In the summer of 1990 Australia gave notice that it would soon require evidence that new medicines were cost-effective before it would allow payment for these medicines under the commonwealth’s public health system. This requirement has attracted the attention of health policymakers in other nations, for which prescription drug costs make up a growing percentage of health expenditures each year. Cost-effectiveness guidelines may represent the “thin end of the wedge” for pharmaceutical companies, who fear that other major buyers of drugs will take Australia’s lead. The guidelines also may represent the “thin end of the boomerang” for governments, in the sense that development of such explicit guidelines may end up costing governments as much as it costs suppliers. In this Peer Review, British analyst Michael Drummond offers his assessment of the Australian guidelines, followed by comments from American researchers Bernard Bloom and Deborah Freund and colleagues.

Basing Prescription Drug Payment On Economic Analysis: The Case Of Australia

by Michael F. Drummond

Australia has long been regarded by the pharmaceutical industry as a difficult country in which to market its products. 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. A medicine must be listed under the PBS if it is to be reimbursed for use in primary care. 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, prices have been set either equal to, or with a small price premium over, those for comparable medicines, or on a “cost-plus” basis for new classes of drugs.

In the summer of 1990 the common-
wealth government issued new draft guidelines for the pharmaceutical industry on preparation of submissions to the PBAC. The main change was that the submissions would now include economic analyses, first voluntary and then mandatory by January 1993. The PBAC might also request an economic appraisal in the interim, if 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 drugs to which a new drug is to be compared 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 setting and defending prices and promoting pharmaceuticals. In some countries studies have been used in price negotiations; in others with free pricing the industry has been encouraged to undertake cost-effectiveness and cost/benefit studies? However, this is different from a formal requirement, and the pharmaceutical industry is concerned that if this approach to granting reimbursement status proves workable, it could be applied by other countries having concerns over cost-effectiveness. More widely, the Australian guidelines represent an example of the use of economic appraisal to encourage a rational diffusion and use of health technology and, as such, require closer examination.

The New Draft Guidelines

A major methodological issue in economic evaluation is the selection of alternatives for appraisal. The Australian guidelines suggest that usually the drug to which a new medicine is to be compared should be the one most widely used in Australia for the relevant indication, and that comparisons with more than one group of drugs will be necessary in some cases. They also acknowledge that in some situations, with “breakthrough” products, no relevant drug comparator would be currently listed. 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 by the manufacturer.

The approach suggested by the guidelines is broadly in accordance with sound principles of economic evaluation, which argue that all relevant alternatives should be considered. This stands in contrast to the alternatives compared in clinical trials of new drugs, where a placebo or baseline therapy is often the comparator. The notion that recommended rather than actual doses should be used in the comparisons is slightly at odds with the practical approach adopted in selecting comparators. However, one defense 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 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.

Another important feature of economic evaluation methodology is the range of costs and consequences considered. The guidelines suggest that a broad viewpoint should be used in assessing costs, 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 funded only 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 nonmedical costs such as social services (home help, day care, Meals on Wheels, and nursing and physiotherapy services) may be relevant. However, they explicitly exclude (except under special circumstances) the consideration of indirect costs and benefits (that is, impact on productivity).

This last recommendation has generated considerable debate. It could be argued on the one hand that losses in productivity (if patients are unable to 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 productivity when workers are off sick. For short-term absence, lost productivity will be made up by colleagues or by the absent worker on his or her return to work; for long-term absence, it 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 productivity 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 company to justify the inclusion of indirect benefits.

Another aspect of the assessment of costs and consequences relates to their measurement in physical units (for example, hours of medical time, years of life gained, or 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 (that is, effectiveness data rather than efficacy data) and those that are important to patients (that is, 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 closer monitoring of patients.

A final 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 has commissioned research to derive a series of unit prices for standardized medical procedures. These will greatly facilitate comparisons between different companies’ submissions and greatly assist smaller companies that do not have the resources to undertake costing studies of their own. The standardized prices will need to be reviewed frequently, however, to ensure that they reflect the real value of health care resources. 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. However, the guidelines recognize that this approach to economic evaluation is still under development.

Many of the measurements in economic evaluations are imprecise; assumptions are frequently made about the value of key parameters. The guidelines suggest that uncertainty in estimations should be allowed for by undertaking a sensitivity analysis, which explores the impact of different estimates on study results. 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 less-severe diseases than those of participants in the clinical trials that 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 a sensitivity analysis of all of 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 major output of economic evaluations is the calculation of a cost-effectiveness ratio, such as the cost per cure obtained, cost per life year gained, or cost per quality adjusted life year gained. Normally, this is expressed on an incremental basis. That is, compared to the alternative, what extra unit of benefit is gained relative to the extra cost? The Australian guidelines give no firm rules for interpretation of the cost-effectiveness ratios. This is in contrast to the recently announced draft guidelines for Ontario, which suggest “threshold” values for cost-effectiveness. 8 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. 9 Such a league table does not now exist for health care interventions in Australia, and further work would be required to generate one. Finally, although the guidelines suggest that a broad range of costs be considered in calculating the cost-effectiveness ratio, it is likely that the government will also be interested in the financial impact on the PBS budget.

