Level 3, 436 Johnston Street
Abbotsford VIC 3067
PO Box 18095 Melbourne VIC 8003
Australia

Tel +61 3 9721 6000
Fax +61 3 8761 2442
www.gsk.com | www.gsk.com.au

5 April 2016

Pharmaceutical Benefits Advisory Committee Guidelines Review
Department of Health
GPO Box 9848
Canberra ACT 2601
Via email to PBSpostmarket@health.gov.au

Dear Review Steering Committee,

GSK welcomes the opportunity to make a submission regarding the draft revised Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines (version 5.0), hereafter referred to as the Guidelines, and we thank the Government for undertaking this important Review.

GSK is a science-led pharmaceutical and healthcare company operating in more than 115 countries around the world. Our mission is to improve the quality of human life by enabling people to do more, feel better and live longer. Here in Australia, we have a proud history dating back to the early 1900s. Today, we strive to improve the wellbeing of Australians by delivering high-quality medicines, vaccines and healthcare products.

When announcing the review, the Minister for Health, the Hon. Sussan Ley stated the Guidelines should incorporate international best practice and remove any unnecessary regulatory burden on the pharmaceutical industry (25 April 2015, press release). The Guidelines are important in providing detailed technical advice on the information required by PBAC to enable them to make a recommendation whether a medication or vaccine should be reimbursed through the Pharmaceutical Benefits Scheme (PBS) or National Immunisation Program. It is important that the Guidelines include methodology that is considered consistent with world's best practice to ensure the best allocation of Government resources, and that the PBAC's standing as a leader in HTA is maintained. This version of the Guidelines has incorporated some changes consistent with best practice but maintained some requirements that may not be considered good practice (e.g. statistical analyses of adverse event data and demographic data). In this example, good statistical practice does not endorse the statistical analysis of adverse event data: individual adverse events are rare and trials are rarely powered to detect these differences. Conversely, analysing a large number of individual adverse events inflates risk of type I error. Clinical evaluation and comparison of adverse events is preferred.

GSK acknowledges that the review has required significant resource with the preparation of multiple important technical issues papers which have each been considered by the Guidelines Review Sub-Committee. The transparency of the review would be enhanced with the public availability of these technical papers.

GSK is concerned that a lack of progress in the Guidelines for the assessment of vaccines threatens to undermine the PBAC and its standing as a leader of Health Technology Assessment (HTA), which benefits Government and taxpayers. Relating to this, GSK has provided commentary on the following topics, for further consideration by the Review Steering Committee:

- Vaccine specific HTA considerations
- Discounting
- Indirect costs and benefits
- Comparator selection

Vaccine specific HTA considerations

In 2006, the Guidelines incorporated an additional section outlining additional information requirements for vaccines. These requirements remain little changed following the review and thus it is unclear whether the Review Committee considered advice/recommendations provided by Medicines Australia, in consultation with Australian Technical Advisory Group on Immunisation (ATAGI) and PBAC (Appendix A) which propose appropriate changes to address the cost, benefits and attributes of vaccines. In recent years some new vaccines have been successfully managed within the existing PBAC system through resubmissions and deliberate efforts by sponsors and Government to overcome the obstacles; however, case-by-case fixes do not serve the Government or taxpayers well. The purpose of the PBAC system is to assist the government in allocating resources to those medicines and vaccines which represent value for money within our health system, consistent with our National Medicines Policy. Where the system provides suboptimal valuation of vaccines, it is offering suboptimal advice to Government on where to direct resources. For patients this translates to delayed, limited or a lack of access to new vaccines.

There are several methods currently used in the health technology assessment of vaccines that may contribute to undervaluation of vaccines and therefore suboptimal access outcomes, which the Guidelines fail to address appropriately.

GSK indicated our concerns regarding the assessment of vaccines in its submission to the terms of the review, including:

- Discount rates
- Indirect costs and benefits for society relating to vaccines

These parameters may not adequately measure the distinctive attributes of vaccines, the value-for-money of which could exceed what is acknowledged by the PBAC at present. Without the necessary revisions to ensure appropriate, robust vaccines valuation, GSK is concerned that some new vaccines may not be made available in Australia.

Vaccination has several distinctive intertemporal features compared to most other health interventions. First, there are often long delays between vaccine administration (when costs are incurred) and disease averted (when benefits are obtained), so benefits are greatly affected by discounting (Jit and Mibei, 2015). Second, vaccines have positive externalities: they not only reduce disease risk in vaccinees but also provide "herd" or community-level protection to others who might otherwise have been infected by vaccinated individuals (Jit and Mibei, 2015). Herd protection from vaccination can persist for years, and indeed indefinitely in the case of eradication. Hence there can be delays between the earlier cost of vaccination and realisation of herd protection effects (Jit and Mibei, 2015). These are some of the reasons why a government is required to have a greater role (responsibility) in decision making for vaccines: they provide benefits on a community level in addition to an individual level.

Discount rates

GSK welcomes the additional discussion around discount rates within the Guidelines, including the ability to support alternative discount methods in Section 3 of the Guidelines for all products. However, the ability to justify alternative discount rates is not new for vaccines, as acknowledged by the previous version of the Guidelines that stated vaccines may be sensitive to the discount rate and requested justification for the use of alternative discount rates, if presented. Consequently there is no change to the Guidelines with respect to discount rates for vaccines. Additionally, though there have been vaccine applications supporting alternative discount rates, there appears to be no examples where these alternative discount rates have been accepted by the PBAC.

Table 1 provides a summary of discount rates recommended by other international agencies and it can be determined that the proposed base case discount rates in the Guidelines remain high by comparison.

Table 1. Summary of International Agency Discounting Recommendations

Country	Discount Rate	Differential Discounting	Rate <5%	Comment
Australia (PBAC)	5% costs, 5% health effects.	No	No	Sensitivity analysis (SA) should include discount on costs and outcomes of 3.5%, 2.5% and 0
UK (NICE)	3.5% costs, 3.5% health effects. 1.5% cost, 1.5% health effects	No	Yes	Where...considered appropriate to undertake sensitivity analysis...because treatment effects are both substantial over a very long period (normally at least 30 years), the committee should apply a rate of 1.5% for health effects and 1.5% for costs.

	because treatment effect >30 years.			
Canada (CADTH)	5% costs, 5% health effects	No (Yes SA)	No	Conduct sensitivity analysis using discount rates of 0% and 3%. When different discount rates are used from those recommended, present results in a sensitivity analysis and justify
NZ (PHARMAC)	3.5% costs, 3.5% health effects.	No	Yes	Rates of 0% and 5% should be used in sensitivity analysis.
15 EU countries	Varies between 3% and 5% both costs and health effects.	No (Yes SA some countries)	Yes in approx. 53%	Most guidelines recommend 3% (Austria, Finland, Germany, Italy, Spain, and Sweden) or 5% (Croatia, Estonia, Latvia, Ireland, Portugal, Russia, and Slovakia). 3.7% Hungary. 4% Norway. Some countries that suggest the same discount rate on health effects and costs, recommend using differential rates in sensitivity analysis. For example, guidelines from Sweden and Spain suggest that the discount rate for health effects is set to 0% in sensitivity analysis.
Belgium Netherlands Poland	3% costs, 1.5% health effects 4% costs, 1.5% health effects 5% costs, 3.5% health effects	Yes Yes Yes	Yes Yes Yes -health effects, No - costs	Lower discount rate for health effects.
Russia	Cost?%, 0% health effects	Yes	Yes	Russia recommends that health effects not be discounted.
Czech Republic, Slovenia Denmark	Rates not specified.	-	-	Recommend discounting but do not recommend specific discount rates.
France	4 to 2.5% revised French guidelines.	Time-varying	Yes	French guidelines recommend a rate of 4% for time horizons less than 30 year with a decline thereafter, down to a discount rate of 2%, however, foreseen that a discount rate will be reduced from 4 to 2.5% in the revised version of the French guidelines.

The Canadian guidelines are currently being updated and this includes a review of discount rates. The discussion paper relating to the Canadian review concludes that the 'the available evidence indicates that the current discount rate of 5% is likely to be substantially higher than the theoretically correct rate' (Paulden et al, 2016).

Applying discount rates of 5% to costs and effects, as proposed in the Guidelines, makes nearly all prevention programmes aiming at long term benefits very cost ineffective. It has been shown that it is highly unlikely that the constant discount rate reflects societal preference (Bonneux and Birnie, 2001).

The higher base-case discount rates, and with no indication that alternative discount rates will be accepted by the PBAC, results in a lower valuation of long-term outcomes such as prevention of infant deaths compared to many other similar national health technology assessment agencies. For example, the use of a 5% discount rate for health outcomes values the prevention of an infant death with a life-expectancy of 82 years, as a saving of 21 life years, whereas, the use of a 1.5% discount rate values this as saving 48 life years in the UK, Belgium and the Netherlands. The inconsistency in discount rates with other agencies could result in some medicines and vaccines being considered cost-effective in other countries but not considered cost-effective in Australia and, as a consequence, not being available (Beutels et al, 2008).

In 2011, NICE amended its advised discount rates for interventions whose treatment effects were both substantial in restoring health and sustained over a very long period following a Citizen's Council review. The Citizen's Council was conducted over 2 days and included education on the reasons for and effects of discounting. The Citizen's Council determined that 'discounting tends to "downgrade" public health benefits - so the tendency is to spend more on treatment than on prevention'. The council was further surprised and puzzled by the effect of discounting when the costs of an intervention are borne in its earliest stages, but the benefits accrue over many years or even decades: as is the case with most preventive and public health projects. They felt that the benefit of these interventions could be undervalued. The council found it odd that health economists should employ a methodology offering such a paradoxical outcome where

treatment is valued over prevention. The council recommended that in circumstances where a particular public health measure is disadvantaged by standard discounting, that this issue is taken into account.

