WHO/IVB/05.19
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Immunization, Vaccines and Biologicals

World Health Organization

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Contents

Acronyms

The following acronyms are used in this document.

AEFI	adverse events following immunization
AHU	air-handling unit
AR	assessment reports
ATT	Access to Technologies (WHO)
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
EMEA	European Medicines Agency
EU	European Union
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GMP	good manufacturing practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IVB	Department of Immunization, Vaccines and Biologicals (WHO)
LSP	lot-summary protocols
MA	marketing authorization
NRA	national regulatory authority
NCL	national control laboratory
PAHO	Pan American Health Organization
PDA	Parenteral Drug Association
PSF	product summary file
PSURs	periodic safety updated reports
QA	quality assurance
QC	quality control
SOP	standard operating procedures
TSE	transmissible spongiform encephalopathy
UN	United Nations
UNICEF	United Nations Children's Fund
USP	United States Pharmacopoeia
VVM	vaccine vial monitor
WHO	World Health Organization

1. Introduction

The World Health Organization (WHO), through its Department of Immunization, Vaccines and Biologicals (IVB), provides advice to the United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies.

The process in place at WHO to assess the acceptability of candidate vaccines for purchase was published initially in the thirty-ninth report of the *WHO Expert Committee on Biological Standardization*, Annex 1 (Technical Report Series, No. 786, Geneva, WHO, 1989). It was further revised twice, in 1996 and 2002, and is replaced by the current document *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (**WHO/IVB/05.19**).

The system in place has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies. In recent years, it has been recognized that the system should be expanded to include other vaccines that countries already use or should use more. This includes vaccines in complex multivalent combinations and products used for outbreaks such as cholera and meningitis. It has also been recognized that countries use the list of prequalified vaccines for guidance on reliable sources of purchase.

The present document is a revision that takes into consideration the recommendations made by an advisory committee of experts convened by WHO in April 2004. The document describes the procedures in place to assess the acceptability, in principle, of vaccines produced from seed to final lot by a single manufacturer in a single site as well as the alternatives of joint ventures between manufacturers, the use of different sites within or outside a given country and also the case of vaccines licensed for the first time in country of origin or elsewhere.

The purpose of the assessment is to verify that the vaccines: (a) meet the specifications of the relevant UN agency; and (b) are produced and overseen in accordance with the principles and specifications recommended by WHO, for good manufacturing practice (GMP),[1] and for good clinical practice (GCP). This is to ensure that vaccines used in national immunization services in different countries are safe and effective for the target population at the recommended schedules and that they meet particular operational specifications for packaging and presentation.

[1] In those aspects where WHO GMP requirements are not detailed enough, other international guidelines shall be followed by the manufacturer – e.g. those of the European Union (EU), Parenteral Drug Association (PDA), and United States Pharmacopoeia (USP) – and appropriate justification for the choice provided. In such cases WHO will assess against the standard used.

The assessment (prequalification) procedure established by WHO for vaccines is based on the following principles:

- reliance on the national regulatory authority (NRA) of the country of manufacture because it meets the published WHO NRA indicators (***http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm***);
- general understanding of the product and presentations offered, production process, quality control (QC) methods and relevance for the target population of available clinical data;
- assurance of production consistency through application of GMP specifications;
- random check-testing of vaccines by independent WHO-contracted laboratories to monitor compliance with tender specifications on a continuing basis;
- monitoring complaints from the field and assisting in the investigation of adverse events following immunization (AEFI).

Since reliance upon effective regulatory oversight by the NRA of the country of manufacture plays a critical role in the system, manufacturers shall: (a) inform their NRA of their application to WHO for the vaccine prequalification by sending a copy to the NRA of the application letter sent to WHO; (b) request the NRA to participate/collaborate in the process; and (c) provide the NRA with the necessary authorization to discuss the relevant files with WHO representatives.

WHO can advise UNICEF and other UN agencies whether vaccines effectively meet WHO-recommended requirements only if the NRA of the producing country exercises independent and appropriate oversight of the vaccines in question and if the vaccines have been assessed through the procedure described in this document.

The fact that certain vaccines are not included in the list does not mean that, if evaluated, they could not be found to comply with the required standards.

As vaccines purchased by UN agencies need to meet WHO recommendations or guidelines (whichever is available), novel vaccines for which such guidelines are not available cannot be evaluated. In cases where a vaccine is made available for a disease of public health importance, the development of such guidelines will be prioritized by WHO and, as soon as a draft document becomes available, this can be used for evaluation for prequalification purposes.

WHO will define, in consultation with UN purchasing agencies and other relevant partners, which vaccines are priority for prequalification and will make this information publicly available. This exercise is required in order to focus the use of resources. The priorities will be redefined at regular intervals to ensure that efforts are put into evaluating those vaccines that are of highest public health importance and most needed in developing countries.

2. Conditions for acceptance of applications

The following are the conditions for acceptance of applications:

- The candidate vaccine falls under the category of priority products as defined by UN purchasing agencies and other partners – e.g. the Global Alliance for Vaccines and Immunization (GAVI).
- The NRA of the producing country is found to meet all the critical indicators defined for prequalification purposes following a WHO independent assessment (***http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm***).

