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

AstraZeneca is a science-led biopharmaceutical company, employing more than 900 people in Australia. Our primary focus is on three important areas of healthcare: Cardiovascular and Metabolic disease (CVMD), Oncology, and Respiratory, Inflammation and Autoimmunity (RIA). We have invested more than $250 million in research and development in Australia in the last decade and invest $4 billion globally every year. AstraZeneca is the largest national manufacturer of pharmaceuticals, providing $725 million of medicines to the local market and greater than $440 million in exports to 30 international markets.

AstraZeneca appreciates the opportunity to provide a submission to the PBAC Guidelines Review. Our submission is in two parts. Part 1 highlights key general points of principal we would like to make regarding the PBAC Draft Guidelines Version 5 ('draft guidelines'). Part 2 contains AstraZeneca comments relating to specific sections of the draft guidelines.

Part 1 – Key general points

We would like to acknowledge the efforts that have been made to date to incorporate sponsor feedback, reflected in the additional guidance around specific technical issues (such as comparator choice, nomination of MCID, indirect comparison etc.). However we would encourage the review to go further and provide a more comprehensive revision of the guidelines in line with the Health Minister's aim to 'maintain Australia's standing as a world leader in health technology assessment'[1] and also address some of the issues raised in the recent Senate enquiry into Access to Cancer Medicines. To this end, and consistent with practices evolving in other international jurisdictions and academic literature, we would like to highlight the following:

1. **Greater weight given to the consumer/taxpayer perspective.** The draft guidelines once again relegate societal perspective analysis to a supplementary status, suggesting that non-health related outcomes should not be included in the arguments supporting the rationale to list the drug (see Part 1 – Section and Part 2 – Section 3). Indeed the new guidelines go even further and narrow the focus in the budget impact analysis from a broad health care cost perspective to just the Australian (Federal) Government health budget (see Part 2 - Section 4). AstraZeneca believes that a societal perspective should be central to the PBAC guidelines, to ensure broader taxpayer consequences are factored into PBAC decision making. Specifically we suggest:

(i) greater detail, emphasis and weight provided to the broader societal consideration of non-health benefits and costs, including productivity gains, reductions in welfare dependence and disability payments for patients and/or their caregivers and;

(ii) explicit guidance on how patient views can be presented, valued, and inputted into a PBAC submission.

2. **Concern regarding change of the criteria for main comparator.** The new wording in the draft guidelines explicitly imply a change in emphasis in the selection of the main comparator from the medicine that is most used in clinical practice to the cheapest alternative (see Part 2, Section 1). AstraZeneca strongly opposes this change in policy.

3. **Additional information requests are overly burdensome and unrealistic**. AstraZeneca appreciates and supports the efforts to make the guidelines more concise, accessible, flow more logically and facilitate clarity around presentation of information for a PBAC submission. However while the document itself is now more streamlined, the additional information requirements are often impractical and onerous. For example the request for unredacted international regulatory documents (Part 1, Section 1) may be difficult to obtain and of little relevance and value in practice. Similarly the requirement that economic models should be assessed by experts to establish validity (see Part 2, Section 3, 3.7) adds significantly to the cost for sponsor companies, generates intellectual property conflicts, stifles innovation and increases workload and timelines to prepare submissions. Moreover it may not deliver any added benefits in terms of either quality of the models presented, or quality of the evaluation.

In addition to these points of principle AstraZeneca would also like to acknowledge the Department of Health's engagement with sponsors to date. We would like to see this continue and in particular, to ensure a smooth transition to the new guidelines once finalised, request that:

(i) Comprehensive training in the new guidelines is provided, including for specific new tools and tests that have been referenced (see Part 2 – Section 2).

(ii) There is a sufficient transition period (at least two PBAC cycles) where either the existing or the new guidelines can be used by sponsors to guide PBAC submission content.

[1] DoH press release, 'Pharmaceutical submission guidelines to be reviewed', April 25th 2015

Part 2 – Comments, concerns and recommendations relating to specific sections of the draft guidelines.

Section 1

General comment

AZ acknowledges the efforts that have been made to make this section more concise, accessible and flow more logically. Similarly we welcome the suggested use of tables and templates to facilitate simplicity and clarity around presentation of information in the submission.

p.16 Justification for the selection of the main comparator

AZ acknowledges and welcomes the additional guidance around treatment of off-label and non-PBS listed medicines. However the statement, '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 and/or reduction in toxicity over that alternative medicine', represents a change in stated policy, and implies the comparator can be selected on pricing/cost grounds and not, as stated in the current guidelines as 'Therapy that prescribers would most replace with the proposed medicine in practice'. AstraZeneca requests that this statement is withdrawn from the guidelines.

