Template for ATAGI pre-submission advice to PBAC

A guide for ATAGI members, ATAGI Secretariat and evaluation groups

Version 3 (Final)

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Purpose

This document is designed to guide the process of ATAGI's pre-submission advice to PBAC (Pharmaceutical Benefits Advisory Committee) for its consideration of vaccine submissions.

PBAC submissions for vaccines to be funded on the National Immunisation Program schedule (the NIP) are preceded by a request for advice from the vaccine sponsor. Because of their technical expertise, ATAGI are uniquely placed to answer questions that require specialist knowledge and experience, and this can help PBAC make decisions about vaccines to go on the NIP.

This template aims to ensure that the key technical issues can be identified for ATAGI's advice prior to the sponsor completing its submission to PBAC. This template is designed to be used by ATAGI members, ATAGI Secretariat staff, and vaccine evaluation groups, who have specialist expertise in the vaccine or the vaccine preventable disease in question.

The new ATAGI process requires sponsors to provide a request to ATAGI for advice that is structured around the PICO criteria (Population, Intervention, Comparator, Outcomes), clinical algorithm and predicted implementation of the vaccine onto the NIP. The process also requires that ATAGI advice to the sponsor and PBAC follows a template, which is intended to provide a synthesis of relevant evidence and to highlight areas of uncertainty. These measures are designed to make ATAGI advice simple to use for both the sponsor and PBAC but also to facilitate the definition of issues that may otherwise emerge as uncertainties later in the PBAC process.

It is recognised that pre-submission advice from ATAGI will be highly specific to the vaccine under review. As such, the required information for proving pre-submission advice from ATAGI is described in general terms in this template, with suggested questions provided so that ATAGI can ensure they provide all the information required by PBAC and its subcommittees to evaluate the vaccine.

It is not intended that the suggested questions in this template should be followed exhaustively. Those questions that ATAGI does not consider relevant should be deleted. Also, if the material in the request is considered adequate, it can be presented using this template either without further comment, or by grouping the relevant questions together with a note 'these issues were adequately addressed.'

When drafting the Advice, authors may wish to include in-text the specific questions posed in the sponsor's Request for Advice, in addition to presenting the consolidated list of questions in the appendix.

Start – Committee-in-confidence

Where appropriate, ATAGI may wish to provide advice to PBAC that is of a sensitive or confidential nature which is not appropriate to be shared with the sponsor. Provide any committee-in-confidence material here for redaction in the version to be shared with the sponsor. Include a reference to the section of this document where this information would otherwise be presented.

This page can be deleted in cases where this does not apply.

End – Committee-in-confidence

1 Overview

Key issues for PBAC to consider

Boxed summary of only the key issues, to be no more than one page

Clinical need and epidemiological objectives
PICO elements
Clinical evidence and model assumptions
Implementation issues
Key areas of uncertainty where there is unlikely to be appropriate evidence in future

Summary of PICO criteria to be addressed in a submission to PBAC

Present the proposed PICO summary table from the sponsor's Request for Advice (Table 2.1-1 in the Advice Request Guideline). More than one table may be appropriate if there are separate target populations (for example, infants; adolescents; elderly).

A separate table reflecting ATAGI's preferred PICO elements may be warranted if it involves substantial amendments or alternative scenarios. Discussion of PICO individual elements should be reserved for Section 2.

2 PICO components and rationale

2.1 Clinical need and epidemiological objectives for the vaccine

Refer to the sponsor's rationale for the vaccine and the clinical claim in Table 2.1-1 of the Request for Advice. This section should be developed at the end of the drafting phase in consultation with the ATAGI discussant(s).

Does ATAGI agree with the sponsor's rationale described in 2.1 of the Request for Advice – in brief, what is the clinical need for this vaccine in each target population group?

Does ATAGI consider that principal benefit is to the individual, rather than the population, for example with a vaccine for travellers, or for cancer patients with specific high risk characteristics? If so, would funding be better suited to the PBS rather than the NIP?

Does ATAGI agree with the sponsor's clinical claim e.g. that the proposed vaccine will replace (based on superiority) or supplement (based on non-inferiority) the nominated vaccine(s) on the NIP?

Is there any supporting advice or policy objective for this particular vaccine, for example from the Chief Medical Officer?

