Target Product Profile and Technical Requirements for Conjugated Pneumococcal Vaccines
Target Product Profile for AMC support

- The specifications relate to the public health impact and suitability of the product, covering measures of vaccine efficacy, safety, dose scheduling, presentation and packaging, and represent the minimally acceptable standard a vaccine needs to meet in order to be eligible for AMC support.

- Developed by WHO at request of AMC secretariat

- [http://www.vaccineamc.org/files/TPP_Master_Table.pdf](http://www.vaccineamc.org/files/TPP_Master_Table.pdf)
Assessment of the TTP

- Independent Assessment Committee (IAC) reviews and decides upon compliance of a vaccine with the TPP.
- Vaccines for supply through AMC should be WHO prequalified (PQ).
- Many of the attributes of the TTP are also reviewed during prequalification.
- IAC has determined attributes that can be assessed based on PQ review and those needing further review by them.
- Following prequalification, WHO prepares a report on how each of the attributes of the TPP has been addressed during the review for PQ and presents this to the IAC.
- The IAC considers this and further reviews the attributes as required.
### TPP attributes – PQ review (1)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Minimally Acceptable Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. Immunogenicity</strong></td>
<td>Immunogenicity should be demonstrated in accordance with WHO criteria, which are based on non-inferiority to a licensed pneumococcal vaccine as outlined in WHO <em>Recommendations for the production and control of pneumococcal conjugate vaccines.</em> (WHO Technical Report Series, No 927, 2005 and any subsequent published guidance).</td>
</tr>
<tr>
<td><strong>D. Safety, reactogenicity and contra-indications</strong></td>
<td>The safety and reactogenicity profile should be comparable to, or better than that of the currently licensed pneumococcal conjugate vaccine. Contra-indications should be restricted to known hypersensitivity to any of the vaccine components.</td>
</tr>
<tr>
<td><strong>F. Interference and co-administration with other vaccines</strong></td>
<td>There should be no clinically significant interaction or interference in relation to safety and immunogenicity with concurrently administered vaccines.</td>
</tr>
<tr>
<td><strong>H. Product presentation</strong></td>
<td>The vaccine must be available in mono-dose or low multi-dose presentations. Mono-doses must be either a single dose vial or a auto-disable compact pre-filled device. Low multi-dose presentations must be formulated and labeled in compliance with WHO policy or guidance.</td>
</tr>
</tbody>
</table>
## TPP attributes – PQ review (2)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>K. Packaging and labelling</strong></td>
<td>Name and labelling must be in accordance with WHO Recommendations for the production and control of pneumococcal conjugate vaccines. (WHO Technical Report Series, No 927, 2005). Packaging must ensure minimal storage space requirements as set out in Guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23).</td>
</tr>
<tr>
<td><strong>L. Product registration and prequalification</strong></td>
<td>The product must be WHO pre-qualified in accordance with Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/IVB/05.19).</td>
</tr>
<tr>
<td><strong>M. Post marketing surveillance</strong></td>
<td>Post-marketing surveillance should be conducted in accordance with national regulatory authorities and WHO prequalification requirements as set out in Guideline for preparation of the product summary file for vaccine prequalification (WHO/IVB/06.16), Guidelines on clinical evaluation of vaccines: regulatory expectations (WHO Technical Report Series, No 924, 2004) and any relevant published guidance.</td>
</tr>
<tr>
<td>Attribute</td>
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</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>A. Vaccine serotypes</strong></td>
<td>The serotypes in the vaccine formulation must cover at least 60% of the invasive disease isolates in the target region, and must include serotypes 1, 5 and 14 which are the most frequent isolates in GAVI eligible countries.</td>
</tr>
<tr>
<td><strong>C. Target population/ target age groups</strong></td>
<td>The vaccine must be designed to prevent disease among children &lt;5 years of age and in particularly be effective in those &lt; 2 years of age.</td>
</tr>
<tr>
<td><strong>E. Dosage schedule</strong></td>
<td>Vaccine scheduling must be compatible with national infant immunization programmes and consist of not more than 3 doses in the first year of life. The first dose must be shown to be administrable at 6 weeks of life or earlier.</td>
</tr>
<tr>
<td><strong>G. Route of administration</strong></td>
<td>Intramuscular or subcutaneous.</td>
</tr>
<tr>
<td><strong>I. Product formulation</strong></td>
<td>Liquid formulation with a standard volume of 0.5 ml/dose.</td>
</tr>
</tbody>
</table>
WHO Technical Recommendations

- TRS 927 Annex 2 (2005) is referenced in the TPP

- Replacement has been endorsed by WHO Expert Committee on Biological Standardization (ECBS) Oct 2010

