Australian Managed Entry Scheme: A New Manageable Process for the Reimbursement of New Medicines?

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**A B S T R A C T**

The global prescription medicines industry argues that it needs high prices for new medicines to meet ever-increasing development costs. While many payers are prepared to pay high prices if they represent good value for money, they first need to feel assured that the value for money estimates are robust. Insofar as new medicines enter the market, limited and uncertain data relating to their performance in normal clinical practice, the value for money case for some medicines may well be driven largely by assumptions than by empirical evidence. The concern to manufacturers is that payers respond to this uncertainty by listing the product at a lower price (which may not satisfy the producer) or not listing the product until more evidence is available (which may not satisfy clinicians and patients). Is there a solution that will satisfy all key stakeholders? Will clinicians and patients continue to have timely access to new medicines and will payers have sustainable reimbursement systems? Will the industry continue to be rewarded with high prices for new medicines so long as they represent good value for money?

In 2011, the Australian Government introduced a managed entry scheme whereby the Pharmaceutical Benefits Advisory Committee will recommend the listing of a new medicine at a price justified by the existing evidence, pending the availability of more conclusive evidence of cost-effectiveness to support its continued listing at a higher price. This commentary examines the Australian Government’s managed entry scheme and issues that are likely to arise from its implementation.

**Keywords:** Australia, decision making

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**Introduction**

The global prescription medicines industry argues that it needs high prices for its new medicines to meet ever-increasing development costs [1]. In some instances, the prices of new medicines are beyond individual patients’ willingness or ability to pay. As a consequence, third-party payers (i.e., governments and other institutions) are under continual pressure to provide their constituents with timely access to new medicines. While many payers are prepared to pay high prices if a product represents “good value for money,” they first need to be satisfied that the estimates of value for money are robust and reasonable. Insofar as new medicines enter the market with limited and uncertain clinical and economic data relating to their performance in normal clinical practice, the value for money case for some medicines may well be driven largely by assumptions than by empirical evidence. The concern to manufacturers is that payers respond to this uncertainty by recommending listing at a lower price (which may not satisfy the producer) or not recommend listing until more evidence becomes available (which may not satisfy clinicians and patients). Is there a solution that will satisfy all the key stakeholders, that is, one in which clinicians and patients continue to have timely access to new medicines, payers continue to have sustainable reimbursement systems, and the pharmaceutical industry continues to be rewarded with high prices for new medicines (so long as they represent good value for money)?

In 2010, the Australian Government and the local pharmaceutical industry announced that they had reached an agreement on the establishment of a managed entry scheme (MES) that would attempt to satisfy the needs of the key stakeholders. The basis of the scheme is that a product will be listed at a price commensurate with it being cost-effective based on the evidence existing at launch. Thereafter, the price of the product will be adjusted (upward or downward) on the basis of cost-effectiveness estimates arising from the generation of further randomized clinical trial (RCT) evidence (postlaunch). This new and innovative policy initiative is likely to be of considerable interest to stakeholders in other jurisdictions who have to deal with the same issues as well as the international ramifications of reimbursement policies in Australia. The purpose of this article was to examine the Australian MES and issues that are likely to arise from its implementation.

**A Framework for Managed Entry**

On May 6, 2010, the Federal Minister for Health and Ageing and the Chair of Medicines Australia, which represents the local medicines industry, signed a memorandum of understanding (MoU) to ensure that all Australians have access to a wide range of subsi-
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MoU would be effective from the date of its execution until June 30, 2011. The MoU will provide some pricing certainty to the innovative pharmaceutical industry and will assist in cutting red tape delivering estimated savings of AU$1.9 billion (US$1.87 billion)."

PBAC takes into account the medical conditions for which the medicine has been approved for use in Australia by the Therapeutic Goods Administration (TGA) as well as its clinical effectiveness, safety, and cost-effectiveness (value for money) compared with other treatments. The Minister of Health and Ageing can list a medicine on the PBS only on a recommendation to do so from the PBAC [6].

When reviewing a submission to list a medicine on the PBS, the PBAC takes into account the medical conditions for which the medicine has been approved for use in Australia by the Therapeutic Goods Administration (TGA) as well as its clinical effectiveness, safety, and cost-effectiveness (value for money) compared with other treatments. The Minister of Health and Ageing can list a medicine on the PBS only on a recommendation to do so from the PBAC [6].

The MoU sets forth provisions that “will help sustain the PBS by delivering estimated savings of AU$1.9 billion (US$1.87 billion).” The savings will be achieved through the expansion of price reform policies introduced in 2007 by the previous government and include expanded arrangements for price disclosure from October 1, 2010, and increased statutory price reductions from February 1, 2011. The MoU will provide some pricing certainty to the innovative pharmaceutical industry and will assist in cutting red tape and improve the time taken to list new medicines on the PBS. After the recent federal election, both political parties agreed that the MoU would be effective from the date of its execution until June 30, 2014 [7].