Furthermore, during the prequalification process, the WHO team will establish an agreement with the NRA for appropriate lot release of all vaccines to be supplied through UN agencies, and sharing of information in case of serious GMP deviations, AEFIs, or withdrawals due to quality issues.

If the vaccine finishing (packaging; or filling/packaging; or formulation/filling/packaging) and distribution are performed in a country different from that of bulk manufacturing, the NRA of the country where the finished product is manufactured must comply with the above-mentioned requirements and commit to perform all post-marketing regulatory functions. For more details, see section 3 step 7, which describes special considerations for vaccines formulated, filled or packaged by different manufacturers in the same or different countries.

Note: An applicant should check with its respective NRA if it has been assessed by WHO. WHO will not be able to process any application until the WHO NRA assessment is conducted.

A marketing authorization (MA) has been granted by the relevant NRA and the post-marketing regulatory oversight is conducted by the NRA of the country of manufacture or that of the country of finishing and distribution. Alternatively, if it is intended that the European Medicines Agency (EMEA) *Scientific Opinion*[2] should serve as a surrogate of the MA, the *Guideline on Procedural Aspects regarding the Committee for Medicine Products for Human Use (CHMP) Scientific Opinion* should be followed in the context of cooperation with WHO for the evaluation of medicinal products intended exclusively for markets "outside the community".

[2] Licensing regulations in the European Union prevent the granting of marketing authorizations to those medicinal products which are not to be used in the European Union territory.

3. Steps of the procedure

For the evaluation of vaccines, WHO requires information related to the manufacturing company and to the product itself. The manufacturer will provide this information in the product summary file (PSF, see Annex 1) and during the site visit. If the manufacturer is not willing to deliver the required information, WHO and the manufacturer will conduct discussions with a view to trying to resolve the situation in a mutually acceptable manner. However, WHO reserves the right to terminate the assessment if, at any time, it is considered that insufficient information has been provided to enable effective completion of the assessment.

1. Official request, response and payment

An application letter is to be sent to the Coordinator, Access to Technologies, Department of Immunization, Vaccines and Biologicals (WHO/IVB/ATT) with a copy to the relevant NRA and UN purchasing agency, with details of country and sites of manufacture, presentations offered and licensing status.

Note: Application letters can be sent at any time and should provide the expected date of file submission. Manufacturers are encouraged to advise WHO as early as possible of their intention to submit a specific vaccine application to facilitate planning.

WHO will send a letter of acceptance or rejection of the application. The applicant, UN agency and NRA will be advised of the acceptance or rejection of the application within two weeks of receipt of the official request.

2. Pre-evaluation meeting

If considered necessary or desirable by either party, and before the actual evaluation process starts, a meeting can be held to discuss the details of the application, between the manufacturer, the responsible NRA (if agreeable to participation), and WHO.

3. Product summary file

A manufacturer for which the procedure is initiated will be requested to:

Prepare and submit two hard copies and an electronic version, preferably in Microsoft Word, of a product summary file, fully up to date and written entirely in English following the WHO format provided below: [3]

Chapter 1: General information
Chapter 2: Personnel
Chapter 3: Premises and equipment
Chapter 4: Vaccine composition
Chapter 5: Production
Chapter 6: Quality control
Chapter 7: Stability
Chapter 8: Clinical experience
Chapter 9: Production and distribution data
Chapter 10: Update of Regulatory Authority actions relevant to the product

The WHO format is required; however, the Common Technical Document (CTD) format can be accepted as long as a detailed cross-referencing of contents and those aspects required by WHO but not included in the CTD requirements are presented. The information to be provided in the file is specified in Annex 1 of this document.

WHO has established three deadlines a year for submission of product summary files: 31 January, 31 May and 30 September.

Upon receipt, the PSF will be screened for completeness and compliance with the required format and contents. The manufacturer will be informed within one month after the deadline if the PSF is accepted for further review or rejected.

1) In case of rejection, an improved PSF may be submitted to meet a subsequent scheduled submission deadline. In case of a second (definitive) rejection, the manufacturer will be informed by letter and required to pay the screening fee (US$ 500).

[3] If the electronic version cannot be provided, three hard copies will be needed.

2) In case of acceptance, the manufacturer will be informed by letter of the acceptance of the file for evaluation and of the names of the experts[4] proposed for the evaluation, together with a copy of their curricula vitae. Simultaneously, an invoice will be sent by WHO requesting payment of the screening and evaluation fees. Manufacturers will be expected to pay the fee and confirm acceptability of the proposed experts within two weeks. Payment of the fees without any further communication will be considered as a *de facto* agreement of the proposed experts; the evaluation will then be initiated.

During the review of the file, emphasis will be placed on assessing the suitability of the vaccine for the immunization services where it is intended to be used, taking into account composition, presentations offered, recommended schedules and clinical data available, labelling (including vaccine vial monitors – VVMs), information provided on package inserts (which shall not contradict WHO model inserts), and packaging and shipping procedures, which shall be in accordance with the latest revision of the WHO *International guidelines on packaging and shipping of vaccines* (WHO/IVB/01.05 or later version). The reviewers will provide WHO with their comments on the acceptability of the information provided and will prepare reports to this effect for WHO.

