules need to be developed for this since no two clinical trials will be exactly equivalent in their methods and setting. The natural tendency will be for companies to take the best possible results for their own product when comparing with another from a rival company. Where there are a number of clinical trials of a particular medicine, there may be a role for meta-analysis.

Another situation in which companies may need to synthesize data is where the therapeutic impact of medicines stretches over a number of years. For example, in the case of cholesterol-lowering drugs a model may need to be developed in order to explore the impact of lowering cholesterol in persons of different age and sex, adjusting for other risk factors (Oster and Epstein, 1987). Given the uncertainties in modelling it might be decided that the intermediate outcome measure, percentage cholesterol reduction, should be used in making comparisons between medicines. However, this may lead to difficulties when, as in this case, there is a non-linear relationship between the intermediate and final outcomes (in length and quality of life).

Finally, rules may need to be developed for undertaking sensitivity analysis. Whereas there is considerable agreement on the need to undertake sensitivity analysis, there is less agreement on which combinations of variables to consider and the ranges of estimates to use. Some sensitivity analyses are more conservative than others. This may be one area where some interchange between applicant companies and the advisers to the PBAC would be advantageous.

3.2 Policy implications

The guidelines have raised considerable scepticism within the pharmaceutical industry, which sees them as yet another mechanism to exert a downward pressure on drug prices in Australia. This view is partly fuelled by the fact that, although companies will be required to demonstrate the value for money from their medicines, these data are merely to secure reimbursement status. Whether higher value for money will be rewarded by a higher price is currently unclear.

This difficulty is compounded by the fact that it will be necessary to assume a price in calculating the incremental cost-effectiveness ratio for a new medicine compared with an existing one. Therefore, does the economic evaluation become an instrument for open price negotiation? At what stage does better value for money justify a higher price? The remit of the Pharmaceutical Benefits Pricing Authority requires it to consider two main criteria in setting prices: gross margin and the comparative prices of products that are considered by the PBAC to have a similar therapeutic effect. The data generated in response to the guidelines could inform difficult trade-offs between additional cost and superior effectiveness, thereby going beyond the notion of similar price for similar therapeutic effect.

Secondly, the process of undertaking economic evaluations adds considerably to the transparency of the decision making process. Although the data submitted to the PBAC will be regarded as 'commercial in confidence' by the Commonwealth government, it is likely that on occasions applicant companies may seek to publish their studies in peer-review journals, particularly when products can be shown to be good value for money. In many ways more transparency is to be welcomed, but a major implication for the PBAC and the pricing committee is that it will highlight

inconsistencies in decision making. In this sense the guidelines place additional demands on the Commonwealth government as well as the industry. Rather than being the 'thin end of the wedge' they may constitute the thin end of the boomerang!

A third implication is that the cost-effectiveness calculations submitted to the PBAC will in part rely on potential savings in health care resources. For example, a new hospital antibiotic may be shown to reduce perioperative infections, thereby reducing patients' need for a prolonged hospital stay. However, managerial action will be required to generate these savings. Therefore, there is a risk that value for money improvements sanctioned by the PBAC may not be realized in practice. New medicines may be a cost 'add-on' to the Australian health care system unless attention is paid to this issue by the Commonwealth and State Governments.

Fourthly, the application of the guidelines represents an ex ante assessment of new medicines. It is well known that some medicines become more widely used than the original indications would suggest. Therefore, a cost-effectiveness study performed in advance for selected indications may not give an accurate estimate of the overall economic impact (Jönsson, 1983; Bulthuis, 1984). Therefore, it may be necessary to re-visit the analysis after a period of time. There is no direct provision for this in the guidelines, but it may be an important feature of their evaluation in the future.

A final policy implication is that it may be difficult in practice to restrict the value for money comparisons to medicines alone. The guidelines acknowledge that in some cases the comparator therapy may be a non-pharmaceutical option. In addition, it is common to make value for money comparisons among medical and

surgical interventions for a given disease grouping. For example, Goldman et al. (1988) evaluated post-infarction prophylaxis with beta blockers and compared the results, in terms of the cost per life year saved, with coronary artery bypass grafting.

