PBAC guidelines should help patients gain the fastest access to the best medicines

MSD Submission to the Public Consultation on

the draft revised PBAC Guidelines (Draft Version 5.0)

5th April 2016

Public

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Timely access to the medicines that Australians need, at a cost individuals and the community can afford is one of the objectives of the National Medicines Policy (NMP)[1]. The guidelines for submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) have an important role to play in achieving this outcome – they provide detailed, valued and important technical guidance for sponsor companies on what information is required by the PBAC and its subcommittees to assist them in making a recommendation to the Government to list a medicine on the PBS.

In attempting to balance health needs and responsible fiscal discipline, the NMP states that access processes should be made as **simple** and **streamlined** as possible, so that subsidisation of medicines is **timely**, mechanisms understood and **unnecessary administrative barriers and expenses avoided**.

In announcing the review on 25th April 2015, the Minister for Health, the Hon. Sussan Ley, highlighted the need "…*to ensure the guidelines remain appropriate*", and noted the timeliness of this review given emerging technologies and expectations regarding subsidy of drugs based on changing evidence. MSD agrees that this review provides an excellent opportunity to make the guidelines contemporary and respected as world's best practice. In doing so, any changes should be consistent with the objectives of the NMP, namely the provision of timely access to affordable medicines. For this reason, MSD recommends that this update:

1 Adopts best practice methodology
2 Guidelines should support evidence and approaches that enable earlier access
3 Removes unnecessary complexity that will not add value to decision-making
4 Refines PBAC submission and evaluation processes & collaboration
5 Monitors implementation to ensure the objectives of the NMP are being fulfilled

1. Guidelines should adopt best practice methodology

Best practice methodology should be included in the guidelines. Failure to do so will result in access delays due to fundamental misalignment on the perceived value of new medicines.

MSD recommendations:

1.1 Selection of the main comparator: the text in the current guidelines (v4.5) should be retained
1.2 Nonhealth outcomes should be incorporated into the base case analysis for a submission
1.3 Methods and approaches on eliciting and quantifying patient preferences should be included
1.4 The half a page limit for describing the expected impact of a proposed medicine on patients and the healthcare system should be removed

[1] Department of Health. National Medicines Policy Document. Available: http://www.health.gov.au/internet/main/publishing.nsf/content/national-medicines-policy

1.1. Retain current comparator guideline

Draft version 5.0 provides revised guidance on the selection of the main comparator, with new and explicit reference to section 101(3A) of the National Health Act 1953 and the addition of:

"Where multiple alternative therapies could be used for the majority of patients, the PBAC cannot recommend a new medicine at a price that is substantially higher than the least expensive alternative medicine unless it is satisfied that the new medicine provides a significant improvement in efficacy or reduction in toxicity over that alternative medicine."[2]

This is a change from the current version of the guidelines (v4.5), where selection of a comparator is based solely on an assessment of the therapy that would be replaced in practice.[3] Health technology assessment requires an assessment of whether the costs of the new intervention provide good use of resources when considering the clinical benefit expected, relative to what is currently used in practice.

MSD is concerned that the proposed changes undermine the scientific and evidence-based principles of this decision to one based solely on cost. Ultimately this will result in access delays due to submissions being rejected as a result of disagreements on comparator selection, uncertainty introduced by the need to present non-randomised comparisons,[4] and comparator erosion becoming more common, making it more difficult to demonstrate value. MSD recommends that the text in v4.5 of the current guidelines be retained, thereby aligning with i) international best practice for the purposes of determining the main comparator, and ii) the remit of the PBAC as specified in the National Health Act.

1.2. Include nonhealth outcomes in base case analysis

Whilst draft version 5.0 provides some guidance on how to incorporate nonhealth outcomes, these can only be included in supplementary analyses:

"If a claim is made for a change in nonhealth outcomes, or the submission identifies health-related outcomes in people other than the patient receiving treatment (eg quality-of-life benefits for family, decreased carer burdens), these should not be included in the base-case evaluation, but may be presented as supplementary analyses (see Appendix 8).

Nonhealth benefits should be considered as part of the base case analysis for determining cost effectiveness. For some medicines, nonhealth-related benefits and associated cost savings can be significant. For example, there are numerous disease-modifying medicines currently being assessed in late stage trials in Alzheimer's disease. The hope is that these medicines delay the onset and/or slow the progression of this debilitating disease. In this instance, the nonhealth benefits - caregiver quality of life, caregiver productivity, reduced use of aged care facilities – might be as important as the direct health benefits. Unless these types of medicines are valued to their full extent through inclusion of nonhealth benefits in the base case analysis, access will likely be delayed.