The time frame for an initial review of a vaccine PSF will be a maximum of three months. A consolidated report will be provided to manufacturers who are expected to submit responses to comments and any complementary information that may be requested as soon as possible. The manufacturer should inform WHO within a month of the estimated timeframe required to address and respond to all queries. The clock is stopped (there is no further action) until reception of the full complementary information.

The complementary information will be submitted in one package in two hard copies and one electronic copy[5] with adequate cross referencing to the original file. If partial responses are received at different times, the review will not start until all of the outstanding items have been covered by the manufacturer. The time frame for review of complementary information will be a maximum of three months.

[4] NRA staff, independent consultants or staff from consulting companies can be appointed as external experts depending on the specific needs. The manufacturer has the right to reject one or more team members if they believe that there may be a conflict of interest situation, in which case WHO will find a replacement. All experts appointed by WHO to participate in the evaluation of a vaccine are required to sign a confidentiality agreement (Annex 2) and to make a written declaration of no conflict of interest for that specific evaluation (Annex 3).

[5] Or three hard copies can be submitted.

4. Initial testing of vaccine samples

As soon as the PSF review is satisfactorily completed, WHO will request the manufacturer to submit to WHO an appropriate number of samples (25 at minimum and 200 at maximum) each of not less than three final lots, for consistency testing. These lots will have been produced after a date defined by WHO and formulated from consecutive bulk lots (in the case of combined vaccines, consecutive bulks will be specified by WHO for one of the components).

These samples shall be accompanied by the respective lot-summary protocols. In some cases, samples of bulk material, and samples of the manufacturers' reference vaccine may be requested. WHO will send the vaccine samples to its contracted laboratories for testing. Tests undertaken will be the most relevant to reflect the quality, safety and efficacy of the vaccine. Usually potency and toxicity are tested; however, depending on the nature of the vaccines, other relevant tests can be performed. The samples subject to testing must comply in all respects with the information and specifications stated in the PSF. They must have been produced under full-scale production conditions, and be a representative sample of the product intended to be marketed through UN agencies. The expected time frame for testing from the date of receipt of sample by WHO to the conclusion of testing by WHO, is three months.

To promote the independence and impartiality of the testing, the list of WHO's contracted laboratories will be kept confidential. Neither the manufacturer nor any other party who may have requested that vaccines be tested through this system will be informed where the testing is actually performed. On request, the manufacturer and the relevant NRA will, however, receive a report of the test results.

5. WHO site visits

The main objectives of the site visit are to assess that the vaccine complies with WHO recommendations for production and control, that it meets the UN tender specifications (which reflect the needs of the immunization programmes at country level), that the company has an adequate quality assurance (QA) system in place, and that the relevant vaccine/s is/are produced in compliance with WHO-recommended GMP. Other important aspects of the assessment include but are not limited to: labelling, packaging and post-marketing surveillance system in place, VVM implementation when required, stability programme, etc.

Site visits are required for all manufacturers applying for the prequalification of new products to be evaluated for purchase by UN agencies. They are necessary as part of the initial evaluation, as follow-up to corrective actions taken by the manufacturer following WHO recommendations and for reassessment purposes. They may also be deemed necessary as a result of complaints or reports of serious AEFI if a quality problem is suspected.

Site visits are an essential part of the assessment performed to ensure that vaccine candidates for purchase by UN agencies (or those that are already being purchased) actually meet (or continue to meet) WHO recommendations and tender specifications. To the extent possible, they build on information gathered through inspections performed by NRAs that meet the critical indicators established by WHO for vaccine prequalification purposes. In such cases, if detailed reports of inspections are made available for WHO review, WHO may decide, in agreement with the manufacturer, to organize a site visit. This would focus only on aspects relevant to the product/s under evaluation that have not been addressed by the NRA that performed the inspection, including all those aspects that are specific to the UN tender specifications.

For a new application, when the reviews of the PSF and testing have been satisfactorily completed, WHO will assemble a team to visit the manufacturing facility. The site visit will take place as soon as possible after satisfactory completion of testing, usually within a time frame of two months. Technical staff from UNICEF or the Pan American Health Organization (PAHO) may elect to join the team if the vaccine in question is under consideration for supply to these agencies. Otherwise, the team will be composed as far as possible of the same experts that have reviewed the file. Team members must have expertise in the areas of production, quality control, quality assurance and GMP. If additional members or replacement members are needed, the curricula vitae of the proposed new members will be submitted to the company for clearance. The team will cover the range of expertise required to assess the vaccine in question from the different perspectives. A WHO staff member will lead the team and the members will act, on a temporary basis, as expert advisers to WHO. In some circumstances, the leadership can be delegated to one of the external experts who will act on behalf of WHO.

The NRA of the manufacturing country is invited to assign one or two staff members to join the WHO team as observers.

A bilateral consultation meeting is held between WHO and the NRA, either at the beginning or the end of the mission. The purpose of this meeting is to discuss regulatory aspects related to the vaccine/s in question. Some examples of the topics discussed are testing and release of vaccine lots for UN agencies, findings of the most recent inspections, update on safety and efficacy data, any variations to the licence that may have been requested, licence renewals, recalls or withdrawal of lots, etc.

