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Pharmaceutical Benefits Advisory Committee
MDP 952
Pharmaceutical Evaluation Branch
Department of Health
GPO Box 9848
CANBERRA ACT 2601

Dear Committee members,

Thank you for the opportunity to provide feedback on the draft revised *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee* (hereafter *PBAC Guidelines draft v.5.0*).

By way of introduction and in the interests of transparency, I am a former evaluator of submissions to the PBAC (1997-2007) who now works part-time as a consultant advising and assisting sponsors with the conduct of health technology assessment (HTA) to inform reimbursement decisions (including submissions to the PBAC). I also work part-time at Deakin University where I am the Unit Chair for the Economic Modelling unit that is offered as part of the Master of Health Economics course. In my capacity as an academic at Deakin University, I was part of a consortium assembled by Deakin University who tendered to conduct the review of the PBAC Guidelines. As a consequence of my experience working in the PBAC Secretariat and the Pharmaceutical Evaluation Section at the Department of Health (from 1997-2001), then as the manager of the Monash Evaluation Group (from 2001-2007) who were contracted to evaluate submissions to the PBAC, and then as a consultant to industry and as an academic at Deakin University (from 2007), I believe I have developed a good understanding of the perspectives of government, the PBAC and the industry in relation to HTA. Although I no longer work directly for the PBAC, I still hold the PBAC and the principles by which it operates, as outlined in the PBAC Guidelines, in the highest regard.

According to the outline of the Pharmaceutical Benefits Advisory Committee Guidelines Review provided at http://www.pbs.gov.au/info/reviews/pbac-guidelines-review [Last accessed: 31 March 2016], one of the aims of this revision of the Guidelines was to *"ensure that the Guidelines are of the highest quality and that they continue to reflect best international practice"*. Also, the revised Guidelines were to *be "more concise, clear, focused and up-to-date"* than the current version. Given these stated aims, many of us who work on submissions to the PBAC had very much been looking forward to the release of the draft Guidelines. Although there are some significant improvements in *PBAC Guidelines draft v.5.0* compared with the current PBAC Guidelines, I am disappointed with several aspects of the *PBAC Guidelines draft v.5.0* that have been released for public comment. Given the page limit for responses, this response focusses on my concerns with *PBAC Guidelines draft v.5.0.*

The most serious concern I have is that several parts of *PBAC Guidelines draft v.5.0* compromise technical principles of HTA in interests of achieving the political objective of minimizing price of new drugs. I very much appreciate the need for this political objective to be satisfied; for example, I recognise that there is an information asymmetry as to the appropriate price that should be included in an economic evaluation of a proposed product. It has become apparent that companies can request and apply inflated prices in their economic evaluations, particularly in their first submissions. I appreciate that the government needs to find ways of achieving prices that are closer to the lowest price at which a

company is prepared to sell. It is in the interests of the Australian taxpayer that the government find "levers" to ensure that it does not pay more than it has to for any pharmaceutical product. However, in my opinion, it is inappropriate for the PBAC to misapply principles of HTA in an attempt to address this issue. Misapplication of HTA principles only undermines the integrity of the PBAC and the high regard in which it is held. It would make more sense to deal with the issue of the price input into economic analyses directly rather than manipulate other aspects of the clinical and economic evaluation to compensate for the problems that have been observed with this input. Two examples (not exhaustive) of places where *PBAC Guidelines draft v.5.0* appear to be attempting to address political issues rather than focussed on HTA best practice include:

- The *PBAC Guidelines draft v.5.0* now appear to require nomination of the "least expensive alternative" as a comparator in several situations. Thus, for example, a sponsor seeking to list a new atypical antipsychotic could interpret the *PBAC Guidelines draft v.5.*0 as requiring comparisons versus antiquated drugs such as chlorpromazine, haloperidol, and thioridazine, which I suspect is not the intent of the revised advice on comparator selection. I suggest to the Committee that the issue of the appropriate comparator has become more controversial since the separation of drugs on PBS into two separate formularies - F1 (which mostly includes patented drugs) and F2 (which mostly includes drugs whose patents have expired). Before this separation, prices of drugs on the PBS that were considered to be of similar safety and efficacy were priced equivalently through a reference pricing mechanism (i.e., the PBS was a system that purchased products on the basis of outcomes). Since the splitting of the formulary, the introduction of price disclosure arrangements has resulted in reductions in prices of drugs in the F2 category. These price reductions do not, typically, flow through to drugs in the F1 formulary even though the drugs may have been listed on the basis of similar safety and efficacy compared to a drug in F2 that has subsequently had its price reduced. Thus, drugs of similar safety and efficacy are not necessarily priced equivalently on the PBS. The determination of the appropriate comparator becomes controversial in the scenario where a new entrant comes into an existing market where there are several potential drugs to be replaced that are of equivalent efficacy and safety but where some are included in the F1 formulary, but others are included in the F2 formulary. The *PBAC Guidelines draft v.5.*0 do need to provide specific guidance for this specific situation but, as discussed above, the blanket advice in the *PBAC Guidelines draft v.5.0* that the *"least expensive alternative medicine"* should be included as a potential comparator is likely to have unintended consequences.
- In the past, consistent with HTA best practice, it was intended that economic analysis should be based on the most likely outcomes to be achieved in practice should a drug be listed as requested. The *PBAC Guidelines draft v.5.*0 seem more intent on requiring submissions to base the economic analysis on the most conservative estimate of outcomes to be achieved in practice. For example, in introducing guidance on adjusting for treatment switching in trials, the *PBAC Guidelines draft v.5.*0 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 best-practice.

Another concern I have is that the process of revision of the guidelines does not permit sufficient opportunity for meaningful consultation with a broad range of stakeholders and technical experts. For example, the imposition of a 5-page limit on submissions responding to the release of the *PBAC Guidelines draft v.5.0* severely limits the amount of detail that a submission (like this one ☺) can provide. Previous revisions of the Guidelines were developed following extensive discussions among a wide range of contributors from industry, government, academic experts in various fields, members of the PBAC and its subcommittees, and the community. In fact, I believe that the resources of the Department were highly and well leveraged in the process because resources (e.g., access to experts) that industry and academia were able to contribute were accessed without cost to government. Although this was a time-consuming process, it was a process that resulted in PBAC Guidelines that were, for the most part, considered to be "cutting-edge" and that resulted in them being well-received by stakeholders. I believe that similar processes were used in the development of the well-accepted reports produced by the Indirect Comparisons and Surrogate to Final Outcomes Working Groups that, as part of the current revision process, have now been incorporated into *PBAC Guidelines draft v.5.0*.