2.2 Population

Describe the following information from the sponsor's Request for Advice:

- The target population and the current Australian Immunisation Handbook recommendations for this disease in each group (Table 2.2-1 of the Request for Advice)
- The target population for whom the proposed vaccine is intended and disease incidence/burden (Table 2.2-2 of the Request for Advice)
- The key sources of epidemiological data used to generate the estimates and any limitations (including information summarised in Table 2.2-3 format adapted for this purpose, if relevant).

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

Target population groups

- *Does ATAGI agree with the choice of target population group(s)? Has the proposal omitted any population groups with substantial incidence of vaccine preventable disease that should be considered?*
- *Does the proposal differ with current Handbook recommendations? Is this adequately justified (or refer to where this is discussed in this advice)*
- *If this vaccine is added to the NIP for the population groups proposed, will there be any changes reflected in the Australian Immunisation Handbook recommendations?*
- *Are there any impending changes to the NIP for other vaccines that are relevant?*
- *Are high risk groups adequately described?*

Disease incidence/burden in the target population groups

- *For each target group proposed, are the estimates appropriate for incidence and burden of disease? Has the sponsor considered morbidity and mortality in these estimates?*
- *Is the disease aetiology multi-factorial and if so has the request adequately described the vaccine-preventable fraction of the population?*
- *What is the likely impact of any under- or over-estimates?*

- *Has the request identified the appropriate sources of data from which estimates are derived? What are the limitations of the data or methodology used to generate it (such as under-reporting, variable case definitions, only data available are out of date)?*

Other issues potentially relevant to the target population

- *If the vaccine targets only specific strains or serotypes, might introduction of the vaccine result in increasing dominance of other strains? What are the implications for individuals infected with disease not covered by the vaccine type strains or serotype(s)?*
- *If relevant: Does the proposed catch-up program identify the appropriate age groups/at risk population?*

2.3 Vaccine Intervention

Present the Vaccine characteristics and dosing presented in Table 2.3-1 of the Advice Request.

When describing the proposed dosing, avoid duplication with the clinical evidence considered in Section 4.2 by including a cross-reference if necessary to where issues relevant to the intervention have been discussed in that section.

Which category does this request relate to (delete those not applicable to this vaccine)?

- *a new vaccine*
- *a vaccine already on the NIP, for a new population (for example, infants in addition to adolescents)*
- *a new vaccine proposed as an alternative to another brand already funded on the NIP*
- *a new combination of existing separate vaccines already on the NIP*
- *a new version of an existing brand on the NIP containing updated or different subtypes*
- *an amendment to an existing vaccine/population listing on the NIP (for example, changing the dose schedule; expanding the age range for over 70s to include 65 years and over)*

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

Proposed doses and schedule (may alternatively be addressed in Section 4.2)

- *Is the proposed timing and frequency of vaccine doses in the proposed schedule (primary dose or series and booster) appropriate given the demonstrated duration of immunity for the vaccine?*
- *Is this timing adequately demonstrated for each vaccine component or vaccine antigen?*
- *Is the number of doses proposed appropriate? Does this apply to each target group or in a subset?*

2.4 Comparator

Present the following from the sponsor's Request for Advice:

- The sponsor's nominated main comparator and any key secondary comparators
- Where the proposal involves multiple target populations, include Table 2.4-1 identifying the comparator for each population or group
- Table 2.4-2 comparing the proposed vaccine with the main comparator vaccine

Comparator information that is commercial-in-confidence should be presented in the Committee-in Confidence section.

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Is the nominated comparator(s) appropriate? Are there others that should be considered (or excluded) and if so why?*
- *Are there any notable features in the proposed vaccine that differ with the comparator: this may include differences in vaccine valency or included target serotypes; different TGA approved indications, or dosing. What are the implications for this or these differences?*
- *Are there any near market comparators that should also be considered?*
- *If the comparator is standard medical management, is this adequately described?*

2.5 Outcomes

Present Table 2.5-1 of the Advice Request Guideline summarising outcomes to be reported from the key trials for intervention and comparator (for each target population where relevant).

Responses to the questions below should validity and limitations of the type of outcomes rather than interpretation of trial evidence. Alternatively, these can be addressed in Section 4.2.