WHO site visits to manufacturing facilities or results of consultations held with the NRA may trigger a follow-up assessment of the NRA for one or more functions. In such cases, these follow-up assessments should be performed within a maximum time frame of six months. The outcome of these follow-up assessments may have an impact on the final decision on the prequalification of the vaccines in question.

As part of the assessment, WHO will negotiate an agreement with the relevant NRA for exchange of information regarding results of national inspections, variations to the licence or cancellations, rejection of lots, recalls and withdrawals, interruptions in production, information on AEFI reported or other matters that could affect the normal supply of vaccine to UN agencies.

The findings and recommendations of the team will be discussed with the company on a daily basis during the site visit. On a case-by-case basis, the team may prepare a work plan, together with the manufacturer, to address critical recommendations and establish deadlines for receiving responses. The executive summary, which includes main findings, recommendations and closing remarks is prepared by the WHO team and left with the manufacturer. The findings and recommendations will be also reported to the company and NRA representatives during the closing meeting, which provides a forum for discussion, questions and clarification of potential misunderstandings. The final decision regarding the acceptability of the product for supply to UN agencies is taken by an ad hoc Expert Committee appointed by WHO for this purpose, on the basis of the final detailed report and advice provided by the team.

The final detailed report providing findings, recommendations and conclusions is prepared by the team, reviewed by the Committee and sent to the company within 30 days of the visit with a copy to the NRA. If minor adjustments need to be made by the manufacturer, WHO will postpone its final recommendations to UNICEF or the other UN agency involved until such adjustments are implemented and verified by WHO.

If the company does not comply with the agreed deadlines, the prequalification process can be terminated.

6. Report and outcome of the assessment

Once WHO considers that the process is complete, and if the outcome is satisfactory, WHO sends a letter to UNICEF and other UN agencies, advising on (a) compliance of the vaccine with both the WHO requirements and the specifications of the relevant UN agency, and (b) the role of the NRA in certifying this. This letter will be copied to the manufacturer, the NRA, the National Control Laboratory (NCL) responsible for lot release and the relevant WHO Regional and Country Offices. The vaccine will then be included in the WHO list of prequalified vaccines at the beginning of the following month. The current list may be consulted at: ***http://www.who.int/vaccines-access/prequalvaccinesproducers.htm.***

The prequalified status of a vaccine is normally valid for a period of two years; however, under certain circumstances, this status can be extended up to five years (see item 12).

For details on notification of changes or introduced variations, consult item 11 (Supply).

7. Special considerations for vaccines formulated and filled by different manufacturers in the same or different countries

There are four basic types of contractual arrangements that describe the relationships between active substance (bulk) manufacturers and finished product manufacturers that influence suitability of a vaccine for prequalification by WHO:

a) *Commodity transaction:* sale and purchase of bulk vaccine on the open market.

Bulk manufacturers and finished product manufacturers working under this type of arrangement would not be eligible to undergo the prequalification process for the products in question.

b) *Contract manufacturing:* a contract manufacturer is a facility that is subcontracted by a vaccine manufacturer to do one or more steps of the process. The vaccine manufacturer is responsible for the product and shall ensure that all steps of the manufacturing process are performed in accordance with the licence specifications and in compliance with GMP.

A candidate vaccine, produced under the conditions of point (b) is suitable for being assessed in accordance with the regular procedure as described in this document. The PSF shall include the complete manufacturing information, and depending on the contract, WHO site visits to contract manufacturing facilities may be required.

c) *Partnership/joint venture:* an arrangement between the bulk manufacturer and the finished product manufacturer, which provides a stable ongoing supply of bulk to the finished product manufacturer. This will usually, but not necessarily, include various services and mutual monitoring mechanisms as well as the bulk vaccine.

d) *Technology transfer:* setting up by a vaccine manufacturer a finishing facility, including construction, training of staff, initial activities in assurance of quality and gradual handover to the finished product manufacturer.

Contractual arrangements of type c) and d) above would enable the finished product manufacturer to undergo the prequalification process, in which case the following criteria would be followed:

- The assessment evaluation will be product specific, just as it is for vaccines produced by one company from the starting materials.
- The bulk material must be already prequalified by WHO for the UN market under the procedure described above (items 1 to 5).
- There must be a long-term (usually not less than two years) contract between the bulk manufacturer and the company where the product is finished. The terms of the contract, regardless of the vaccine, shall include the criteria described in the document *Guidelines for bulk procurement of oral polio vaccine*, Task Force on Situation Analysis, 29–30 November 1993 (CVI/TFSA/94.4) and shall define the liabilities. This contract must be submitted to WHO for review as part of the assessment procedure.