I am also of the view that *PBAC Guidelines draft v.5.0* fail to facilitate more concise, clear, and focussed submissions to the PBAC. The expansion in the knowledge base relating to HTA has resulted in an increase in the complexity of methods and

techniques that can be, and are, applied in the discipline. In response, submissions have become much longer and more complex. Consequently, Commentaries critiquing submissions have become longer as they try to systematically comment on each of the issues and analyses presented in a submission. Paradoxically, the presentation of a greater volume of information to the PBAC does not necessarily translate to a better understanding of a drug, its clinical place, its comparative efficacy and safety, and whether it provides value for money for Australians. Frequently, analyses, submissions and Commentaries incorporate substantial amounts of extraneous information that is of only peripheral relevance to decision-making. At times, this is due to requests for information in the PBAC Guidelines. One of the key objectives of the review of the PBAC Guidelines was stated to have been more concise, clear, and focused Guidelines. Achieving this goal in the face of an HTA knowledge base that continues to expand is a challenge but, in my opinion, could have been achieved by using a more "skeletal" form for the PBAC Guidelines combined with greater use of cross-referencing to stand-alone "living" technical or educational documents that can be continuously reviewed and updated over time. In addition, it is my opinion that an opportunity has been missed in the development of the revised Guidelines to encourage sponsors preparing submissions be more judicious in determining the level of detail that is presented in relation to a specific issue – more detail should be encouraged when the issue "matters" (i.e., when outcomes of an analysis are sensitive to the issue) but less detail is necessary when the issue is only of peripheral interest (i.e., has no or marginal impact on analyses). The role of the PBAC Guidelines could have been revised to be more focussed on ensuring that the Guidelines explain the principles by which the PBAC operates (i.e., 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, which results in the Guidelines being interpreted as being overly prescriptive. To give two examples (not exhaustive) to illustrate the point I am trying to make:

- Section 3.2 of *PBAC Guidelines draft v.5.0* requests that results of a literature search for reports of relevant economic evaluations. Requesting the conduct of a systematic review of published relevant economic evaluations is an example of a case where the guidelines result in the presentation of large amounts of extraneous information in both submissions and Commentaries that is peripheral to the PBAC's consideration. In my view, the problem arises because there is no description of the principles behind or reasons for this request. My recollection is that this section was included in the previous major revision of the Guidelines as a means of encouraging sponsors to consider published economic evaluations to make sure that they had not failed to consider aspects of modelling that it might be important to capture (e.g., to check that no important health states were inadvertently omitted from a Markov model). It was not intended that sponsors should be constrained by the available evaluations (i.e., the potential for better models to be developed than those reported in the literature should not be limited). I am not sure that it was ever intended that a systematic search of the literature should be presented in a submission nor evaluated nor considered by the PBAC.
- Related to the previous point, the *PBAC Guidelines draft v.5.0* have now introduced a Model Validation section. Although model validation (in terms of assessment of structure, inputs, and outputs) should be a necessary step in the model development process, and some requests in this new section are reasonable and appropriate (e.g., validation of outputs against empirical data), some requests in this section will result in large increases in the amount of information presented to the PBAC that, again, are unlikely to be important for on PBAC decision-making. For example, providing detail on which experts have been asked to judge the appropriateness of the conceptual model, etc, is only valuable if the PBAC has a list of "approved experts". Furthermore, the development of a model is typically an iterative process so just providing a description of the model development process is frequently likely to result in many pages of additional information that is likely to be of only peripheral interest to decision-making. The important question is whether the PBAC considers the model that is ultimately used to conduct analyses to be appropriate.
- The *PBAC Guidelines draft v.5.0* includes a requirement for submissions presenting a patient-level simulation model to also present a *"cohort-based model that implements a nested, less complex model structure"*. It is reasonable for the PBAC to expect that a cohort model should be used where possible because such models are more transparent and are less "data hungry" than patient-level models. However, there will be occasions where use of a cohort-based model is not appropriate as it may require oversimplification of the decision problem or, alternatively, would result in a model with an unmanageable number of states. In such cases, and provided sufficient data are available to

populate the model, an individual-level state-transition model will be more appropriate. If requirements are included in the *PBAC Guidelines draft v.5.0* that the submission: (i) present adequate justification for presentation of a patient-level model; and (ii) demonstrate that sufficient data are available to populate such a model, then it is redundant for the PBAC Guidelines to also require presentation of a cohort model as it will already have been determined that the cohort model is inadequate for the purposes of economic evaluation. The presentation of a second model will increase the amount of superfluous material presented in submissions that is likely to be of marginal interest to the PBAC.

Another concern I have is the return to a structure that separates the clinical and economic evaluations (i.e., that returns to a submission structure that was recommended in 2002) without wide consultation and debate, and, therefore, potentially inadequate consideration given to the potential ramifications of returning to such a structure. Some members of the Department and the PBAC may recall that the 2002 PBAC Guidelines had four sections: Section 1, which was for presentation of the details of the proposed drug and its proposed use; Section 2, which was for presentation of the clinical evidence; Section 3 that was for presentation of the modelled economic evaluation; Section 4 for presentation of the financial analyses. In 2006, Section C was introduced as a place for information that was important for the development or "bridging" of the clinical evaluation to an economic evaluation and was a section that required input and consideration by both people involved in the clinical aspects of the submission and people involved in the economics aspects of the submission. My recollection is that the stimulus for the introduction of Section C in the Guidelines was that, with the prior structure, there was a tendency for sponsors, evaluators and discussants at meetings of the technical sub-committees to bifurcate aspects of the submission into "clinical" and "economics" issues and to have different people focus on these parts of the submission independently. In several (I would venture to say many) instances, this led to a disjointed overall submission or evaluation such that it left PBAC in the difficult position of having to reconcile disjointed information on a drug. Although I don't have evidence to justify this statement, my view is that the introduction of Section C led, over time, to a substantial reduction in the presentation of disjointed submissions (which meant fewer disjointed Commentaries). Similarly, it is my opinion that it resulted in greater continuity in the discussion at ESC because both clinical and economics discussants considered the information presented in Section C. I am concerned that the removal of Section C has the potential, over time, to result in the loss of continuity between the clinical and economic evaluation due to the different sections being considered the domain of different people. I believe it would be a mistake to believe that the system has matured to a point where it is no longer necessary for this "bridging" section in the Guidelines. My experience is that it is the actual requirement to draft a Section C that 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 and that, in the absence of this section, such collaborations become less likely. In re-distributing information currently presented in Section C to Sections 2 and 3, it is my view there has been a narrow consideration of investigations that have been presented in Section C. For example, issues of the relationship between the evidence used in the model compared with the evidence presented in Section B (e.g., four trials may be presented in Section B but only one of those trial is used to provide inputs to a model [e.g., due to availability of individual patient data] such that it is therefore necessary to consider whether the treatment effect observed in that trial is representative of results observed in the other three trials). This narrow interpretation means that it is now not clear where certain analyses should be presented – Section 2 or Section 3.