Of particular interest in this article are clauses 26 and 27 of the MoU, which relate to the development of a MES for the listing of (certain) new medicines; these are reproduced in Figure 1.

The MES is the result of ongoing discussion between PBAC and the Department of Health and Ageing (DoHA) with members of the local medicines industry to enhance the quality and strength of the evidence provided by applicants (i.e., members of the local medicines industry) to the PBAC to support their submissions to list new medicines on the PBS.

The local medicines industry has been pursuing improved PBS listing arrangements, such as an MES, for some time. The industry has agreed to further price reductions for their existing medicines in the MoU to improve their chances of being able to list their new medicines.

The introduction of the MES is one of a number of activities between the government and the pharmaceutical industry to identify and address areas of clinical, economic, and/or financial uncertainty associated with new medicines. Some of the recent activities undertaken to address clinical and economic uncertainty include horizon scanning, meetings between the national regulator (TGA), the PBAC Secretariat, and individual pharmaceutical companies to discuss the design of phase III clinical trials, the development of parallel registration (TGA) and reimbursement (PBAC) processes, and the enhanced postmarket monitoring of medicines [8,9].

Risk-sharing agreements have been used by the DoHA, ostensibly administered by the Pharmaceutical Benefits Pricing Authority, for many years as a tool to manage the financial uncertainty surrounding the listing of new medicines on the PBS. As the Pharmaceutical Benefits Pricing Authority notes in its 2010 annual report: “Increasingly, the PBPA considers deeds of agreement containing risk sharing arrangements to contain overall costs of drugs on the PBS and to manage the financial risks to the Government resulting from uncertainty about drugs utilization. At 30 June 2010, there were 90 deeds of agreement in place or in development” [10].

In February 2011, the DoHA released a framework for the introduction of an MES for submissions to the PBAC for the listing of a new medicine on the PBS. [8] A submission will be considered by the PBAC for an MES under the following conditions:

1. The PBAC accepts that there is a high clinical need for the proposed medicine in the indication requested by the sponsor. The consideration of clinical need would involve an assessment of the prevalence and severity of the disease, whether alternative therapies are available, and the extent to which the proposed medicine is expected to meet the residual need.
2. The PBAC considers that new clinical data will resolve the issues of uncertainty in relation to the extent or value of the clinical effect, which would hence otherwise prevented an initial positive recommendation. For the (RCT)-based MES, this means that a trial protocol is available for the consideration of the PBAC at the time of the original submission and that the PBAC is satisfied that the results will be available within a reasonable time frame (such as the period covered by the deed of agreement [DoA], usually 4 years) to enable the reporting of results aimed at resolving the outstanding area(s) of uncertainty, noting that, in the future, there may also be other circumstances in which either non-RCT-level evidence may be appropriate, such as data collection for the purpose of confirming cost-offsets in economic analyses.

3. Implementation will be via a confidential DoA between the sponsor and the government, as an administrative tool to ensure clear understanding by all parties of the obligations under the MES framework and to ensure that the proposal, if adopted, is being used in conjunction with other existing tools designed to manage the entry of a new medicine, as appropriate[11].

4. Any subsequent review by the PBAC of the evidence specified by the DoA would also include a consideration of all other relevant evidence at that time, including evidence from any Risk Management Plan where mandated by the TGA.

The framework does not state who will propose a listing under the MES. A sponsor could ask the PBAC to list a new medicine under a MES; this is unlikely to happen in the initial submission because it may request a PBS listing at a high price as its initial strategy. There are no details as yet on the MES in the PBAC guidelines.

As part of the initial MES submission, the PBAC will consider the usual clinical and economic evidence available when it reviews the initial submission, as well as the additional section in the submission dedicated to the provision of additional evidence in a resubmission under the MES framework.

Such a thorough and comprehensive submission package is intended to enable the PBAC to do the following:

1. Make a positive recommendation based on current evidence at a price it considers acceptable in view of the evidence available at the time of the initial submission.
2. Identify the key areas of uncertainty for decision making (which may or may not be identical to the uncertainties identified in the submission by the sponsor).

While a future price cannot be specified or guaranteed at the time of the initial listing, the PBAC, in line with its practice of making consistent and reasonable decisions, will reconsider a managed entry resubmission and a price change in the event that the identified uncertainties are resolved by the additional clinical data [8].

A DoA will be used to manage/share the risk associated with a managed entry listing. Table 1 outlines what needs to be specified in a DoA.