A European Vaccines Economic Community made up of European experts from academia, national public health or health technology assessment bodies from relevant national and international health authorities developed a consensus framework for health economic evaluation of vaccines (Ultsch et al 2015). Expert opinion from this group recommended:

- differential discount rates for costs and effects if the time horizon is long (>20 years)
- the discount rate of health effects could be around 50% of the discount rate for costs
- constant discount rates over time should not be applied in models with a long time horizon (> 20 years)

GSK proposes that the base case discount rates in the PBAC Guidelines should be:

i. Reduced to be consistent with the majority of other HTA agencies
ii. Allow for differential discounting for interventions with long-term outcomes (not only vaccines)
    a. consistent with empirical studies of societal values (Beutels et al, 2008)
    b. to avoid a paradoxical outcome where treatment is valued over prevention (NICE Citizen's council)
    c. improve equity from an intergenerational perspective (Jit and Mibei, 2015), and
    d. is already accepted in some countries as appropriate for all health economic evaluations (Jit and Mibei, 2015)
    e. is supported by health technology expert opinion (Ultsch et al 2016).

Indirect costs and benefits

Vaccination programmes are a cornerstone of an efficient public health programme. Preventing disease is preferable to treating illness as it avoids unnecessary suffering, paying for health care cost that could have been avoided, and generates social benefit such as reduced work loss and/or productivity. Vaccines have been acknowledged as one of the best investments for acquiring good health that a government, a social insurance fund, an employer, a family or an individual can make.

The full economic and societal value of vaccination is complex to assess. Preventing disease in children can also reduce absenteeism for parents who otherwise would take days off work to care for their sick children, leading to a substantial societal burden. Preventing disease in working adults reduces absenteeism, enhancing productivity and contributing in turn to economic growth. Quality of life is essential at all ages. It is fundamental in children for their life opportunities, educational achievements, and healthy wellbeing. Additionally, preventing common diseases in adults and the elderly also contributes to their quality of life and helps ensure healthy ageing for growing ageing populations. These wider economic and societal values, although difficult to measure, should be taken into consideration in assessments of the economic value and cost-effectiveness of vaccination programmes (Postma MJ et al, 2015). Prevention of disease in children can also impact the individuals' lifetime earnings (and corresponding burden on social security systems) because of improved educational achievement or avoided disabilities.

GSK suggest the PBAC Guidelines include more detailed guidance on assessments relating to the full economic benefits of a new medicine or vaccine which includes the consideration of non-health benefits and costs, including productivity gains, reductions in welfare dependence and disability payments. The Guidelines would be improved if advice is included on the inclusion of quality of life impacts on caregivers such as the parents of sick children. GSK believes these should not be relegated to a 'supplementary' consideration.

Comparator selection

GSK refers to commentary within the Medicines Australia submission to the review in relation to comparator selection and concerns that the proposed new wording has the potential to:

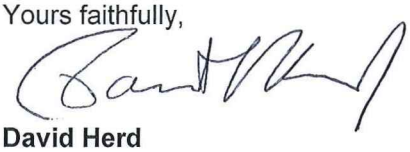
- further exacerbate existing concerns regarding comparator erosion and linkages between the F1 and F2 formularies;
- raise reference pricing implications for all PBS-listed medicines linked by therapeutic relativity if a new proposed drug is compared with the least expensive comparator within a reference group;
- further devalue innovation; and/ or
- delay access to new medicines
- create additional regulatory burden through the need to present comparisons with multiple agents.

GSK recommends that the Version 4.5 text be retained in Version 5.0 of the PBAC Guidelines, thereby aligning with i) international best practice for the purposes of determining the main comparator, ii) the remit

of the PBAC as specified in the National Health Act and (iii) the intention of the review to reduce regulatory burden.

The Guidelines should be constantly and regularly reviewed to incorporate new methodology and standards. This review provides an opportunity to update the Guidelines to maintain the PBAC's reputation as world-leading in pharmacoeconomic assessment. GSK encourages further consideration where the Guidelines are inconsistent with leading health technology expert recommendations such as those for discounting. This will avoid situations where new therapies are not available due to differing assessment requirements.

Yours faithfully,



David Herd
Director, Healthcare Environment
GSK Australia

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MAVIG'S PROPOSED CHANGES TO THE PBAC GUIDELINES FOR VACCINE EVALUATION

The 2005/06 federal budget stated

> "*The Australian Technical Advisory Group on Immunisation will receive additional support to strengthen their ongoing role in providing evidence-based clinical advice on the medical administration of vaccines. The Pharmaceutical Benefits Advisory Committee will assume responsibility for evaluating the cost-effectiveness of new vaccines in order to provide a more consistent and transparent process for recommending vaccines for Australian Government funding.*"

To date, sponsor applications for re-imbursement for vaccines have been written using the standard PBAC guidelines for pharmaceuticals. However assessment of the safety, efficacy and cost-effectiveness of vaccines requires considerably different methodology to that used to assess pharmaceuticals. Accordingly, MAVIG believes that an appropriate approach for the assessment of vaccines may be to develop separate guidelines that address those issues that are appropriate to vaccines as the changes required are numerous. This document reviews the current PBAC guidelines and outlines the areas that inadequately address the key issues for assessing the safety, efficacy and cost-effectiveness of vaccines. If it is not feasible to produce a separate set of guidelines for vaccines, the issues raised in this document could be incorporated into one or (preferably) more appendices.

A few practical issues affecting the feasibility of adapting the pharmaceutical guidelines for vaccines have also been identified. The cost of products listed on the PBS are published and are available for incorporation into submissions to the PBAC for new pharmaceuticals. In contrast, prices of vaccines listed on the National Vaccination Schedule (NVS) are not published, making the estimation of the cost-effectiveness of a proposed vaccine difficult. Similarly, usage statistics are available for all products listed on the PBS, but not for those on the current NVS. This would need to be addressed for the new NVS program.

1 DETAILS OF THE PROPOSED VACCINE AND ITS PROPOSED USE ON THE PBS/NVS

1.1 PHARMACOLOGICAL CLASS AND ACTION

Give the brand name and Australian approved name for the proposed vaccine. What disease(s) is/are prevented by the vaccine? What are the characteristics of the vaccine? Is the immunising agent live, attenuated, killed, absorbed/non-absorbed, viral or bacterial? What formulation(s) (ampoule, vial, pre-filled syringe etc), and pack size(s) is proposed for PBS/NVS listing?

In some cases, different forms of immunising agent, for example live, attenuated, killed, absorbed/non-absorbed, viral or bacterial may offer advantages in safety and effectiveness. In addition, the presentation of the vaccine, (ie pre-filled syringe), may also provide advantages in administration. The form of the vaccine might also affect the perceived risks and benefits of immunisation to individuals and impact on the acceptability of an available vaccination.

1.2 INDICATIONS

State the indication(s) approved by the TGA (or recommended by the ADEC or by the TGA delegate or, if none are specifically mentioned in the TGA delegate's report, the indication(s) as contained in the draft product information supplied). Then state whether the vaccine is to be listed on the PBS and/or the NVS. If PBS listing is sought, what type of restriction is sought? If a restricted listing is sought, suggest a wording for the requested restriction. If an unrestricted listing is sought, identify the main indication(s). If the vaccine is to be listed on the NVS, describe the proposed program delivery system and the target population.

1.3 TREATMENT DETAILS

What is the proposed course of treatment/prevention? Describe the vaccination schedule with doses, primary immunisation and possibly booster vaccinations recommended in the current TGA-approved product information.

Provision should be made in the guidelines for inclusion of information regarding the Program delivery system eg schools, clinics etc. This has important implications for the eradication/prevention of diseases in the community and the effectiveness of making the vaccine

available. In addition the program delivery system has important implications in terms of administration and cost.

1.4 CO-ADMINISTERED AND SUBSTITUTED THERAPIES

What other vaccines, if any, are likely to be prescribed with the proposed vaccine?

List the therapies, particularly existing PBS and NVS vaccines, which are likely to be prescribed for use in conjunction with the proposed vaccine, as part of the standard immunisation schedule. This should include drugs which are likely to be used to manage side effects of the proposed vaccine if applicable. Provide the details requested in Section 1.3 for each drug and vaccine included in the economic evaluation.

If the proposed vaccine is listed, what therapies, if any, are likely to be prescribed less for the target patient population:
(a) for the therapeutic indication; or
(b) for the treatment of side-effects of current therapies?

List the therapies and/or vaccines, particularly existing PBS and NVS vaccines, which are likely to be substituted by the proposed vaccine. Provide the details requested in Section 1.3 for each vaccine included in the economic evaluation.

Optimising the vaccine administration schedule is important in achieving maximum protection, whilst minimising adverse events and inconvenience for recipients. These features may all impact on effectiveness in actual clinical practice. How the vaccine fits into the current administration schedule is therefore an important characteristic.

The potential for the novel vaccine to be co-administered with other vaccines and the effect this may have on safety and immunogenicity should be addressed in the application due to the potential for immune interference.

1.5 MAIN COMPARATOR

Of the substituted vaccines, identify the main comparator(s) and justify the selection.

The following will assist in selecting the appropriate comparator.

(a) If no currently listed vaccine is available, the main comparator will usually be standard medical management (this could include a surgical procedure or conservative management). This should be clearly and consistently defined in both the submission and the comparative randomised trials.

(b) If the proposed vaccine provides immunity against a disease for which a vaccine is already listed, the main comparator will usually be the vaccine, which is prescribed on the PBS/NVS for the largest number of patients. If a sponsor is in any doubt the advice of the PBAC Secretariat and/or the Pharmaceutical Evaluation Section may be sought (see below).

