Submission to the Public Consultation on the draft revised Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines (Draft Version 5.0)

5 April, 2016

Medicines Australia is the peak organisation representing the research-based pharmaceutical industry in Australia. Our members comprise over 80% of the prescription medicines market by value and play an integral role in delivering better health outcomes for Australians. Medicines Australia's members include the vast majority of sponsors who seek to make their medicines available to Australian patients via the Pharmaceutical Benefits Scheme (PBS) via a submission to the PBAC.

Introduction

Medicines Australia welcomes the public consultation on draft Version 5.0 of the Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines. The PBAC Guidelines Review (hereafter the review) is an important and timely opportunity to maintain Australia's standing with world leaders in Health Technology Assessment (HTA).

The PBAC Guidelines 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. The Guidelines are also informative for the evolution of HTA methods, health policy and clinical trial design domestically and internationally. It is for these reasons that it is important that they are contemporary, comprehensive, and consistent with world's best practice. Indeed, in announcing the review on 25 April 2015, the Minister for Health, the Hon. Sussan Ley, stated that *"This review demonstrates a proactive approach from the PBAC to ensure the guidelines remain appropriate"*, and "*It is particularly timely given emerging technologies and international calls for Governments to subsidise drugs based on changing evidence…*"

Medicines Australia acknowledges its ongoing contribution to the review, through its membership of the Guidelines Review Steering Committee (GRSC) and representation on the Drug Utilisation Subcommittee (DUSC) and Economic Subcommittee (ESC) of the PBAC. However, it is worth noting that comments from DUSC and ESC will not include Medicines Australia's views, which will be provided separately on behalf of our members. As part of membership to the GRSC, Medicines Australia submitted a comprehensive technical review of draft Version 5.0 of the PBAC Guidelines directly to the GRSC and Adelaide Health Technology Assessment (AHTA) for consideration in February 2016.

The purpose of this submission is to respond to the public consultation and provide a broader appraisal of the review and the revised guidelines on behalf of our members, and to identify key areas where further work should be conducted.

Medicines Australia recommends that the review:

1. Consider the draft Version 5.0 against the initial goals for the review, including achieving world's best practice Guidelines;
2. Assess key guidance in the draft Version 5.0 requiring further consideration; and
3. Consider appropriate transition arrangements and education for users of the Guidelines.

Recommendations

1. Consider draft Version 5.0 against the initial goals for the review, including achieving world's best practice methods Guidelines

Medicines Australia supports the general process for the review to date, including formal public consultation on areas of the Guidelines requiring updating, and the current public consultation on draft Version 5.0. The review has been well served by the formation of a steering committee consisting of experts in HTA and considerable experience with PBAC submissions across government, academia and industry. The committee's primary role has been to provide direction to AHTA in conducting the review. Medicines Australia has welcomed the willingness of the GRSC and AHTA to consider the industry's position and recommendations and to incorporate a good number of these throughout the review.

While acknowledging the significant body of work completed in just over 6 months, Medicines Australia is however concerned that the following have been given inadequate consideration by the GRSC and AHTA:

i) submissions to the review's first call for public consultation,
ii) recommendations from the Senate Community Affairs References Committee's inquiry into "Availability of new, innovative and specialist cancer drugs in Australia"[1], and
iii) review and incorporation of international best practice HTA methods.

There are two common themes from initial submissions to the review, the Senate report, and evolving HTA processes internationally. These relate to i) the changing landscape of clinical trial design/clinical

[1] http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Cancer_Drugs/Report

trial evidence and ii) the need for greater patient and clinician input throughout the HTA decision making process. Medicines Australia believes that more thorough consideration of these factors is required to ensure the revised Guidelines meet the stated goal of world's best practice.

Medicines Australia acknowledges that the review is intended to be completed by mid-2016 with the finalised Guidelines to be published shortly thereafter. However it argues that full deliberation of the above should be prioritised ahead of pre-specified timeframes, and if necessary, the timelines for the review should be extended.