It is important that the revised Guidelines continue to provide up-to-date advice on the appropriate presentation of information to the PBAC in submissions. Thus, it was hoped that advice would be incorporated (either directly or in an associated technical document) on presentation of information to the PBAC where advances have occurred in methods and techniques that are applied in HTA. The *PBAC Guidelines draft v.5.0* incorporate advice on one additional new technical area (i.e., approaches to dealing with treatment switching in trials) but there remains no advice in the Guidelines on, for example:

- presentation of evidence from trials that incorporate multiple stages or adaptive or rule-based designs;
- whether the PBAC considers propensity score methods are appropriate to adjust for differences in covariates across patients in whom the intervention and comparator were assessed and any specific requests the PBAC has when presenting such analyses;

- whether the PBAC considers outcomes from discrete choice experiments and other techniques (e.g., patient value mapping) that are being used internationally to understand the value of a treatment are valuable and any specific requests the PBAC has when presenting such analyses;
- whether the PBAC would value the presentation of analyses that incorporate the impact of an intervention on the health-related quality of life of carers of patients, which will be particularly important for interventions used in people who are dependent on others for completion of tasks of daily living (washing, dressing, feeding, toileting, moving around) e.g., children, some with mental health conditions, some frail and elderly;
- advice on presentation of information for drugs that fall into, what I term, the "no man's land of comparative effectiveness" i.e., where the evidence is insufficient for concluding non-inferiority but also there is insufficient evidence to conclude that the comparator is superior (and therefore deserving of a price premium).

Other issues I have with the released draft of the *PBAC Guidelines draft v.5.0* are minor such that they should be relatively easy to correct. Examples of minor issues that I have identified (but please note that I have not been exhaustive due to page restriction limits on submissions) include:

- There are inconsistencies in the definition and application of important terms both within the document and with internationally accepted definitions and applications. These inconsistencies have the potential to confuse readers who are looking for guidance on the presentation of information to the PBAC.
  - A simple but powerful example is that the *PBAC Guidelines draft v.5.0* repeatedly refer to the term "patient-relevant outcome". This term is defined in *Glossary: Key terms for preparing submissions to a health technology assessment (HTA) advisory committee for funding of a medicine, medical service or prosthesis (Version 1) February 2013* [available at: http://www.pbs.gov.au/industry/useful-resources/glossary/Glossary-of-Terms_Final-15Apr-13.pdf; Last accessed: 1 Mar 2016] as an "umbrella term covering any health outcome that is perceptible to the patient …". According to this definition, although a change in HbA1c might be considered clinically meaningful, it would not be a "patient relevant outcome" as it is unlikely to be directly perceptible to a patient. Yet, in Table A.1.1 of *PBAC Guidelines draft v.5.0*, the instructions are to provide a table which outlines "the critical patient-relevant outcomes" and an example of HbA1c is provided as an example of a patient-relevant outcome.
  - The implied definition of patient-reported outcomes as quality of life instruments (on p.57) is incorrect. Quality of life assessments are only a subset of patient-reported outcomes. PRO is an umbrella term that covers a whole range of potential types of patient self-reported assessments e.g., symptoms, functioning, etc.
- There are a number of oversights in updating of the Guidelines. For example, the *PBAC Guidelines draft v.5.0* (on p.138) refer sponsors to the Pharmaceutical Benefits Pricing Authority for advice, which is defunct. In addition, the Guidelines have not been updated to reflect different requirements due to the implementation of Revised Arrangements for the Efficient Funding of Chemotherapy Drugs (e.g., an alternate table to the one presented at Table 1.4.1 (on p26) is needed for chemotherapy drugs).

As noted previously, although this submission makes numerous comments on *PBAC Guidelines draft v.5.0*, these should not be considered an exhaustive list of issues as my ability to provide feedback has been severely hampered by the 5-page limit imposed on submissions. Given constraints on my time but especially considering that that these additional pages may be ignored, I have attached a marked-up copy of only Section 1 of the Guidelines to illustrate how a 5-page limit constrains the amount of feedback can be provided. I would be pleased to provide marked-up copies of other sections if it is considered valuable.

Yours sincerely,

Lili Bulfone
Shoten Pty Ltd

Section 1 Context

Section 1 includes details of the medicine and its proposed use.

Introduction

Section 1 of a submission to the PBAC establishes the context for the submission.

A description is requested of:

- the clinical issue that the proposed medicine is expected to address (Subsection 1.1)
- the way the medicine will be used (Subsection 1.2)
- the regulatory status of the proposed medicine (Subsection 1.3)
- the proposed PBS listing (Subsection 1.4).

Flowchart 1.1 summarises the information requested for Section 1 of the submission.

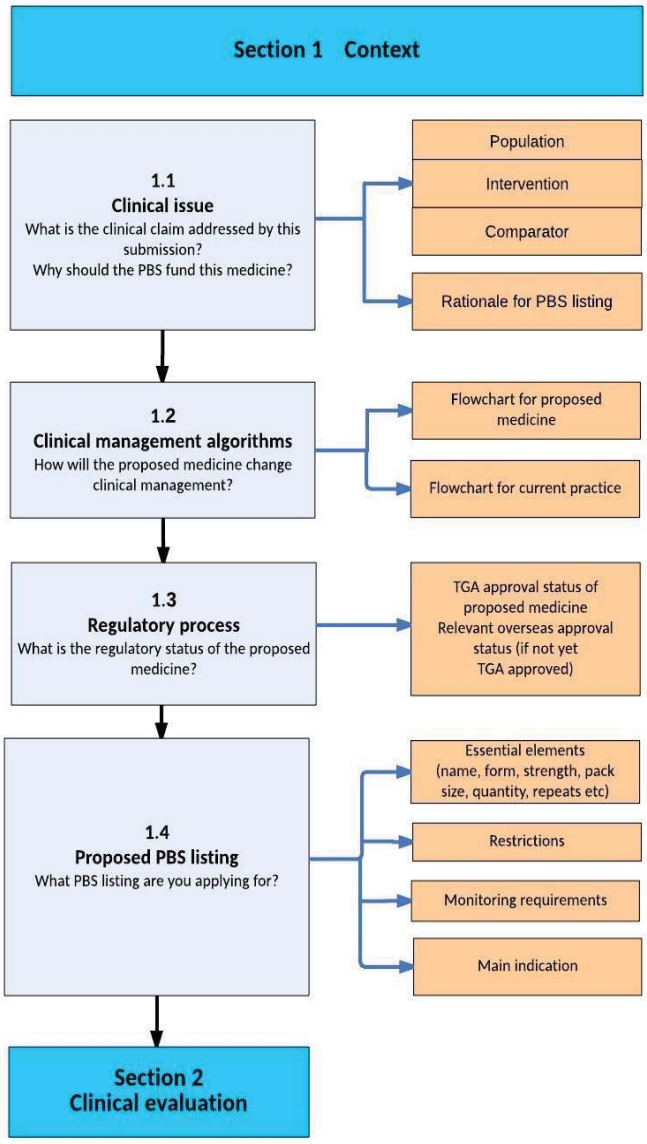
Notes: If the submission is requesting listings for multiple patient indications, present separate Sections 1 to 4 in separate submissions

The singular term 'comparator' is used to denote one or more comparators. If there is more than one main comparator, provide all the requested information for each comparator.

Commented [A1]: 'disease or condition' as in other parts of the Guidelines?

Commented [A2]: This could be an extreme requirement in some cases e.g., if the same trials form the evidentiary basis for the clinical claim for the different indications. For example, cholesterol-lowering agents are frequently trialled for use in multiple indications (e.g, primary hypercholesterolaemia and familial hypercholesterolaemia). Requiring separate submissions in these instances seems an overkill.