For effectiveness studies the comparator should be another vaccine that protects against the same disease or promotes a similar antibody response, if available. However different vaccines may provide clinical protection for the same condition, but actually target different antigens and/or different levels of antigens.

In the case where a vaccine is indicated for a disease not currently covered by other vaccines, the choice of comparator is more complex. This is particularly true for vaccines for maintenance of eradication of disease, for diseases treated and prevented by measures other than vaccination and for vaccinations against epidemics. In this case the baseline population risk would not be the current low risk of disease, but a higher risk where there is no herd immunity.

1.6 DIFFERENCES BETWEEN THE PROPOSED DRUG AND THE MAIN COMPARATOR

What are the main differences in the indications, contra-indications, cautions, warnings and adverse effects between the proposed drug and the main comparator? Do the vaccines attenuate the same antigens? What are the main differences in the characteristics of the vaccines? Are there differences in the strength of the vaccines, scheduling of doses, routes of administration or fit with the current vaccination schedule of the vaccines?

These can generally be determined by a comparison of the current TGA-approved product information for the respective drugs.

Differences in formulations may need to be considered where there is evidence for differences in immunogenicity and safety. These may include features such as storage, shelf-life and route of administration.

2 DATA FROM COMPARATIVE RANDOMISED TRIALS FOR THE MAIN INDICATION

2.1 DESCRIPTION OF SEARCH STRATEGIES FOR RELEVANT DATA

Describe the search strategies used to retrieve relevant clinical and economic data from the published literature, the Cochrane Controlled Trials Register and from unpublished data held by the company.

Selection of trials for analysis must start with a consideration of all relevant trials that enable a comparison between the proposed vaccine and the main comparator for the main indication. An adequate search strategy must be used to locate these trials. This should involve at least three approaches: a search of the published literature (see Appendix B for details of how to describe this search); a search of the Cochrane Controlled Trials Register; and a check with the sponsor's head office and other subsidiaries of the company for further trials (which may be unpublished).

This search should aim to identify studies that describe all relevant attributes of the vaccine including immunogenicity, clinical efficacy, duration of protection and safety.

2.2 LISTING OF ALL COMPARATIVE RANDOMISED TRIALS

It is recognised that randomised trials are not always available for vaccines. If there are no randomised trials of either the proposed vaccine or the main comparator, state this and then list all non-randomised studies that are relevant to the main indication.

Randomised controlled studies are important in establishing vaccine efficacy. The choice of endpoints, such as disease incidence or immunological surrogate marker values for protection or both endpoints, may depend on whether an established qualitative and quantitative surrogate for protection exists or has yet to be established. For vaccines with a new conjugate, containing a known antigen for which the protective antibody level is established immunogenicity studies may be suitable in establishing efficacy. The choice and feasibility of randomised controlled studies will depend upon the indication sought, vaccination strategy and type of prophylaxis (ie pre-exposure protection or community protection).

Vaccine performance includes a range of different characteristics that are typically tested for in different types of vaccine studies, and on a time continuum from the first studies that support registration and adoption into public health programs. These characteristics include, immunogenicity (ie, the ability of the vaccine to stimulate the immune system), the duration of immunity that is granted; rate of and level of severity of adverse events, and the proportion of cases that are prevented through the vaccine (Jefferson and Demicheli, 2005). Randomised controlled trial (RCT) data are not always available for the assessment of these different characteristics and indeed may not be optimal or feasible. The strengths and weakness of experimental (RCT, controlled clinical trial [CCT] and community intervention trials) and non-experimental trials (cohort and case-control studies) in relation to their objectives are outlined in **Table 1.**

Table 1 Strengths (indicated by the + symbol) and weaknesses (indicated by the − symbol) of experimental (RCT, CCT, and community intervention trials) and non-experimental (cohort and case-control) study designs in relation to their objectives

			Side effect		
Study design	*Immunogenicity testing*	*Duration of immunity*	*Frequent and/or short terms*	*Rare and/or long terms*	*HB case prevention*
RCT	+++	−	++	−	±
CCT	++	−	++	−	±
Community intervention trials	++	−	++	+	+++
Cohort	−	+++	+++	+++	+++
Case-control	−	−	+	+++	+

Source: Jefferson and Demicheli (1999)

Abbreviations: CCT, controlled clinical trial; RCT, randomised controlled trial; HB, hepatitis B

It is frequently not feasible to determine vaccine efficacy in RCTs for either direct protection (individual) or indirect protection (population), due to the large sample size and length of time required for such studies. In addition, duration of immunity and the need for boosting, key components of vaccine effectiveness, are typically determined in observational cohort studies and studies of phased vaccine introduction following licensure of the vaccine.

Another measure of efficacy is through the direct assessment of transmission risks in Secondary Attack Rate Studies. The first (or primary) case within a defined group (such as a school or family) is identified and people infected by this individual (called secondary cases) are documented. The portion of individuals infected divided by the proportion of individuals that are susceptible is the secondary attack rate.

Since RCTs are not always the optimum source of evidence, in some situations, non-experimental designs may be considered appropriate. For example:

(i) When an experiment is impossible (ie, the aim of the evaluation is to assess the population effectiveness of vaccine).
(ii) When an experiment is not necessary (which is sometimes the case);
(iii) When an experiment is inappropriate (ie, due to the trial population not being large enough to detect the event or the outcome, ethical considerations or refusal by participants to partake in the study).
(iv) When the vaccine needs to be assessed in terms of infrequent adverse events;
(v) When the vaccine prevents rare events (Jefferson and Demicheli, 2005).

In practice, vaccine efficacy is frequently assessed across time, with different study designs addressing different characteristics.

Although Appendices P–R of the current guidelines address the inclusion of data from non randomised trials, ideally guidelines for vaccine applications would address the requirements for assessing the pivotal trials that have supported registration (eg immunogenicity and safety trials) as well as the requirements for assessing trials of other characteristics of the vaccine if available (eg duration of protection, transmission rates). For example European regulatory authorities provide guidance on when immunogenicity data are sufficient:

- there is a well-established correlation between an immune response and clinical protection
- the disease of interest had a very low incidence
- the efficiency study is not a feasible comparison of the immunological response to a comparator with clinical efficiency data.

2.3 SELECTION OF THE COMPARATIVE RANDOMISED TRIALS

Describe how the comparative randomised trials for reporting have been selected from the results of the literature search. In a technical document or an attachment to the submission, provide the full results (printouts) of the searches. Justify the exclusion of all remaining citations from these searches. List the key trials that remain for further reporting in Sections 2.4 to 2.9.

2.4 ASSESSMENT OF THE MEASURES TAKEN BY INVESTIGATORS TO MINIMISE BIAS IN THE COMPARATIVE RANDOMISED TRIALS

Provide information on the measures taken to minimise bias in each of the randomised trials listed in response to Section 2.3.

It is recognised that randomised trials are not always appropriate for vaccines. If non randomised trials are included, use the methodology presented in Appendices Q and R to describe each trial, noting that these Appendices should be adapted for the assessment of vaccine trials.

2.5 CHARACTERISTICS OF THE COMPARATIVE RANDOMISED TRIALS

Provide information on other characteristics of each of the randomised trials listed in response to Section 2.3.

It is recognised that randomised trials are not always appropriate for vaccines. If non randomised trials are included, use the methodology presented in Appendices PR to describe each trial, noting that these Appendices should be adapted for the assessment of vaccine trials.

2.6 ANALYSIS OF THE COMPARATIVE RANDOMISED TRIALS

State how the outcomes of each of the randomised trials listed in response to Section 2.3 were analysed.

It is recognised that randomised trials are not always appropriate for vaccines. If non randomised trials are included, use the methodology presented in Appendices PR to describe each trial, noting that these Appendices should be adapted for the assessment of vaccine trials.

2.7 RESULTS OF THE COMPARATIVE RANDOMISED TRIALS

Present the results of each type of patient-relevant outcome of each trial (or meta-analysis) separately as the extent of any differences in outcomes between the proposed vaccine and the main comparator in terms of their natural units.

It is recognised that randomised trials are not always appropriate for vaccines. If non randomised trials are included, use the methodology presented in Appendices PR to describe each trial, noting that these Appendices should be adapted for the assessment of vaccine trials. Results from studies that describe all relevant attributes of the vaccine including immunogenicity, clinical efficacy, duration of protection and safety should be presented.

2.7.1 Efficacy data

It is unclear what outcomes the PBAC might consider to be sufficient for demonstrating the efficacy of vaccines. RCT data are sometimes available for immunogenicity data but not for clinical protection data. However, European regulatory authorities indicate clinical efficiency data is not required when:

- there is a well-established correlation between an immune response and clinical protection
- the disease of interest had a very low incidence
- the efficiency study is not a feasible comparison of the immunological response to a comparator with clinical efficiency data.

It therefore would seem appropriate for such immunogenicity outcomes to be considered acceptable evidence of the efficacy of vaccines submitted to the PBAC. However the current guidelines do not make provision for the inclusion of data demonstrating the correlation between an immune response and clinical protection, which would be required for an economic model demonstrating cost-effectiveness.

The impact of a vaccine on the burden of disease extends beyond those receiving the vaccination to the whole population through indirect effects or herd immunity. Maintaining a certain level of immunity in the population is important because very few vaccine-preventable diseases can be totally eradicated (Kohl *et al.,* 2003). Where available, evidence should be presented evaluating the effects of herd immunity. This characteristic is often an important consideration in vaccine cost-effectiveness.