[2] Guidelines for Preparing a submission to the PBAC, Version 5.0 (draft for public consultation) page 16
[3] https://pbac.pbs.gov.au/section-a/a4-main-comparator.html
[4] Clinical studies tend to compare a new interventions to best available therapy rather than cheapest therapy; the implication is that submissions would need to rely on non-randomised comparisons.

1.3. Include methods for incorporating patient values

Incorporating the patient perspective on the value of medicines is increasingly being recognised as a critical element of health technology assessment. For example:

- Canada has a formalised process through which patient input is derived – in their decision-making framework[5] "alignment with patient values" sits alongside "cost effectiveness", with the framework noting that no element over-rides another.
- FDA has developed a structured process for eliciting patient preferences (shared recently with attendees of the forum Room with a Patient View, Sydney on 25th to 26th February 2016).

In contrast, v5 of the PBAC guidelines does not provide any additional information on how the patient perspective can be incorporated into the submission, nor how it will be considered in decision-making. A description of methods (e.g. qualitative or quantitative) and approaches that could be used to measure patient value should be included in an attachment to the guidelines. Any approaches used should include clear guidance to assist the consumer navigate the process and provide their input in a meaningful way. An example of an approach that was used to elicit and quantify preferences of Australian patients suffering from chronic lymphocytic leukaemia was recently presented at ISPOR in 2015[6].

1.4. Remove the half page limit for describing the rationale for PBS listing

The inclusion of a section intended to present and justify why Government should subsidise the proposed medicine, by looking at "*the expected impact of the proposed medicine in terms of patients' health, health-related costs or cost offsets, and the impact on issues such as access or equity*", is a welcome addition. Given its importance to decision-making, the current half a page limit is unreasonable and should be removed.

2. Guidelines should support evidence and approaches that enable earlier access

MSD recommendations:

2.1 Consider all adjustment for treatment switching approaches on their own merits on a case-by-case basis; move this section to an appendix.
2.2 Acknowledge that the use of nonrandomised comparisons is reasonable when a proposed new therapy provides an important clinical benefit in an area of high unmet need; include appendix to provide guidance on the use of observational data to inform estimates of effectiveness
2.3 Include an appendix to describe managed access programs

2.1. Consider all adjustment for treatment switching approaches on their own merits

The inclusion of methodological guidance on how to adjust for treatment switching (crossover) is a welcome addition to v5 of the guidelines. However, MSD is concerned that the guidance relegates methods recognised

5 https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20(pERC)/pcodr_perc_deliberative_frame.pdf

6 Glase KM et al. 2015. A systematic quantitative approach to incorporating the patient perspective into health technology assessment decision making. ISPOR Philadelphia. PHP180.

by international experts as being valid and appropriate – e.g. inverse probability of censoring weights (IPCW) and rank-preserving structural failure time (RPSFT) model – to second choice. These methods should be considered as suitable as other adjustment methods. It should be left to the sponsor to propose and justify the chosen approach on a case-by-case basis. Given this is an evolving field, it would be better if this section is presented in an appendix, to facilitate more regular updates to keep in line with world's best practice.

2.2. Include approaches to facilitate better use of non-RCT data for important new drugs in areas of high unmet need

The draft updated guidelines acknowledge that there are situations were nonrandomised comparisons can provide useful information, for example in rare conditions. Another circumstance that should be included is when the proposed new therapy provides an important clinical benefit in an area of high unmet need.

In these situations, regulatory pathways across the globe have evolved to provide mechanisms for earlier registration, for example breakthrough designation / priority review mechanisms in the US, the EAMS scheme in the UK, provisional registration in the EU, etc. Generally, these mechanisms allow for initial registration using less robust evidence from Phase I or Phase II single arm studies, with confirmatory evidence to be provided once available. It would make sense that in situations such as these, reimbursement decisions should not have to wait for information from the confirmatory trials.

Recognising that non-randomised studies may be used either to complement the evidence base represented by randomised controlled trials or as the source of evidence for a specific effectiveness parameter if randomised data are not available, NICE recently commissioned Technical Support Document No. 17 – "The use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data" (Faria et al. 2015).[7]

The objectives of this guidance document are to (i) summarise commonly available methods to analyse comparative individual patient data (IPD) from non-RCTs to obtain estimates of treatment effect to inform NICE Technology Appraisals (TAs) and (ii) to propose a set of recommendations to improve the quality and transparency of future assessments.