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Does the sponsor's clinical claim rely on true vaccine effectiveness outcomes or surrogate measures? If clinical evidence reports immunological correlates of protection, are these acceptable as surrogates?*
- *Where the clinical evidence identifies a threshold or titre level – is this cut-off appropriate as a measure of protection?*
- *Where different measures of efficacy or immunogenicity are presented, or using different assays methods, what are the relative merits of each?*
- *In terms of safety, will data be presented regarding longer term or low frequency events?*
- *Are there specific safety outcomes relevant to the vaccine preventable disease that should be considered (intussusception is typically specifically reported for rotavirus vaccines; febrile seizures are of particular interest for meningococcal vaccines)? Are any of these unavailable from the clinical evidence?*

- *Have potential safety outcomes been reported for all relevant target populations? Are there any potential gaps in data on safety, and if so, what are the implications of these?*

3 Clinical Management

3.1 Clinical management algorithms

Present the clinical algorithms from Section 3.1 of the Request for Advice showing current practice and how this will change on funding of the proposed vaccine on the NIP.

Suggested questions for ATAGI advice (as appropriate to this vaccine):

- *Do the clinical management algorithms capture the appropriate level of detail? Is there any non-NIP vaccination that should be included?*
- *If standard medical management is the nominated comparator, is this adequately reflected?*

3.2 Proposed NIP listing

Present the following from the sponsor's Request for Advice:

- Table 3.2-1 of the Advice Request Guideline describing the proposed NIP listing
- Description of any proposed catch-up program

Does ATAGI have any comments on the proposed NIP listing for the primary (ongoing) program that have not been covered in Section 2?

3.2.1 Catch-up program

- *If proposed, is the duration and target age-group of the catch-up program appropriate?*
- *Will delivery of the catch-up program differ from the primary program (or can it be delivered at the same time as or with minimal additional resources as the primary program?)*
- *Has the sponsor described the impact on overall coverage, if so with what evidence?*

3.3 Relationship with other listed vaccines or medicines

Describe the relationship between the proposed vaccine and vaccines currently available on the NIP outlined in Section 3.3 of the Request for Advice.

Suggested questions for ATAGI advice:

- *Will the vaccine proposal affect other vaccines already funded on the NIP (not including market share)? Will the listing of the new vaccine as proposed require amendment or removal of any existing vaccine listings?*

- *Will the new vaccine be used interchangeably with the comparator? If so, is dosing and administration the same? Can the new vaccine be used to complete a dose series commenced with an existing vaccine?*

3.4 State and Territory immunisation programs

Present Table 3.4-1 describing relevant State and Territory vaccination programs if applicable.

Is a similar immunisation program being undertaken in the States and Territories? How does this proposal differ? Assuming these jurisdictional programs will be discontinued on listing of the proposed vaccine, which individuals will no longer be eligible for the vaccine?

4 Clinical evidence

4.1 Relevant trials and other clinical information

Present the following from the sponsor's Request for Advice:

- The master list of trials (Table 4.1-1 of the Advice Request)
- The characteristics of key randomised trials (Table 4.1-2)
- Sources of evidence for each target population (Table 4.1-3)

Has the sponsor identified all the relevant clinical trials and other clinical evidence?

Is any of the evidence in unpublished trials that are unlikely to be available?

Are there any significant gaps in the evidence for certain target population groups? If so, are there any sources of early phase or unpublished data that could be used instead?

4.2 Clinical evidence

Present the key clinical evidence from the sponsor's Request for Advice, including the following (and other information where relevant or in consultation with the ATAGI Discussant(s)):

- Present Table 4.2-1 that summarises the key efficacy and safety outcomes for the key trials
- Describe the patient-relevant efficacy outcomes will the sponsor report in the submission for the vaccine, and for the comparator? This is including primary effectiveness (disease incidence; disease mortality/morbidity), secondary effectiveness (for example, hospitalisations)
- Describe the surrogate/immunogenicity outcomes that will be reported
- Present summary outcomes from indirect comparisons where relevant
- Describe any potential risks of harm to patients in the long term

- Describe rates of vaccine failure for both the proposed and comparator vaccines
- Describe evidence supporting any herd immunity assumptions

