ρ

PBS Post-Market Review Team
Department of Health and Ageing
MDP 900
GOP Box 9848
CANBERRA ACT 2601
Via email to: PBSpostmarket@health.gov.au

1 April 2016

Dear Sir/Madam

Re: Public Consultation on the Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines Review

Roche welcomes the review of the Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines, acknowledging the need for the Guidelines to represent best practice and facilitate access to innovative medicines. The goal of aligning with international best practice is important and commendable. However, Roche is aware of best practice approaches in other countries performing health technology assessment (HTA) that are not reflected in the revised Guidelines. It is recommended that further consideration be given to globally accepted approaches and methods.

Roche recommends that the review of the Guidelines considers the following, particularly in light of the recommendations of the Senate Community Affairs References Committee 's Report on the "Availability of new, innovative and specialist cancer drugs in Australia"[1]:

- International best practice in HTA methods should be followed where appropriate.
- The broad societal value of medicines, beyond health outcomes, should be considered in a transparent and balanced way in the evaluation of medicines.
- The proposed selection of the main comparator based on the least expensive alternative does not support innovation.
- Increased clarity on the role and acceptance of different levels of evidence, given the recommendation for more flexible evidentiary requirements in the Senate Report, particularly for rare diseases.
- The review of the PBAC Guidelines should occur alongside a review of PBAC processes, including an increased role for patients and clinicians in HTA decision-making.
- The review of the PBAC Guidelines should occur alongside a review of medicines reimbursement policy, including the interpretation of current legislation.

Many of these issues were identified by stakeholders during the review's first call for public consultation in September 2015. Although several issues have been addressed to some extent in the revised Guidelines, further consideration is required before the Guidelines are finalised and implemented.

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

Roche Products Pty Limited
ACN 000 132 865
4-10 Inman Road
(PO Box 255)
Dee Why NSW 2099
AUSTRALIA

International best practice

The inclusion of well-documented, well-supported, clear and transparent methodologies that represent international best practice will increase the quality, consistency and alignment of HTA in Australia. For example:

- the broader concept of value and therapeutic innovation that is taken in countries such as France and Germany
- global best practice on appropriate crossover adjustment methodologies, such as those recommended by UK expert health economist Nicholas Latimer and utilised by other HTA decision-makers, such as NICE[2].
- the more flexible use of managed entry and real-world data in The Netherlands and Italy
- the use of discrete choice experiments, which have been used in other jurisdictions such as Germany, as a methodology for ensuring patient preferences are incorporated in a rigorous and robust way in the evaluation process for new medicines.

Value and criteria for PBAC assessment

The revised Guidelines note that '*The PBAC is required under s. 101(3A) of the National Health Act 1953 to consider the effectiveness and cost of the proposed medicine compared with alternative therapies. When the proposed medicine is substantially more costly than an alternative therapy, the committee will not make a positive recommendation unless it is satisfied that the proposed medicine provides a significant improvement in efficacy and/or reduction in toxicity over the alternative therapy*' (page 16 of the revised Guidelines). "*Under the National Health Act 1953, the primary objective of the PBS is to improve health, so the PBAC primarily focuses on health outcomes*" (page 19). While *the Act* highlights the need for improved efficacy and reduced toxicity, it does not explicitly preclude the consideration of broader societal perspectives. However, the revised Guidelines state that the primary focus of the PBAC is on (clinical) efficacy and toxicity and mandate an assessment using a "health care system perspective" for considering costs and benefits (page 85). A "societal perspective" can be presented, however, incorporating broader, non-health outcomes for carers and patients (e.g. work productivity) is relegated to a "supplementary analysis" (pages 19 and 85). The revised Guidelines do not explain how the PBAC will consider such supplementary information or how it would be used in decision-making. For some medicines, non-health-related benefits and cost savings can be considerable (e.g. the impact of antimigraine therapy on work productivity or Alzheimer's therapy on caregiver time). Not including these components of value presents equity issues for those patients who are unfortunate enough to be diagnosed with a disease where the value is measured in a non-standardised way. A broader perspective on value was a key recommendation of the Senate Report on Access to Cancer Medicines in Australia[1], and therefore, it is critical that this broader perspective is appropriately acknowledged across Sections 2 to 5 of the revised Guidelines.

