Process for WHO to Develop Target Product Profiles (TPP) for the Advance Market Commitment (AMC) international initiative.

Specific application to a Pneumococcal Vaccine

WHO's constitution requests the Organization to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". Accordingly, it is one of WHO's core mandate to set norms for areas of public health, based on the most complete and reliable scientific evidence available (11th General Programme of Work, 2006-2015).

The Fifty-third World Health Assembly in its resolution WHA53.12 on the Global Alliance for Vaccines and Immunization (GAVI), further requested the Director General of WHO to promote and to monitor strictly the quality assurance of vaccines.

Following on these principles, the World Health Organization supports the AMC through the establishment of Target Product Profile (TPP) specifications using established WHO processes, including validation of the TPP by its Strategic Advisory Group of Experts (SAGE) on immunization. This will be accomplished notably by seeking advise from the best experts representing the required specialties and ensuring an appropriate regional balance.

The TPP will be described in terms of public health impact (level of effectiveness or efficacy, as appropriate, in the target population against a defined endpoint). Limits will be set on minimum duration of immunity and maximum number of doses to induce protection. The TPP will take into consideration available delivery systems in terms of immunization schedule (number of doses and timing of vaccination), route of administration, temperature sensitivity of the product, presentation, and absence of interference with other essential health interventions in the target population.

Key elements of the process:

The activity will be implemented by the WHO Department of Immunization, Vaccines and Biologicals.

Upon request of the Independent Assessment Committee (IAC), or if not yet constituted, by the Donor Committee (DC), WHO will initiate the process, which is expected to last no more than 6 months and will result in the submission to the IAC of a TPP endorsed by SAGE and approved by Director WHO.
The process includes the following steps:

1. selection of a panel of technical experts, representing the keys areas required to formulate the TPP, to participate in an *ad hoc* expert advisory committee;
2. review and endorsement of the proposed expert committee by SAGE, and the IAC (if constituted);
3. consultation with *ad hoc* expert committee on necessary background documents required to formulate a TPP;
4. preparation of key background papers to inform the setting process on major technical issues to be considered;
5. *ad hoc* technical expert open consultation, with participation of an IAC representative and other observers, resulting in the formulation of a draft consensus TPP;
6. stakeholder consultation of draft consensus TPP;
7. informal consultation at ECBS;
8. submission of the consensus TPP to SAGE for validation. It is proposed that a representative of the IAC participates in the SAGE deliberations;
9. SAGE endorsement of TPP (with or without modifications in the TPP(s) proposed by the ad hoc expert advisory group) and recommendation to the WHO Director-General;
10. approval of the TPP by the Director-General;
11. communication of the TPP to the IAC;
12. Approval of the TPP by the IAC

**Procedural Issues:**

*Ad hoc TPP setting consultation format:*

Consultations will take place through meetings of the TPP *ad hoc* expert committee. Decision-making will be by consensus. The chair will address disagreements through discussion between the parties. The opposing viewpoints will be discussed in the panel and resolution reached through consideration of knowledge and evidence.

*Selection of experts for the TPP ad hoc expert committee:*

Experts to serve on the committee will be identified through the secretariat, based on the required technical profile (annex 1), with due consideration geographical representation, and in accordance with established WHO procedure. After clearance for conflict of interest, the committee members will be approved by SAGE. The names of the experts will be published on the AMC website.

*Handling of conflicts of interest:*

Conflict of interest for TPP expert committee members will be handled as described in the Terms of Reference of SAGE (Annex 2). The selection of the experts involved in the process will attempt to nominate people as free of conflicts as possible. However, any potential conflict of interest will be handled by full disclosure of financial or other
relevant interests, and open consultations and meetings to ensure full transparency. Members with a conflict of interest on a particular issue will be asked to recluse themselves during all discussion on that issue.

Secretariat

The secretariat for the TPP setting process will be hosted in WHO at the Initiative for Vaccine Research (IVR). The secretariat will regularly inform the IAC and DC on the status of the TPP setting process.

TPP setting process for a Pneumococcal Vaccine

I. Steps of the TPP development process

1. Appoint a WHO focal point (P-staff) to coordinate the process, plus assign secretary (G-staff) to assist with administrative and logistics support and under the direct supervision of the coordinator, IVR/IMR (March 2007)

2. Form small TPP meeting planning group (January 2007) (4-6 persons, mix of in-house relevant WHO staff, and AMC secretariat) to
   - develop outline of meeting objectives and agenda
   - coordinate the formulation and convening of experts on ad hoc TPP expert panel
   - coordinate the commissioning and production of background papers by expert consultants (in consultation with ad hoc TPP expert panel)
   - liaise with AMC secretariat

3. Submit list of members for the ad hoc TPP expert panel to SAGE (March 2007) for approval. Given the high level of technical expertise required, potential members will be contacted directly by the secretariat, without a call for nominations. Appoint after review for conflict of interest.

