Submission to the Call for Public Comment: Pharmaceutical Benefits Advisory Committee (PBAC) Submission Guidelines Version 5.0

April 2016

About HTAccess Consulting

After conducting several Health Technology Assessments for review by both the PBAC and MSAC, HTAccess Consulting was established to provide technical support to organisations engaging with the PBAC or MSAC. This submission draws on experiences and reflections on the preparation of submissions to the PBAC covering a wide variety of therapeutic areas. This has included the development of several co-dependent submissions for consideration by both the PBAC and MSAC.

Response to Request for Public Comment

HTAccess Consulting has reviewed all of the draft documents associated with the preparation of a submission to the PBAC that were released for public consultation in February and March 2016 and provides feedback on the proposed draft documentation below.

Comparator selection

The guidance on comparator selection outlined in the draft PBAC guidelines results in a situation whereby multiple comparators would appear to be required for most PBAC submissions. Indeed, consideration of the breadth of factors would suggest the nomination of a single comparator would be largely restricted to cases where there is either only one alternative therapy listed on the PBS, or there is an emphatic market leader for current parity-priced PBS-listed treatments in a given therapeutic area. The circumstances under which either of these criteria would be met would be limited.

The inclusion of multiple comparators has proportional impact on the length and complexity of a submission to the PBAC. Further, personal experience on the nomination of multiple comparators suggests that this often results in the need to incorporate evidence with varying degrees of scientific rigour in the PBAC submission. Issues relating to the quality of evidence available especially arise in circumstances when clinical trial programs for comparator treatment(s) were performed a long time ago and in historic clinical management contexts. This often leads to there being limited exchangeability between historic and contemporary trial results which, in turn, compromises the ability to robustly assess the comparative efficacy and safety of a new treatment with *all potential comparators* according to guidance in the draft PBAC guidelines. In these instances, the value of presenting data for comparator treatments 'just in case' the PBAC may view a given treatment as a potentially relevant comparator is drawn into question.

It is acknowledged that there are instances where the nomination of multiple comparators is clearly appropriate. As such, the draft PBAC guidelines could benefit from providing more explicit or quantitative advice regarding the circumstances under which the nomination of multiple comparators is required. As an example, clarifying the draft guidance that presentation of multiple comparators may be required "when there is no

clear market share for one particular comparator" or "when there is a substantial difference in the cost of a treatment course across the comparators" to include a specific market share threshold and/or a specific difference in absolute cost of treatment could be considered for inclusion in the final PBAC guidelines. This would give sponsors great clarity as to when the nomination of multiple comparators is genuinely useful for PBAC decision-making.

A further mechanism to reduce the uncertainty regarding comparator selection would be for the Department to provide firmer (and potentially binding) advice to sponsors on this matter as part of the pre-PBAC submission meeting process. My personal experience, and the anecdotal feedback received from others, is that the Department is averse to providing sponsors with explicit guidance on the matter of comparator selection. A consequence of this risk averse position appears to be that the Department tends to advise sponsors to include a comparator 'just in case' the PBAC deems it to be informative. The conservative advice often provided by the Department suggests that articulating more explicit criteria on comparator selection in the final PBAC guidelines would facilitate more constructive discussions between sponsors and the Department on this matter.

Whilst acknowledging the need for the PBAC guidelines to remain flexible enough to accommodate the breadth of submissions considered by the PBAC, the publication of more explicit and transparent guidance on comparator selection as part of the final version of PBAC guidelines and/or a change in Departmental policy regarding the nature of advice given to sponsors could benefit sponsors, the Department and the PBAC alike.

Economic evaluation

Time horizon

The draft PBAC guidelines outline that "the default is a lifetime horizon, although shorter horizons may be used for interventions that do not affect mortality and have temporary quality-of-life effects" (p. 99). This guidance is inconsistent with the broader methodological literature regarding the appropriate time horizon for an economic evaluation. Typically, the wider literature does not specify a default time horizon but, rather, outlines that the time horizon of an economic model should be long enough to capture relevant differences in costs and outcomes across the interventions under consideration (Caro et al., 2012; Gray et al., 2010). For some chronic conditions, or for the assessment of treatments for patients with a terminal illness, a lifetime horizon would indeed be appropriate, however shorter (i.e. non-lifetime) time horizons would be appropriate for a significant number of economic evaluations submitted to the PBAC.

The specification of a default lifetime time horizon also appears to contradict PBAC preferences in this area. For example, as outlined in the Public Summary Document for Nitisinone (November 2012) the sponsor used a 100-year time horizon, however it is outlined that "a shorter time horizon than 100 years – for example, 22 years to coincide with the actual clinical experience of the drug – may be more appropriate to correspond

to current clinical experience with the drug, given the lifetime effects of the drug are unclear" (p.12 of Nitisinone PSD, November 2012). More contemporary examples of the PBAC challenging the use of lifetime time horizons are given as part of the PBAC's consideration of sofosbuvir (July 2014) and daclatasvir (March 2015) where lifetime time horizons were used by the sponsors, however the PBAC considered that a 30-year time horizon would be more reasonable.

Preservation of the guidance provided on time horizon selection for economic models outlined in version 4.4 of the PBAC guidelines which did not specify a default time horizon would help maintain consistency on the appropriate time horizon for economic modelling described in the PBAC guidelines and the wider methodological literature.