- The finished product manufacturer shall have authorization from the vaccine manufacturer producing the bulk to export the final product. A proper assessment of this authorization shall be undertaken by the UN purchasing agencies before commitment to purchase. In the case where purchased bulk antigen A is used for combination with antigens B and C from other sources, proper authorization by the bulk producer of antigen A for combination (and possible limitations for distribution of the combined vaccines) is required. Such a "mixed" combined vaccine will also require a clear demonstration of the efficacy and safety of the intended combined vaccine.
- Each product for which the antigen(s) come(s) from a different manufacturer of bulk is considered as a unique product and will be prequalified separately.
- If imported bulk antigens are formulated differently from the same vaccine produced by the originating vaccine manufacturer and licensed in the country of origin (e.g. different stabilizers, different adjuvants, different preservatives and different excipients), these vaccines will be considered unique products and may require preclinical and clinical evaluation.
- The vaccine production process should be overseen by an independent and functional regulatory authority assessed against published WHO indicators, the options being:
    i) The NRA of the country where the bulk is produced (in the case of the bulk), and the NRA of the country where the finished product is manufactured (in the case of the final product). In this option, both authorities must demonstrate to WHO the required technical expertise and the fields of responsibility of each manufacturer, and each NRA must be precisely defined (e.g. in the case of the NRAs, which authority takes responsibility for each of the regulatory functions).
    ii) The NRA of the country where the final product is manufactured oversees the process from seed to finished product (performs all the WHO-recommended regulatory functions). In this case, this authority must demonstrate to WHO the appropriate expertise for this purpose.
- The product summary file shall be submitted to WHO by the finished product manufacturer, providing details of all the information required in a regular PSF (Annex 1) in relation to the company, general information on bulk material (confidential information is not required), cross reference to the prequalified bulk vaccine PSF, finished product specifications, and detailed information related to all steps to be performed by the finished product manufacturer.
- A sample of not fewer than three consecutive lots shall be submitted to WHO for independent testing of consistency of final product characteristics (actual number to be decided on a case-by-case basis). Lot-summary protocols (LSP) as well as lot-release certificates granted by the NRA for these lots shall be submitted together with the samples.
- A technical audit (site visit) of the finished product manufacturer's facilities shall be carried out by WHO, and the NRA that takes responsibility for overseeing of the product will be invited to join the team as observers.

- If both the bulk manufacturer and the finished product manufacturer are seeking prequalification at the same time, technical audits (site visits) will take place for both the bulk manufacturer and the finished product manufacturer. In both cases the relevant NRA/NRAs will be involved.
- The finished product manufacturer is required to state on the vaccine box labels the source of the bulk material.
- The prequalification status for vaccine finished product manufacturers will last for two years as long as the contract between the bulk manufacturer and the company where the product is finished remains active.

8. Special considerations for fast-track procedure

The implementation of a fast-track procedure may be required under special circumstances. This procedure is applicable to vaccines that are part of the routine immunization programmes or those that are used only as an emergency response, but not applicable in the case of novel vaccines not yet introduced or partially introduced into the routine immunization programmes.

In agreement with UN purchasing agencies or other partners, the fast-track procedure can be considered in the following situations:

- An acute shortage[6] of a vaccine that puts at risk the global supply of routine immunization programmes.
- An emergency situation or outbreak of a disease for which there is no prequalified vaccine, or its availability is not sufficient and an additional source of the same vaccine is required.

In those cases where the fast-track procedure is followed, the established deadlines for submission of PSFs do not apply.

The procedure will permit a review of the product summary file in parallel with the licensing process by the relevant regulatory authority and the testing of samples, thus minimizing timelines for completion of the review and testing. The site visit could take place while the results of tests are pending. If clinical trials are ongoing, the technical part of the dossier can be reviewed while awaiting the receipt of the clinical information.

There should be maximum flexibility in this process. For example, consideration could be given to information provided by the relevant regulatory authority with the manufacturer's permission (including inspection reports), and to results of tests performed by the relevant regulatory authority/control laboratory.

Depending on the circumstances and workload, a different fee may need to be charged for this procedure (see item 16).

[6] As agreed with UN purchasing agencies and other partners.

9. Special considerations for accepting submissions before the licence is granted

Under special circumstances, the prequalification evaluation can be initiated before the national licence is granted. This provision can be applied, in agreement with the UN purchasing agencies and other partners, under the following circumstances:

- The vaccine is a priority vaccine for introduction into the routine immunization programme; and
- Availability of the vaccine in question is a substantial limiting factor for the timely introduction of the vaccine into routine immunization programmes.
- This provision does not apply to novel vaccines not yet introduced in the immunization programme.

In such cases, the manufacturer may submit the PSF while the licensing process at national level is still in progress. The review of the PSF by WHO experts will be performed in parallel with the regulatory review by the NRA. If clinical trials are taking place, the technical part of the dossier can be reviewed pending the receipt of the clinical information. However, the testing of samples and the site visit will take place only once the MA of the product has been granted. The final WHO opinion on the acceptability of the product for UN purchase will be given once the product has been granted the MA, the clinical data have been reviewed, and the site visit and testing have been completed and found satisfactory.

10. Special considerations for accepting submissions of vaccines that have been licensed in countries different from that of manufacture

In some cases, vaccines that are manufactured in one country (country A) can be finished (packaged, or filled, labelled and packaged, or formulated, filled, labelled and packaged) in a different country (country B) by the same or different manufacturer. The vaccine would then be distributed only from the country where the finished product is manufactured (country B). In such cases, the vaccine must have been licensed in country B, the regulatory authority of country B must have been assessed by WHO and found to meet all the critical indicators as defined by WHO for prequalification purposes and must have agreed to exercise the ongoing regulatory overseeing of the product for export through UN agencies. In those cases where the finishing and distribution is done by a different manufacturer – see item 7 c) and d) – provisions stated under item 7 apply as well.