Broader comparisons make sense in that an undue concentration on pharmaceuticals may lead to suboptimization. Also, in the long run, virement should be possible between different health care budgets. However, the implication for the Commonwealth government is that the application of the cost-effectiveness guidelines to pharmaceuticals may raise questions about other expenditure, for example on physicians' services. It may also have implications for the State governments in their funding of hospital services. The guidelines will also highlight different rates of inflation between medicines and other categories of health care spending.

4. CONCLUSIONS

The Commonwealth of Australia has taken a major step in being the first country in the world to require data on cost-effectiveness prior to the reimbursement of pharmaceuticals. The implementation of the guidelines will place considerable demands both on the industry and the Commonwealth itself. Indeed, the mode of implementation of the guidelines is probably as important as the guidelines themselves. Much will be learned as companies submit economic evaluations and the PBAC scrutinizes them. In particular, much will be learned about the robustness of economic evaluation methods and their potential for informing policy decisions about the rational diffusion and use of health technology.

If the guidelines are implemented sensibly they could form the basis for better decisions about the rational diffusion and use of medicines, and for setting the balance between expenditure on pharmaceuticals (under the PBS) and on other health care resources. On the other hand, if implemented inappropriately, the guidelines will be nothing more than an expensive way of slowing down the entry of new medicines into Australia and of reducing pharmaceutical expenditure. Only time will tell.

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APPENDIX 1: TEN QUESTIONS TO ASK OF ANY PUBLISHED STUDY

1. Was a well-defined question posted in answerable form?
 - (a) Did the study examine both costs and effects of the service(s) or programme(s)?
 - (b) Did the study involve a comparison of alternatives?
 - (c) Was a viewpoint for the analysis stated or was the study placed in a particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?
 - (a) Were any important alternatives omitted?
 - (b) Was (should) a "do-nothing" alternative (have been) considered?

3. Was there evidence that the programme's effectiveness had been established? Was this done through a randomized, controlled clinical trial? If not, how strong was the evidence of effectiveness?

4. Were all important and relevant costs and consequences for each alternative identified?
 - (a) Was the range wide enough for the research question at hand?
 - (b) Did it cover all relevant viewpoints (e.g. those of the community or society, patients and third-party payers)?
 - (c) Were capital costs as well as operating costs included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, days lost from work or years of life gained) prior to valuation?
 - (a) Were any identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
 - (b) Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?
 - (a) Were the sources of all values (e.g. market values, patient or client preferences and views, policy makers' views and health care professionals' judgements) clearly identified?
 - (b) Were market values used for changes involving resources gained or used?
 - (c) When market values were absent (e.g. when volunteers were used) or did not reflect actual values (e.g. clinic space was donated at a reduced rate) were adjustments made to approximate market values?
 - (d) Was the valuation of consequences appropriate for the question posed (i.e. was the appropriate type, or types, of analysis - cost-effectiveness, cost-benefit or cost-utility - selected)?

(Continued)

APPENDIX 1: TEN QUESTIONS TO ASK OF ANY PUBLISHED STUDY

7. Were costs and consequences adjusted for differential timing?
 - (a) Were costs and consequences that occurred in the future "discounted" to their present values?
 - (b) Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
Were the additional (incremental) costs generated by the use of one alternative over another compared with the additional effects, benefits or utilities generated?

9. Was a sensitivity analysis performed?
 - (a) Was justification provided for the ranges of values (for key parameters) used in the sensitivity analysis?
 - (b) Were the study results sensitive to changes in the values (within the assumed range)?

10. Did the presentation and discussion of the results of the study include all issues of concern to users?
 - (a) Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
 - (b) Were the results compared with those of other studies that had investigated the same questions?
 - (c) Did the study discuss the generalizability of the results to other settings and patient/client groups?
 - (d) Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences or relevant ethical issues)?
 - (e) Did the study discuss issues of implementation, such as the feasibility of adopting the "preferred" programme, given existing financial or other constraints, and whether any freed resources could be used for other worthwhile programmes?

Source: Drummond et al. (1987).