Flowchart 1.1 Overview of information requests for Section 1 of a submission to the PBAC



1.1 Clinical issue addressed by the submission

INFORMATION REQUESTS

Summarise the clinical claim

Tabulate the proposed population, intervention, comparator and outcomes for the proposed medicine, and present the overall clinical claim.

Describe the population

Describe the target Australian population that it is proposed would receive treatment for their disease or condition with the proposed medicine, and identify any relevant population subgroups.

Describe the proposed intervention and comparator

- Describe the pharmacological action, therapeutic class and biological plausibility of the proposed medicine.
- Identify and justify the main comparator, describe any other relevant comparators (including future comparators), and tabulate key differences between the proposed medicine and the main comparator.

Provide a brief rationale for PBS listing

Describe the intended use of the proposed medicine in the target Australian population.

Commented [A3]: Inconsistency in draft - "Outcomes" is not listed in Flowchart 1.1 above or discussed in the main body of this section of the Guidelines.

Commented [A4]: This sentence is not quite right - maybe *"biological plausibility of activity of the proposed medicine"*?

Clinical claim

Tabulate the proposed population, intervention, comparator and outcome(s), and the overall clinical claim for the proposed medicine in Table 1.1.1.

Table 1.1.1 Components of the overall clinical claim addressed by the submission

Component	Description	Example
Population	Briefly state the target population	Patients with type 2 diabetes for whom adequate control with metformin or a sulfonylurea has not been achieved
Intervention	Briefly describe the intervention	[medicine XXX] 100 mg mane
Comparator	Briefly describe the comparator	[medicine YYY] 25 mg bd
Outcomes	Briefly state the critical patient-relevant outcomes	• Change in HbA1c from baseline measured at 6 months • Weight loss from baseline to 6 months • Hypoglycaemic events in 6 months
Clinical claim	State the clinical claim that the submission presents: In [population and health issue], [proposed medicine] is no worse than/as effective as/more effective than [main comparator] at improving/reducing [outcome(s)]	In people with type 2 diabetes for whom adequate control with metformin or a sulfonylurea has not been achieved, [medicine XXX] is more effective than [medicine YYY] at reducing HbA1c, and increasing weight loss after 6 months, although this results in more hypoglycaemic events

Commented [A5]: I am not convinced that the example helps as it potentially constrains the appropriate presentation of information.

Commented [A6]: Should mode of administration, duration of treatment and other circumstances of use be specified here?

Commented [A7]: As per previous comment

Commented [A8]: Inconsistency here – "patient-relevant outcomes" are required yet the example includes change in HbA1c, which is not an outcome that is likely to be directly perceptible by the patient (i.e., it is not a patient-relevant outcome according to the definition in the glossary).

Commented [A9]: No room here for less effective agents for which there may still be a clinical need. Also what to do about drugs that fall into "no man's land of comparative effectiveness" i.e., where there is no statistically significant difference between the proposed drug and comparator such that the evidence would not support a claim for superiority of the comparator but where the 95% confidence interval around difference in effectiveness crosses the MCID such that a claim that the proposed drug is no worse than the comparator is not justified.

Population

Target Australian population

The target population is defined as the people with the specific disease or condition that will be treated with the medicine if it is listed as proposed.

Provide a brief overview of the disease or condition that will be treated by the proposed medicine. Include enough detail of diagnosis, symptoms, prognosis and other related issues to assist the assessment of the submission.

Describe the characteristics of the Australian population who would be treated with the proposed medicine, such as their age, sex, important comorbidities and disease-related characteristics. Sources of data should be provided, and should preferably include Australian datasets, or studies involving Australian participants. Indicate the incidence and prevalence of the disease or condition in Australia using data from a reputable source, such as those listed in 'Sources of epidemiological data for use in generating utilisation estimates'.

Where studies involving Australian participants are not available, discuss whether population or subgroup characteristics are likely to be representative of the Australian setting. Data should be presented as percentages and means with estimates of uncertainty (eg interquartile range, standard deviation and ranges), where possible.

Relevant subpopulations

If a specific population group (eg specific age group, sex, comorbidity) is to be targeted for treatment with the proposed medicine rather than the broader population, indicate whether the usual course of the disease – or the available treatment options for that subgroup – differs from that of the broader population. If the broader population is to be targeted, define any important subgroups for which there may be a different use of the proposed medicine, a different comparator or a different treatment effect.

Intervention and comparator

Pharmacological action and therapeutic class of the proposed medicine

Present the therapeutic class, Anatomical Therapeutic Chemical (ATC) classification and a description of the pharmacological action of the proposed medicine. Tabulating this information to enable a comparison of the proposed medicine with the nominated comparator would be helpful.

When discussing pharmacological action, ensure that adequate detail is provided to support the targeting of the group of patients described in the proposed listing. If the listing is a subgroup of a broader indication, it is particularly important that the mechanism of action for the particular subgroup is described, and contrasted with the complement for that subgroup.

Biological plausibility for the use of the proposed medicine in the intended population

Discuss the pharmacological, biological and clinical plausibility for targeting a subgroup, or state when evidence for any of these is unavailable.

Justification for the selection of the main comparator

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.

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.

Commented [A10]: The term "broader population" in this paragraph is confusing. Is that term supposed to be a reference to the population that would be covered by the TGA-registered indication? If so, might be better to make the reference population "the population for which TGA registration has been sought" rather than "broader population".

Commented [A11]: If a table comparing the proposed drug and the comparator is necessary, would make sense to request this after the comparator has been nominated.

Commented [A12]: Will mechanism of action change in subgroups? I can understand relative and absolute treatment effects being different in subgroups but can't think of examples where mechanism of action is different.

Commented [A13]: Inconsistency – heading suggests for the "intended population" but paragraph states for "targeting a subgroup". Is this discussion required only when targeting a subgroup?

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.

Within this context, the main comparator is defined as the therapy that prescribers would most likely replace with the proposed medicine in practice, should it be listed on the PBS. The identification of the therapy most likely to be replaced should be consistent with current Therapeutic Goods Administration (TGA) marketing authorisation and PBS listings for the appropriate patient indication and line of treatment. The main comparator should be consistent with the positioning of the proposed medicine in the intended clinical management algorithm, as presented in Subsection 1.2. Where the medicine most likely to be replaced is not PBS listed or TGA registered, state this and present evidence that it is widely used for the proposed indication

In general, most comparators are identified in one of the following three categories:

- **Existing pharmacological analogues.** If the proposed medicine is in a therapeutic class for which pharmacological analogues are already listed, the main comparator is usually the analogue prescribed on the PBS for the largest number of patients for the same indication.
- **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.
- **No currently listed medicine.** If the proposed medicine is for an indication for which there are no currently listed PBS medicines, or the proposed medicine will be used in addition to – rather than replace – a medicine, the main comparator would usually be standard medical management (this could include a nonlisted medicine, a surgical procedure, best supportive care or conservative management). In the absence of a PBS-listed medicine, clinical practice may be to use a medicine that is not PBS listed. In this circumstance, the medicine used in clinical practice may be the appropriate main comparator.

