



Submission to the Public Consultation on the draft chapter “*Product Type 4 – Hybrid Technologies and Co-dependent Technologies*” of the draft revised Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines (Draft Version 5.0)

11 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.

The Pharmaceutical Benefits Advisory Committee (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 Pharmaceutical Benefits Schedule (PBS). As new technologies are developed and drug discovery and research becomes more intricate and targeted, it is vital to constantly and regularly review the Guidelines, processes and standards that govern the system. In this context, the review provides an important opportunity to update the PBAC Guidelines to ensure Australia's reputation as having a world-leading HTA system is maintained.

Medicines Australia acknowledges it has been invited to be an ongoing contributor to the review, through its membership of the Guidelines Review Steering Committee (GRSC). As member of 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. Medicines Australia has also provided a public submission to the broader consultation on the draft revised PBAC Guidelines Version 5.0.

This submission is in response to the draft of '*Product Type 4 – Hybrid Technologies and Co-dependent Technologies*' chapter of the draft revised PBAC Guidelines Version 5.0. Medicines Australia notes that this document represents significant progress in providing clarity on the guidance for preparing a submission to the PBAC that involves hybrid technologies or co-dependent technologies. Medicines Australia also notes that further guidance such as this has been called for by the industry during the early stages of the PBAC Guidelines Review. Notwithstanding this, Medicines Australia intends for this submission to highlight outstanding areas for further work for the betterment of this chapter of the draft Guidelines.

In particular, Medicines Australia calls for:

1. Further clarification on the processes and timelines to ensure timely access to targeted medicines;
2. Further clarification and alignment of PBAC and Medical Services Advisory Committee (MSAC) co-dependent technology information requests; and
3. Appropriate education for users of the hybrid and co-dependent submission chapter of the Guidelines and ongoing consideration of efficiencies in the co-dependent technology assessment process.

1. Further clarification on the processes and timelines to ensure timely access to targeted medicines

To date, assessments of co-dependent technologies have primarily involved drug/test combinations where new medicine requires the use of an associated pathology test to determine the eligible population. This requires consideration by both the PBAC and the MSAC. There is currently no single document, or separate process that accommodates co-dependent technology reimbursement submissions and covers all of the procedural requirements and types of evidence requested by both committees. Instead, guidance is split across the co-dependent technology chapter of the draft PBAC Guidelines, and Appendix 7 of the '*Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Service Type: Investigative (Version 2.0)*'.

Medicines Australia notes that there are substantial differences between submission processes, timelines and information requests outlined in the PBAC and MSAC guidelines. Importantly, the MSAC submission process requires early engagement to enable the Protocol Advisory Sub-Committee (PASC) to agree on the scope of the application (i.e.

population, intervention, comparator and outcomes criteria) prior to lodgement of a reimbursement submission. This does not seem to be acknowledged in the draft PBAC Guidelines, despite the fact it substantially lengthens submission timelines and requires significant time and resources to be invested by sponsors, the Department of Health and PASC members.

Furthermore, there are currently varying levels of understanding and expectation across industry on the process for co-dependent submissions. Feedback from Medicines Australia members is that the discrepancies between PBAC and MSAC submission cut-off dates, meeting dates, evaluation timelines and post-recommendation PBS/MBS listing processes create unnecessary confusion around the procedural elements of the co-dependent technology framework, and can lead to delays in patient access to targeted medicines.

In order to address these issues, Medicines Australia recommends that both sets of guidelines:

- Present a clear and consistent definition across the MSAC and PBAC Guidelines of what constitutes a co-dependent technology, including practical examples of relationships determined to be co-dependent or not co-dependent and the reasons for the determination (this is included in the MSAC Guidelines (page 6) and could be replicated in the PBAC Guidelines);
- More clearly outline the preferred format and structure for an 'integrated' co-dependent submission that meets the expectations of both a major submission for PBS listing of the medicine and also a submission-based assessment (SBA) for the MBS listing of the co-dependent diagnostic test; and
- Provide clearer guidance for timelines and processes applicable to both committees, including:
 - Pre-submission processes required to define the PICO criteria for the submission
 - Processes for pre-ESC and pre-PBAC/MSAC commentaries
 - Post-PBAC/MSAC listing processes.

Whilst there are benefits in early engagement through the MSAC process this often leads to lengthy protocol development processes, and potential mismatch between MSAC and PBAC submission cut-off and meeting dates. It is important to ensure that drug-test pairings are not penalised by greater complexity and longer timeframes to patient access than pharmaceuticals that do not require an associated test. In addition to this, further guidance on the intended process and timings following a positive recommendation from the PBAC/MSAC for the reimbursement of a pair of co-dependent technologies could potentially lead to faster listing times.

2. Further clarification and alignment of PBAC and MSAC co-dependent technology information requests

Types of submissions

Whilst it is encouraging that the draft PBAC Guidelines recognise that different information requests are relevant in different situations, there is a need for further clarification about the information requests to be addressed for each submission type. Medicines Australia recommends that the review:

- Use the description of the requirements in terms of biomarker, test and medicine instead of denoting each option as 'integrated' or 'co-ordinated'. This would make it easier to determine when each submission type should be used. Alternatively, the Guidelines could add the requirements to the heading – i.e. Type 1a submission – new biomarker, new test, new medicine etc.