2.7.2 Duration of protection

The duration of protection will impact on vaccine effectiveness. This is frequently managed by formal surveillance studies on the need for boosters. As this long-term efficacy data will usually not be available for new vaccines, mathematic modelling might on occasion be used to help to

predict (at least provisionally) the need for and timing of boosting (EMA, 2005). However, there are many factors that models cannot adequately take into account and therefore recommendations for boosting should be confirmed by appropriate surveillance studies following the adoption of the vaccine into public health programs. This surveillance is typically the role of public health bodies such as the National Centre Immunisation Research and Surveillance.

2.8 INTERPRETATION OF THE RESULTS OF THE COMPARATIVE RANDOMISED TRIALS

Based on the results of the trials presented in Section 2.7, state the category which best describes the proposed vaccine.

(a) The proposed vaccine has significant clinical advantages over the main comparator:

- (i) it is significantly more effective than the main comparator and has similar or less toxicity; OR
- (ii) it has similar effectiveness to the main comparator, but has less toxicity; OR
- (iii) it is significantly more effective than the main comparator, but has more toxicity.

(b) The proposed vaccine is no worse than the main comparator in terms of effectiveness and toxicity.

(c) The proposed vaccine is less effective than the main comparator, but has less toxicity.

Section 2.8 of the PBAC guidelines states “A claim of no advantage must also be based on the results of well-conducted studies, preferably "head-to-head" randomised trials.” However, it is very rare for "head-to-head" RCTs to be conducted for vaccines. Frequently such comparisons are based on the results of immunogenicity studies. Consequently it may be difficult for sponsors to accurately compare vaccines for the same disease.

2.9 PRELIMINARY ECONOMIC EVALUATION BASED ON THE EVIDENCE FROM THE COMPARATIVE RANDOMISED TRIALS

Provide a preliminary economic evaluation of substituting the proposed drug for the main comparator based on the results of the randomised trials presented in Section 2.7.

3 MODELLED ECONOMIC EVALUATION FOR THE MAIN INDICATION

3.1 NEED FOR A MODELLED EVALUATION

Justify the decision as to whether or not to present a modelled economic evaluation.

The need to perform a modelled economic evaluation is stronger when evaluating vaccines than when evaluating treatments. Vaccine trials typically include a limited number of participants and are of relatively short duration, compared to the follow up period evaluated. In addition, vaccine trials frequently report immunogenicity endpoints, which may require modelling to the final outcomes of clinical and economic interest. Further, trials typically account for a limited range of costs, effects, and program options, which would need to be explored thorough a model. Modelling may also include analysis of retrospective cost and outcomes data from different sources.

3.2 POPULATION USED IN THE MODELLED EVALUATION

What population has been used as a basis for the calculation of costs and outcomes?

3.3 APPROACH USED IN THE MODELLED EVALUATION

Describe the type of economic evaluation that was modelled (see Appendix K) and the approach used.

The approaches to modelling an economic evaluation are varied. The following list is not exhaustive, but include one or more of a spreadsheet; a decision analysis; a Markov process or a Monte Carlo simulation, *stochastic model* or *deterministic model* and either *static model* or *dynamic model*.

Dynamic models can be used to capture the effects of herd immunity - the indirect protection of susceptible individuals (see below). Using herd immunity, the rate at which susceptible individuals become infected depends on the number of infectious individuals in the population. Using a dynamic model, distinct periods of infection post-vaccination can be determined (eg, epidemics and endemic equilibriums). A dynamic model also assesses age effects. A routine

infant vaccination will increases the mean age of infection through a cohort effect (the infection becomes concentrated in older cohorts) or herd immunity effect (susceptible individuals are less likely to come into contact with infected individuals, and tend to be older when infected).

Static models use a fixed infection rate so that the number of deaths prevented per immunised individual is independent of the number of individuals vaccinated. The cost-effectiveness of the vaccine is therefore independent of coverage (assuming no fixed costs in setting up the program). A static model is justified when evaluating a vaccine having low coverage or not preventing the circulation of the pathogen.

Since the benefits of the vaccine impact on the population at large as well as the individual receiving the vaccine (a public good), the model should adopt a societal perspective. Immunisation provides direct benefits to the individual who is vaccinated as well as provides positive externalities to the broader community, whose total risk of contracting avoidable disease is reduced as fewer people are able to transmit the disease.

The type of analysis used could be a cost-effectiveness analysis (CEA), or cost-utility analysis (CUA) with outcomes expressed as quality-adjusted life years (QALYs). Quality of life gains are an important benefit for vaccines aimed at infections that lead to long lasting complications.

A decision analysis model is not the only way in which the cost-effectiveness of a vaccine can be assessed. Life years and QALYs may not be the most appropriate method nor capture all health benefits from the vaccine, such as avoidance of disruption to daily life including time away from work due to illness, anxieties from fear of contracting the disease and fear of developing side effects. Therefore, other types of analyses could be used to complement a CEA or CUA.

One alternative is a willingness to pay (WTP) analysis within the context of a cost benefit analysis (CBA). Although CBA is not encouraged by the PBAC for the purposes of assessing the cost-effectiveness of pharmaceuticals, CBA is a valuable method of assessing the cost-effectiveness of vaccines. WTP might be an appropriate tool to account for patient costs, and intangible benefits that are not captured by the quality-adjusted life years (QALY) measure in a modelled evaluation.

A second alternative is a discrete choice experiment (DCE) within a CBA. A DCE uses hypothetical examples of vaccine attributes (e.g. rates of efficacy and side effects, and method of administration), to which participants in the experiment can relate. Participants are forced to trade off between the values of different attributes rather than simply accepting the program that is offered.

Guidance should be provided in the guidelines on how to conduct these types of studies.

3.4 VARIABLES IN THE MODELLED EVALUATION

All variables in the model must be listed and documented. It would be preferable to do this in a table. Each variable's name (and definition as necessary), quantity and source must be provided.

3.4.1 Mortality rates

Specify the source of life expectancy estimates (mortality rates) and describe how these have been adjusted for use in a model with a long time horizon and (potentially) cohorts of different generations.

3.4.2 Costs

In contrast to products listed on the PBS, the prices of vaccines on the NVS are not published and are not available to other sponsors. This issue needs to be addressed in order for accurate costs to be included in the economic analyses.

Guidance should be provided as to which costs should be considered when evaluating a new vaccine that is delivered in conjunction with an existing vaccination schedule. However, the decision to adopt or not adopt a vaccination program should be based on the efficiency of the program at the steady state level and all marginal costs should be accounted for (excluding one off set-up costs). Where a vaccine is administered in conjunction with other vaccines (i.e. a single vaccination shot), costs for the evaluated vaccination must be disentangled from costs related to existing vaccinations.

Vaccines may involve different resources than curative treatments and may be administered in non-clinical settings, such as community centres or schools. Whilst it is unrealistic to expect a

systematic micro-costing study to be carried out, the key resources of the vaccine programme should be costed out and tabulated. To ensure consistency and comparability within and between submissions to the Pharmaceutical Benefits Advisory Committee, the *Manual of Resource Items and the Associated Costs* should be updated to include costs for health-related services specific to vaccines.

Since indirect costs can have a significant influence on the cost-effectiveness of vaccines, the guidelines should specify that sponsors should include indirect economic outcomes in an economic evaluation of a vaccine. It has been recommended that economic evaluations of vaccines should include productivity losses (Beutels *et al* 2003), particularly for vaccines that target children or young adults, since the effect of preventing death in young adults may substantially lower the cost-effectiveness due to their greater net contribution to the economy (compared to elderly members of society). Guidelines should outline acceptable methods to estimate indirect costs, such as human capital, friction costs, and willingness to pay methods.

3.4.3 Burden of disease

Identification of the number of cases prevented by a vaccine is often key in the assessment of its economic value. **Section 2.7** presents data to support the efficacy of the vaccine in preventing the disease. If included in the model, an assessment of the epidemiological evidence for the incidence of the disease in the Australian population should be included. These may include surveys, routine surveillance data and seroprevalence studies. The results of the studies described above should be presented with an estimate of the number of incident and prevalent cases in the population for whom reimbursement is sought. The results of the clinical trial data presented in **Section 2.7** should be applied to the incident and prevalence estimates to estimate the number of cases avoided by the listing of the vaccine on the PBS/NVS.

3.4.4 Indirect effects or herd immunity / herd protection

Indirect effects or herd immunity / herd protection may be one of the main outcomes of a public vaccination program. Herd immunity should be included in models of vaccination of programmes that have a demonstrated herd immunity effect and for which the projected coverage rate is high enough to justify such herd immunity. If relevant, outline the sources of evidence used to demonstrate the impact of herd immunity, the results obtained with similar vaccines and the approach used to incorporate herd immunity into the economic model.

Indirect effects or herd immunity / herd protection may be one of the main outcomes of a public vaccination program. Herd immunity could be included in models of vaccination of programmes where projected coverage rate is high enough to justify such herd immunity. If relevant, outline the approach used to incorporate herd immunity into the economic model and the assumptions on the impact of herd immunity.

3.4.5 Duration of protection

Information on the duration of protection and the need for boosters is frequently only determined by surveillance studies following the adoption of the vaccine into public health programs. If relevant, outline the assumptions on duration of protection and the approach taken to modelling duration of protection.

3.5 STRUCTURE OF THE MODELLED EVALUATION

The model's structure must be described.

Identify the options considered and justify the option chosen when designing the model. Consider implicit assumptions built into model structures and comment if appropriate. Indicate whether the modelled outcomes represent the final outcomes of treatment. Where appropriate, explain and justify the linking of measured short-term and/or surrogate outcomes to the modelled final outcomes, including a justification for how these are quantified over time. Define and justify the appropriate time horizon for follow-up.

Describe how the dynamics of the model function. If herd immunity has been included in the model, describe how it has been incorporated. Where outcomes have been quantified over time, explain the underlying assumptions and rationale.