Model validation

As a general comment on the information requests on model validation, the draft PBAC guidelines provide extensive guidance to applicants regarding structural and methodological approaches that should be employed when developing an economic model for consideration by the PBAC. In cases where applicants have followed the advice specified in the draft PBAC guidelines, and provided justification for their approach as required, it should follow that the economic model is 'valid' for the purposes of PBAC decision-making. As such, the conduct of further model validation steps would seem to add little overall value to the submission.

The nature of the information requests associated with model validation also raise several issues that are likely to make it impractical for sponsors to be able to meet the model validation requirements set out in the draft PBAC guidelines. A key issue relates to the identification of suitably qualified, independent experts that can judge the validity of an economic model prior to submission to the PBAC. Due to the niche nature of the industry in Australia, a substantial proportion of people with suitable expertise to assess model validity would currently be working either in industry, the Department, or in academic centres involved in the assessment of PBAC submissions. As such, the identification and engagement of independent experts to assess model validity of economic models submitted to the PBAC will be a serious challenge for sponsors.

The questions in the model validation section of the draft PBAC guidelines also appear duplicate the role that the PBAC submission evaluation groups and the Economics Sub-Committee play in the assessment of a PBAC submission. Specifically, the Department of Health webpage outlines that "The Economics Sub Committee (ESC) of the Pharmaceutical Benefits Advisory Committee (PBAC) assesses clinical and economic evaluations of medicines submitted to the PBAC for listing, **and advises PBAC on the technical aspects of these evaluations**"[1] (emphasis added). As ESC is an independent panel comprised of health economists and other clinical experts that provides advice to the PBAC

[1] http://www.pbs.gov.au/info/industry/listing/participants/economics-subcommittee-esc, accessed 4th April 2016

on technical aspects of PBAC submission, it is debatable whether the model validation process requested in the draft PBAC guidelines actually addresses an existing gap in the independent expert review of economic models submitted to the PBAC.

Notwithstanding the practical challenges associated with validating economic models in the fashion requested in the draft PBAC guidelines, many aspects of economic model validation are currently fulfilled by the role of the evaluator groups and ESC. Therefore, it is unclear whether the model validation requirements set out in the draft PBAC guidelines will assist in decision-making or simply adds another layer of complexity that will lead to further uncertainty.

Co-dependent technologies

The updated policy allowing lodgement of an integrated co-dependent submissions for consideration by both the PBAC and MSAC is welcomed.

Overall, the draft guidelines for preparing submissions for co-dependent technologies to the PBAC may benefit from more clearly describing the process and format requirements associated with preparing and lodging a major submission for a co-dependent technology. For example, confirmation that the PBAC requirements for report formatting and publication prevails for integrated co-dependent submissions as outlined in the Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee-Service Type: Investigative (Version 2.0) could help clarify the Departments expectations for applicants who refer to the PBAC guidance on co-dependent technologies.

A general reflection on the integrated co-dependent technology information requests outlined in P4.2 of the draft PBAC guidelines is that they ask questions on overlapping aspects of co-dependent technologies at various points throughout the document. As an example, Item 4 (0) asks for a description of the biomarker. Subsequently, Item 8 (0) asks if there is a clear definition of the biomarker. Another example is that Item 14 (T) asks if the proposed test is an additional or replacement test, however information on the most widely used tests in current practice is not requested until Item 27 (T). Given the high degree of overlap between these questions, the inconsistencies in the location where aspects of test characteristics are requested in the draft guidelines risks leading to the development of submissions that, whilst fully compliant with the guidelines, lack a sense of overall cohesion.

It is suggested that in finalising the information requests for co-dependent technologies, further consideration is given to reviewing the order and format of the information requests with a view to developing a more parsimonious information request section for co-dependent technologies. A suggest layout would be to streamline and group information requests on aspects of co-dependent technologies under specific headings, such as:

- Details of the biomarker
    - This section would define the biomarker, estimate the prevalence of the biomarker in the MBS-eligible patient population, and outline if the biomarker is a known prognostic indicator for the disease area in general.
- Details of biomarker testing options
    - This section would describe the proposed and current (if any) testing options for the biomarker, including the specimen type that is tested and whether testing is performed only at the time of diagnosis or throughout patient management.
- Evidence of biomarker test performance
    - This section would present the evidence reporting on the analytic performance of the test for which MBS listing is being sought, including assessments of comparative test performance to alternate testing methodologies (if applicable).
- Evidence of improved patient outcomes stemming from changes in patient management on the basis of biomarker test performance
    - This section is largely represented by the information requests regarding the efficacy and safety of the therapeutic intervention outlined in Section 2 of the draft PBAC guidelines. These information requests could be supplemented by an assessment of potential additional safety consideration associated with biomarker sample collection procedures.

Concluding Comments

It is noted that many of the information requests outlined in Section C of version 4.4 of the PBAC guidelines have been relocated to Section 2 or Section 3 of the draft PBAC guidelines. The proposed new format allows for sponsors to discuss issues of data applicability in Section 2 in closer proximity to the data itself, and issues of data translation and pre-modelling studies in Section 3 in closer proximity to the description of the economic model itself. Personally, I feel that the proposed format is more logical than current arrangements where the discussion of data applicability, translation and pre-modelling studies are provided as a stand-alone Section C and will result in more cohesive submissions in the future.

Thank you for the opportunity to provide feedback on the draft PBAC guidelines (version 5.0) being developed by the Guidelines Review Steering Committee. I hope these comments have been informative. I would be happy to offer clarification or expand on any of the comments made in this submission if requested by the Department.

Toby Gould
Principal Consultant
HTAccess Consulting

References

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