2. Assess key guidance in the draft Version 5.0 of the Guidelines requiring further consideration

Medicines Australia seeks to emphasise key Guidance issues needing re-consideration, including:

- Revised guidance on the selection of the Main Comparator;
- Guidance not adequately covered in draft Version 5.0; and
- Procedural elements not adequately covered in draft Version 5.0.

Revised guidance on the selection of the Main Comparator (page 16)

Version 5.0 provides draft 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 inclusion of the specific text outlined below:

> *"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 compares with text in Version 4.5 of the PBAC Guidelines regarding choice of Main Comparator referring to:

> *"Therapy that prescribers would most replace with the proposed medicine in practice if the PBS subsidises the proposed medicine as requested[3]*."

Medicines Australia vigorously opposes this proposed addition to the PBAC Guidelines and explicit focus on the "least expensive alternative medicine", citing interpretation and selection in this manner has the potential to:

- further exacerbate existing concerns regarding comparator erosion and linkages between the F1 and F2 formularies;
- raise reference pricing implications for all PBS-listed medicines linked by therapeutic relativity if a new proposed drug is compared with the least expensive comparator within a reference group;
- further devalue innovation; and
- delay access to new medicines.

Medicines Australia recommends that the abovementioned Version 4.5 text be retained in Version 5.0 of the PBAC Guidelines, 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.

Medicines Australia has consistently raised identification and agreement of the Main Comparator as a significant issue for the industry. Medicines Australia intends to work with government in 2016 to address the policy settings and legislative basis for the selection of Main Comparator.

Guidance not adequately covered in draft Version 5.0

Areas of the PBAC Guidelines that have been consistently raised by members as requiring updating and/or clarification include the Main Comparator, indirect comparisons, surrogate-to-final outcomes, patient cross-over in clinical trials, discount rates and financial estimates spreadsheets. Medicines

[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

Australia acknowledges that there has been positive movement on some of these areas, however recommends that further attention is required prior to finalising these areas of the Guidelines.

Medicines Australia considers that there is still an opportunity for betterment of draft Version 5.0 through the inclusion, or expansion, of guidance specific to the following key topics that have been raised again by members as not being fully addressed:

i) *Evolution of clinical trial design –* Medicines Australia acknowledges that the draft Guidelines reference different levels of clinical evidence, such as non-randomised controlled trials, and the role they play in particular settings. However, it is uncertain how such different levels of evidence will be assessed by the PBAC. Medicines Australia reiterates the need for specific guidance on how such information will inform pragmatic decision making with regards to 'fit for purpose' evidence. This is especially relevant in light of evolving regulatory decision making processes across the globe (including the TGA), which are trending towards providing accelerated registration, based on earlier non-phase III data, for promising breakthrough therapies for unmet clinical need.

Evolution in clinical trial design has been recognised by the Minister for Health, the Hon. Sussan Ley (refer to quote in Introduction) and more recently the Senate Community Affairs References Committee, whose report on "*Availability of new, innovative and specialist cancer drugs in Australia"*[4] recommended that the Australian Government initiate a comprehensive review of the system for the registration and subsidisation of medicines – with a focus on the adoption of more flexible evidentiary requirements.

Medicines Australia appreciates that flexibility and pragmatism does occur in an ad-hoc manner within the current PBAC decision making framework, however believes that greater recognition of evolving clinical trial design within the structured framework of the Guidelines will assist sponsor companies better present available clinical trial data. Examples of the need for further guidance on evidentiary requirements, standards and methods relate to studies that are adaptive in nature, have a paucity of data, and/or treat rare diseases.

ii) Improved patient & clinician involvement – Medicines Australia recognises the great advances over the last decade in terms of improved patient and clinician involvement in the PBAC decision-making process. However, it is believed that further improvements to patient and clinician input can be informed through examination of the guidance of other HTA jurisdictions (e.g. NICE – National Institute for Health and Care Excellence, SMC – Scottish Medicines Consortium, CADTH – Canadian Agency for Drugs and Technologies in Health).