The appropriate time horizon for follow-up relates to the disease and treatment patterns and an estimation of the time period(s) in which the outcomes are expected to occur from the natural history of the disease. In a vaccine model, outcomes might be expected to occur over a long time horizon, if individuals are vaccinated against a disease having a lifetime risk. A rationale for the time horizon should be presented, relating to the risk of the disease against which the individual has been vaccinated.

Future costs and benefits of health care expenditure are discounted to take into account both the social opportunity cost of investment and the social rate of time preference. With vaccines, the bulk of costs are incurred at the beginning of treatment, whereas health outcomes can extend many years into the future, even possibly to future generations. Thus, discounting health outcomes will tend to devalue vaccination efficiency, whereas competitive alternative treatments (such as curative treatments with short-term consequences) will seem to be more efficient.

Discounting costs and outcomes at the same rate assumes that people and society have exactly the same trade-offs between health and wealth, and ignores the possibility that health gains may be considered as a real capitalization of the future and future generations. Evidence suggests that individuals' time preferences are not constant but decrease with time. Hence, in a vaccine model covering a long time horizon, the discount rate should tend to zero as time tends to infinity (Beutels *et al* 2003, Tasset *et al* 1999).

3.6 RESULTS OF THE MODELLED EVALUATION

Present the results of the model firstly in disaggregated form, then in increasingly aggregated form (with discounting as appropriate, see Appendix L). Present the appropriately aggregated and discounted results separately for outcomes and resources and separately for the proposed drug and its main comparator. Finally, present the incremental cost of achieving each additional unit of outcome with the proposed drug when substituted for the main comparator.

If the model estimates change over time, present key outputs (such as incremental costs, incremental outcomes and incremental cost-effectiveness) on a graph with time on the x-axis against the changing outputs on the y-axis.

The presentation of disaggregated results depends on the type of model. For example, where possible, present the quantity of each type of resource provided in its natural units as well as its cost valued in dollar terms, and/or present the costs and outcomes associated with each branch in the tree of a decision analysis.

If the proposed vaccine is both more expensive and more effective, it is helpful to know how much more it costs to achieve the extra units of outcome in the form of an incremental ratio. Where provided, incremental ratios should be highlighted.

3.7 SENSITIVITY ANALYSES OF THE MODELLED EVALUATION

One-way sensitivity analyses must be conducted on all variables using extreme values. Present in tabular form and as a tornado diagram. Conduct two-way sensitivity analyses on all variables shown to be sensitive in the one-way analyses. Present in tabular form and as graphs.

Compare any aspect of the model's results against any corresponding results obtained empirically and comment on any differences. It may be helpful to examine the sensitivity of the model to any changes in assumptions concerning the structure of the modelled evaluation which are important but debatable.

These analyses are important to determine how sensitive the evaluation is to changes in the variables that have been used in the evaluation. If discounting has been necessary, the robustness of the conclusions to different discount rates (including a zero discount rate on non-monetary outcomes alone and on both costs and outcomes) should be tested.

A sensitivity analysis should be conducted where the indirect effects in a dynamic model are varied. Additionally, the cost per unit of indirect costs (eg, productivity loss per unit of time) should be varied.

If discounting has been necessary, the robustness of the conclusions to different discount rates (including a zero discount rate on non-monetary outcomes alone and on both costs and outcomes) should be tested. Discounting costs and outcomes at the same rate assumes that people and society have exactly the same trade-offs between health and wealth, and ignores the possibility that health gains may be considered as a real capitalization of the future and future generations. With vaccines, the assumption of health capitalization is the basis of the public health paradigm.

From a public health perspective, the diminishing risk is considered through a global, not individual, impact. Hence, over time, vaccination programs will be considered as effective in that it reduces the relative risk of disease. Therefore in addition to including a zero discount rate for

health outcomes, sponsors should consider presenting results using a variable discount rate that tends to zero over time (Beutels et al., 2003; Tasset et al., 1999).

4 ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

The use and financial implications of funding a vaccine depend on several key variables:

- unit cost of the vaccine;
- the number of doses required to fully immunise a person;
- storage and waste management;
- cost of administering the vaccine, including provider time, staff and materials and transport;
- whether the vaccine is a combination vaccine or a mono-valent vaccine;
- how the vaccine fits into the current vaccination schedule; and
- epidemiological data to estimate immunisation coverage rates and birth cohorts.

From a societal perspective, vaccines usually provide a public health benefit. Hence, most universal vaccination programmes are delivered in non-clinical settings, such as schools or community centres, and may differ between states/territories. Hence, administering the vaccine would involve different cost than the administration of curative treatments in clinical settings. There also may be costs associated with maintaining a reserve stock to ensure availability of the vaccine.

Unlike curative treatments, vaccines have a substantial upfront cost while benefits and cost-offsets attributable to the vaccine are likely to be recognized far into the future. This time lag would have a significant impact on financial projections, as there would likely be few cost offsets during the time horizon typically used to forecast the financial implications of curative treatments.

Further, unlike products listed on the PBS, usage statistics are not readily available for vaccines listed on the current NVS. This makes it difficult for sponsors of new vaccines to accurately estimate the expected market size of a new vaccine. In addition, the choice of vaccine for a disease is frequently chosen by a tendering process at state level, post listing on the NVS. Therefore although it may be possible to estimate the expected market size for vaccines against a particular condition, the market share for individual products cannot be easily estimated.

For vaccines considered therapeutically interchangeable with already listed vaccines, where the proposed price is the same, there is unlikely to be a significant change in the size of the market, assuming steady state. The financial implications of listing such vaccines are likely to be cost-neutral, however from a public health perspective it is desirable to have multiple products available to prevent supply issues.

Given the time lag between when costs are incurred and cost-offsets are realized, it may be appropriate for sponsors to use a longer time horizon when forecasting the financial impact of a vaccine. This would provide decision makers with a more complete picture of the long-term financial implications of the vaccine.

Guidance also should be given regarding which government costs should be considered.

The calculation of the financial implications of listing vaccines on the NVS may be difficult to determine. Where there are multiple vaccines for the prevention or eradication of the same condition, the use of specific brands of vaccine is often determined by a tendering process. Therefore, although the total market size for vaccination against a disease may be known, the market share for individual products may not be known at the time of submitting to the PBAC. Further, where a vaccine against a particular condition is already available, and the proposed vaccine can be considered therapeutically equivalent and has the same cost as the listed product, the financial implications of listing are likely to be cost-neutral.

4.1 ESTIMATED EXTENT OF USE OF THE PROPOSED DRUG

Estimate the likely prescription volume of the proposed drug on the PBS/NVS for at least each of the first two full years from the date that it is listed on the Schedule.

An epidemiological approach should be adopted to estimate the likely patient numbers projected to be eligible for the proposed vaccine and its comparators. Where the proposed vaccine can be considered therapeutically equivalent to a currently listed product, provide details of the usage of the currently listed vaccine (if available). If it can be demonstrated that the use of the currently listed vaccine is stable and the cost of the two vaccines is equivalent, it may not be necessary to present further calculations. In this case, use of the proposed vaccine could reasonably be expected to substitute for the already listed vaccine with no addition to the market size.

Estimate the likely patient numbers for each proposed indication for PBS or NVS listing for the vaccine. Where a number of products provide immunity against the same condition, estimate the total market size. If possible, also estimate the market share for the proposed vaccine.

4.2 ESTIMATED EXTENT OF SUBSTITUTION OF OTHER DRUGS

Estimate the change in the extent of use of other drugs using the information provided in Sections 1.4 and 4.1.

4.3 ESTIMATED FINANCIAL IMPLICATIONS FOR THE PBS/NVS

The time horizon for this analysis should be until the proposed drug is predicted to have achieved a peak or stable market share under the proposed PBS/NVS listing. Products listed on the NVS do not result in any increase in cost to the PBS.

4.4 ESTIMATED FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

The financial implications for the government may include the costs of the program delivery system eg, clinics, schools etc. Generally it is not feasible to capture these costs. Other government health related cost offsets should also be included.

AGENDA ITEM 2

POST-ATAGI VACCINES APPENDIX

The ESC is requested to review the following draft appendix on the application of the PBAC Guidelines to the specific circumstance of vaccines, including their consideration for funding under the National Immunisation Program (NIP) and to consider recommending their endorsement by the PBAC.

Background

The ESC has overseen several iterations of the guidance to be given to applicants for vaccines to be considered by the PBAC for listing on the PBS or funding under the NIP.

These iterations have involved sessions discussing options with the Medicines Australia Vaccines Industry Group (MAVIG) in August 2005 and November 2005 and with the Australian Technical Advisory Group on Immunisation in November 2005. Other comment is being sought from other parties through the Immunisation Section of the Australian Government Department of Health and Ageing.

The attached version reflects the discussions with representatives of MAVIG and of ATAGI with representatives of the ESC in November 2005. It also incorporates input from the ATAGI meeting held in later November attended by the PBAC Chair, the PBAC Secretary and the ESC Secretary.

It removes the notes in drafting, although they are retained for information in a separate page at the end.

MAVIG have been provided with a copy of this later version and have indicated that they may wish to communicate via a letter to be tabled at the ESC meeting.

ADDITIONAL INFORMATION REQUIRED FOR VACCINES

REFER: Section 1.1

This appendix applies to submissions for vaccines seeking listing under the PBS or seeking funding under the National Immunisation Program (NIP).

These additional requests for information are not exhaustive, but are to clarify the needs of the PBAC when applying the general approach of these Guidelines to the specific circumstances of vaccines. They are not an alternative set of requests and the remainder of the Guidelines remains relevant to vaccines.

The order of this Appendix follows the order of the main sections of these Guidelines.