The final Section of the revised Guidelines (Section 5) allows for sponsors to outline "equity principles, 'rule of rescue' and other relevant factors that can affect the PBAC's assessment of proposed medicines". However, as with the societal perspective, it is not clear how these will be considered or weighed against traditional cost-effectiveness criteria.

[2] http://www.nicedsu.org.uk/Crossover%20and%20survival%20-%20final%20DSU%20report.pdf

Support for innovation

Roche is concerned that the revised Guidelines include elements, such as comparator erosion, that will impede future access to innovative medicines and continued improvement in health outcomes. The revised Guidelines state that "*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*" (page 16).

This interpretation of *the Act* is questioned, as the choice of comparator as the least expensive alternative medicine is not specified: '*101(3A) For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing* ***the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations***.'

The text in the current PBAC Guidelines regarding choice of main comparator refers to "*therapy that prescribers would most replace with the proposed medicine in practice if the PBS subsidises the proposed medicine as requested*" . It is recommended that the current guidance remains to ensure alignment with best practice internationally as highlighted by the European Network for Health Technology Assessment[3].

Roche is concerned that the choice of the least expensive alternative medicine as the main comparator, regardless of the extent of use in clinical practice, will lead to inequity of access to new medicines. Medicines that are submitted to the PBAC while all comparator therapies are under patent and in the F1 formulary will continue to demonstrate cost effectiveness against prices for the standard of care, which are set to generate a return on investment. However, as soon as one therapy in a reference group is exposed to generic or biosimilar competition, moves to the F2 off-patent formulary and incurs a price reduction, new innovative molecules will be required to demonstrate cost-effectiveness against this significantly lower price, regardless of the extent of use of this low cost alterantive in clinical practice. This shift in the comparator price could occur in a matter of months, potentially creating a barrier to innovation from the moment the first generic or biosimilar in a therapeutic area gains PBS listing. However, what is welcomed is that the revised Guidelines acknowledge that: '*In situations where the proposed medicine has more than one alternative therapy and there are distinct groups of patients in whom one alternative therapy, but not the other(s), is appropriate, and those alternative therapies have different prices, then the new medicine's price can reflect the proportions of the treated population in which the different alternative therapies are appropriate*' (page 16). In this situation, the lowest cost comparator may be used in only a subgroup of patients treated with the proposed drug and therefore a weighted price is appropriate, or the lowest cost comparator may be used in a different patient population to the proposed medicine, and therefore is not relevant.

Fit-for-purpose levels of evidence

Roche appreciates the PBAC's willingness, as outlined in the revised Guidelines, to consider different standards of evidence, such as non-randomised studies (pages 30 & 45), surrogate outcomes and secondary outcomes that are "patient relevant" (page 50). However, it is unclear how this evidence will

[3] http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Choice_of_comparator.pdf

be considered, given that the PBAC focuses on minimising uncertainty, which is more likely to be present in non-randomised trials. This poses a significant risk to the evaluation of medicines for rare diseases, which are unlikely to be accompanied by randomised trial evidence. This is particularly important and challenging in a Global environment of accelerated regulatory approval for innovative medicines with high unmet need that are based on adaptive and earlier phase clinical trials. While fit-for-purpose evidentiary requirements was a recommendation of the Senate Report[1], guidance on the appropriate approach to take in the setting of evolving trial design is lacking in the revised Guidelines.

Guidelines that are presented in a more modular or scalable fashion (i.e. allowing sponsors to select the components that are relevant to the product in question) would allow more "fit-for-purpose" submissions, in line with the Government's commitment to reducing "red tape", as recommended in the Senate Report.

It is noted that in some instances the revised Guidelines impose limits on how sponsors can present submissions, which may further limit flexibility and ability to tailor submissions to address the specific research question. For example, the 'Rationale for PBS listing' is to be limited to less than half a page (page 19) and non-health outcomes as 'supplementary analyses' (pages 19 & 85).

Process improvement

Roche recognises that the process for assessment and appraisal of medicines is out of scope for the Guidelines review, and as such tiering of submissions or other efforts to ensure the system is fit-for-purpose are not able to be considered. However, a review of both methodologies and process needs to be considered in tandem if Australia is to be a benchmark for best practice HTA.

As Roche noted in the first public consultation: 'Alongside the Guidelines Review of methodologies, the planned review of reimbursement processes needs to ensure:

- the perspectives of all relevant stakeholders are taken into consideration in a timely way; and
- the decisions should reflect the needs and values of the Australian population.