The Senate Community Affairs References Committees report on "*Availability of new, innovative and specialist cancer drugs in Australia"*[5] also recommends "*enhancing and formalising mechanisms for consumers and clinicians to play a more central and substantial role in the evaluation of new medicines and new indications for already listed medicines*."

iii) Inclusion of methods related to broader value of medicines – Medicines Australia calls for inclusion of contemporary and thorough guidance on assessments relating to the full societal impact of a new medicine i.e. the consideration of non-health benefits and costs, reductions in welfare dependence and disability payments for patients and/or their caregivers. Greater attention to these factors has consistently been called for by the industry and other key stakeholders. Medicines Australia does note that guidance on patient-relevant and societal factors has been included in draft Version 5.0 (e.g. patient preference, productivity gains, other indirect costs) however, it is disappointing that these have been relegated to areas of "supplementary" consideration[6]. The draft Guidelines do not outline how the PBAC will consider such supplementary information in its decision-making process. There may be instances in the future where broader societal costs are a primary consideration for new medicines and this potential should be recognised in the Guidelines.

iv) Inclusion of methods specific to biosimilar submissions - Medicines Australia has also previously called for guidance on the evidentiary requirements for biosimilar medicines, in particular the evidence reviewed by the TGA and evidence considered by the PBAC in determining

[4] http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Cancer_Drugs/Report
[5] http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Cancer_Drugs/Report
[6] Guidelines for Preparing a submission to the PBAC, Version 5.0 (draft for public consultation) page 19

biosimilarity versus substitutability. Consideration should be given to instances where biosimilar medicines may need to follow the major submission pathway depending on the clinical assessment necessary for the purpose of substitution and prescribing directions. Further guidance on this would be welcomed in the final Version 5.0 and is particularly relevant as more biosimilars will shortly be seeking registration and reimbursement.

In addition to these issues and based on feedback from its membership, Medicines Australia is concerned that the revised guidelines create further regulatory burden for sponsors, evaluators and the PBAC. In particular, Medicines Australia notes that the revised wording relating to comparator selection results in the potential need for sponsors to undertake comparisons against multiple comparators, in addition to the need for multiple economic analyses and evaluations.

Procedural elements not adequately covered in draft Version 5.0

While the review has been specific to methodologies within the PBAC Guidelines, it is impossible to ring-fence the update from other inter-related guidance. As such, Medicines Australia welcomes the initiation of the Review of the Manual of Resource Items and their Associated Costs and the inclusion of co-dependent technologies guidance within the current draft version 5.0 of the PBAC Guidelines.

However, Medicines Australia is disappointed that work specific to updating guidance related to pre- and post-PBAC processes has not begun. Feedback from the Medicines Australia membership is that clarity around pre- and post- PBAC processes is as important as the PBAC Guidelines themselves; however, is distinctly lacking.

To date, there has been little transparency of the progress on addressing the recommendations related to procedural improvements and evolutions suggested by stakeholders during the initial public consultation process. Whilst Medicines Australia understands that there is work underway through various forums, Medicines Australia wishes to reiterate the key issues raised by the industry and other stakeholders throughout the review, including:

- Providing mechanisms for greater clinician and patient involvement along the continuum of the PBAC evaluation process, including capturing patient experiences, as well as a better understanding of the decision making process itself and its outcomes (as mentioned above);
- Providing a mechanism for minor submissions and vaccine submissions to progress via the parallel process pathway as currently occurs for major submissions;
- Exploring, in partnership with industry, a process for the tiering of submissions with the intention of a fit-for-purpose PBS application process, by providing more resources and evaluation time for complex submissions and streamlining simple submissions;
- Implementation of an online portal for the provision of PBAC submissions and correspondence during the process between the PBAC Secretariat and the sponsor;
- Reviewing and improving the current process for PBAC hearings for sponsors and formalising consumer hearings to optimise value for the PBAC during the decision making process; and
- Providing clarity with regards to post-PBAC pricing processes, including timing of deliverables and communication and alignment within different areas of the Pharmaceutical Evaluation Branch.