- Incorporate practical examples to explain each type of co-dependent submission, and acknowledge that there are situations where a submission or resubmission may only have to be considered by one committee (i.e. PBAC or MSAC but not both)
- Tabulate the information requests relevant for each type of submission in a format similar to either Appendix 7 of the current MSAC Guidelines for Investigative Medical Services or (Table 2 in Merlin 2013¹)
- Provide more linkages between PBAC and MSAC guidance documents

Additional clarification

Medicines Australia member companies note that there are some sections of the draft co-dependant chapter that could be made clearer and more user-friendly. In particular, it is noted that:

- Item 5(T) requests that the sponsor describe the evidentiary standard test method in sufficient detail that a laboratory technician would be able to perform it. The rationale for requesting this level of detail is unclear, and may prove challenging in cases where Australian molecular pathology laboratories utilise in-house developed test methods rather than commercial test kits.
- Item 19(O): Diagrams to depict the various trial designs would be helpful.
- Item 19(O) and 30 (O): How ethical is a double-randomised controlled trial where patients are randomised to the test/no test and to the drug/main comparator if the proposed targeted therapy was specifically designed and developed to work only in biomarker positive patients?
- Item 25(T) requests that the QUADAS-2 tool is used to assess the quality of diagnostic accuracy studies presented in the submission. This should be updated to align with the MSAC Guidelines, which note that there are several quality assessment instruments available for accuracy studies including the Standards for Reporting of Diagnostic Accuracy (STARD) initiative and the ACCE3 Model Project (for genetic tests).
- Item 33(O): Where a drug has been specifically designed and developed to work only in biomarker positive patients, is the background prognostic effect not relevant given that in a study of only biomarker positive patients, the prognostic effect would be assumed to be the same in both treatment arms?
- Section 3, Item 37(O); (iii) states that 'a scenario analysis is provided where the proposed medicine is used without testing in order to show the extent of improvement in the ICER associated with using the test'. This is not relevant where the targeted therapy has been specifically designed and developed to work only on a particular biomarker. The drug would not be used without the test.
- Item 38(O): Non-health-related impacts of diagnostic testing may include the societal impact to caregivers and work productivity of improved outcomes associated with use of targeted therapy.
- Item 39(O): The inclusion of the calculations of PPV and NPV in the chapter are welcomed.
- Section 4 outlines information requests for establishing the predicted use of co-dependent technologies and the financial implications to the Federal Health Budget. The PBAC's 'Utilisation and Cost Model Spreadsheets for Major PBAC Submissions'

¹ Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing personalized medicines in Australia: a national framework for reviewing codependent technologies. *Med Decis Making*. 2013 Apr;33(3):333-42

standardised Microsoft Excel template should be updated to reflect the need to incorporate use of diagnostic tests alongside targeted medicines in certain instances.

- If the diagnostic test and the targeted medicine are not owned by the same company, the co-dependent process requires two (or more) commercial entities to develop the single reimbursement dossier in order to determine a single estimate of cost-effectiveness and a single estimate of the impact to the Federal Health Budget. In developing this reimbursement dossier, it is unavoidable that confidential scientific evidence, commercial forecasts and prices are shared between these commercial entities. Whilst this is unavoidable in those circumstances, some flexibility in the submission process may be necessary to prevent commercial-in-confidence information being shared unnecessarily.

3. Appropriate education for users of the hybrid and co-dependent submission chapter of the Guidelines and ongoing consideration of efficiencies in the co-dependent technology assessment process.

It is now increasingly common for medicines, in particular cancer medicines, to have an associated diagnostic test or treatment-associated device to ensure the medicine is used where most effective. It is therefore important to recognise that there are unique potential benefits of targeted therapies to patients; by receiving treatments better targeted to their needs, in addition benefits to the broader healthcare system; by more coordinated and targeted distribution of health care expenditure and resources.

Given the diversity of industry experience in developing and lodging co-dependent PBAC/MSAC submissions, Medicines Australia recommends that extensive education be offered to ensure a common understanding and interpretation of the 'Hybrid technologies and co-dependent technologies' chapter of the draft revised PBAC Guidelines.

Medicines Australia notes that feedback from members who have used the co-dependent process is that it is overly resource-intensive and complex for both the sponsor and the Department of Health. Some sponsors have noted that the additional complexity in terms of applications and consideration for two separate Committees is for little added value, increases red-tape and reduces the timeliness and certainty around the reimbursement of targeted medicines in Australia.

Whilst outside the remit of the current review, Medicines Australia encourages ongoing consideration of the validity of the current structure for the assessment of co-dependent technology submissions. With the goal of ensuring that drug-test pairings are not disadvantaged by greater complexity and longer timeframes to patient access than non-co-dependent medicines.

Medicines Australia supports timely access to innovative, safe, effective and targeted 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. Medicines Australia welcomes the additional guidance provided for hybrid technologies and co-dependent technologies in addition to consideration of the comments in this submission.