1. Details of the proposed vaccine and its proposed use on the PBS or NIP

1.1 Pharmacological class and action
As part of the information in Section 1.1, provide the number, identification and amounts of antigens in the proposed vaccine; the formulation of the proposed vaccine, and any information regarding any expectation of a limited initial supply where relevant. Other relevant characteristics to be presented include the disease(s) to be prevented by the vaccine and the defining characteristics of the vaccine, including whether the immunising agent is live, attenuated, killed, absorbed or non-absorbed and viral or bacterial and a description of any cold storage requirements which might apply to its distribution.

Appendix A gives details of the additional information requirements of submissions containing fixed combination vaccine products. For (b) of this appendix, the component products should preferably be listed on the PBS or funded under the NIP at the time the submission is lodged. For (e*), the combination vaccine should provide clinically acceptable effectiveness for each of the individual components.* ~~there should be no loss of beneficial effectiveness of the components (within current non-inferiority standards).~~ Appropriate evidence comparing the fixed combination vaccine product with each of its individual components would usually be required. *Provided a clinical advantage (improved coverage, less injections) or cost savings (improved delivery, reduced visits) can be demonstrated for a proposed combination vaccine this will support pricing above the sum of the individual components.*

MAVIG notes that the fixed combination vaccine products and the cross reference to Appendix A in the Guidelines for additional requirements have been added to this draft for discussion.

MAVIG recognises that ESC has subtly changed the words of point (e) of Appendix A of the PBAC Guidelines for vaccines and would ask for further clarity around this. Appendix A (point e) of the PBAC Guidelines notes:
'there should be additive (not necessarily synergistic) beneficial effectiveness of the components'

For vaccines this has been changed to:
'there should be no loss of beneficial effectiveness of the components (within current non-inferiority standards'.

MAVIG note that immunogenetic response within vaccine combinations can be lower than the response from individual components. However this is considered acceptable by regulatory authorities so as long as it is above the clinically accepted thresholds for each of the antigens. The most recent example of this is with the approval of DTPa combination vaccines containing Hib. MAVIG recognise that this may be the reason for ESC proposing a different criterion for point (e), however a better approach may be to word it as follows: (e) the combination vaccine should provide clinically acceptable effectiveness for each of the individual components.

MAVIG also notes that Appendix A of the PBAC Guidelines specifies that the pricing of combination products will normally be no greater than the sum of the individual components (at the current price to pharmacist level). Where a higher price is requested, this must be supported by evidence of enhanced clinical outcomes and acceptable cost effectiveness.'

MAVIG argues that the criteria as implied in the current wording is too stringent for sponsors to demonstrate an acceptable cost-effectiveness at a higher price, and would suggest that Appendix A is revised accordingly.

MAVIG notes that combination vaccines may improve clinical outcomes through improved coverage and compliance, however data to support this, will not be through the required level of evidence (randomised controlled clinical trials) required by the PBAC for primary decision making. MAVIG request that this is recognised in Appendix A of the PBAC Guidelines and allow for better compliance or coverage to be demonstrated using other data sources (ie observational studies) and used as the basis to seek a higher price. In fact, this situation is not unique to vaccines, and a broader discussion is required with industry.

It is well recognised that fewer injections at any given visit will lead to less trauma and less side effects. This will lead to improved efficiencies in delivery and reduced visits and costs, as parents are commonly opting to split the visits if multiple injections are required[1] *. The current Appendix A notes that 'benefits in patient convenience or cost savings to the PBS…will be regarded as supportive but not necessarily an adequate basis for listing'. MAVIG disagrees with this, and would argue that if these benefits can be demonstrated then these factors should also be acceptable in supporting a higher price. MAVIG proposes the addition of the following sentence at the end of the above paragraph.*

"Provided a clinical advantage (improved coverage, less injections) or cost savings (improved delivery, reduced visits) can be demonstrated for a proposed combination vaccine this will support pricing above the sum of the individual components."

And the removal of the following two sentences

1. *"where a higher price is requested, this must be supported by evidence of enhanced clinical outcomes and acceptable cost effectiveness"*

[1] *56% of parents have suggested that they will take their child to 2 separate visits if 3 injections are required Madlon-Kay DJ and Harper PG (1994). Too many shots. Parents, nurses and physicians attitude to multiple simultaneous childhood vaccination. Arch Fam Med 3: 610-13.*

2. *"where benefits in patient convenience or cost savings to the PBS or the patient are claimed, these should be demonstrated and will be regarded as supportive but not necessarily an adequate basis for listing".*

This is also consistent with the note further on in the vaccine Appendix Section 3.3 which states cost benefit analyses are potentially useful to estimate the value of the consequences of the proposed vaccine that may not be captured by other means, for example changes to injection frequency and adverse effects.

MAVIG also points out that the benefits of combination vaccines in improving public health outcomes is widely accepted by immunisation and public health experts (see for example CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines 1998). There are recent examples where combination vaccines have enhanced the effectiveness of the national immunisation program in Australia.

- *ATAGI recommended the introduction of Inactivated Polio Vaccine (IPV) when the Western Pacific Region was declared polio free at the end of 2000. Their advice was that Australia should switch as soon as suitable cost effective IPV containing combination vaccines become available. This advice implicitly supported that the introduction of the new antigen (IPV is injectable and was replacing oral polio vaccine given separately) could only acceptably be achieved by having that antigen in a combination vaccine as there are then no additional visits, no additional needles for the child or any of the associated programme costs. In this particular case there were also cost savings attributable to the removal of OPV from the immunisation schedule. Costs saved which were associated with OPV vaccine administration were estimated to be $7 per dose of which only 36c was the cost of the vaccine[2].*
- *Combination vaccines of measles, mumps, rubella combined with varicella are likely to be introduced in the near future and may allow further optimisation of schedule and possibly a reduction in the number of immunisation visits scheduled.*

MAVIG also points out that combination vaccines are technically very difficult to develop. This is recognised in the CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (1998), where it notes that the presence of more than one component often causes an interaction, leading to either a diminished or an increased response to individual components, compared to when specific components are administered alone. Such interactions are often immunological in nature, but problems may also be caused by chemical and physical interactions between the different components of the vaccine. For example there may be competition of absorption sites on the adjuvant. In the case of live virus vaccines, interference between different virus strains used in combinations, or induced by concomitant exposure to extraneous infection, may suppress proliferation of the vaccine strains resulting in sub-optimal response.

Immunological interference is a broad description of a multitude of interferences, the nature of which is often only partly understood. On or more of the following phenomena may be

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- [2] *Tucker, Isaacs & Burgess (2001). Cost effectiveness analysis of changing from live oral poliovirus vaccine to inactivated poliovirus vaccine in Australia. ANZ J of Public Health Vo, 25 no 5, 411-416.*

involved: antigenic competition, epitope specific suppression, an adjuvant effect exerted by specific components of the combined vaccine and an adverse adjuvant reaction.
To account for these complexities, each combination vaccine must be developed and studied individually in terms of quality, stability, safety, clinical tolerability and efficacy/immunogenicity.

It is for these reasons, that the research and development program for combination vaccines is typically many-fold more extensive (and expensive) than for combination pharmaceutical products. Vaccine manufacturers would not undertake this development without an expectation of being able to recoup the costs.

1.2 Indications

As part of the information in Section 1.2, indicate whether the submission is for listing on the on the PBS or funding under NIP, with a rationale. It would be expected that a vaccine would be proposed for funding under the NIP where there is expected to be an additional health benefit to the community following use of the proposed vaccine which would be improved by maximising coverage rates in the identified individuals. More specific considerations favouring a submission for NIP funding include:

(a) the target is a broader population in which there is either no need to assess risk factors for the disease in each individual, or the assessment of risk factors at an individual level is straightforward (for example, age, gender, ethnicity, geography);
(b) there is a reason to maximise population coverage due to either the severity or prevalence of the condition in an unimmunised population in order to achieve the full community benefit;
(c) the proposed vaccine protects against infection;
(d) the proposed vaccine needs only to be delivered as a single dose or a few doses; and
(c) the efficacy of the proposed vaccine is sufficient.

An additional factor that might be considered in supporting a request for funding under the NIP is where there are putative advantages of increasing herd immunity, particularly where these advantages are supported by clinical evidence (see additional requests below in relation to Section 3.4 for the presentation of such advantages and evidence). PBS listing might be favoured when the proposed vaccine is 'discretionary' for the majority of the population, or the assessment of risk factors is less straightforward (for example, an assessment of immune system status is required).

Explain and justify any restrictions on subsidised use of the proposed vaccine to certain populations, seasons, geographical distributions, and ethnic groups. See additional requests below in relation to Section 3.2 on the presentation of epidemiological evidence to support the request for these restrictions.

If a catch-up program is also requested, define and justify its duration from commencement of the overall funding arrangement and its extent in terms of extra targeted population groups.

Describe any requested PBS restriction or NIP scheduling in relation to the TGA-approved indication and also the Australian Immunisation Handbook, with an explanation and justification for any discrepancies. Where the relevant indication or part of the Handbook is not finalised, refer to the latest draft version and any other relevant advice about any anticipated changes to the draft.

Explain the relationship between the proposed vaccine and vaccines currently available on the NIP (and/or the PBS as relevant) in terms of both their antigen content and their dosage schedules (see also additional requests below in relation to Section 1.5).