For a manufacturer with subsidiaries in different parts of the world that do different manufacturing steps, if the bulk is not licensed in the country of manufacture, the NRA of the country where the finished product is manufactured would need to exercise the full regulatory process of technical review, clinical review and regulatory inspections of the facilities in the originating country in order to grant the MA. This is different from a finished product manufacturer that buys prequalified bulks of a vaccine that has a marketing authorization in country of origin and requests prequalification of final product.

11. Supply

All lots of prequalified vaccine shipped in response to orders placed by a UN agency must have been released in advance of shipping by the NRA. A copy of the lot-release certificates will be kept by the manufacturer and sent, on request, to the UNICEF Supply Division or to the Coordinator, Access to Technologies, Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva (WHO/IVB/ATT). In addition, a suitable number of samples (defined during the assessment process) of each vaccine lot supplied to the UN agencies will be retained by the manufacturer, to be made available to WHO/IVB/ATT for testing on request.

The manufacturer shall inform WHO/IVB/ATT immediately after approval (within a month)[7] of any changes/variations that must be notified or submitted to the NRA in the formulation, presentation, methods of manufacturing or quality control and specifications, facilities, or for any other aspects which might (a) result in a change of safety and/or efficacy of the vaccine, or (b) change the basis of the regulatory approval by the NRA. All other changes can be reported to WHO on an annual basis. The rationale for the changes must be provided. The data that support the changes must be introduced in the PSF update submitted by the company at the time of the next reassessment. Such modifications may necessitate a further assessment or interim site visit by WHO to assure continued compliance with WHO recommendations.

If the labelling specifications are changed or model inserts are updated as part of a new tender period, manufacturers shall comply with the revised tender specifications for the new tender period. The updated versions of labels and model inserts must be reviewed by WHO before implementation.

If the manufacturing country regulations do not require approval by the NRA of changes that fall under categories (a) and (b) stated above, WHO shall be informed of the proposed changes before these are implemented on products supplied to UN agencies.

[7] Notification to WHO by letter/explanatory note attaching copy of the approval by the NRA.

12. Reassessments

a) Reassessments will be done in the following situations:

i) At regular intervals, usually every two years, with the possibility of an extension of up to five years for vaccines that have been prequalified for more than two years, and have been reassessed at least once after initial evaluation, if:

- there have been no significant changes or additions to the approved processes and procedures listed in the national authorization of the manufacturing and testing facilities;
- there have been no significant changes in the product indications, patient groups, or consumer warnings as compared to those mentioned in the marketing authorization;
- there have been no recalls of the product(s) and there have been no withdrawals or cancellations of registration licences related to quality issues since the previous reassessment evaluation;
- significant changes to the product or its manufacturing processes or facilities (which can potentially have effects on the product's quality, safety or efficacy) have been notified to WHO immediately after approval by the relevant NRA (with explanatory information to justify the change), and WHO has not found that these changes require a reassessment in a shorter time frame;
- no confirmed incidents related to non-compliance with quality specifications of tenders have been received by WHO with regard to the product(s) since the previous reassessment evaluation;
- no significant complaints from the field or reports of AEFI attributable to quality of the product(s) have been received and confirmed by WHO;
- post-marketing surveillance or studies conducted by or otherwise obtained by the manufacturer or the NRA in regard to the product(s) have shown no significant increase in any expected or unexpected adverse events in an established or any other patient group;
- communication between the relevant NRA and WHO is good (as defined per agreement made at the time of initial evaluation, see item 5) and WHO is routinely informed in cases of problems identified by such NRA.

ii) If the vaccine fails to meet the WHO recommendations and/or the specifications of the offer to bid.

iii) When no supply to the UN has taken place for a period equal to, or greater than, two years.

iv) In the case of a suspension of production, after production is re-established and before purchase by the UN agencies.

v) When, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made. See also item 11 (Supply).

b) Routine reassessments performed as defined above, require:

i) Submission of information on the items that have been changed with appropriate referencing to the existing file (in case of two-year reassessment); and submission of an updated PSF (Annex 1), (in case of a five-year reassessment).

ii) Testing of new samples, usually from three lots chosen by WHO.

iii) Consultation with the NRA on outstanding issues with the vaccine(s) supplied to UN agencies.

iv) A site visit to the manufacturing facilities, ideally with participation of representatives of the local NRA. The purpose of the visit will be primarily to verify that the vaccine continues to meet the WHO recommendations and the specifications of the relevant UN agency, and that it complies with current GMP standards. Furthermore, these site visits provide an opportunity for the manufacturer and the team members to discuss any changes which may be foreseen in production and/or quality control methods, as well as any new specifications and/or issues regarding introduction of new policies or strategies proposed by WHO.

v) WHO may consider streamlining a site visit for re-assessment under special circumstances. In such cases, if detailed reports of inspections performed by regulatory authorities meeting all critical indicators are made available for WHO review, WHO may decide in agreement with the manufacturer to organize a site visit that focuses only on those aspects relevant to the product/s under reassessment that have not been addressed by the NRA that performed the inspection, including all those aspects that are specific to the UN tender specifications.

