Submission to the Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines Review
[redacted]

The authors of this document are individual consultants who, collectively, have decades of experience with health technology assessment (HTA) in the industry, government and academic sectors. The authors have a significant interest in the development of PBAC Guidelines that are at the leading-edge of international best practice, but that do not unnecessarily increase the administrative burden for government, the PBAC and its sub-committees, the evaluation groups or industry.

The first section of this submission will provide general comments on the revised draft Guidelines (version 5.0) including the authors' views on whether the Guidelines have met the stated objectives of the Review. The following sections will focus on more specific issues in relation to relevant sections of the draft Guidelines.

There are many improved aspects of the draft Guidelines compared to the previous version, such as frequent reference to what the PBAC have found most useful in their deliberations of HTA submissions and why. However, due to the 5-page limits imposed on submissions, the focus of this submission is on areas of the draft Guidelines that the authors believe require either revision or present opportunities to reduce the burden on stakeholders without loss of relevant information for PBAC decision-making.

General Comments

The stated objectives[1] of the Guidelines review include: ensuring "that the Guidelines are of the highest quality and that they continue to reflect best international practice" and "to develop a more concise, clear, focused and up-to-date methods Guidance". No detail is available from government documents outlining key measures that would need to be met to ensure that the new Guidelines will achieve the stated objectives. Thus, it is difficult to determine whether the objectives were met. Prior to ratification, the draft Guidelines should be compared to guidelines from the UK, Canada and Europe (those countries identified in the terms of reference) to check whether the PBAC Guidelines measure up in terms of world's best practice and achieve international consistency. It is important to note that best practice needs consideration of the latest clinical and economic evaluation methods, which may not yet be reflected in existing international guidelines.

In terms of the objectives that relate to international best practice, the influence of international practice and guidelines on the revised Guidelines appears to be limited. There is little reference made to international developments in guidelines such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) consensus publications on best practice approaches to economic modelling (https://www.ispor.org/workpaper/practices_index.asp).

Key general points on the draft Guidelines include:

- Given the title of the PBAC Guidelines is "Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee", the primary target audience for the Guidelines is sponsors who prepare and submit applications to the PBAC for listing on the Pharmaceutical Benefits Scheme (PBS). The target audience for the draft Guidelines as they are currently written is ambiguous and requires clarification. There appears to have been limited direct inclusion of industry and patient/consumer organisation personnel in the review process with only one industry representative and no patient/consumer representative on the Guidelines Steering Committee (out of 13 members). The underweighting of industry and consumer involvement should concern the PBAC because version 5.0 might not fully reflect the concerns of these important stakeholder groups. Furthermore, the opportunity for these stakeholders to respond to the Guidelines is severely hampered by a 5-page limit on submissions.
- Although the draft Guidelines are somewhat shorter than the current version, they include more requests for information that increase the volume of information that a submission will present. For example, there is an increased requirement to present systematic reviews to justify inputs to economic analysis (regardless of the sensitivity of the analysis to the input); increased information requirements to justify the structure of a model used to conduct economic analysis, and the range of occasions where comparisons

[1] Source: PBAC Guidelines Review website (http://www.pbs.gov.au/info/reviews/pbac-guidelines-review)

against multiple comparators need to be presented has been expanded. The presentation of a greater volume of information to the PBAC does not translate to a better understanding of a drug, its clinical place, its comparative efficacy, safety, and cost-effectiveness if the additional information being presented is peripheral or extraneous to these considerations. It is our opinion that the revision of the Guidelines presented an opportunity, not only to declutter the Guidelines themselves, but to also declutter submissions by encouraging a greater focus on information that is central to PBAC decision-making and discouraging (or, at least, demoting) the presentation of information that is peripheral to decision-making.