MAVIG notes the additional points added into the most recent draft for discussion (March 2006). We previously noted the intent of this section is to reflect Government policy on what may be funded under NIP. MAVIG has a major concern – the wording of this section now implies that a vaccine will not be considered for NIP funding unless there are additional health benefits to the community (ie to the unimmunised) over and above that to the individual immunised. Although there typically may be additional health benefits to the unimmunised in a national program, this has not been a necessary criterion for a national program previously in Australia, and is not recognised as a necessary criterion in other western countries with similar health care systems. MAVIG refers ESC to Erickson et al, (2005). Vaccine 23;2005; 2470 – 2476 for a discussion on the criteria for a national immunisation program. One of the key questions is whether the burden of disease is sufficient to warrant a national control program. National immunisation programs are then seen to maximise the public good, by maximising coverage.

MAVIG also stands by our previous recommendation that given the list of criteria above is unlikely to be exhaustive, the title 'More specific considerations favouring a submission for NIP funding include' be changed to 'These may include'.

MAVIG also urgently seeks clarification of several points in this section:

- *point (c) "the proposed vaccine protects against infection". The intent of this is not clear. If it is intended to exclude therapeutic vaccines (those used to treat, as apposed to prevent, disease) then it would be preferable to explicitly state this. The vaccine against shingles[3] is an example where the vaccine does not protect against infection. In shingles, the infection occurred earlier (chicken pox) and the disease is a re-activation of this infection. The mechanism of action of the vaccine is not well understood. However, the vaccine should be considered on its merits of clinical and cost-effectiveness for a national program.*
- *point (d) "the proposed vaccine needs only be delivered as a single dose or a few doses". Again, the intent of this is not clear. As above, if it is intended to exclude therapeutic vaccines then it would be preferable to explicitly state this.*
- *point (e) "the efficacy of the proposed vaccine is sufficient". Vaccine efficacy will underpin an assessment of cost-effectiveness, but the intention behind "sufficient" efficacy being a consideration for NIP funding, in and of itself, is not clear.*
- *"PBS listing might be favoured when the proposed vaccine is 'discretionary' for the majority of the population..." The word 'discretionary' is clearly intended to convey a specific meaning but what this is, is not clear. Is it intended to reflect when the vaccine is not cost-effective for the majority of the population?*
- *The word putative, and in what context this is being used?*

MAVIG understands that the extent of advice provided by ATAGI prior to a submission is still under discussion. However, under its Terms of Reference ATAGI is best placed to determine whether or not a particular vaccine is likely to meet the criteria for NIP funding and will specifically provide advice to the PBAC on this (Term of Reference 5). It is appropriate that

[3] *Oxman et al(2005). N Engl J Med. 352:2271-84*

this advice is also made available to the sponsor prior to a submission. MAVIG therefore still recommends that wording such as the following be added after option C.
'ATAGI advice should be sought prior to an application for listing under the PBS or the NIP'.

1.3 Treatment details
As part of the information in Section 1.3, specify the proposed schedule of administration (including details of doses and whether primary immunisation and/or booster vaccinations is requested) and any consequential programmatic requirements for administration (eg within and/or beyond current NIP arrangements). Identify and justify any differences from treatment recommendations in the TGA-approved product information and/or the Australian Immunisation Handbook (or the latest draft version of either document where these are not finalised). Specify any new or additional requirements that are likely to have an impact on financial implications of listing the proposed vaccine. Indicate when such programmatic requirements are expected to extend to also include other particular delivery systems (which may vary across states and territories) such as through clinics, community centres and schools.

1.4 Co-administered and substituted therapies
As part of the information in Section 1.4, specify whether the proposed vaccine is to be available as a substitute for existing products or is to be added to current arrangements for either the NIP or the PBS.

1.5 Main comparator
As part of the information in Section 1.5, define the main comparator in terms of the currently available vaccine most likely to be replaced in practice, including by identifying any differences in antigen content. Present a table if this would assist in comparing the content and characteristics of the vaccines (for example, the antigens attenuated by the vaccines, the strength of the vaccines, the scheduling of doses, the routes of administration and the fit with the current vaccine schedule). If a table comparing vaccine content and characteristics is presented, and if the trials presented in Section 2 use other vaccines, then consider including these other vaccines in this comparative table. If the alternative vaccine is not currently funded, the advice of the Department may be sought. If there is currently no vaccine available, then the main comparator will usually be standard medical management.

2. Data from comparative randomised trials for the main indication

2.6 Analysis of the comparative randomised trials
As part of the information in Section 2.6, if immunogenicity outcomes are the primary outcomes of the comparative randomised trials, then the prognostic validity of these surrogate outcomes in relation to more directly patient-relevant outcomes needs to be established, particularly in the context of a claim of therapeutic superiority. Additional advice is found in Appendix O.

Guidelines to determine the prognostic validity of immunogenicity surrogate endpoints are currently being updated in Appendix O and MAVIG would like the opportunity to review these recommendations as part of this review. It is anticipated that the wording of the guidelines will acknowledge that immunogenicity markers are often primary outcome measures of vaccine studies and are an appropriate endpoint to demonstrate the correlation between an immune response and clinical protection.

For the proposed vaccine, demonstrating the prognostic validity of an immunogenicity outcome from a vaccine trial usually requires separate analyses (a) showing that a threshold level of antibody response predicts a particular extent of protection and thus a subsequent magnitude of reduction in cases of the disease presenting in each of one or more manifestations and (b) assessing whether there is any limit to the duration of this predicted effect or waning of the effect over time *where data are available.* .

MAVIG note that in most cases, an assessment on the duration of protection will usually be incorporated into an economic model, as such analyses would require long-term surveillance data, which is often only sourced post-licensure and generally not be available for new vaccines. Additionally, long-term surveillance will require the involvement of the National Centre for Immunisation Surveillance and Research (NCIRS) or another similar surveillance body, necessitating the need for further clarification regarding acceptable interaction between sponsors and NCIRS for surveillance purposes. Therefore, recommend that the words 'where data are available' is added to the end of the sentence.

If there are regulatory standards for immunogenicity that would inform the assessment of the validity of a surrogate outcome, they should be provided, although regulatory requirements may not always satisfy the requirements needed to map the direction and magnitude of a change in the surrogate immunogenicity outcome to the duration, magnitude and severity of one or more changes to subsequent clinical outcomes for inclusion in an economic evaluation.

As vaccines are generally given to a 'well' population, potential harms should be adequately described, including how adverse events were ascertained in the trials and information on adverse events that might have arisen following any launch of the proposed vaccine in other markets.

Apply this clinical evidence to any extra population identified in any requested catch-up program. For example, justify any claim that vaccine effectiveness is similar in both the primary and catch-up populations.

Section 2.8 of the current PBAC guidelines states "A claim of no advantage must also be based on the results of well-conducted studies, preferably "head-to-head" randomised trials". It is proposed that the current wording is amended to acknowledge that such trials are rarely conducted for vaccines and most comparisons are based on immunogenicity studies.

3. Modelled economic evaluation for the main indication

3.2 Population used in the modelled evaluation

The base case of the modelled evaluation should be for the primary population. Present and assess the appropriateness of available evidence to estimate the epidemiology of the disease in the Australian population and any sub-groups as identified by restrictions requested in response to Section 1.2. Possible sources of epidemiological evidence include routine surveillance data, seroprevalence studies and surveys.

Where appropriate use sensitivity analyses presented in response to Section 3.7 to examine the sensitivity of the base case of this model to the marginal costs and benefits of different options of adding a catch-up program and then (a) extending the catch-up population and/or (b) lengthening the duration of the catch-up program.

MAVIG recommend the change above, as catch-up programs are not always going to be necessary.

3.3 Approach used in the modelled evaluation

There are generally two types of models used to estimate the epidemiological impact of vaccination programmes, static and dynamic models. Static models are those in which the force of infection (probability per unit time that a susceptible person acquires infection) is constant over time. These are usually structured as decision analysis models or Markov models. *Although static models are not designed to follow the transmission of disease over time between vaccinated and unvaccinated individuals, they can integrate the impact of herd immunity by assuming a reduction in disease incidence of the unvaccinated population using published epidemiological data.* ~~static models ignore herd immunity effects (see below)~~. Dynamic models are those in which the force of infection is dependent on the number of infectious persons in the population at each time point, and this number would be expected to decline following immunisation. Dynamic models allow for the assessment of herd immunity and also the assessment of age shift *in the absence of published epidemiological data*. Dynamic models should be considered when the force of infection is likely to change following immunisation (ie if the proposed vaccine blocks transmission of infection and coverage is extensive) and the risk and/or severity of the disease is age-dependent.

MAVIG suggest the wording above better reflects the use of static models

In situations where a small proportion of the population is to be immunised, either through low coverage or targeted immunisation, or the proposed vaccine does not prevent circulation of the pathogen, then herd immunity effects would be expected to be negligible and so a static model would tend to be more appropriate.

Study design: in addition to the usual requirements, submissions may need to consider a joint analysis. This refers to an analysis of all affected vaccinations if the cost of delivery and/or coverage rate across multiple vaccinations is likely to be affected by a new proposed strategy. For example, this might apply when the proposed vaccine is multi-valent and could change the number of needles to be injected at one or more steps in the vaccination schedule.

Cost-benefit analyses (CBA) are potentially useful to estimate the value of the consequences of the proposed vaccine that may or can not be captured by other means, for example, changes to injection frequency and adverse effects. ~~but the usual requirements for presenting a CBA noted in Appendix K would apply.~~

MAVIG supports the use of cost-benefit analyses in vaccine economic evaluations as cost-benefit analyses are capable of providing the most comprehensive consideration of the costs and benefits of intervention programs, as it attempts to weight all of the outcomes associated with a program through a single monetary outcome. It is particularly useful in vaccination programs as it allows for the valuation of not only the prevention of a disease to the individual but also the implicit or explicit impact of that disease to the family and society in

general. Preventative programs are like insurance policies and the monetary value given to the benefits of vaccines are a good indication of what society are willing to pay for future societal good health.

