Submission to the PBAC Guidelines Review Public Consultation

1. Introduction

Janssen (Janssen Cilag Pty Ltd) welcomes the public consultation on the proposed Pharmaceutical Benefits Advisory Committee (PBAC) guidelines (v 5.0). Janssen is the sponsor of innovative medicines that are listed on the Pharmaceutical Benefits Schedule (PBS) and in the past five years alone have lodged over 50 submissions to the PBAC (10 for the listing of new medicines previously unavailable to Australian patients). The team who write submissions within Janssen have over 50 years of experience in health technology assessment (HTA) and some members of the team have been involved in writing PBAC submissions since 1999. Furthermore, as an international company, Janssen is experienced in methodologies utilised by HTA systems around the world.

Janssen and their parent company Johnson and Johnson, are internationally committed to fostering the world's best practice of HTA and actively participate in and sponsor collaborations such as the Greenpark Collaboration on cross-over and locally *"Room With A Patient View* conference" which examined the need for and how to engage patients in health care decision making.

Janssen strive to bring timely access of our innovative medicines to Australian patients and acknowledge that this is also the goal of the PBAC, the Department of Health and the Australian Government. Janssen therefore welcomed the terms of reference to the guidelines review, namely:

- developing a more concise, clear, focused and up-to-date methods guidance; and
- that the guidelines continue to reflect best international practice.

It is unclear how the proposed guidelines meet the terms of reference, indeed Janssen would argue that in their proposed current state they do not. Given that the submissions in this consultation period are limited to five pages, Janssen are unable to comment on every issue of concern, however will broadly note areas of key concerns and provide general comments as well as some final conclusions and recommendations. However it is unclear how the proposed guidelines meet the terms of reference.

2. Overall Comments

The proposed guidelines do not appear to have achieved the objective of concise, clear, focused guidelines. Improving the conciseness and clarity, should not be just about reducing the number of pages in the guidelines but also about making the guidelines more accessible, specifically they should be written in plain English. Janssen understand that there will always be a need for technical language and jargon. However, even experienced submission writers have had trouble reading the proposed guidelines and interpreting some sections. We recommend that the proposed guidelines could benefit from editorial review.

Additionally, whilst the authors of the guidelines may consider that the objective of de-cluttering has been met there appears to have been no thought given about what a submission prepared according to the proposed PBAC guidelines would look like. Whilst the guidelines review committee and the PBAC are likely to argue that these are intended as guidelines and not as a *recipe book* for writing a submission, it is important to acknowledge that despite there being minimal "must do's" the Guidelines are presented in such a way that inexperienced submission writers will present everything, thereby increasing the size and complexity of submissions and subsequently the time needed for a proper evaluation. Sponsor's will present everything requested in the guidelines because they become afraid that if something is not

provided it becomes an opportunity for the PBAC to reject a submission because of "uncertainty". This will lead to delays in access.

Janssen agrees with the issues raised and the solutions offered in the submission to the PBAC Guidelines Review by Crowley, Bulfone, Noble and Wonder. We agree with both the general comments and the identified issues for Sections 1 through to Section 4.

3. Areas of key concern

3.1 Patient involvement

One area where Australia is undoubtedly and clearly behind international practice is consideration of the patient (consumer) voice as a valid and important component of HTA decision making. Janssen note that there was no consumer representative present on the steering committee and consider that this was a missed opportunity. Janssen notes that there have been recent advances in the PBAC process by including some form of "Consumer hearing", however it is unclear what weight these hearings have had on the decision making process.

Many HTA systems (NICE, SMC, CADTH) formally incorporate patient view. NICE in the UK has employed several measures, including a Citizen's Council. Canada, particularly in the area of oncology, has a formalized process through which patient input on drug reviews and feedback on recommendations is obtained to ensure patients' experiences (both good and bad) of living with cancer and undergoing treatment are routinely considered.

The stated objective of the PBAC guidelines review was to ensure that the guidelines are world's best practice HTA. However, the lack of consumer involvement in both reviewing the proposed guidelines and the exclusion of their view as part of the formal decision making process cannot be interpreted as best practice.

Janssen agree with the views expressed by Noble Pharma Consulting in its submission to the consultation process. Specifically, the suggestion of incorporating into the guidelines the use of discrete choice experiment methods to systematically capture and quantify the patient perspective. This suggestion is consistent with work Janssen has commissioned within Australia in using DCE methodology to elicit and quantify patient values in a systematic way for the purpose of treatment evaluation (Glase, Walters et al 2015).