13. Monitoring continued compliance with specifications through random testing of samples

Samples of lots supplied through UN agencies will be selected, at regular intervals (at least once a year), for independent testing of final product characteristics. An appropriate number of lot samples (between 50 and 100 depending on the vaccine) selected by WHO from a list of products supplied to UN agencies will be requested from the manufacturer. These will be sent by WHO to their contracted laboratories for testing. Upon request by WHO, the manufacturer or NRA, as appropriate, will provide lot summary protocols and information on lot release for review. The vaccine manufacturer and the relevant NRA may request the report of the test results. Manufacturers will, in any case, be contacted for follow-up actions in case of failure to meet specifications.

In the event of failure to meet the established criteria for reassessment or testing, WHO will investigate the problem and provide the UN agency with written information, copied to the manufacturer and the NRA, on the actions that need to be taken.

14. Monitoring complaints or AEFI from the field

Complaints from the field concerning vaccines supplied by UNICEF will be communicated via the field officers to the UNICEF Supply Division in Copenhagen. The Supply Division will then request the intervention of WHO to investigate the complaint and ensure that, if necessary, a further in-depth investigation is performed. Complaints communicated by any other route to the manufacturer or NRA shall also be relayed immediately to WHO, through the UNICEF Supply Division in Copenhagen to allow the investigation procedure to begin.

In the case of vaccines purchased through other UN agencies, the information shall be communicated through the relevant purchasing agency to WHO, so that the investigation process can be started. After investigation, WHO will provide UNICEF or the other UN agency involved with a written report of the problem and include recommendations for action, if any. WHO will then be available as a technical resource while UNICEF or the other UN agency implements the recommendations.

WHO will make a copy of its investigation report available to: the manufacturer; the NRA; the regional offices of the country involved in the complaint/AEFI and of the country of manufacture; and to other NRAs, if relevant.

15. Recommendations for action in cases of failure

In the event of situations as described in points 13 and 14 above and depending on the nature of the failure to meet the established criteria, WHO may include a recommendation that manufacturer's lots of vaccines be more closely monitored during a probationary period, or that purchase of the vaccine by UN agencies be suspended pending investigation and resolution of the problem, or if a formal reassessment is required, until this has been completed. WHO will inform the relevant NRAs about problems in the field or failure to meet established criteria.

16. Costs

The cost of the activities required to assess the acceptability, in principle, of candidate vaccines for UN agency purchase is covered by the manufacturers. It will be split into a screening fee and an evaluation fee. Both will be paid after the screening of the product summary file has been completed. If the screening process is not satisfactory, the manufacturer will be charged only the screening fee of US$ 500. The current cost of the initial evaluation of a candidate vaccine is US$ 25 000 for traditional vaccines and US$ 66 500 for combinations and novel vaccines (see table below). The expenses related to the site visit will be charged on a cost recovery basis. The evaluation of a vaccine will commence only after payment of the above fee and receipt by WHO of the product summary file.

The cost of activities required to keep the WHO list updated (reassessments) is charged to the manufacturers on the basis of an annual fee of US$ 8 000 for traditional vaccines and of US$ 14 000 for combinations and novel vaccines. The expenses related to the site visits are charged on a cost recovery basis. The table below shows the list of traditional and novel vaccines. The reassessment fees are charged to the manufacturers at the beginning of every calendar year. The reassessment process will not be initiated until the corresponding fee is paid to WHO. Failure to pay could ultimately lead to withdrawal of the vaccines from the list.

In all cases where follow-up site visits and other additional activities and resources are required for special reasons (e.g. failure to meet the criteria), these will be charged separately on a cost recovery basis.

These fees came into effect on 1 January 2005 and will be revised after two years.

Table: List of vaccines

Traditional vaccines	Combinations and novel vaccines
• BCG vaccine • Diphtheria–tetanus toxoids (DT/dT) • Diphtheria–tetanus–wholecell pertussis (DTwP) vaccine • *Haemophilus influenzae* type b (Hib) vaccine • Hepatitis B vaccine (HepB) • Inactivated polio vaccine (IPV) • Measles vaccine • Measles–rubella(MR) vaccine • Meningococcal A+C polysaccharide vaccine • Meningococcal A+C +W polysaccharide vaccine • Mumps vaccine • Measles–mumps–rubella (MMR) vaccine • Oral polio vaccine (OPV) • Wholecell pertussis vaccine • Rubella vaccine • Rabies vaccine • Tetanus toxoid (TT) vaccine • Yellow fever vaccine	• Oral cholera vaccines • DTwP–HepB vaccine • DTwP–Hib vaccine • DTwP–IPV • DTwP–HepB–Hib vaccine • DTwP–IPV–HepB vaccine • DTwP–IPV–HepB–Hib vaccine • Other combinations • Other possible candidate vaccines in the future, for example: – Diphtheria–tetanus–acellular pertussis (DtaP) vaccine and – DtaP-based combinations – Meningococcal conjugate vaccines – Measles aerosol vaccine – Rotavirus vaccine – Japanese encephalitis vaccine – Pneumococcal conjugate vaccine – Malaria vaccine – Dengue vaccine – Human papillomavirus (HPV) vaccine – HIV vaccine – TB vaccine – Others