Appendix K of the guidelines does not provide any requirements for CBA. Rather it notes the following:

'In contrast to other forms of analysis, cost-benefit analyses (CBA) express all outcomes in monetary rather than physical units. This requires a monetary valuation of these outcomes and CBA relies heavily on calculations of indirect costs and benefits, principally changes in production capacity. Such analyses are not likely to be helpful to PBAC in its deliberations and are not encouraged'.

This is contradictory to the statement above that states that ' CBA are potentially useful', and therefore needs further clarity for sponsor companies. MAVIG seeks advice from ESC regarding this contradiction, and suggests that reference to Appendix be removed. .

MAVIG suggests that the caveat 'but the usual requirements for presenting a CBA noted in Appendix K would apply' be removed.

Refer to Appendix L if changes to indirect outcomes (particularly changes in productivity) are claimed.

Given than indirect outcomes are variables within modelled economics, MAVIG question whether this discussion should be in Section 3.4.

Appendix L notes that 'in general changes in productive capacity as an outcome of therapy are not encouraged in submissions to the PBAC. However if considerations of such indirect benefits can be justified in the submission, the following standard economic practice should be adopted'.

MAVIG have noted in previous correspondence that the wording in Appendix L is negative and discouraging of sponsors to claim indirect benefits. ESC has noted in our previous meeting that this is not the intent. Therefore, a better discussion of the intent of Appendix L is suggested. This could include a discussion around the perspective of the guidelines being societal, and a clear definition of what the PBAC means by this, and guidance on the level of evidence required, and preferred methodology that would be acceptable to the PBAC when claiming indirect benefits.

For population based programs, MAVIG would argue that all models take a societal perspective, which would include both direct and indirect costs and benefits, based on the best available data.

3.4 Variables in the modelled evaluation

Include additional program costs where these are expected to change with the introduction of the proposed vaccine. For example, include the costs of additional ACIR payments if additional encounters are required to give the proposed vaccine. There may also be changes for the delivery of the proposed vaccine through clinics, community centres and schools. If it is considered essential to initiate a surveillance program as part of funding the proposed vaccine under the NPS, also include the costs of the resources for such a program.

MAVIG believe that an assessment as to whether a surveillance program is 'essential' and what the costs related to such a program will be, is clearly the role of NCIRS/ATAGI in 'providing surveillance of vaccine-preventable diseases and adverse events after immunisation'. Therefore, these requirements should not be included in PBAC submissions.

Furthermore, as noted in the correspondence sent to MAVIG by Jennie Roe from the Population Health Division (date 17 Jan 2006), NCIRS are excluded 'from providing advice to individual vaccine sponsors on preparation of submission to the PBAC' due to 'strict conflict of interest rules'.

Present systematic overviews of any and all available supporting evidence on variables expected to impact on overall vaccine effectiveness, including any waning or limited duration of vaccine effectiveness (such as any surveillance studies on the need for booster doses) and/or herd immunity implications (such as observational studies). The quality of these studies should be presented and assessed separately as described in Appendices P, Q and R.

3.5 Structure of the modelled evaluation
The duration of a model should be justified, as the cost-effectiveness ratio for vaccination programs generally reaches a plateau after a length of time and the time span of a model should not be limited to a time before a plateau is reached. Presenting Markov traces of key variables such as the incremental cost-effectiveness ratio over time will assist in assessing the impact of varying the time horizon of the model.

Explain and justify the approach taken in the mathematical modelling of consequences such as any waning or limited duration of vaccine effectiveness and/or herd immunity implications.

3.7 Sensitivity analyses of the modelled evaluation
Due to the multitude of uncertain parameters, present multivariate sensitivity analyses in addition to univariate sensitivity analyses. As models of vaccines may be particularly sensitive to the discount rate used for calculating the net present value of health outcomes, sensitivity analyses varying this rate should be presented, together with any arguments seeking to justify a rate other than the 5% per annum requested in Appendix L.

MAVIG recognises ESC consideration in allowing for sponsors to justify a lower discount rate. Ideally, however MAVIG continues to argue that a lower discount rate should be used for population based vaccination programs and a rate of 3% is used as base case rather than 5%. This discount rate should be applied to both costs and outcomes, and as suggested by Drummond et al (1997) an analysis using 0% discount rate should also be provided to enable decision makers to assess the overall sensitivity of the choice of discount rates.

Why a lower discount rate
Shaffer et al (1996; p77) note that because of individuals' attitudes toward society, consideration of children as part of future society, and feelings of altruism toward humanity, the societal discount rate is lower than an individual's personal discount rate or a private-sector discount rate. This has also been supported in the literature where it has been argued that society is more than a collection of individuals and their view of the future may not be the same as an individual. This is particularly evident with immunisation programs where

herd immunity has led to a reduction in risk on a population basis, rather than just to the individual.

Sheldon (1992) argues that the practice of discounting future streams of costs and benefits is principally justified by the fact that individuals have a positive time preference, preferring consumption sooner rather than later. However discounting weights public decision-making in favour of interventions resulting in short-term benefits and against longer-term benefits and therefore, discriminates against preventive and other public health programmes. The author also argues that health policy should have a longer time horizon, reflecting social values rather than individual preferences and demonstrates that factors which make discounting the future rational from the individual's point of view are shown to be irrelevant to a societal perspective.

Bos et al (2005) have reviewed the impact of discounting health gains for vaccination programs, diabetes intervention and cancer interventions. The authors note that in prevention programs with distant future health gains, such as infant vaccination programs, discounting health effects has a strong impact on the results of cost-effectiveness analyses. This is also supported by Brouwer et al (2005) and Milne (2005). Bos et al (2005) note that in their review, the impact was so large that the discount rate may clearly have influenced decision making. For curative interventions (diabetes and cancer) the discount rate is likely to be much less influential on decision making. Therefore, the authors conclude that the same discount rate for health and monetary effects may lead towards favourable decisions for curative compared with preventative interventions. This is particularly important when decisions will be made by the same decision makers, ie PBAC.

References:
Bos JM, Postma MJ and Annemans L (2005). Discounting health effects in pharmacoeconomic evaluations: current controversies. Pharmacoeconomics 23(7): 639-49.
Brouwer WBF, Niessen LW, Postma MJ and Rutten FF. Need for differential discounting of costs and health effects in cost-effectiveness analyses. BMJ 331: 446-8.
Milne R (2005). Valuing prevention: discounting health benefits and costs in New Zealand. New Zealand Medical Journal 118 (1214): 1-4.
Shaffer PA and Haddix AC (1996). Time preference. In Preventative effectiveness: a guide to decision analysis and economic evaluation. Editors Haddix AC, Teutsch SM, Shaffer PA and Dunet DO. Oxford University Press.
Sheldon TA (1992). Discounting in health care decision making time for a change. J Pub Health Med 14: 250-56.

4. Estimated extent of use and financial implications

4.1 Estimated extent of use of the proposed vaccine
Estimates of use should be based on data from current estimates of vaccinated cohorts where the proposed vaccine is to replace an existing product, with allowance for estimates of wastage and usage beyond the target population. The advice of the Department, particularly the Immunisation Section, should be sought. If catch-up cohorts are to be included, this needs to be explained and justified and, consistent with the additional requests above for information in response to Section 3.2, should be presented as a series of marginal analyses examining the impacts of various options for catch-up programs.

If the proposed vaccine is indicated for a new disease, use standard population estimates, with further modification as necessary if restricted to specific target populations. See also additional requests above for information in response to Section 3.2.

4.3 Estimated financial implications to the NIP
When appropriate, this section should adopt the perspective of the NIP, not the PBS.

4.4 Estimated financial implications for government health budgets
This section should include costs of administration either through the main vaccination programs or through other systems, such as general practice.

The costs associated with program delivery are not available in the public domain and therefore will be difficult for sponsors to include. Further guidance on how such costs will be provided to sponsors is requested.

Cost consequences to government budgets beyond the health sector (such as clinics, community centres and schools) could also be identified and estimated for separate presentation in response to this section. These may vary across states and territories.

It is unclear from the proposed wording how sponsors will capture the abovementioned costs, and whether such information will be provided by the Department, either on a case-by-case basis at the sponsor's request, or as an inclusion in the Manual of Resource Items and Their Associated Costs. It is assumed that sponsors will not be required to actively source cost data beyond the health sector, particularly when considering that such costs may differ between states and territories, and wording to verify this assumption is required.

Note in drafting: *Appendix O is being revised separately and will provide a more detailed explanation of presenting a basis to determine prognostic validity.*

Note in drafting: *Section 3.3 of the* PBAC Guidelines *is currently under revision, and the relationship between the text referring to Section 3.3 in this Appendix and the text being developed in Section 3 and its associated appendices will require cross-checking.*

Note in drafting: *Appendix K of the* PBAC Guidelines *currently discourages use of monetary valuation of health outcomes. This is also currently under revision and this separate substantive review will guide the final wording of the text in this paragraph.*

Note in drafting: *Appendix L of the* PBAC Guidelines *is also currently under revision and this separate substantive review will guide the final wording of the text in this paragraph. This separate review may provide further guidance on the nature of evidence which would more convincingly support such claims.*

Note in drafting: *important program costs which might vary require further examination, including impacts on clinics, community centres and schools. As these are better identified, the* Manual of Resource Items and their Associated Costs *will need updating.*

Note in drafting: *Sections 1.6, 2.1 to 2.4, 2.7 to 2.9, 3.1, 3.2 and 4.2 were also reviewed, but vaccine-specific advice was not thought necessary. In addition, some terms should be defined in the* Glossary *accompanying the* PBAC Guidelines. *These include immunogenicity, herd immunity (the indirect protection of non-vaccinated susceptible individuals), catch-up programs and joint analysis.*