4. Sub-contract the production of relevant working papers in consultation with ad hoc expert committee (March - April 2007)

5. Develop agenda for and convene consultation meeting. Invite observers to be present as liaisons (IFPMA, DCVMN, SAGE, UNICEF, WB, GAVI, BMGF, MSF, GFTAM, IPA etc) (April - Mai 2007)

6. Hold consultation (September 2007)

7. Solicit feedback from stakeholders on draft consensus TPP (industry, government, civil society)

8. Informal consultation at ECBS (October 2007)
9. Present proposed TPP to SAGE for their deliberation and approval (November 2007).

10. Adjust TPP according to SAGE recommendation and submit to WHO Director General (November 2007).

11. Submit TPP to IAC for approval (November 2007)

II. Key issues for which working papers will need to be developed for discussion of the TPP for a Pneumococcal vaccine (to be confirmed with ad hoc expert panel)

*Pneumococcal disease epidemiology*

Age specific disease incidence and mortality
Serotypes causing disease: by age, geographic region, temporal variation (including outbreak associated serotypes)

*Evaluative Question: Vaccine performance and Public Health impact indicators*

- Vaccine performance indicators
  - Specific efficacy end-points: invasive disease, pneumonia, nasopharyngeal carriage (marker for indirect effect)
  - Safety
  - Vaccination schedules and durability of protection

- Public health impact outcome measures - mortality, disability, hospital use, replacement disease

*Normative Criteria/Issues:*

Programmatic issues related to in-country health intervention delivery programs, i.e. National Immunization Programs, EPI.

- Formulation, presentation, cold chain requirements, integration into EPI delivery system, absence of interference with EPI vaccines.
ANNEX 1:

Desired profile of experts for the ad hoc expert advisory committee(*):

1. Disease burden, epidemiology, pneumococcal disease & clinical trials

Extensive experience in infectious diseases epidemiology, with focus on developing countries; sero-epidemiologic studies, experience in measuring acute respiratory infectious disease burden; lead investigator in large scale vaccine trials, including pneumococcal vaccines;

2. Immunology

Extensive experience in immunology of pediatric infectious diseases, specialized knowledge in immunity to encapsulated bacteria, and immune responses to conjugate vaccines, standardized measurement of immune responses.

3. Vaccine formulation and design

Knowledge of conjugation technologies for carbohydrates and proteins, conjugate vaccine characterization, quality control of vaccines, vaccine stability and presentation.

4. Manufacturing

Background in industrial scale vaccine production, in particular of conjugate vaccines, production scale up, technology transfer, presentation and packaging

5. Vaccine regulation

Regulatory experience with established authorities; evaluation of vaccine dossiers for marketing authorization, experience with WHO Expert Committee on Biologicals Standardization and other relevant WHO committees; knowledge of WHO prequalification.

6. Vaccine utilization and delivery

Developing country experience in relation to pediatric vaccine delivery, including logistic and operational issues, new vaccine introduction decision making, programmatic planning and impact monitoring.

7. Health economics and statistics/modeling

Health economical assessment of vaccine utilization in developing countries, experience with WHO endorsed methodologies and concepts in relation to costing and calculation. Understanding of clinical trial design and analysis, and statistical analysis of
complex datasets (specifically including meta-analysis), as well as mathematical modeling of vaccine impact and infectious diseases in developing country scenarios

8. Public health

Broad background in child health in developing countries, experienced in assessing longitudinal health and demographic data, sound understanding of developing country health systems and systems barriers to intervention delivery, experienced with intervention impact assessment.

(*) The total number of experts of the ad hoc group should not exceed 14 members. Three official observers will be invited from IAC, UNICEF and WHO-SAGE. Additional technical resource persons can be invited as observers as needed. WHO conflict of interest criteria will be applied.
ANNEX 2 (conflict of interest)

DECLARATION OF INTERESTS FOR WHO EXPERTS 17 Jan - 16 Feb 06

The assistance of distinguished authorities knowledgeable in a variety of medical and scientific professions is essential to the solution of international health issues. It is expected that persons qualified to serve as an expert for the World Health Organization (WHO) may have private interests related to the subject of their expertise. At the same time, it is imperative that situations be avoided in which such interests may unduly affect, or may be perceived to affect, an expert's impartiality or the outcome of work in which he/she was involved.

To assure the highest integrity, and hence public confidence, in the activities of the Organization, WHO regulations and policies require that all experts serving in an advisory role disclose any circumstances which could give rise to a potential conflict of interest (i.e., any interest which may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). Accordingly, in this Declaration of Interest form, you are requested to disclose any financial, professional or other interest relevant to the subject of the work or meeting in which you will be involved and any interest that could be significantly affected by the outcome of the meeting or work. You are also asked to declare relevant interests of others who may, or may be perceived to, unduly influence your judgment, such as immediate family members, employers, close professional associates or any others with whom you have a substantial common personal, financial or professional interest.