- The document is overly cumbersome and the flow, at times, is disjointed and needs significant editorial improvement. The guidelines are a complex read containing a combination of technical background material as well as specific guidance on what to present and how to present information relevant to the clinical, economic and financial analyses. They may be improved by having a medical writer review the draft and simplify the language used. We suggest that the Guidelines could substantially be decluttered by having the Guidelines focus on the 'why' and 'when' information is needed by the PBAC rather than to provide detailed technical advice on the 'what' needs to presented and 'how' it should be presented. The 'what' to present and 'how' to present in a submission could be included by cross-referencing of stand-alone living documents. For example, the draft Section 2.3 could be condensed to a few sentences explaining that the PBAC values evidence from studies that have a low risk of generating biased estimates of outcomes more highly than evidence from studies that have a high risk of generating biased estimates of outcomes and that, for this reason, sponsors are requested to conduct and present an assessment of the risk of bias in a study. Appropriate cross-references to other documents that explain how this assessment could be conducted and presented could then be provided (e.g., to Chapter 8 of the Cochrane Handbook for RCTs or the relevant ACROBAT-NRSI publication when assessing non-randomised studies). Alternatively, if these documents are considered to be insufficient for PBAC purposes, a specific, separate, stand-alone "technical guidance document" could be developed for this purpose which can then be updated as necessary. This approach would ensure that the Guidelines themselves are not interpreted as being overly prescriptive, and it would be clear that the associated technical documents are intended to be more educational in nature.
- Section C of the current version of the Guidelines has been removed with some content moved to the new Sections 2 and 3 of the draft Guidelines. There are some investigations that would, to date, be included in Section C but where the most appropriate positioning in the new format is not clear, e.g., assessment of applicability of evidence incorporating a stopping rule. Although the relocation of some information to Section B is appropriate (e.g., subgroup analysis where the clinical claim is specific to the subgroup), it is our view that Section C should be reinstated as it provides a clear bridge between the clinical and economic sections of a submission. This section fosters collaboration and discussion between those involved in the clinical aspects and economics aspects of the submission and ensures consistency and continuity between the clinical and economics sections of a submission.
- The draft Guidelines do not currently provide a framework for sponsors to address the place of future product/technology types that have unique characteristics and may require different approaches to assess their associated benefits and resources (e.g., immunotherapies, cellular therapies).

Section 1

The primary issue of concern in Section 1 of the draft Guidelines is the choice of comparator. A few minor issues are also briefly flagged below.

Choice of comparator (pages. 16-18)

In principle, it is the authors' view, consistent with international HTA practice and guidelines, that the choice of comparator should be the intervention (which, in some cases, may not be a medicine), that the new medicine is most likely to replace in clinical practice. Frequently, this will correspond to the medicine with the current highest market utilisation share. Occasionally the market shares of current leading medicines may be fairly evenly split between two or more products, and in such a circumstance multiple comparators may be appropriate (though, on occasion, this can be simplified back to one comparator if the products/medicines have been determined to be interchangeable and/or listed on the basis of cost-minimisation analysis).

In contrast, the draft Guidelines indicate comparisons against multiple comparators may be required when there is a substantial difference in the cost of a treatment course across the comparators. Specifically, the Guidelines state, *"Where multiple comparators with large disparities in cost are available, and these are equi-effective in the target population, sponsors should be prepared to provide both a comparison against the comparator with the greatest market share and a comparison against the most cost-effective comparator".* The draft Guidelines make reference to s.101(3A) of the National Health Act in this section, but the wording of this section of the Act does not explicitly require the PBAC to take into account the cost effectiveness versus the least cost comparator. In some cases, the least cost comparator will be so underutilised it will be irrelevant from clinical effectiveness, economic and financial perspectives. Thus, this requirement is contrary to the generally accepted approach for determining the appropriate main comparator. In this case, it appears to us that comparisons against low-priced comparators (e.g., generic medicines that have had their prices eroded by application of price disclosure arrangements) are being contrived to lower the acceptable price for a new drug. The use of the least expensive comparator could lead to unintended and unwelcome consequences for PBAC, e.g., it is unlikely that the PBAC would normally want to spend its limited time considering comparisons of a new antipsychotic against drugs that have been superceded in practice (e.g., due to unacceptable safety profiles) as would be required given the specification in the Guidelines for submissions to include a comparison against the "least expensive alternative". In addition, the evidence base to inform meaningful clinical comparisons and economic analyses is likely to be limited in the case of older, less expensive products.