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. Further methodological issues no doubt could have been addressed, in particular those relating to the difficulties of conducting economic analyses alongside clinical trials."" However, the major issues raised by the guidelines are not methodological. Rather, they relate to the logistical problems the guidelines pose, for both the industry and the PBAC, and the way the guidelines will be applied in determining reimbursement status for new medicines.

Main Implications Of The Guidelines

The draft guidelines raise a number of logistical issues for pharmaceutical companies. In particular, they imply that, in the medium to long term, modifications will be required in clinical trials programs. First, additional data on resource consumption will need to be collected. Although it will require additional time and effort, this should be relatively easy to accomplish. More fundamental are the likely modifications required in the choice of comparator therapy and the length of patient follow-up. In the extreme, additional clinical trials may be required to satisfy the new cost-effectiveness criteria, as opposed to the more familiar efficacy and safety criteria required for licensing. These trials will have current therapy, not placebo, as the comparator and will follow patients longer to record essential clinical and economic outcomes. For example, clinical trials of new prophylactic antibiotics will not cease data collection when the patient becomes infected. They will follow the course of disease to establish the costs of treatment.

The companies also may need to undertake further analyses following the clinical trials. For example, extrapolation may be required from the trial setting, which may or may not be in Australia, to regular Australian clinical practice. The problems and prospects for such extrapolations are only just being explored. Also, where the clinical trials measure intermediate endpoints, such as percentage reduction in serum cholesterol, modeling approaches will be required to project long-term outcomes in mortality and morbidity. 10 These data inevitably will be regarded with more skepticism than is afforded to directly observed data from intervention studies. Therefore, the external validity of models will need to be
established wherever possible.

The guidelines also will raise logistical issues for the government. It will need to invest resources in the skills and expertise required to assess submissions made by the companies. It will also need to decide on the extent to which it will enter into dialogue with applicant companies, to ensure that submissions are of the required standard. It may also require additional clinical assessments of company submissions, since the data on the likely relative effectiveness of new drugs in regular clinical use may be different from those already submitted in licensing applications.

The choice of comparator is likely to become a central issue in the assessment of company submissions. Although the guidelines state that the comparator must be the most frequently used drug (or other therapy) for the condition concerned, the tradition to date has been to make comparisons between agents in terms of their pharmacological properties. The application of cost-effectiveness thinking potentially broadens the debate, to encompass non-pharmacological comparators as well. Furthermore, in assessing the likely clinical alternatives, does one consider that treatment patterns may be changing? For example, the most widely used drug for hypertension may currently be a beta blocker, whereas in the future it may be an angiotensin converting enzyme (ACE) inhibitor.

Finally, to make comparisons in terms of value for money, the PBAC needs a series of benchmarks. Should these derive from previous PBAC decisions, which relate primarily to drugs already listed, or should they be based on "league tables" built on cost per quality-adjusted life year, which have well-publicized weaknesses?

The major implications of the guidelines relate to policy. On a general level, it is likely that expectations differ, both within government and outside. Some may view cost-effectiveness criteria as a way to cut costs; others may view them as a way to encourage a rational use of health care resources. The two are unlikely to be the same. Further, companies may view cost-effectiveness studies as a way to justify higher prices.

The link between cost-effectiveness data and pricing decisions requires additional thought and discussion. This is compounded by the fact that companies need 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.

In the short run, it is unlikely that the cost-effectiveness data will determine a new medicine's price directly. However, they do tend to raise a different set of issues relating to pricing. For example, in agreeing to list a new drug, is the PBAC accepting the price given in the cost-effectiveness study? Should companies be bound by the price they propose in their submission? Should a range of prices be assumed, to assess how the cost-effectiveness of a new medicine varies?

Therefore, production of cost-effectiveness data is likely to add considerably to the transparency of listing and pricing decisions. Although data submitted to the PBAC are confidential, applicant companies may seek to publish their economic studies in peer-reviewed journals, particularly when products can be shown to be good value for money. A major implication for the government is that inconsistencies in decision making will be highlighted. Therefore, the new draft guidelines impose extra burdens on government as well as on companies.

**Issues For The Future**

The Commonwealth of Australia has taken a major step in being the first nation to require data on cost-effectiveness prior to
the reimbursement of pharmaceuticals. Implementation of the guidelines will place considerable demands on both the industry and the commonwealth. Indeed, the mode of implementation 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.

All views expressed here are the sole responsibility of the author. The author thanks Vanessa Windass for secretarial assistance.

NOTES

10. Drummond and Davies, “Economic Analysis alongside Clinical Trials.”