Where possible, the main comparator should be in a similar form to the proposed medicine (eg sustained-release tablets or oral pressurised inhalation); however, this criterion is secondary to the fundamental consideration of which therapy will be replaced in clinical practice.

If a PBS-listed comparator is perceived as having a substantial disadvantage compared with the proposed medicine (ie has a less favourable toxicity profile, is delivered in a less acceptable form or has substantially poorer therapeutic effectiveness), the proposed medicine may be used in a larger number of patients than the currently listed comparator. If

Commented [A14]: These two paragraphs are confusing and are an example of where the Guidelines try to introduce levers to push prices of new drugs down but where the lever introduces issues for HTA. Marginal analysis compares the marginal costs and benefits generated by a scenario where a proposed drug is available compared to the current scenario where the drug is not available. The appropriate comparison in a marginal analysis is thus one of the world with the new therapy with the current world without the new therapy, with the comparator being the therapy (which can include no therapy) most likely to be replaced in the "new" world. The suggestion here that a comparison is required against "least expensive alternative medicine" is not appropriate where the least expensive alternative medicines are not used and such guidance is likely to lead to unnecessarily messy and complicated submissions (e.g., in schizophrenia, chlorpromazine and thioridazine would be the "least expensive alternative medicines"); Is it the intent that a submission for a new antipsychotic should require a comparison against these rarely used agents?? Identification of the appropriate comparator should simply be based on consideration of the therapy most likely to be replaced. It is acknowledged that there will be occasions where pricing is an important consideration BUT I believe this has only become a consideration because price disclosure arrangements only apply to drugs in the F2 classification - if drugs have been listed on the basis of equivalence with a drug that has been transferred to the F2 formulary, then, in the now theoretical world where the PBAC "pays for outcomes", the same price paid to achieve the particular outcome generated by the lowest price item should be paid by all drugs that have been determined to be equivalent to that drug. To try to address this issue with the wording proposed here just introduces more problems. It would be more appropriate to simply highlight the problem that exists because of the F1 and F2 split and explain the situation where the lowest price comparator should be used.

Commented [A15]: Redundant assuming that line of treatment is part of the indication.

Commented [A16]: This sentence probably fits better under the third bullet point below.

If non-PBS comparators can be used, guidance should be provided in the Guidelines on what to assume and what to do about cost-effectiveness of the non-PBS comparator e g., would this need to be established first (such that, effectively, a sponsor is required to present the case for cost-effectiveness firstly for the non-PBS listed agent and then for the proposed drug)?

Commented [A17]: Population?

Commented [A18]: See comment above.

there are differences between the currently listed comparator and the proposed medicine, discuss the effect on the number of patients that are likely to be treated. Present:

- a comparison of the proposed medicine with standard medical management (including watchful waiting)
- a comparison of the proposed medicine with the nominated main comparator.

When this situation arises, the main comparator should be clearly and consistently defined both in the submission and in the supporting evidence base (ie direct randomised trials).

Commented [A19]: Wouldn't this fit better under the next heading with the discussion of multiple comparators?

Multiple comparators

Where multiple comparators exist, the PBAC would prefer that all of those that are potentially relevant are included in the submission. Comparisons with multiple comparators may be less relevant when there is convincing evidence of therapeutic equivalence between these comparators.

The presentation of multiple comparators may be required in the following instances:

- when there is no clear market share for one particular comparator
- when it is likely that different comparators are used in different subpopulations of the proposed target population (eg according to disease severity)
- when there is a substantial difference in the cost of a treatment course across the comparators.

Commented [A20]: See comment at bottom of p16

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.

Commented [A21]: See the comment at the bottom of p16

The submission should present a comparison against each comparator, rather than a comparison against a weighted or mixed comparator.

Future comparator(s)

If there is a reasonable expectation that a medicine will enter the Australian market in the near future for the proposed indication, this may be regarded as a supplementary comparator.

This could include therapies that are currently undergoing TGA registration, or that have recent or current submissions to the PBAC for a PBS listing.

Commented [A22]: I suggest this paragraph be cut. Although there can be an expectation that a competitor's medicine will enter the Australian market, 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 release of the PBAC agenda (i.e., after the lodgement of the submission).

Comparison of the proposed medicine and the main comparator

Tabulate evidence that highlights any differences between the proposed medicine and the main comparator (and supplementary comparator, if relevant) in Table 1.1.2. Where characteristics are the same, state this. Provide references to the sources of the data in table notes.

Table 1.1.2 Comparison of the proposed medicine and the main comparator

Comparison	Description for the proposed medicine, main comparator and supplementary comparators (if applicable)
Course of treatment[a]	[Describe the course of treatment for the proposed medicine and the course of treatment for the main comparator (and supplementary comparators, if applicable)]
Course of treatment[a] for concomitant or subsequent medicines that are included in the economic evaluation	[Describe the course of treatment for concomitant or subsequent medicines for the proposed medicine and the main comparator (and supplementary comparators, if applicable)]
Proposed/approved TGA indications (and PBS restrictions, if applicable)	[Describe any differences in the indications or restrictions between the proposed medicine and the comparator]
Toxicities that may result in differences in use	[Describe any differences in toxicities between the proposed medicine and the comparator that may result in differences in use]
Any differences ~~that may result~~ in ~~changes in~~ patient compliance	[Describe any differences in formulation, pill burden, frequency of dosing etc between the proposed medicine and the comparator that may impact on patient compliance with the treatment course for the condition]
Evidence of a difference in time-dependent alteration of dose	[Describe where doses are likely to change over time for the proposed medicine and the comparator, particularly if this is likely to occur for one medicine and not another]
Any differences that may result in different populations using the medicine	[Describe any differences (eg mode of administration, metabolism pathways, number of pills) between the proposed medicine and the comparator that may result in different populations using the medicine]
Any differences that may result in growth in the market	[Describe differences in the medicines that may result in growth in the market if the proposed medicine is listed]

[a] When describing a course of treatment, include the following information:
- dose and manner of administration
- dosing frequency per day or other appropriate time interval
- duration of course
- anticipated frequency of repeat courses of treatment.

Commented [A23]: May be better to have separate columns for the proposed drug and comparators for some comparisons (e.g., course of treatment) where descriptions are being requested for each therapy but to have merged cells for others where the focus is to be on the difference across the two therapies (e.g., key differences in toxicity profiles).

Commented [A24]: May be appropriate to include pre-medications here too.

Commented [A25]: of

Commented [A26]: of

For the proposed medicine, confirm that these details are consistent with those recommended in the relevant TGA-approved product information or, if this is not available at the time of finalising the submission, in the most recent draft product information, together with the most recent written recommendation(s) of the TGA delegate or Advisory Committee on Prescription Medicines, if available.

Rationale for PBS listing

Provide a brief rationale for the proposed use of the new medicine in the target Australian population. Under the *National Health Act 1953*, the primary objective of the PBS is to improve health, so the PBAC primarily focuses on health outcomes. Briefly outline the expected ~~impact~~ consequences of the proposed medicine eg ~~in terms of~~on patients' health, on carers' health, ~~-~~health-related costs (including~~or~~ cost offsets), ~~and the impact on issues such as~~ access to or equity in the distribution of treatment. **Limit your response to less than half a page.**

Details of non-health-related impacts of the proposed medicine should only be presented as supplementary analyses in Section 3 or discussed in Section 5.