Other issues of concern in Section 1 are:

- The request for unredacted regulatory documents from other countries may not be practical as such information and documentation is often not available and may never be available to sponsors.
- On page 15, the clinical claim (to be summarised in Table 1.1.1) does not include a consideration of comparative safety
- Under the sub-heading of future comparator(s) (page 18), the second paragraph (or both) should be removed. Although the general request for the sponsor to include an additional comparator where the sponsor has an expectation that a competitor's medicine will be considered by the PBAC imminently is reasonable, the specific request to include therapies undergoing TGA registration is not a reasonable expectation given that the TGA doesn't publicly release the list of drugs currently undergoing evaluation. Similarly, drugs that will be considered at the same time as the proposed drug will often not be known until the release of the PBAC agenda (i.e., after the lodgement of the submission).
- Under the heading of Rationale for PBS listing (page 20), the new Guidelines state that submissions should not discuss non-health-related impacts. However, we feel that non-health-related outcomes should not be required to be omitted as they are often relevant to the patient and can form an important component of the rationale for PBS listing.
- Definition of the term "proposed patient indication" and the distinction between "indication" and "population" in this phrase is unclear e.g., within the section entitled 'Proposed patient indication' (page 30).

Section 2

Several issues in Section 2 that require additional discussion and review before the Guidelines are finalised, particularly with regard to switching, minimal clinically important difference (MCID), post-marketing surveillance (PMS), and translation of clinical trial data to Australian practice. These are addressed below.

Switching (pages 76-80)

Allowing patients on a comparator medicine to switch to a new investigational medicine after the latter has demonstrated superior efficacy is a particular issue in oncology trials. Failure to statistically adjust for switching potentially biases estimates of overall survival benefits against the investigational medicine (which can have implications for cost-effectiveness analysis). When switching is allowed within a clinical trial, several techniques can be applied to the economic analysis. The draft Guidelines request "the most conservative end of the 95% confidence interval for the treatment effect be applied" in economic analysis. From a technical point of view, the application of extreme values in an economic evaluation would be unlikely to be considered

appropriate. Furthermore, such advice is not consistent with international best practice, e.g., as contained in Latimer & Abrams. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching.

Minimally Clinical Important Difference (MCID) (pages 56-57)
Establishing the MCID for the primary outcome is essential, as the Guidelines point out (p56 and Appendix 3). The MCID is also integral to establishing the non-inferiority margin (Appendix 4) and the Guidelines stipulate that this margin 'must' be justified (p51). We suggest that it is impractical to specify an MCID for all outcomes and suggest that this only be required for the 'primary' outcome of interest and not all outcomes as directed in the draft Guidelines (p56). To require that MCIDs be investigated and justified for all outcomes is overly burdensome and may not contribute useful information for decision-making purposes. Additionally, it would be helpful if the guidelines could provide a 'link' or make reference to a separate document prepared by the Department of Health that acts as a repository of accepted measures and values for MCIDs, as previously accepted by the PBAC. This information is not consistently reported in the PBAC Public Summary Documents. This would help to cut down on uncertainty and the workload burden.

- On the issue of MCID, the authors also suggest the following:
  - Reference could be made in the Guidelines to EMA guidance on non-inferiority margins.
  - The Guidelines should also provide guidance (e.g., in a separate technical document) on the approach that should be adopted when there is no established MCID for the outcome of interest
  - The Guidelines should provide guidance on what to do with products that are not non-inferior (i.e., where the lower confidence limit is exceeded) but are no worse than the comparator (i.e., where there is insufficient evidence to demonstrate the statistical superiority of the comparator). Accordingly, the categories provided in the Clinical Claims section should be expanded. It may be useful to draft a technical document that presents approaches that can be used to present therapeutic conclusion.
  - Though not related to MCID, a similar repository could be established for accepted health utilities.

Post-Marketing Studies (PMS) (page 85)
Another area of concern is the suggestion that the efficacy of a proposed medicine be evaluated in a post-marketing surveillance study where the efficacy of the medicine in the Australian population or maintenance of response beyond the clinical trial period is uncertain. In general, there will always be an element of uncertainty with respect to the effectiveness of a new medicine in the longer term. The concern here is that post-marketing studies to follow up efficacy are complex and expensive to design and execute. There is also limited local expertise in the PMS field. Without clear criteria as to when such studies are required and why they are required there is a risk that they will not provide useful information and will add to the burgeoning cost and burden of bringing a new medicine to market. As an additional point, the authors of this submission have no concern around post-marketing surveillance for safety purposes and acknowledges that the process and governance around such surveillance is already in place with the TGA.