p.18 Multiple Comparators

Similarly to the above one of the criteria for when multiple comparators are required includes 'when there is a substantial difference in the cost of a treatment course across the comparators'. This again implies a change in policy and implies the comparator can be selected on pricing/cost grounds and not, as stated in the current guidelines as 'Therapy that prescribers would most replace with the proposed medicine in practice'. AstraZeneca requests that this statement is withdrawn from the multiple comparator criteria.

p.18 Future Comparators

AstraZeneca is concerned about the apparent formalisation of this concept into the guidelines. Moreover it is not clear how this would work in practice i.e. what evidence/data is required and how this will influence PBAC decision making. In addition, Sponsors would not be aware of the TGA status of future competitors, given that this information is not in the public domain and there would be no guarantee that potential future competitors would seek or obtain local registration or PBS listing. AZ proposes that the reference to therapies that are currently undergoing TGA registration be removed.

p.20 Rationale of PBS Listing

Contrary to the guidance provided in this section, we believe non-health outcomes must be included in the rationale for PBS listing since such broader societal impacts can be critically relevant.

p.23 Section 1.3 Regulatory Process

The draft Guidelines request unredacted registrations reports from FDA and EMA. AstraZeneca is concerned about the request for evaluation reports from FDA and EMA as these reports represent a snap-shot in time from an overseas evaluation which may or may not be relevant to the registration environment in Australia. Further in the "Document Table" on page 7 it is suggested that the FDA and EMA Assessment Reports are required if the medicine is not TGA registered. However this scenario would by default occur within the TGA/PBAC parallel process. Under this scenario the Delegate's Overview would be provided one week prior to the PBAC meeting at which the submission is being heard, making the request superfluous. Moreover this request will create further work for the evaluator who will not be an expert in regulatory matters. AstraZeneca therefore requests that the requirement to provide unredacted registration reports from FDA and EMA be removed from v5.0 of the guidelines.

Section 2

General comment

Reference is made in several places throughout Section 2 to particular tests, tools or comparisons that could be presented. Many may be unfamiliar with these approaches and AZ proposes that education on these tools and/or tests be provided if it is expected that they are to be included in submissions. For example:

- AMSTAR, ROBIS tools to assess the quality of a systematic review, p44
- ACROBAT-NRSI tool to assess sources of bias, p44
- Begg test, Egger test to assess publication bias, p60
- MAIC, STC comparisons as approaches for comparing single arm studies, p62

p.37 Search results

"Where multiple reasons for exclusion exist, excluding on the basis of an incorrect comparator should be done last". AstraZeneca would like clarification on the justification for why excluding on the basis of an incorrect comparator should be done last. .

p.38-39 Option to present supplementary evidence
"Separately identify and list the supplementary randomised trials" This sentence should read 'supplementary evidence' rather than 'supplementary randomised trials' since the evidence will not necessarily be randomised trials.

p.58 "Present the forest plots for the meta-analyses in an attachment to the submission". Forest plots were previously included in the main body of the submission and allow quick visual assessment of results. Please consider moving this back to main body.

p.79 Treatment switching in trials

"Where it is unclear whether the estimate is conservative, consider using the most conservative end of the 95% confidence interval for the treatment effect in an economic analysis".

AZ requests that the economic analysis should be based on the most likely outcomes to be achieved in practice rather than the most conservative should a drug be PBS listed as requested.

Section 3

p.87 Introduction
Discussion of therapeutically inferior products seems to be unnecessary. These are acknowledged to be rare cases as legislation prevents PBAC from recommending the listing of inferior products on the PBS.

p.96 Perspective of evaluation
As outlined in Part 1 of this submission, AstraZeneca believes the societal perspective should be central to PBAC consideration and such concerns should not be relegated to supplementary concerns given some interventions have significant economic and social consequences for society beyond patient health outcomes and health care budgets.

p.96 Discounting
Three different sensitivity analyses for discounting are proposed, in addition to the 5% base case discounting rate. This adds additional complexity for the modelling results and sensitivity analysis to be presented and it is difficult to see how this adds additional value for decision making. We suggest using one agreed, realistic rate less than the 5% which is unfeasibly high.

p.98 Literature review
Please provide further clarity on the scope for the literature search. Should this be restricted to published models or should other models considered by other HTA Agencies (e.g. NICE, CADTH be included).

p.99, and Section 3.7 Validation of the economic model

According to these draft Guidelines conceptual models should be assessed by experts to establish face validity. In practice for AstraZeneca and many other Sponsors external consultants (Global and local level) are frequently requested to construct economic models or adapt a Global model. A literature review of published models and justification of the model structure is usually conducted by experts in the field. Therefore the draft Guidelines concept of external validation by yet another external expert appears to be a redundant concept. Moreover this would add significantly to the cost for Sponsor companies, generate intellectual property conflicts, stifles innovation and increases workload and timelines to prepare submissions and ultimately may not deliver any added benefits in terms of quality of the models presented for evaluation. Independent validation of the model structure is, and should be, performed during the independent evaluation of submissions. Some practical issues with this suggestion may not have been fully considered. Expert consultants, be they independent companies or academic centres, are unlikely to offer their expert opinion without charging for their time, and yet the commercial arrangement may impact independent validation. This additional requirement for validation simply adds another layer of unnecessary process, when the overall approach should be simplification where possible. This whole Section is at odds with the general advice to select the least complicated model techniques where possible.