It is important that the Australian community has a voice in determining what is value for money in HTA. These values can only be derived through a process that allows active participation by citizens and a clear set of decision-making principles reflecting society's preferences. These decision-making frameworks have been considered in other HTA countries. In the UK, patients and citizens are involved in setting decision-making criteria and participate on the HTA Committee. In Canada, patients participate on the HTA Committee and, as part of the pan-Canadian Oncology Drug Review, patient advocacy groups provide input at the beginning and throughout the evaluation process. This is a point of difference with the Australian system, where input from patient groups is only considered immediately prior to PBAC consideration in the form of Public Comments and Consumer hearings. Involvement of the community throughout the evaluation process is key to ensure a clear, consistent and effective process of valuing medicines more broadly.'

There is a need to establish a process for tiering of submissions, with a more comprehensive evaluation proposed for complex applications and innovative medicines that are often associated with higher budget impact and therapeutic value, versus a less comprehensive evaluation for treatments associated with a low budget impact, treatments for rare diseases and those with a comparable clinical benefit and cost to existing therapies.

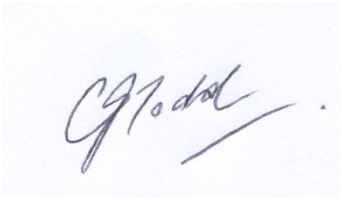
Policy review

Roche recognises that the timing of the Guidelines review imposes limits on what can be achieved, as the Guidelines must reflect the current policy and legislative settings, some of which is open to differing interpretation. Roche considers that a more comprehensive review of the Guidelines should occur after, and be informed by, broad consideration of the objectives, process and assessment criteria for the Australian HTA system.

Conclusion

Development and implementation of world-class PBAC Guidelines for HTA evaluation of medicines can facilitate optimal access and appropriate use of innovative medicines and enable the best possible outcomes for Australian patients. This is a shared goal for all stakeholders.

Yours sincerely



Carlene Todd
Director, Market Access and Pricing
Roche Products Pty Limited

Appendix of additional technical comments:

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
About the Guidelines, page 4	Key factors influencing decision-making by the PBAC	'Other less ready quantifiable factors that also influence PBAC decision-making are…'	Calling out these factors in a transparent way is an important step forward.
About the Guidelines, page 5	Key points for preparing a PBAC submission	'Information requirements **must** be followed'	Add: 'Unless adequate justification is provided for the exclusion of this information, in line with the research question being posed.' As outlined on page 4 of the Guidelines.
Part A: Submission Executive Summary, page 10	Checklist for the Executive Summary of a major Submission		The factors that the PBAC takes into account in their decision-making process need to be considered in the Executive Summary (e.g. equity and availability of effective alternatives' (pages 4-5 of the Guidelines). This should be added to the checklist.
Section 1: Context, pages 12-15	1.1 Information Requests and Table 1.1.1.	'Tabulate the proposed population, intervention, comparator and outcomes for the proposed medicine, and present the overall clinical claim'	Inconsistent with Flowchart 1.1 (page 13), which only includes Popualtion (P), Intervention (I), and Comparator (C). Outcomes (O) are not included in Flowchart 1.1.
1.1. Clinical issue addressed by the submission: Intervention and comparator, page 16	Justification for the selection of the main comparator	'New therapeutic class: If the proposed medicine is in a new therapeutic class, but there are other, widely used medicines listed for the proposed patient indication, the main comparator would usually be the medicine prescribed on the PBS to treat that indication for the largest number of patients'	The Comparator section is confusing as this text recommends the <u>most commonly used</u> as the comparator, whereas page 16 recommends the least expensive. Further clarity needed on the recommendations in the Comparator section.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
1.1 Clinical issue addressed by the submission: Intervention and comparator, page 16	Multiple comparators	'Where multiple comparators exist, the PBAC would prefer that all of those that are potentially relevant are included in the submission'.	The Comparator section is confusing as this text recommends the most commonly used as the comparator, whereas page 16 recommends the least expensive. Further clarity needed on the recommendations in the Comparator section.
1.2 Clinical management algorithms, page 20			Discussing treatment algorithm before the comparator is identified will assist readability, given it provides a more logical flow of events regarding how the comparator is chosen.
Section 2: Clinical Evaluation, page 30			Recommendation: Section 2 be called 'Evaluation of Outcomes' It is important that the broader definition of value beyond just clinical outcomes is captured in the evaluation of benefits, given the predominance of this discussion during the Senate Inquiry and the recommendation to consider broad evidence in the Senate Report.
Section 2: Clinical Evaluation, page 30	Flowchart 2.1: Overview of information requests for Section 2 of a submission to the PBAC		As in the current Guidelines, is there a place for new medicines that are clinically inferior but less expensive, especially if other treatments are contraindicated?