Section 3
There are a number of issues in relation to Section 3. Key issues are addressed below. It is the authors' considered view that the additional requirements of the economic modelling section will add at least 50% more time and cost to the preparation of the submission. Examples of the additional requirements included in the Guidelines that are onerous include the requirement to present additional literature reviews/systematic reviews to validate inputs to the economic analysis (regardless of the sensitivity of the analysis to the variable) and requirements in relation to steps to validate the structure of a model. Proficient modelling skills within industry, government and academic evaluation centres are significantly limited, and the additional requirements in relation to modelling appear not to recognise this capability and capacity limitation.

Other specific comments are highlighted below.

Cost-consequences analysis (page 94)
It is important to emphasise, as the Guidelines do, that a cost-consequence analysis should not be the only analysis performed (it is usually provided as a supplementary analysis). However, such assessments can be particularly beneficial in describing costs and benefits not readily captured in a formal economic evaluation. A

cost-consequence analysis represents an avenue for input from patient stakeholder groups, and the methodology within that section of the Guidelines should be explored further. For example, including quality of life decrements associated with carers of the patient group in question is problematic in a traditional cost-utility approach. In such circumstances, a cost consequence analysis may provide a more transparent and intuitive avenue for understanding costs and benefits for a broader range of stakeholders.

Cost-benefit analysis (page 95)

On page 95 of the draft Guidelines, it is stated that a cost-benefit analysis (CBA) is not preferred. However, the authors believe that the methods involved in CBA such as discrete choice experiments (DCE) among others can be informative with regard to how much emphasis patients place on specific attributes or outcomes associated with alternative interventions. This may be a simple ranking of the importance of different disease characteristics or attributes of a medicine from a patient perspective, or it could go one step further and provide a willingness to pay for the different attributes (or avoidance of disease characteristics) in question. These results need not be 'wrapped-up' in an overall CBA result but could be better used as supplemental evidence to explore what is most important to a patient in an economic evaluation.

Perspective of the economic analysis (page 96)

The authors believe that a societal perspective is the most important perspective to use in a scheme that is financed by the taxpayer. This perspective should form the 'base-case' of any economic evaluation to the PBAC. Anything less than this results in devaluing aspects of the impact of disease on different stakeholder groups and jurisdictions. As some diseases have broader impacts on a wider set of stakeholders than others, a societal perspective will ensure such disease areas do not 'lose-out' during economic evaluation in comparison to disease areas where the costs and outcomes are more patient-centric.

Time horizon (page 99)

The authors agree with the PBAC Guidelines that the time horizon examined by an economic evaluation should be sufficient to capture all important differences in costs and outcomes between the intervention and the comparator and that the default time horizon should be a lifetime (although a shorter horizon may be used for interventions that do not affect mortality and have temporary quality-of-life effects). However, the statement that "A model that predicts that 50% of patients with an advanced cancer survive for 10 years is not invalid because a lifetime horizon was selected, but because the input data predict implausible outputs" should be deleted or, at least, revised. The statement, as written, inappropriately predetermines that a new intervention to treat patients with advanced cancer could never result in this outcome. It is not beyond the realms of possibility that revolutionary treatments will be developed in the future.

Other issues on modelling

The definition of terms and consistency with other HTA jurisdictions would be helpful. The authors disagree with the need to perform a cohort model if a patient-level simulation model is undertaken. It is reasonable to expect that a cohort model should be used where possible because such models are more transparent and less data hungry than patient-level models. However, there will be occasions where the use of a cohort-based model will not be appropriate as it may require oversimplification of the decision problem or will result in a model with an unmanageable number of health states. In such situations, and provided sufficient data is available to populate the model, an individual level state transition model would be more appropriate. If requirements are included in the Guidelines, which state that the submission should: 1) present justification for a patient-level model, and 2) demonstrate that they have sufficient data to populate such a model, then it is redundant to also ask for presentation of a cohort model. The user has already determined that the cohort model is inadequate for the purposes of economic evaluation.

Cost minimisation analysis (CMA) (page 132)

The interpretation of this section of the Guidelines is that any new medicine seeking listing should be less expensive than what is currently available. This appears to indicate a significant policy shift by the Government. In the past the price of a new medicine listed on the basis of a CMA could be based on equivalent resource use with the new medicine.

In the second line of page 132, the word 'superior' should be removed.