1.2 Clinical management algorithms

INFORMATION REQUESTS

Present clinical management algorithms for current practice and the proposed medicine

Use a flowchart to show the current clinical practice for the disease or condition in the Australian target population, and clinical practice if the proposed medicine is listed.

Compare the two algorithms

Describe the changes to Australian practice that would be expected if the proposed medicine is listed.

List other relevant therapies

Identify all other therapies commonly used in the current clinical algorithm (PBS-subsidised and non-PBS-subsidised) and in the intended clinical algorithm (eg comparators, co-administered therapies and other medicines that are likely to be prescribed less often or more often).

Clinical management algorithms for current Australian practice and the proposed medicine

Present a flowchart that depicts current management of the disease or condition in the target Australian population in the absence of the proposed listing of the new medicine, and a flowchart describing the eligible patients and the circumstances of use of the proposed

Commented [A27]: Why is there a page limit here? The instructions say brief; maybe emphasize that word but not a fan of specific page limit.

Commented [A28]: I don't understand why these elements should not briefly be discussed. There may be instances where it is appropriate to consider non-health outcomes in the valuation of a medicine and where those outcomes may provide at least some of the rationale for listing the drug on the PBS e.g., drugs that negate the need for patients in rural/remote areas to travel into a city to receive the comparator drug.

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medicine if the listing is implemented as requested. The two algorithms may be captured on a single flowchart, if appropriate.

The flowchart(s) should be informed by the following sources:

- a literature review of relevant published clinical management guidelines (preferred). The PBAC has a preference for independent, up-to-date evidence-based clinical practice guidelines developed for Australia or relevant to the Australian setting. Include a copy of the literature review and guidelines as an attachment to the submission
- an expert panel and/or a well-designed survey (if current clinical management guidelines are not available). Present details of who the survey was sent to, who responded, and the survey questions and responses in an attachment to the submission. See Appendix 1 for further advice on expert panels and surveys.

Identify the following criteria and characteristics in the flowchart(s):

- all relevant diagnostic criteria and/or tests to determine the target population (including tests to exclude patients, or inform continuation criteria or stopping rules). Reference Medicare Benefits Schedule (MBS) items, where appropriate, and state clearly when a test is not currently reimbursed through Medicare
- important characteristics of patients (eg risk factors, severity of disease) and circumstances of use of the medicine
- the prescriber, and whether any special training requirements or specialised facilities are required. Provide a justification for these below the algorithm
- all treatments, including any required previous therapies or required co-administered therapies, and any consequences for subsequent therapy options. Give particular consideration to whether a proposed medicine is likely to replace a currently available option, or whether it is likely to displace that option to a later line of therapy
- all streams of health care resource provision, both before and after the point in the algorithm that the proposed medicine is introduced.

It is important that the clinical management algorithms adequately capture the steps (diagnostic and therapeutic) that define the population that would be eligible for treatment, as well as all relevant downstream changes to patient management (such as changes to the use of other medicines). In many cases, an appropriate approach is to extend the clinical algorithm to the expected end of the disease process, capturing all the treatment options. If the clinical algorithm for the proposed medicine and the comparator are expected to be the same after a particular point in the algorithm, the algorithm may be truncated if the submission clearly indicates that clinical management is identical after that point.

It may not be appropriate to capture all relevant details within the flowchart(s). When this is the case, provide a description or justification for the details excluded from the clinical management algorithm.

The population, and the use of the proposed medicine and the main comparator(s) in the clinical management algorithm should be consistent with those described in Subsection 1.1.

The submission should provide a robust justification for the positioning of the proposed medicine in the clinical management algorithm from the options available, and explain why alternative positions for the proposed medicine in the clinical management algorithm are inappropriate.

Variation of a current PBS restriction

Submissions can seek a variation of the current PBS listing of a proposed medicine. If the variation represents a new clinical indication, this should be treated in the same way as if the submission were requesting a listing of a new medicine. The clinical management algorithm should represent only patients with the new indication.

If other variations to the PBS restriction are requested, the proposed clinical management algorithm should reflect the change in practice that would occur if the restriction were to change. Such variations could include:

- relaxation or removal of one or more restriction criteria
- relaxation or removal of one or more continuation criteria
- request to change the listing to permit patients to access treatment earlier in the management algorithm (ie moving from last line to an earlier line of therapy).

For any proposed change to the listing, the clinical management algorithm should be restricted to patients whose management will change. Patients who receive the same treatment regardless of the proposed change to the listing should be clearly separated, or excluded from the algorithm.

Comparison of the two algorithms

Summarise the differences between the current and proposed clinical management, as depicted in the algorithm(s). Any changes in the pattern of health care delivery should also be mentioned.

Other relevant therapies

Identify those medicines and other health care interventions that would be prescribed less or more often as a consequence of listing the proposed medicine.

If relevant therapies are identified as being prescribed more or less often but are excluded from the economic evaluation or financial analyses, provide justification for this exclusion.

Commented [A29]: This section needs some restructuring. Suggest that the section starts of by acknowledging that there are two types of submissions that seek extension of a PBS restriction: (i) those that seek to relax existing restrictions; and (ii) those that seek listing for a different indication.

I can understand that the management algorithm only needs to reflect patients with the new indication for the latter of these types of submission. However, in the case of the former, I can envisage occasions where it would actually be appropriate to present the algorithm for the clinical condition (as requested in the previous subsection) even though the submission will focus on effectiveness and cost-effectiveness of the proposed therapy in the **additional** population to be covered by the modified restriction e.g., submissions that request first-line listing where the therapy is currently listed for second-line use.

Commented [A30]: pattern of use of health care resources

1.3 Regulatory process

INFORMATION REQUESTS

Tabulate the TGA regulatory milestones for the proposed medicine

State the date of TGA approval or indicate the progress of the application for registration.

Commented [A31]: status

List the TGA-approved indications

Provide: (i) details of the (proposed) indication; (ii) details of the (proposed) dose and method of administration; (iii) a copy of the (draft) product information; (iv) details of any concerns raised by the TGA and how they have been/will be addressed, (v) details of the risk management plan, and (vi) details of any (proposed) conditions of registration.

Indicate whether overseas regulatory approval has been obtained

Provide information on the overseas registration status of the medicine.

TGA approval

All new pharmaceutical products must be registered on the Australian Register of Therapeutic Goods (ARTG) by the TGA before being marketed in Australia.

Complete the information requested in Table 1.3.1 and provide relevant documents with the submission. For submissions undergoing parallel processing, provide regulatory documents in Table 1.3.1 to the Pharmaceutical Evaluation Branch as they become available.