3.2 Comparator

Janssen are concerned by the apparent change in the definition of comparator and the apparent reinterpretation of the National Health Act in order to justify the change in comparator definition. Version 5.0 provides draft revised guidance on the selection of the Main Comparator, with new and explicit reference to section 101(3A) of the National Health Act 1953 and the inclusion of the specific text outlined below:

> *"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 or reduction in toxicity over that alternative medicine."*

This compares with text in Version 4.5 of the PBAC Guidelines regarding choice of main comparator referring to:

> *"Therapy that prescribers would most replace with the proposed medicine in practice if the PBS subsidises the proposed medicine as requested."*

Janssen strongly believe that the comparator should be the treatment that will be most likely replaced in clinical practice. Changing this moves away from international HTA practice for definition of comparator and could be interpreted as an exercise in cost-containment.

Janssen agrees with the concerns and potential impacts discussed in the Medicine's Australia submission.

3.3 Cross-over

Janssen acknowledge that there is no single best method of adjusting estimates of overall survival in all studies with treatment switching (ie cross-over). Each approach has limitations and underlying assumptions that may or may not hold. The draft guidelines request that multiple methods of adjustment are provided including simple and complex methods. Of concern, the draft guidelines propose that *"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".* Janssen do not consider this appropriate as the most conservative estimate when multiple estimates are provided may not be the most methodologically appropriate estimate. Equally, the cost-effectiveness could be more favourable, yet the guidelines do not propose applying the opposite, more favourable limit of the 95% confidence interval. This advice is not consistent with international best practice (Latimer and Abrams, 2014).

Janssen note that the Department of Health and the University of Adelaide both participated in the Greenpark Collaborative & Bellberry initiative for outlining the best practices in treatment switching in oncology trials project and are surprised that there is no cross-reference to these recommendations particularly given that the guidance is expected to be published later this year.

The PBAC will increasingly find itself evaluating submissions with substantial cross-over especially in the oncology setting. Jonsson, Sandin et al 2014 describe that *"Crossover is .. of concern in health economics and outcomes research because of its potential to affect estimates of efficacy and cost-effectiveness (CE). If an investigational drug reduces mortality, ITT analysis will underestimate the treatment effect in the presence of crossover and will likely lead to an overestimate of the incremental cost-effectiveness ratio (ICER). As a result, the decisions by pricing and reimbursement agencies regarding access to new therapies may not maximize health outcomes with the available resources if crossover is not corrected for."* It is critically important for the Guidelines to demonstrate best practice on this issue.

3.4 Time horizon

Janssen agree consistent with best practice that the time horizon 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 horizon unless where inappropriate. Janssen are concerned however with the second paragraph of the time horizon section on the proposed guidelines (p 99) which states that: *"The validity of a model with a lifetime horizon is determined by the population of the model, not the choice of a lifetime horizon. 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.". Janssen believe that this could be interpreted by a Sponsor to mean that the PBAC will never accept a time horizon beyond 10 years for advanced cancer. New transformational cancer treatments in advanced cancer could appropriately require a time horizon beyond 10 years. Janssen therefore requests that this paragraph be removed from the proposed PBAC guidelines or if it is the intent that the PBAC will never allow a time horizon beyond 10 years that the rationale for this is justified.

3.5 Cost minimisation

The Section on cost minimisation (Section 3B) appears to suggest that a cost-minimisation is the appropriate economic evaluation for a product that is therapeutically superior (p132). Janssen request that this be amended.

Of greater concern however, is the following statement on page 133: *"In all cases, assumptions of noninferiority or superiority, with respect to both effectiveness and safety, will need to be well justified for the cost-minimisation approach to be considered acceptable. However, assuming that the PBAC does accept such claims, a therapy providing acceptable outcomes in terms of both effectiveness and safety at a lower cost is preferable."* This could be interpreted to mean that any new medicine seeking listing should be less expensive than what is currently available. This is inappropriate and would violate best practice HTA. This appears to indicate a significant policy shift. Janssen therefore requests that this paragraph be removed from the proposed PBAC guidelines or if it is the intent that the PBAC will never list a cost-minimised drug at the same price but indeed require a lower price that the rationale for this is justified.

3.6 Post market surveillance

The draft guidelines suggest that *"Where the efficacy of the drug in the Australian population or maintenance of a response beyond the clinical trial period is uncertain, a pharmacovigilance study designed to monitor the clinical event rates predicted in the economic evaluation is appropriate.*
Present the details of any proposed postmarketing surveillance study (pharmacovigilance study), including the method of data capture, the outcomes of concern and how the results of the study will be communicated. Assess whether the interpretation of the results would be affected by the subsequent listing of another medicine in a similar population." Janssen agrees with the submission by Crowley, Noble, Bulfone and Wonder which notes there will always be an element of uncertainty and agrees with the recommendation that there should be cirteria as to when and why such studies are required.