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
Section 2: Clinical Evaluation, page 34	Search criteria; randomised trials Search terms	'List all randomised trials containing the proposed medicine. If relevant randomised trials are located that directly compare the proposed medicine with the main comparator, trials that compare the medicine with an alternative comparator can be excluded in Subsection 2.2' 'The search strategy should not include terms for the comparator (unless a search is conducted for trials suitable for an indirect comparison; see Subsection 2.2'	It is unnecessary to include ALL randomised trials of the proposed drug. To streamline the submission and evaluation process, it is appropriate to only include the trials that compare the proposed drug versus the main comparator in Section 2.1. This is inconsistent with the recommendation on page 29: "The search process described in Subsection 2.1 requests that submissions first search for randomised trials that compare the proposed medicine with the main comparator". Text should read: "The search strategy SHOULD include terms for the comparator"
2.2 Identify relevant trials, page 38	Option to present supplementary evidence	"… in certain circumstances, it may be reasonable to justify the inclusion of supplementary study data"	This is an appropriate place to discuss evidence that relates to broader non-health outcomes. Consider description as 'supplementary evidence' rather than 'supplementary randomised trials'. Will not necessarily be randomised trials.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
2.3 Trial design and execution, page 45	Systematic reviews and meta-analyses	'Where individual trials are not able to be retrieved and the submission relies on a pooled treatment effect from the published systematic review and meta-analysis, the submission should clearly report the risk of bias assessment undertaken by the authors of the systematic review, and also assess the quality of the systematic review using a validated tool (such as AMSTAR[6] or ROBIS[7])'	Education needed on validation tools, such as AMSTAR and ROBIS.
2.3 Trial design and execution, page 45	Approach 2: nonrandomised studies	'Nonrandomised studies can, however, provide useful information in the following situations:…'	Add the following bullet point: 'Where there is a high unmet need, a molecule has gone through fast-track regulatory approval, and a managed access program is proposed based on phase I or II data, in anticipation of later phase III evidence'.
2.3 Trial design and execution, page 45	Approach 2: nonrandomised studies	'The submission may wish to address possible sources of bias according to the domains described by the Cochrane Collaboration's ACROBAT-NRSI tool[8]'	Education needed on the ACROBAT-NRSI tool.
2.4 Trial characteristics, page 50	Outcomes	'The PBAC considers the following outcomes to be relevant, and these should be listed and clearly defined for each included trial:…'	An appropriate place to discuss evidence that relates to broader non-health outcomes.
2.4 Trial characteristics, page 52	Non-inferiority margins		Determination of non-inferiority margins needs to be based on both statistical and clinical reasoning.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
2.5 Trial results: whole trial population, page 54	Presentation of indirect comparison	'Subsection 2.5 is intended to capture the results from the studies for the whole trial population. Where the submission is based on a subgroup, meta-analysis or indirect comparison, or requires adjustment for treatment switching, this will be addressed in Subsection 2.6. Regardless of the overall approach taken in the submission, the results for the whole trial population should be presented.'	It is unclear whether the results are to be presented in Section 2.5 for the separate trials of the proposed drug and of the main comparator prior to conducting an indirect treatment comparison. This needs to be made more explicit here.
2.5 Trial results: whole trial population, page 57	Adverse events	'As a minimum, the following categories of adverse events should be reported:…'	Appropriate to include treatment-related adverse events.
2.6 Trial results: additional analyses, page 58	Information requested	'Describe and justify the use of analyses that were not prespecified in the included studies but are relevant to the submission, including…'	Analyses that were pre-specified should also be included here. Suggest deleting the text 'that were not prespecified', and add a separate sentence requesting further justification if the results were not pre-specified. Even if the analyses are pre-specified, biological plausibility needs to be provided. Test for interaction analyses also need to be provided to justify the use of a subgroup. Add text "Test for interaction analyses' (as outlined on page 58).
2.6 Trial results: additional analyses, page 63	Indirect comparison methodology	'More complex methods, such as NMA, may be presented as a supplementary analysis'	Suggesting that these types of analyses can only be presented as a supplementary analysis undermines the potential relevance of this type of approach that is well accepted in other HTA jurisdictions. Suggest removing this sentence given that this type of analysis may be the only relevant assessment available.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
2.6 Trial results: additional analyses, page 67	Adjustment for treatment switching		Move to an Appendix given the technical nature of this discussion to 'declutter' the Guidelines as per the intent/principle of the Review.
2.6 Trial results: additional analyses, page 69	Adjustment for treatment switching	'More complex methods, such as inverse probability of censoring weights (IPCW) or a rank-preserving structural failure time (RPSFT) model, have assumptions that are difficult to validate'	These approaches have been assessed and used internationally and both have their merits, depending on the circumstances and data available in the trial. These methods should not be discredited in the PBAC Guidelines given that international experts have deemed them as representing world's best practice. These methods should be deemed acceptable in appropriate circumstances and outlined with references to published technical approaches in an Appendix.
2.6 Trial results: additional analyses, page 69	Adjustment for treatment switching	'If complex methods are used, the PBAC prefers to see the results of several commonly used methods, and clear justification where a method is not used. Where more complex methods are presented, also present the results of simpler methods as a reference.'	This is not appropriate, as the applicability and feasibility of IPCW and RPSFT are typically mutually exclusive. Simple methods are usually not appropriate and may introduce considerable selection bias. The presentation of simple approaches does not add any certainty or value to validate a complex method.