Table 1.3.1 Progress of TGA application for registration of proposed medicine

Regulatory milestone	Date scheduled/received/expected	Reference to attachment
TGA registration	[insert date]	[insert reference]
If not yet TGA registered:	[insert date]	[insert reference]
• Lodgment of TGA dossier	[insert date]	[insert reference]
• TGA clinical evaluator's report	[insert date]	[insert reference]
• TGA delegate's overview	[insert date]	[insert reference]
• ACPM meeting	[insert date]	[insert reference]

Commented [A32]: what is the difference between scheduled and expected?

Regulatory milestone	Date scheduled/received/expected	Reference to attachment
• Delegate's decision	[insert date]	[insert reference]

ACPM = Advisory Committee on Prescription Medicines

Commented [A32]: what is the difference between scheduled and expected?

TGA-approved indications

State the indication(s) approved by the TGA. These are identified in the 'Indications' section of the product information and are listed in the ARTG.

If TGA approval has not been finalised, provide the proposed indication and the latest draft product information. These should be consistent with any reports or advice received in the regulatory process to date. Clearly state when the TGA evaluator's report, delegate's overview or ACPM advice would impact on the proposed indication or product information

Commented [A33]: This sentence is unclear to me. Does it means when these documents are scheduled to arrive or does it mean **how** those documents might impact on the PI.

Overseas approval status

Provide information on the overseas registration status of the medicine, including registration conditions or boxed warnings that may apply. Provide the unredacted registration reports from the Food and Drug Administration and/or the European Medicines Agency. If the final reports are unavailable, provide the most recent interim reports.

Commented [A34]: "and" or "or"

1.4 Proposed PBS listing

INFORMATION REQUESTS

List the essential elements of the requested PBS listing

State the essential elements of the requested listing, including the proposed medicine's name, restriction, manner of administration, form, maximum quantity, number of repeats, dispensed price, proprietary name and manufacturer.

Define and justify ~~any~~ the proposed restriction(s) ~~in the requested PBS listing~~

State the type of restriction and suggested wording. Describe the intention of the requested restriction, discuss the alternative options that were considered, and justify the need for any proposed grandfathering provisions.

Justify any proposed continuation criteria

If continuation criteria are proposed, justify their inclusion.

Describe any assessment or monitoring requirements

If the requested restriction requires a diagnostic test, indicate whether the test is available and subsidised on the MBS for the intended purpose of the restriction; if not, address the codependency issues that arise (Part B, P4).

Identify any multiple listing scenarios

Indicate whether multiple listing scenarios are presented.

Identify the proposed patient indication(s)

If an unrestricted listing is requested, identify the proposed patient indication(s).

Describe any special pricing arrangements

Explain any proposed special pricing arrangements.

Essential elements of the requested listing

Complete Table 1.4.1 for the requested listing. If any special pricing arrangements are proposed, complete Table 1.4.1 showing both the published price and the special pricing arrangement (a description of the special pricing arrangement should be provided later in this subsection).

Commented [A35]: This summary is too narrowly focussed on diagnostic tests. There will be occasions where the assessment or monitoring requirements may not involve the use of a diagnostic test e g., baseline assessment and monitoring of LFTs may be needed for a drug that has the potential to cause changes to LFTs.

Commented [A36]: Population?

Commented [A37]: Population?

Commented [A38]: Isn't this already covered by the second point in this list of information requests

Commented [A39]: Aren't two tables needed here – shouldn't a separate table be added to this section for drugs listed in the EFC supplement?

Table 1.4.1 Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
[Australian Approved Name, form(s), strength(s)]	[n]	[n]	[n]	[$]	[Brand name, manufacturer]

Maximum quantities and number of repeats

Demonstrate consistency between the maximum quantities and dosage recommendations using the following principles:

Commented [A40]: For drugs included in the EFC supplement, will need to present justification for maximum amount and repeats instead

- For an acute-use therapy, demonstrate that the requested maximum quantity is consistent with the likely use of the proposed medicine for a normal course of therapy (in accordance with any clinical practice guidelines identified in Subsection 1.2).
- For a chronic-use therapy, demonstrate that the maximum quantity is consistent with the likely use of the proposed medicine for one month of therapy between each dispensing by the pharmacist, and that the number of repeats (usually) permits six months of therapy between each prescription by the prescriber.

Justify proposed deviations from this general approach – for example, to minimise wastage or to facilitate intermittent therapy, as appropriate in particular circumstances (see also Subsection 1.1).

Demonstrate that the requested maximum quantities and the requested numbers of any repeats are consistent with the TGA-approved dosage recommendations (see also Subsection 1.3).

Requested restriction(s)

Medicines can be listed on the PBS General Schedule (section 85) either as unrestricted benefits (which have no restrictions on therapeutic use for the purposes of subsidy) or as benefits that have restrictions on therapeutic use for the purposes of subsidy. There are different levels of restriction, including:

- 'Restricted' benefits, which can only be prescribed for specific therapeutic use
- 'Authority Required (streamlined)' or 'Authority Required' benefits, which have restrictions on use, and require authorisation before prescribing by either a streamlined authority code or approval from the Australian Government Department of Human Services or Department of Veterans' Affairs.

Medicines can also be listed under a section 100 arrangement that provides for different distribution arrangements (such as distribution of highly specialised drugs from hospital outpatient departments).

Restricted benefits and Authority Required listings

A submission requesting a Restricted benefit or Authority Required listing is specifically seeking PBAC endorsement of use of the proposed drug for ~~within~~ the specifically requested restriction and of ~~to~~ exclusion of ~~de~~ use of the proposed drug beyond that restriction. The wording of the restriction should identify the use that **should** eventuate and be consistent with the TGA-approved indications (and other sections of the product information). The PBAC recognises that restrictions may increase the administrative burden associated with prescribing and would prefer, where a restriction is required, that the complexity of the criteria be weighed against the risk and consequences of use outside the target population.

The PBAC ~~would consider~~ weighs the appropriateness of a request for an Authority Required benefit on initial listing against the following two key principles:

- There is potential for use in a population in which the proposed medicine is not cost-effective or where the PBAC has not yet determined it to be cost-effective.
- There is potential for a high cost per patient or high total opportunity cost to the health system.

In addition to the principles above, submissions may need to consider other important factors for an Authority Required listing. These are:

- quality use of medicine factors
- safety factors
- administrative burden.

If a Restricted benefit or Authority Required listing is considered appropriate, address the following:

- Describe the intention of the requested restriction.
- When formulating the requested restriction, discuss alternative options that would be acceptable to the sponsor. It may be useful for the PBAC to consider these in order to arrive at the simplest but most effective restriction to administer.
- Discuss the trade-offs between the clinical preference for a simple restriction and a complex restriction to limit the use of the proposed medicine to the target population.
- Justify the requested restriction level, method of applying the restriction and criteria proposed in the restriction.

Complete the restriction template from the Department of Health, available at [*link to be inserted when this document becomes available*]. This document provides guidance on how to formulate the restriction wording and justify restriction criteria.

Commented [A41]: From a clinical perspective? Or from a cost-effectiveness perspective? (a restriction may be appropriate from a cost-effectiveness perspective but not from a clinical perspective)

Commented [A42]: Maybe start this paragraph by explaining that the perfect storm for leakage occurs when it is appropriate from a clinical or patient perspective to use the drug in a wide population or to continue the drug longer than proposed stopping rules would allow but where the drug is only cost-effective in a subgroup with certain eligibility and/or continuation rules applied.