Such process improvements are consistent with the findings and recommendations of the Senate Community Affairs References Committee for Inquiry: *Availability of new, innovative and specialist cancer drugs in Australia, which recommended "options for improving the operation of assessment processes"*[7].

Medicines Australia calls for the Department/Government to initiate in a timely manner a review and update of pre- and post PBAC processes, in collaboration with the industry and other key stakeholders.

3. Consider appropriate transition arrangements and education for users of the guidelines

There is a significant lead time for sponsors in preparing submissions to the PBAC, therefore guidance on the transitional arrangements between Version 4.5 and Version 5.0 of the Guidelines will need to be made clear for sponsors and other key stakeholders. Medicines Australia recommends a period of no less than two PBAC cycles to enable transition across to Version 5.0 of the Guidelines.

[7] http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Cancer_Drugs/Report

Furthermore, there are efficiencies to using legacy guidelines in instances where multiple submissions to PBAC may be required.

Once finalised, it will be necessary to implement regular monitoring and reporting on how the PBAC Guidelines are being used in practice. Rolling updates of methodologies are also recommended to ensure the Guidelines remain consistent with the updated literature. Medicines Australia understands the approach taken by the UK's National Institute for Health and Care Excellence (NICE) Decision Support Unit, enables methodologies to be updated easily outside of the Guidelines document itself. As outlined in its initial public submission to the review, adopting this type of approach would reduce red tape and ensure the Guidelines remain contemporary and 'world's best practice' through more regular updating.

As with previous significant changes to policy or Guidelines, Medicines Australia recommends that considerable education be offered to industry, evaluators and other key stakeholders. It is imperative to ensuring a common understanding and interpretation of the Guidelines, including their intersection with the PBAC remit, as outlined in Section 101 of the National Health Act (1953). Previous releases of PBAC Guidelines updates have been associated with joint stakeholder workshops. Medicines Australia recommends similarly that this occur with the roll-out of Version 5.0 of the PBAC Guidelines. Such workshops could include best practice examples/case studies of how to apply the guidelines once finalised.

Summary:

As new technologies are developed and drug discovery and research becomes more intricate, it is vital to constantly and regularly review the Guidelines, processes and standards that govern the system. The current review provides an excellent opportunity to update the PBAC Guidelines to ensure Australia's reputation as having a world-leading HTA system is maintained into the future.

Medicines Australia has engaged proactively and in good faith throughout the review, and acknowledges that a review of this nature is multifaceted and complex, and that the issues raised in this submission may not be exhaustive.

Medicines Australia is pleased that a good number of its recommendations and views have been taken on board and implemented into the Guidelines so far, and has generally supported the level of engagement with stakeholders and process for the review.

Notwithstanding, the feedback from members and other stakeholder is that the revised Guidelines represent a missed opportunity to deliver world's best HTA practice or advice. To that end, Medicines Australia encourages further dialogue throughout the remainder of the review on those recommendations that have not yet been adequately implemented, including those raised in this submission.

Medicines Australia also seeks to further address the legislative and policy settings underpinning the guidelines that may impede the realisation of world's best practice, such as the wording on the selection of the main comparator. Medicines Australia will endeavour to pursue this issue following the review in 2016 through such forums as the Access to Medicines Working Group (AMWG) or with the Minister for Health.

Medicines Australia supports timely access to innovative, safe and effective medicines and recognises that this is a shared goal of the Government, PBAC, patients, medical practitioners, and the pharmaceutical industry. Central to this goal is a predictable, reliable and robust PBAC process, underpinned by world's best practice evaluation methods and Guidelines.