2.6 Trial results: additional analyses, page 69	Adjustment for treatment switching	'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, if presented'	This is not reasonable. The most conservative method is not necessarily the most realistic or certain estimate, based on the appropriateness of the methodology used. Recommend that this sentence be removed.
2.7 Applicability of the trial evidence	Information request	'Identify any treatment effect variation in subgroups, compare the subgroups with the Australian population, and discuss how this is reflected in the therapeutic claim and economic analysis.'	There is a need to not just compare subgroups with the Australian population, but also compare the whole of trial population (when used) with the Australian population. Suggest rewording so there is clarity that the relevant trial population is compared with the Australian population.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
2.7 Applicability of the trial evidence, page 72	Subgroups showing treatment effect variation		This section is only relevant IF there are differences between the trial population and the Australian population. Where there are no notable differences, test for interaction analyses are not relevant. This needs to be clarified upfront, given the purpose of this section is to determine whether the trial represents clinical practice.
2.7 Applicability of the trial evidence, page 72	Comparison of trial setting and Australian setting		This section is confusing and requires simplification. The first step is to determine whether there are any differences between the trial population and the Australian population. The analysis will be limited by the available Australian data. Only IF there are differences, should test for interaction analyses be performed for the relevant subgroups that show differences between the trial and clinical practice. If the whole trial population is used (and there are no subgroup analyses performed in Section 2.6), these analyses are not needed if the whole of trial population and the Australian population are shown to be comparable.
2.8 Interpretation of the clinical evidence, page 75	Information requests		The value of a the proposed medicine comprises both health and non-health outcomes that should be captured, as outlined in the Senate Recommendations to the Inquiry on Access to Cancer Medicines. It is important that other non-clinical outcomes are considered in the interpretation of the evidence and can inform the economic evaluation.
2.8 Interpretation of the clinical evidence, page 76	Therapeutic conclusion		Guidance needs to be included on drawing a therapeutic conclusion of superiority from an indirect treatment comparison (ITC), network meta-analysis (NMA) and mixed treatment comparison (MTC).
Section 3: Economic evaluation, page 77	Introduction	'The economic evaluation initially depends on whether the therapeutic conclusion shows that the proposed medicine is…. • therapeutically inferior to the main comparator'	This is inconsistent with Flowchart 2.1, page 30, which does not include 'therapeutically inferior to the main comparator' as a possible therapeutic conclusion.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
Section 3: Economic evaluation, page 77	Cost-minimisation requires cost savings	'When the proposed medicine is concluded to be therapeutically superior or noninferior and is anticipated to provide cost savings to the health system, a cost-minimisation approach is appropriate'	This text is confusing and suggests that new medicines that have not demonstrated clinical superiority (but may be innovative in other respects) must offer savings. This is likely to limit availability of different treatment options and the ability of clinicians to optimise treatment for individual patients. Why would a cost-minimisation analysis be appropriate when a treatment is superior and provides costs-savings? To be clarified whether this is an error.
3.1: Overview and rationale of the economic evaluation, page 87	Modelled economic evaluation (including stepped adjustments to a trial-based evaluation)	'3. Extrapolate health care resource use and health outcomes (for the proposed PBS use) as required over the appropriate time horizon (detailed in Subsections 3.2 and 3.5).'	It is more appropriate to apply this as Step 2. Incorporation of proposed Step 2 issues will often only be relevant over time exceeding the trial based results.
3.2 Computational methods and structure of the economic analysis, page 88	Time horizon of the evaluation	'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'	This is a very welcome change from the current Guidelines.
3.2 Computational methods and structure of the economic analysis, page 95	Extrapolation	'Generally, transition probabilities should be derived from observed time-to-event data to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free'	Median time to follow-up as the truncation point for extrapolation has been removed from the revised Guidelines. However "become unreliable" is unspecific and will again give room for debate on the appropriate time point for Kaplan Meier truncation.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
3.2 Computational methods and structure of the economic analysis, page 96	Extrapolation	'A range of alternative survival models should be fitted to the observed data. The range of models to be tested should include more flexible extrapolation approaches with multiple points of inflexion (eg piecewise spline models), which better facilitate extrapolation based on the section of the Kaplan–Meier curve that is most representative of long-term survival'	This approach contradicts the use of as much Kaplan Meier data as possible as proposed for the selection of the truncation point for extrapolation.
3.7 Model validation	Information requests		The value of this validation exercise is not clear. Validation is part of the evaluation. There will be significant additional work and resources required (in terms of potential external validation, expert involvement) and impact on the timelines for model development. Who is the appropriate expert?
3.8 Uncertainty analysis, page 107	Defining sensitivity analyses to be undertaken	'If undertaking a probabilistic sensitivity analysis on a cohort-based state transition model, the number of iterations (sets of randomly sampled input parameter values included in the analysis) should provide stability in the model outputs across multiple analyses using alternative random number seeds'	No guidance is provided on the importance of probabilistic sensitivity analysis (PSA) and how it will influence decision making. The Guidelines only require univariate/multivariate sensitivity analyses. If and how will PSA be used and perceived in the future?