p.99 Validity of model horizon
In the current environment of significant advances in cancer treatments, a cohort of advanced cancer patients who may have a durable response to treatment over many years should not automatically be considered implausible. The future prospects may vary by tumour type, but it should not be assumed that a significant treatment benefit is generally implausible in advanced disease.

p.102-3
Demographic and disease specific characteristics of the trials have previously been considered in Section 2, in addition to the applicability to the Australian population has now been assessed in Section 2.7. Therefore in the interest of being concise and improving the flow of information this section should not re-iterate this but only discuss any differences identified in 2.7 that would require translation in Section 3.3.

p.102 Sources of data
The Guidelines do not acknowledge the practical issue that sometimes assumptions need to be made in economic modelling. If there are assumptions that cannot be supported by literature references these should still be stated as assumptions and can be tested in sensitivity analyses.

p.106 Transition probabilities
Please can more guidance be provided for how confidence intervals should be incorporated into the model when transition probabilities are derived from Kaplan-Meier survival analyses in a partitioned survival model.,?

p.108 Parametric model fitting
The Guidelines suggest a range of best-fitting models should be tested in sensitivity analysis. Again, the use of a range of parametric models adds to the complexity of the economic model. Please consider limiting this to justification of the base case parametric model (if there is a clear best fit parametric model) and selection of next best fit in sensitivity analyses if all statistical techniques and visual inspection suggest there is little difference.

p.130 Section 3.10
This Section appears to repeat information already provided earlier in Section 3 and as such is redundant in the written explanation of the economic model. This summary could be incorporated as a worksheet in the model for easy reference instead, rather than repeat information in what will become a very long Section 3.

p.138 Cost minimisation results
The first sentence should read Pharmaceutical Benefits Pricing Section (?), however the whole sentence seems unnecessary/unclear in intent.

Section 4

General comment

The narrowing of the focus from all health budgets to just Australian Government health budgets in Section 4 is a worrying departure from normal health economic practices. This will lead to inconsistent conclusions between Sections 3 and 4 (See Part 1 of the submission also).

The current guidelines recommend a disaggregation of PBS/MBS and other Gov't health budgets. AZ proposes that this should be retained so that cost to Australian Government should not influence PBAC decision making.

Introduction "Presenting both (market share and epidemiological) approaches and demonstrating a concordance of comparable results across the approaches might reduce uncertainty in the utilisation and financial estimates". It is unclear if this adds any value and if one method has been ruled out then both should not need to be presented. AZ proposes that this should remain unchanged from v 4.4.

p.153 'For these calculations, use constant prices'. This remains a questionable feature of the Australian system especially for situations where known statutory price reductions will occur. It should also be noted that this contradicts the advice provided for combination items, where it is suggested that the impact of future statutory price reductions should be presented in expenditure estimates. (Page 177 P1.1 Listing fixed dose combination products – Financial implications section). AZ proposes that known price reductions should be included in the analysis.

p.163 "Summarise the results of any calculations (e.g. sensitivity or scenario analyses) to quantitatively examine the impact of uncertainty in Spreadsheet 5 of the standardised Excel workbook. Do not include the supporting calculations in that spreadsheet. If additional calculations need to be explained, a separate workbook should be provided for any analysis other than the base-case (most likely) analysis. Spreadsheet 1 of the separate workbook should highlight the differences from the base-case workbook". Separate workbooks add complexity and can lead to errors, formulas not being updated etc. We suggest rewording to: "If additional calculations need to be explained, a separate ~~workbook~~ *sheet* should be provided for any analysis other than the base-case (most likely) analysis. ~~Spreadsheet 1 of the separate workbook~~ *The new sheet* should highlight the differences from the base-case workbook".

Section 5

p.173 "No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients".

We suggest that the pharmacological alternative referred to should be PBS medicines only i.e. the wording should be changed to "No *PBS listed* alternative exists in Australia to treat patients…"

Appendices

1-Expert Opinion

The inclusion of 'consumer' i.e. patient, as a source of expert opinion may be a suitable way to add validity to patient input. There is a specific note regarding the sponsor of Advisory Boards regarding the difficulty of assessing the generalisability of such opinion. This devalues the most frequent source from whom input is sought. Impact on the cost of expert opinion as a more market research, random sample approach is required. Additionally guidance on what is considered large or small samples of prescribers is required.

5-Factors that may cause heterogeneity of treatment effect

This new appendix is welcomed and provides a useful reference for describing potential confounders when combining trials in a meta-analysis, performing indirect comparisons of randomised trials or network meta-analyses, or comparing variables from the clinical trial setting with the population in the economic model.