In the interests of ensuring that the PBAC guidelines remain aligned with world's best practice, MSD proposes the inclusion of an appendix covering these aspects in v5 of the guidelines.

2.3. Include an appendix to describe managed access programs

Managed entry schemes were introduced in 2011 as "*a mechanism whereby the PBAC may recommend PBS coverage at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price*".[8] In March 2015, the PBAC considered and made revisions to a draft 'Framework for the Managed Access Programme for submissions to the PBAC'.[9]

[7] Available: http://www.nicedsu.org.uk/TSD17%20-%20DSU%20Observational%20data%20FINAL.pdf
[8] Available: http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-PBAC-submissions
[9] Available: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/11-03-appendix-a-managed-access-programme-draft-framework.pdf

In the last year, a number of important new medicines (e.g. pembrolizumab, crizotinib, trametinib) were subsidised on the basis of the principles outlined in the managed access program framework.

Given the opportunity that this framework provides to facilitate earlier access to important new medicines, and given the need to provide guidance in regards to the concepts and principles that should be considered, it would help if this framework is described in an appendix to the guidelines.

3. Remove unnecessary complexity that will not improve decision-making

There are a number of instances in the draft revised guidelines where new information or analyses requests have been introduced that will not improve decision-making. On the contrary, they are likely to create unnecessary complexity, and will impose significant additional red-tape for sponsor companies. This could result in access delays, either through increased rejections resulting from the inability of sponsor companies to comply with all of the new requirements, or alternatively delays in submitting applications in order to address the onerous information requests. Examples of non-value adding Information requests follow.

MSD recommendations:

3.1 Remove requirement to provide FDA or EMA assessment reports (page 7)

TGA assessment reports are already provided with the submission; assessment reports from overseas authorities are less relevant to inform decisions in the Australian context.

3.2 Remove requirement to provide supplementary comparisons to future comparators (page 18)

It is difficult to predict whether or not a potential future comparator is under TGA review and/or whether a subsidy application has already been submitted. Regardless, a formal comparison of two new medicines is not critical to decision-making, especially since in the large majority of cases both medicines would present an economic analysis against the same common comparator. In these instances, PBAC has regularly formed a pragmatic view on the comparative effectiveness and safety of these new therapies, particularly if the products belong to the same class.

3.3 Streamline information requests in sections 2 and 3

Section 2 and 3 of the draft revised guidelines have substantially increased the information requests to support the clinical and economic analyses, respectively. In regards to the latter, the new draft guidelines now include an additional, time-consuming validation step. These additions create the risk that submissions might end up being delayed in order to comply with the new requirements, or be rejected due to uncertainties / incomplete analyses – both these circumstances will result in delayed access to important new medicines.

4. Refine PBAC submission and evaluation processes & collaboration

Whilst this review's primary focus is updating of methodological guidance, an overhaul of current processes is crucial if this review is to provide Australians with the fastest possible access to the medicines that they need. Below are a number of proposals that would help achieve this aim.

MSD recommendations:

5.1 Implement fit for purpose assessment process, e.g. tiering of submissions, rolling submissions
- Reduce red-tape for simple reimbursement submissions
- Longer, more highly consultative evaluation pathway for the early consideration of important new medicines

5.2 Increase transparency and predictability of post-PBAC processes

5.3 Implement parallel-processing for minor submissions

5.4 Co-dependent assessment pathway including PASC and MSAC steps, should be further streamlined to avoid unnecessary delays

5. Implementation should be monitored to ensure the objectives of the NMP are being fulfilled

Introduction of the new guidelines is a significant change – appropriate training for industry and evaluation groups would need to be provided, and transition arrangements implemented.

Equally important is the need to observe and measure the success of the PBAC guideline update. Ultimately, if this fails to enable the funding of important new medicines in a timely manner, it would have been a futile exercise.

To monitor this, MSD proposes that a review is done by respected international experts on the implementation of these guidelines with respect to their use in submissions and their impact on decision-making, and compare this with overseas best practice HTA approaches. This review would be done 2 years post-implementation, with the report and feedback provided to industry. This could then inform further refinements to the guidelines as needed.

MSD recommendations:

5.1 Conduct appropriate training for industry and evaluation groups

5.2 Implement reasonable transition arrangements

5.3 Conduct a review by respected international experts on the implementation of these guidelines with respect to their use in submissions and their impact on decision-making, and compare this with overseas best practice HTA approaches