3.7 Economic Model

Janssen note that Section 3 introduces a large number of additional requirements when compared to the previous guidelines, in particular additional literature searches and formal validation of the model. Janssen agree that it is good practice to validate models however, the extent of the validation proposed in the guidelines is extraneous to decision making. For example on page 118 Sponsors are asked to address the following: *"Have experts been asked to judge the appropriateness of the conceptual model? (If yes, who are they? why are they expert? to what extent do they agree that the conceptual model is appropriate? If no, why not?)."* It is unclear what information would need to be provided to provide comfort to the evaluator and PBAC that the expert is indeed an expert. We request that Section 3 of the proposed guidelines is reviewed, asking whether the additional requirements add to decision making.

3.8 Risk Share Arrangements

Of particular concern to Janssen is the guidance (p154) that *"Thresholds applied in risk-sharing arrangements should correspond with the most likely usage estimates for the PBS or RPBS reported in Subsection 4.2".* Janssen notes that expected patient uptake rate is a proportion of the overall cost-effective eligible patient population. A cap based on expected uptake may result in a situation whereby financial penalties are imposed on a Sponsor for use within the intended restriction. Janssen request that this section of the guidelines be amended to more accurately reflect that the intention of risk share arrangements is not to penalize the Sponsor for appropriate cost-effective use but rather to manage risk of use outside of the intended restriction. A more reasonable statement in the guidelines would be *"Thresholds applied in risk-sharing arrangements should correspond with the level of the eligible patient population."*

3.9 Minimally Clinical Important Difference (MCID)

The draft guidelines suggest that "for each outcome relevant to the submission, nominate and justify the minimal clinically important difference (MCID)". Janssen again agrees with the submission by Crowley, Noble, Bulfone and Wonder on this issue and reiterate that requiring MCIDs be investigated and justified for all outcomes and is unlikely to add useful information for decision making.

3.10 Extraneous information requests

Janssen note that there is an increase in the information expected to be presented in a submission, including but not limited to: 1) increased requirement to present systematic literature reviews to justify economic analysis; 2) increased information requirements to justify structure of a model; 3) Bayesian Information Criterion as well as Akaike's Information Criterion when determining goodness of fit; and 4) provision of statistical code, output and notation explaining variables used when establishing the comparative treatment effect.

Providing this information requires additional workload and is excessive for the Sponsor, evaluators, Subcommittees and the PBAC. It is unclear how the presentation of this information translates to a better understanding of the drug, its clinical place, its comparative efficacy, safety and cost-effectiveness and ultimately how it assists in better decision making. Janssen fear that the focus on information that appears to be peripheral to decision making will increase rather than reduce uncertainty and hinder rather than aid the PBAC in decision making.

Janssen requests that the guidelines are critically reviewed to determine whether the additional information requests add to or whether they are peripheral to decision making.

3.11 Transition arrangements

Janssen agrees with the Medicine's Australia's recommendation regarding potential transition for any new guidelines.

4 Conclusion and recommendations

Janssen has discussed the proposed guidelines with staff members involved in HTA in other countries as well as with a number of internationally renowned HTA experts. The overwhelming impression is that Australia had been at the forefront of economic evaluations in the 1990's and that there is a huge competence in HTA in Australia, however the proposed guidelines are considered to at best address previous problems but at worst are perceived as ignoring issues that will arise in the future. There is a fear that HTA in Australia is going backwards not forwards.

Janssen are concerned that whilst the guidelines should strive to present world's best practice and allow the timely reimbursement of cost-effective medicines the proposed guidelines will instead increase uncertainty, promoting a tick box for the evaluator whereby pragmatic and commonsense decision making becomes impossible with the end-result delayed access for Australian patients to innovative medicines.

In conclusion, Janssen recommend that the draft guidelines as they currently stand should not be adopted but rather be subjected to further discussion and review by a broader number of stakeholders, including consumers over an extended period and in a more consultative manner.

References

Jönsson L, Sandin R et al. Analysing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value in Health 2014; 17: 707-713

Latimer NR & Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching (2014).

Glase K, Walters, N et al. A systematic quantitative approach to incorporating the patient perspective into health technology assessment decision making. Poster presented at ISPOR 2015