The following information will be disclosed in a PBAC Public Summary Document and published on the DoHA Web site:

1. The successful submission/package as a managed entry type of submission
2. The uncertainties identified at the time of the initial consideration by the PBAC
3. The time frame for resubmission to the PBAC

A Public Summary Document associated with the resubmission would note the subsequent evidence as agreed under the DoA and any other available evidence considered by the PBAC. Information consistent with the commercial-in-confidence framework and unpublished data will not be included in the Public Summary Documents [8,12].

### Concerns About the Proposed MES in Australia

#### Inclusion of stakeholders

Insofar as the PBS has many stakeholders, it has been argued that the MoU should have been more inclusive. While the Generic Medicines Industry Association, the body that represents the local generic prescription medicines industry, was not a co-signatory of the MoU and has been a vocal critic of it, there are no signs to indicate that it has any major objections to clauses 26 and 27. This is not unexpected given the members of the Generic Medicines Industry Association are unlikely sponsors of new medicines [13].

While clauses 26 and 27 confer certain obligations on it, the PBAC was also not a co-signatory. It could be argued that PBAC’s interests were represented by the minister and DoHA, despite the fact that the PBAC was established as an independent committee. The introduction of an MES is essentially a policy issue, and it is not PBAC’s role to determine policy. Nonetheless, its implementation may well present some procedural challenges that could have
been considered through consultation in advance of the signing of the MoU.

**Sufficient and sustainable for the PBAC?**

While the introduction of an MES is a new policy option, is it the best possible solution to the problem? The evidence requirements of the PBAC have existed for almost 20 years, and the international prescription medicines industry has been somewhat reluctant to respond fully to the requirements. It does not necessarily make sense for a manufacturer to do so if the evidence requirements of the PBAC are unique. But recent developments indicate that this is not the case. The industry’s focus has shifted from “why” to “what” additional evidence should be generated and “when.” It could be argued that the relevant clinical evidence should be generated in phase III rather than in phase IV as implied in the MoU. Such criticisms may be founded in some instances but not in others; the expectation that all phase III clinical trials should be final outcomes trials is perhaps an unrealistic one. Nonetheless, other ongoing local and international developments, such as early payer engagement, should lead to an improved understanding on what clinical evidence can and should be produced in the pivotal phase III clinical trials [9].

The MES is different to a procedure the PBAC has used from time to time to facilitate the initial and ongoing PBS listing of certain new medicines. In 2001, the initial submission to list imatinib on the PBS for patients with chronic myeloid leukemia in the chronic phase who had failed treatment with interferon-α was supported by the results from an uncontrolled phase II study with a surrogate measure, the proportion of patients who achieved a major cytogenetic response after 12 months, as the primary outcome measure [14]. The PBAC was concerned about the uncertainty surrounding the relationship between the surrogate measure and survival and thus the estimated (modeled) incremental gain in survival with imatinib over its comparator, hydroxyurea. [15]. The listing of imatinib was delayed while the PBAC sought further evidence and advice to validate major cytogenetic response as a surrogate measure as well as further survival data from the ongoing phase II study. The availability of an MES could have facilitated its earlier listing. It is also different to the PBS listing of bosentan for patients with pulmonary arterial hypertension in 2004 where the source of evidence on its clinical performance to support its continued listing was a local patient registry [16,17].

Some key elements, such as “high clinical need” and “fit-for-purpose evidence,” have not been defined and may be disputed. In the end, the PBAC will be the judge. The initial deed will need to consider all possible clinical scenarios. Clause 27 indicates that the main focus is likely to be the magnitude of the incremental clinical effect (i.e., efficacy).

There is no mention in the framework on whether the comparator in the clinical trials needs to be a current relevant active treatment or whether placebo will be acceptable. Likewise there is no mention on whether the trial should be designed/powered for superiority or noninferiority. It is reasonable to assume that active comparator trials designed for superiority will be more suited to an MES and thus be acceptable to the PBAC.

While not explicitly stated, it is likely that the evidence provided in the initial submission to support the listing of the medicine will be on an acceptable surrogate outcome whereas the evidence provided in the resubmission to support the medicine’s continued listing will be on a payer-relevant (i.e., final) outcome. There could be some initial challenges if the PBAC is not that familiar with the surrogate outcome or has been inclined not to accept it in the past for other medicines.

Problems may also arise if the results from the relevant clinical trial indicate a different comparative safety profile (i.e., there are unforeseen safety issues) and an unexpected risk-benefit trade-off will need to be made.