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
Section 4: Predicted use of the medicine in practice, page 124	Introduction	'Where both epidemiological and market-share approaches are possible, the PBAC prefers that both are presented, with a comparison of the results and an interpretation of any discrepancies. Where only one approach is presented, the submission should clearly justify why this has been done'	Requiring both approaches should not be the default position. Instead,the submission should clearly justify why one particular approach was presented, rather than why two have not been presented. Providing both approaches is excessive and adds considerable work for limited additional value.
4.1: Justification of the selection of data sources, page 129	Commissioned data	'When presenting commissioned data, provide the relevant correspondence requesting the data, including the precise questions asked of the experts, disease registry or study investigator'	It is appropriate to provide methodology, however provision of correspondence requesting the data is not necessary. Instead of 'source correspondence', research questions and data requests should be specified.
4.2 Estimation of use and costs of the proposed medicine, page 131		'For conditions that may have less clear parameters for diagnosis or a subjective element in their diagnosis, consider the impact of misdiagnosis of patients for the purposes of rendering them eligible for the proposed medicine'	This would likely represent double counting as there will already be an element to this in official figures used to estimate incidence and prevalence. There is also uncertainty in applying any misdiagnosis parameters to patient numbers.

Guidelines Section, Page #	Topic/Issue	Text from the revised Guidelines	Comment/recommendation
4.3 Estimation of changes in use and cost of other medicines, page 139		'On the basis of the estimated utilisation changes, estimate the costs in each year over five years for each of the forms and strengths of each of the medicines substituted, decreased and increased.'	Present 6 years of predicted use rather than 5 years, as requested in post-PBAC utilisation estimates discussions.
4.5 Estimated financial implications for the Australian Government health budget, page 143	Net implications for Australian Government health budget		Guideline Sections on State/Territory Government health budgets and the Combined Government health budget have been removed. Is this no longer a requirement?
4.6 Identification, estimation and reduction of uncertainty, page 145	Factors that could affect the extent of usage within the requested restriction	'The duration of therapy might be longer than expected from the randomised trials, particularly when trials are truncated' 'There might be a likelihood of doses increasing over time'	Duration might be longer as suggested, but may also be shorter in real world scenarios, especially given potential compliance issues. Doses may also decrease over time due to compliance considerations.