Commented [A43]: I don't think the two items listed are actually "principles"; they are something more like "factors".

Commented [A44]: As per previous comment

Grandfathering

An Authority Required restriction might need to include 'grandfathering' provisions for individuals who commence therapy before the requested PBS listing is implemented. When this is likely to be the case, the submission should address the following:

- Provide details of the patients (such as estimated numbers, disease characteristics and information relevant to the requested restriction) currently receiving the proposed medicine and the scheme(s) through which the medicine is available. Where available, provide the eligibility criteria for provision of the medicine through the scheme.
- Explain why patients currently receiving the proposed medicine would not be able to access the proposed medicine according to the requested restriction (where patients would be eligible, no grandfathering clause is required).
- Provide a justification for a grandfathering provision that would enable patients currently receiving the proposed medicine to access it through the PBS. The justification may include
  - evidence that patients cannot cease treatment to ascertain eligibility
  - evidence that patients would have been eligible according to the requested restriction at the time of initiating the medicine
  - any other relevant factors.

Where a grandfathering provision is requested, the estimated number of patients currently receiving the proposed medicine should be clearly identified and counted in Section 4 of the submission.

Other issues

If a requested restriction is likely to have implications for the restriction of another PBS-listed medicine (eg its initiation or continuation criteria), discuss these implications.

A number of factors may prompt the PBAC to review the requirement for a pharmaceutical benefit to have an Authority Required listing (eg if the PBAC is considering an application for an additional product for PBS subsidy for the same indication/restriction as an existing listing).

Justification for continuation criteria

Continuation criteria should only be applied when eligibility criteria alone cannot adequately identify patients for whom use of the proposed medicine would be acceptably cost-effective at the price requested. It is preferable that medicines are cost-effective for the treatment of all patients who continue to receive net benefit from treatment.

Commented [A45]: Listing only one scenario where continuation criteria "should only be applied" might not be appropriate e g., application of continuation criteria might also be appropriate from a quality use of medicines perspective

Justify the need for continuation criteria and present the proposed wording in a separate restriction for continuing treatment (identified in the 'Treatment phase' of the restriction template {*link to be inserted when this document becomes available*}). Each element in the continuation criteria should be justified on clinical grounds, be unambiguous, use objective rather than subjective measures, and explain and justify the thresholds applied with any

tests. State whether the continuation criteria are consistent with the clinical evidence presented in Section 2.

Continuation criteria are unlikely to be suitable if there is evidence that breaks in therapy are likely to cause rebound of the condition, increase risks of toxicity associated with subsequent recommencement, or reduce the likelihood of benefit from subsequent recommencement. Continuation criteria may not be acceptable where the criteria involve subjective assessments or are likely to result in prescribers seeking to maintain subsidy despite the continuation rules.

Present a risk assessment of the proposed continuation criteria.

Commented [A46]: What does this mean?

Assessment and monitoring requirements

Note: This section may be revised to be consistent with the 'Codependent technologies' product type (Part B, P4), which is a section currently being drafted and will be released for public consultation after consultation on the full guideline has commenced.

Indicate whether any assessments or monitoring are required to demonstrate patient eligibility for the proposed medicine. If so, determine what tests are available to make these assessments and whether they are subsidised via the MBS or through another ongoing subsidised arrangement. If listed on the MBS, supply the details of the relevant MBS item. If such a test is not readily or equitably accessible, or has not been assessed for its performance in detecting or monitoring the biomarker, address the codependency issues that arise in the form of an integrated submission (Part B, P4).

Commented [A47]: This term seems narrow

Commented [A48]: This section is too narrowly focussed on diagnostic tests. There will be occasions where the assessment or monitoring requirements may not involve the use of a diagnostic test e g., baseline assessment and monitoring of LFTs may be needed for a drug that has the potential to cause changes to LFTs; administration of an instrument e g., to assess PASI in psoriasis

If the requisite diagnostic or monitoring test has been assessed for performance and is MBS listed, there are still implications associated with its use in various sections of the submission:

Commented [A49]:

- The implications of misclassification arising from both false positive and false negative tests and assessments should be considered, because these can affect the effectiveness of treatment and the incremental cost-effectiveness of the proposed medicine. Poor test performance can also affect the numbers of treated patients. Information on the performance of relevant MBS-listed tests should be provided in Section 2 of the submission, and inform the economic evaluation (Section 3) and predicted use of the medicine in practice (Section 4).

Commented [A50]: The test may be measuring a level of something. The concept of false/true positives/false negatives may not apply.

- If resource use for assessments (eg a diagnostic test or the time to conduct a diagnostic questionnaire) is expected to change as a result of implementing the requested restriction, the costs associated with these changes should be included in the economic evaluation (Section 3) and inform the budgetary considerations for predicted use of the medicine in practice (Section 4). For example, the resources might not be provided routinely in current practice, but would need to be provided to demonstrate eligibility for a requested restriction.

Commented [A51]: assessments?

- If the assessment involves any risk of harm to the individuals examined (eg by requiring a biopsy), the risk of ~~associated~~ negative consequences for the patient's health ~~impairments~~ should be discussed and quantified in Section 2, and the associated

provision of any further resources to treat potential harms should also be included in the economic evaluation (Section 3).

Multiple listing scenarios

The clinical management algorithm for the requested restriction specifies the preferred listing scenario for the proposed medicine. However, as part of justifying the requested restriction in response to Subsection 1.4, more than one listing scenario might have been canvassed as being appropriate for PBAC consideration.

If alternative listing scenarios have been proposed, ensure that these scenarios are examined in alternative analyses presented in Sections 3 and 4. The preferred approach would be to present a single model that is capable of presenting multiple scenarios, rather than separate models with different structures.

Proposed patient indication(s)

The proposed patient indications should be consistent with the (proposed) TGA-approved indications listed in Subsection 1.3, and the population and treatment details described in Subsection 1.1. The proposed patient indication is the indication that is likely to account for the largest proportion of patients treated (as identified in Section 4). If there is no clear 'main' indication, the submission should repeat Sections 1 to 4 for each indication, in separate submissions. If a sponsor is in doubt, seek advice from the Pharmaceutical Evaluation Branch.

For an Unrestricted listing, there is no mechanism for the PBS to reinforce consistency between the TGA-approved indications, or to minimise use in indications outside the proposed patient indication. Therefore, the proposed patient indication should be defined as what would eventuate in the absence of a Restricted benefit.

Special pricing arrangements

Provide details of any special pricing arrangements. Ensure that Table 1.4.1 has been completed to show both the proposed published price and the price associated with any special pricing arrangements.

Commented [A52]: Population?

Commented [A53]: As per earlier comment - This could be an extreme requirement in some cases e.g., if the same trials form the evidentiary basis for the clinical claim for the different indications. For example, cholesterol-lowering agents are frequently trialled for use in multiple indications (e.g, primary hypercholesterolaemia and familial hypercholesterolaemia). Requiring separate submissions in these instances seems an overkill.

Commented [A54]: Restriction?