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Are the efficacy data adequate to support the sponsor's clinical claim? Specifically:*
  - *Is evidence available for each target population group?*
  - *If direct evidence (intervention vs comparator) is unavailable, what are the limitations of the indirect comparison?*
  - *Dose the proposed dose schedule reflect the dose and dose intervals studied in trials?*
  - *Is the evidence adequate to demonstrate duration of protection and what conclusions can be drawn regarding waning of immunogenicity?*
  - *For trial data reporting disease incidence, are the outcomes reported by vaccine type disease? If not, how likely is it that outcomes are equally applicable to the vaccine type (or serotypes)?*
  - *Other comments as to the adequacy of clinical evidence for each of the target groups?*
- *Are the safety data adequate to support the sponsor's clinical claim? Specifically:*
  - *Is the safety profile of the vaccine about the same, better or worse the comparator? Or is it no worse than but different to, the comparator (if so describe the difference in adverse events).*
  - *Has the sponsor adequately considered adverse events characteristic of the comparator?*
  - *Are data available for long-term safety outcomes or low frequency severe adverse events?*
  - *Comment if safety data were inadequate to make an assessment of the clinical claim*
- *Is any observable difference in outcomes (either efficacy or safety) between target groups or high risk groups?*
- *What are the estimated rates of vaccine failure in each target population group?*
- *Is there evidence of effectiveness (c.f. efficacy) when used in population programs (Australia or other countries)? Is there evidence to support compliance to the vaccine course?*
- *What is the evidence of any critical indirect outcomes, if relevant:*
  - *To support herd immunity assumptions?*
  - *Replacement disease (for diseases characterised by more than one strain or serogroup)?*
- *For strain- or serogroup-specific vaccines, is there any benefit in terms of cross-reactivity to other strains?*
- *If this is a combination vaccine or it is proposed to be co-administered with other vaccines (at the same NIP time point): Are the proposed interaction studies for co-administered / components of combination vaccines adequate? What are the implications of missing or inadequate studies?*

4.3 Translation of evidence

Present the following from the sponsor's Request for Advice:

- The Tables described in 4.3 of the Advice Request Guideline comparing the Trial setting and the Australian treatment setting for each of the PICO elements (Tables 4.3-1 to 4.3-4).

Has the sponsor identified the key differences between the clinical evidence and the Australian setting? Have extrapolations or historical data been used – are these appropriate? What are the key differences and what are the implications for the economic model assumptions?

Is the trial population representative of the Australian target group in terms of baseline characteristics and disease risk?

Is incidence of the vaccine-preventable disease in the clinical trial population representative of its epidemiology in Australia?

5 Proposed economic model and assumptions

Present the following from the sponsor's Request for Advice:

- Present the structure of the proposed economic model given in Figure 5.1-1
- Present the associated inputs/variables in Table 5.2-1 of the Request for Advice.

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Does the model include all the relevant health states? For example, is any state missing that would represent a source of infection?*
- *Are the other model assumptions supported by the evidence? For example, consider the values assigned to variables such as rate of infection, rate of hospitalisation versus disease incidence; rate of permanent injury versus mild impairment / full recovery; case fatality or death rate; probability of vaccine failure, seroconversion rate; duration of immunity.*

6 Expected use and implementation

6.1 Estimated use

Present the estimates of use in Table 6.1-1 from the sponsor's Request for Advice.

With reference to the questions suggested below, consider different scenarios for uptake (for example, to inform sensitivity analyses) and the factors that are likely to drive these, including the evidence to support these.

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Do the utilisation estimates align with the epidemiological evidence and proposed dosing?*
- *What is the expected uptake given the program delivery context for each target group?*
- *Are the estimates for the catch-up cohort reasonable?*
- *Any other comments on drivers for immunisation coverage?*

6.2 Implementation

Refer to information presented in 6.2 of the Request for Advice, consider what should be presented here in light of the suggested questions below and in consultation with the ATAGI Discussant(s).

Suggested questions for ATAGI advice (delete as appropriate to this vaccine):

- *Would this vaccine be associated with any change to administration costs; additional training requirement for providers or storage/cold chain requirements?*
- *Are there any time-sensitive matters that will affect implementation?*
- *Will this vaccine require any additional measures for implementation to manage vaccine safety such as adverse event surveillance or prophylactic medicines to minimise events such as fever?*
- *Will the addition of this vaccine to the NIP require a change to any existing vaccine (or scheduled doses) or components thereof?*
- *Is there relevant international experience that should be considered for the implementation of this proposed vaccine?*
- *For childhood immunisation, does the proposed frequency fit with existing NIP schedule time points or will an additional GP visit or school program be required?*
- *If the proposed vaccine is a new combination that will replace separate vaccines currently on the NIP, are there any disparities in NIP schedule time points and how should these be resolved?*

7 Any other relevant information

Include any comments here if the sponsor has presented information in Section 7 of the Request. Otherwise this section can be deleted.

Appendix 1: Consolidated list of sponsor's questions with ATAGI answers

Present the table of sponsor's list of questions from the Guideline appendix. These should be answered in the appropriate part of the ATAGI advice; the list consolidates all the questions and identifies where these are addressed.