**Reasonable for industry?**

The MES is likely to be an option only for the sponsors of certain new medicines, that is, those that will be used long term (either continuously or intermittently) to treat patients with chronic diseases where it is unreasonable to expect long-term outcomes data at the time of an initial PBAC submission. Like the imatinib example, a crucial issue may be the acceptance by the PBAC of the surrogate measure from the phase III trial. The difference here is that the resubmission will be supported by data from a proper outcomes trial rather than by longer-term follow-up data from the phase III trial. The 2008 Surrogate to Final Outcomes Working Group report to the PBAC noted that the task of evaluating surrogate measures does not have a simple solution. Nonetheless, the Surrogate to Final Outcomes Working Group developed an evidence framework and agreed that some guidance can be given regarding the relative importance of the different dimensions in the framework, with not all dimensions contributing equally to the overall assessment. In the framework, randomized trial data is rated more highly (i.e., provides stronger support) than nonrandomized data [18].

Sponsors will need to give serious thought as to when to request consideration of an MES. Should they request this when submitting their initial submission or later if and when the submission hits challenges after evaluation by the Pharmaceutical Evaluation Section to the point that there is a real risk that the submission will be rejected by the PBAC? Why would a sponsor propose a low price for a new medicine upfront without having received any feedback on how the submission has fared? An MES submission might not be subject to cost-recovery measures if it meets the current exemption criteria [19].

**Will it impact prices?**

Sponsors will probably agree to an initial “low” price for a new medicine only if they are satisfied that there is a reasonable chance that they will be able to achieve a fairer (higher) price after the supply of the results from the clinical trial to the PBAC in a resubmission. While it will not be possible for the DoHA to state exactly what price will be offered, it will need to be reasonably clear on this.

Sponsors will agree to an initial “low” price for a new medicine only if they are sufficiently confident that it will not have an effect on its price in other countries through international reference pricing. Confidence will be higher if the initial price is not publicly disclosed.

The results from the clinical trial may indicate a price reduction rather than a price increase. There is no discussion in DoHA’s MES framework on this scenario. It is not clear what sponsors would do here. Provisional listings are not possible under the current legislation. If the trial shows that the medicine performs poorer than expected, then a price decrease may well be sought. If the results indicate a benefit only in a particular patient subgroup, then the medicine’s continued listing (at any price) for this patient subgroup is a possibility; this will probably occur only if the subgroup has been prespecified in the clinical trials protocol. If the government and medicine’s sponsor cannot agree on the actual price decrease (this should be considered in the DoA), then the medicine will probably be delisted. (The formal procedure is that PBAC make a recommendation to delist for the minister to consider.)

**Competitive effects on industry**

A subsequent initial submission from another sponsor seeking the listing of a different medicine to treat patients with the same dis-
ease/condition as a medicine already listed under an MES could have the potential to alter the extent of future clinical need but not the health gain. The first medicine will have the requisite clinical trial underway, whereas the competitor might not have a similar ongoing RCT. There could be several possibilities. For example, the competitor medicine may have

1. Data on the surrogate measure that supported the listing of the first medicine with an ongoing clinical trial that will provide similar evidence in the resubmission for the first medicine.

2. Data on the surrogate measure that supported the listing of the first medicine with an ongoing clinical trial. The application to the PBAC would be based on a cost-minimization analysis in comparison with the first medicine by way of the surrogate outcome.

3. Data on a final outcome.

The price of the second medicine will be determined by using the usual criteria; the key drivers will be the comparability of the two medicines and the degree of confidence the PBAC would have that the incremental modeled health quality-adjusted life-year gain for the first medicine in its initial submission and confirmed by the supply of RCT data in a resubmission could be extrapolated to the second medicine to maintain the cost-minimization analysis of the initial submission.

**Better access for clinicians and patients**

Continued timely access to new medicines is a goal of the MES that is shared by all stakeholders. There is no agreed local definition of “timely access.” One approach could be to measure the time from the initial PBAC submission to PBS listing. It is not possible to measure this now for new medicines given submission dates are not made public. Nonetheless, they can be inferred with reasonable accuracy. It is unclear what level of improvement of access would be seen as being meaningful.

Protracted discussions on some of the finer points of the DoA may result in delayed listing/access. Key aspects of the DoA will not be made public, and so one will not be able to determine what the cause(s) of the delay is. Because all deeds are confidential, there will not be a learning effect for other sponsors who might be interested in the MES concept.

**International considerations**

The MES is yet another interesting Australian health care policy experiment. The specific dual requirements for high-level (i.e., RCT) clinical evidence and a low initial price with an explicit mechanism for a potential price increase on the basis of the RCT evidence indicate an operating model that is novel. It is too early to speculate on its likely acceptance and use. It may be an option that payers in other jurisdictions could implement, once early to speculate on its likely acceptance and use. It may be an option that payers in other jurisdictions could implement, once

**Conclusion**

The MES framework looks promising on paper, but the real problems may surface only in its implementation. It may well spark a lot of interest but might engage only a few takers in the short term. There are no examples to date. Local and international observers might not be able to learn that much from the players given the key aspects of any MES are likely to be locked up in a DoA.

**REFERENCES**