Kindly complete this form and submit it to WHO Secretariat, well in advance of the meeting or work. You are also asked to inform the Secretariat of any change in this information that occurs before or during the course of the meeting or work. If WHO considers that a potential conflict of interest exists, one of several outcomes can occur, depending on the circumstances involved: (i) you may be invited to continue to participate in the meeting or work, provided that your interest would be publicly disclosed; (ii) you may be asked not to take part in the portion of the meeting, discussion or work related to your interest, or not participate in related decisions; or (iii) you may be asked not to take part in the meeting or work altogether. Non-completion of the DOI form would preclude further consideration of an expert's participation.

Experts are requested to agree that any relevant conflicts may be publicly disclosed to other meeting participants and in the resulting report or other work product. The Secretariat will assume that you consent to such a disclosure, unless you check "no" in the space provided on the last page of this form. The information disclosed by you may later be made available to persons outside of WHO if the objectivity of the work or meeting in which you are involved is questioned and the Director-General considers disclosure to be in the best interests of the Organization, although only after discussion with you.

Date and title of meeting or work, including description of subject-matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached):

________________________________________________________________________

________________________________________________________________________

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.
The term "you" refers to yourself, your employer and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your minor children). "Commercial entity" includes -- aside from any commercial business -- an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources having an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

**EMPLOYMENT AND CONSULTING**

Within the past 3 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or negotiation for future work.

1a Employment

1b Consulting, including service as a technical or other advisor

**RESEARCH SUPPORT**

Within the past 3 years, have you or your department or research unit received support or funding from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or award for future research support.

2a Research support, including grants, collaborations, sponsorships, and other funding

2b Non-monetary support valued at more than US$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)

**INVESTMENT INTERESTS**

Do you have current investments (valued at more than US$10 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? You may exclude mutual funds, pension funds or similar investments that are broadly diversified.

3a Stocks, bonds, stock options, other securities (e.g., short sales)

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures)

**INTELLECTUAL PROPERTY**

Do you have any current intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (also include pending applications)

4b Proprietary know-how in a substance, technology or process

**PUBLIC STATEMENTS AND POSITIONS (during the past 3 years) (questions relate to balanced composition of committee or group)**

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?

5b Have you held an office or other position, paid or unpaid, where you may be expected to represent interests or defend a position related to the subject of the meeting or work?

5c Have you served as a principal investigator, a lead expert in an expert committee or...
scientific or advisory group, and/or a member of a steering committee, an advisory board or equivalent body in relation to the same product or subject matter?

**ADDITIONAL INFORMATION**

6a  *If not already disclosed above, have you worked for the competitor of a product which is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a financial or commercial competitive advantage?*

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<th>Yes</th>
<th>No</th>
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6b  *To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, financial or professional interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?*

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<th>Yes</th>
<th>No</th>
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6c  *Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?*

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<tr>
<th>Yes</th>
<th>No</th>
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7. **TOBACCO OR TOBACCO PRODUCTS** (answer without regard to relevancy to the subject of the meeting or work)

*Within the past 3 years, have you had employment or received research support or other funding from the tobacco industry or had any other professional relationship with an entity, directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?*

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<th>Yes</th>
<th>No</th>
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**EXPLANATION OF "YES" RESPONSES:** If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. **If you do not provide, the amount or value of the interest, where requested, it will be assumed to be significant.**

<table>
<thead>
<tr>
<th>Nos. 1 - 4: 7</th>
<th>Name of company, organization, or institution</th>
<th>Belongs to you, family member, employer, research unit or other?</th>
<th>Amount of income or value of interest (if not disclosed, is assumed to be significant)</th>
<th>Current interest (or year ceased)</th>
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<tr>
<td>Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.</td>
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</table>
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details

CONSENT TO DISCLOSURE. The Secretariat will assume that you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product, unless you check "no" in the space provided here. If you check "no", the Secretariat will not disclose the information without your prior approval, although this may result in your not being able to participate in the meeting or conference.  No:  □

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information due to the fact that I acquire additional interests, I will notify the responsible staff of WHO and complete a new declaration of interests detailing the changes. This includes any change which occurs before or during the meeting or work itself and through the period up to the publication of the final results.

Date: ______________________
Signature __________________________________
# ANNEX 3

Proposed Budget for TPP process (indicative)

<table>
<thead>
<tr>
<th>Items</th>
<th>Budget (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaries for WHO P-staff and G-staff for 8 months</td>
<td>200,000</td>
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<tr>
<td></td>
<td>100,000</td>
</tr>
<tr>
<td>Background Papers: 3-4 papers Support for expert teams; travel for primary research and analysis, support for administration, 50,000 US$ per key areas of analysis/ per paper</td>
<td>150,000</td>
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<tr>
<td>Meeting costs for ad-hoc consultation.</td>
<td>100,000</td>
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<tr>
<td>Follow-up technical and administrative support to complete process</td>
<td>25,000</td>
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<td></td>
<td>575,000</td>
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