- [http://www.who.int/biologicals/areas/vaccines/pneumo/Pneumo_final_23APRIL_2010.pdf](http://www.who.int/biologicals/areas/vaccines/pneumo/Pneumo_final_23APRIL_2010.pdf)
Replacement WHO recommendations

- Refinements to section A: Manufacturing Recommendations

- New sections:
  - B: Non-clinical evaluation of new pneumococcal conjugate vaccines
  - C: Clinical evaluation of new pneumococcal conjugate vaccines

- Recommendations for National regulatory Agencies now in section D
Immunogenicity based clinical assessment

- PCV7 (Wyeth) was licensed on efficacy studies

- New PCVs clinical assessment based on immunogenicity studies

- Non-inferiority to currently licensed vaccine to be demonstrated

- Investigation of concomitant use

- Immune memory
What happens when PCV7 no longer available as a comparator?

- Use a comparator that has been directly compared to PCV7 during clinical development
- Consider the available effectiveness and safety data (post licensure) of the comparator
- Consider comparator with highest number of serotypes in common
Immunological assay

- WHO reference ELISA uses 0.35 μg/mL threshold.

- Use of alternative assay is acceptable if it can be demonstrated that the threshold used is comparable to the threshold in the WHO assay.

- Measureable immune response to each serotype in vaccine required

- Primary analysis:
  - The percentage of subjects with IgG ≥ threshold AND
  - The serotype-specific IgG GMC ratios

- Secondary analysis:
  - IgG concentrations
  - OPA data
Vaccination schedules

- Currently PQed vaccines have demonstrated effectiveness at 6, 10 and 14 week administration. This allows concomitant immunisation with other EPI vaccines.

- Other schedules have been used in different countries

- WHO has coordinated a study on optimising pneumococcal immunization schedules

- This will be reviewed by WHO Strategic Advisory Group of Experts (SAGE) in November 2011
PQ process revision


- Revised procedure endorsed by ECBS Oct 2010, with scheduled implementation in Jan 2012

- Revision submitted to committee can be found at http://www.who.int/biologicals/expert_committee/WHO_BS_10_2155.pdf

Submission of application letter

- Is vaccine a priority for PQ?
  - Yes: Acceptance of intention to submit
  - No: Reject Application

Product Summary File Submission

- Is PSF complete?
  - Yes: Mandatory PSPQ characteristics met?
  - No: Critical data missing?

- Is Vaccine has unique/innovative PSPQ characteristics?
  - Yes: Programmatic suitability?
  - No: Accept PSF for review

- Fee Request & Receipt

- Additional Data Request

- Is critical data missing?
  - Yes: Mandatory PSPQ characteristics met?
  - No: Critical data missing?

Accept PSF for review

- Fee Request & Receipt

PSF evaluation process

- Testing process
  - Three months
  - Site audit process
  - Three months

- NRA consultation

No hoc committee recommendation

- Review by ad hoc committee on PQ and PSF
  - Yes: Product satisfactory
  - No: Product unsatisfactory

- PSF review, testing and site audit all satisfactory?
  - Yes: Product satisfactory
  - No: Product unsatisfactory

Listing of PQ product on website

Process Termination

Site audit process

*Based on two rounds of PSF data evaluation

Maximum time: Three months

One month (or up to four months if PSPQ SC advice required)

This shape indicates a process delay point where action by the manufacturer is required. Time between request to the manufacturer for information and its supply are not part of the process time indicated.
Accepted PSF

Manufacturer accepts reviewers /pays fees

Data evaluation

Report

Additional Data Required?

Yes

Request/supply of Additional Data

Yes

review by ad hoc committee
(see main process chart)

No

refer to ad hoc vaccine PQ committee ?

Yes

Is data satisfactory?

No

Yes

Satisfactory Completion of PSF evaluation process

Process termination

This shape indicates a process delay point where action by the manufacturer is required. Time between request to the manufacturer for information and its supply are not part of the process time indicated.
Accepted PSF

Request samples/reference/reagents for testing with relevant documentation

Samples sent to contract laboratories

Report

Test data satisfactory?

Yes

Process terminated

No

Further testing required?

Yes

refer to ad hoc vaccine PQ committee?

No

No

review by ad hoc committee (see main process chart)

Satisfactory Completion of Testing Process

Three months

This shape indicates a process delay point where action by the manufacturer is required. Time between request to the manufacturer for information and its supply are not part of the process time indicated.
Satisfactory Completion of PSF review

Schedule site audit

Site audit

Draft Report (delivered at exit meeting)

Final Report

Critical deficiencies found?

Yes

Process terminated

No

Additional Data Required?

Yes

Request/supply of Additional Data

Review of additional data satisfactory?

Yes

Satisfactory completion of site audit process

No

Follow-up site visit required?

Yes

Two months

No

One month

This shape indicates a process delay point where action by the manufacturer is required. Time between request to the manufacturer for information and its supply are not part of the process time indicated.