17. Confidentiality

Information to which WHO requires access for the purpose of assessing or reassessing the acceptability in principle of a vaccine for purchase by UN agencies may include confidential information. However, if, in the opinion of the manufacturer, any information to be submitted to WHO and its expert team members in the course of the (re)assessment procedure includes confidential information; the manufacturer must advise WHO thereof in writing, prior to or at the same time as the disclosure, duly identifying the confidential information in question. Notwithstanding the foregoing, WHO and its expert team members will treat all information submitted to them either as written documents or during site visits as confidential, in accordance with the terms set forth below.

WHO will treat information so identified contained in the product summary file (Annex 1) and information disclosed during site visits as confidential and proprietary to the manufacturer and, in this connection, take all reasonable measures to ensure (a) that such information ("the Confidential Information") is not used for any other purpose than the (re)assessment procedure described in this document, and (b) that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO and/or its expert team members will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

a) was known to them prior to any disclosure by the manufacturer; or

b) was in the public domain at the time of disclosure by the manufacturer; or

c) has become part of the public domain through no fault of WHO and/or any of its expert team members; or

d) has become available to WHO and/or any of its expert team members from a third party not in breach of any legal obligations of confidentiality to the manufacturer.

18. No conflict of interest

The team of experts selected for a specific evaluation process includes experts in the field of production, quality control, clinical evaluation and GMP. These experts are selected by WHO and act as WHO temporary advisers or consultants. Prior to formalizing arrangements with such experts, WHO will require them to complete the WHO declaration of interests form. In addition, the agreement between WHO and such experts will include similar obligations of confidentiality and non-use as contained in point 17 above, as well as a conflict of interest undertaking. Through this conflict of interest undertaking, the aforesaid experts agree to discharge their functions exclusively as advisers to WHO. They also confirm that they have no financial interest and/or other relationship with a party, which:

a) may have a vested commercial interest in obtaining access to any confidential information disclosed by the manufacturer in the course of the (re)assessment procedure described in this document; and/or

b) may have a vested interest in the outcome of the (re)assessment procedure, including, but not limited to, parties such as the manufacturer of the vaccine(s) that is (are) being assessed or manufacturers of competing vaccines.

WHO will advise the manufacturer in advance of the composition of the evaluation team, and provide curricula vitae of the temporary expert advisers included in the team. The manufacturer will then have the opportunity to express possible concerns regarding any of the expert team members to WHO. If such concerns cannot be resolved in consultation with WHO, the manufacturer may reject an expert team member, within, at the latest, 15 days of receipt of the proposed team composition.

Annex 1:
The product summary file

The product summary file (PSF) is a brief (1–2 volume) summary dossier containing current information on the product to be supplied to UN agencies. It presents information on the product composition, manufacturing procedure, testing, stability, labelling, clinical experience and available post-marketing safety information.

For initial product assessments, a product summary file shall be submitted for each vaccine to be assessed. For combination vaccines, information shall be submitted on each of the component vaccines and on the combination itself. If a combination vaccine is being evaluated and the monovalent versions of the antigens contained in the combination are also being evaluated, the information provided for the monovalent vaccines (up to concentrated bulk) can be used for the assessment of the combinations, or conversely, the information on each antigen provided in the PSF of the combination vaccine can be used to assess the monovalent vaccines (up to concentrated bulk level).

The product summary file is expected to contain the following elements:

Chapter 1: General information

1.1 Provide brief information on the company (including name and address of the site, including telephone, fax and 24-hour telephone numbers, and the principal contacts of the company), and relation to other sites where steps of the process or testing activities may be conducted.

1.2 List pharmaceutical and non-pharmaceutical manufacturing activities carried out at the site as licensed by the national regulatory authority. This information shall also be provided for contracted manufacturers.

1.3 Provide a short description of the site (size, location and immediate environment). List of buildings on the site(s), or a site plan, identifying the manufacturing, control, and storage activities in each building.

1.4 State the number of employees engaged in the production, quality control, storage and distribution.

1.5 List outside scientific, analytical or other technical assistance in relation to manufacture and analysis, including equipment and/or other facility maintenance and validation. In case of contract manufacturing and contract testing of part of the process, provide information on the way in which GMP compliance of the contract acceptor is assessed.

1.6 Give a short description of the quality management system of the firm responsible for manufacture.

1.7 Give a short description of the internal audit system and programme for auditing suppliers of raw materials.

Chapter 2: Personnel

2.1 Provide an organizational chart showing the relationships between different areas, including quality assurance, production and quality control, with identification by name of key personnel (Head of Production, QA, QC, Warehousing, Engineering).

2.2 Give qualifications, experience and responsibilities of key personnel.

2.3 Outline arrangements for basic and in-service training and how records are maintained.

2.4 Describe requirements for personnel engaged in production, particularly relating to requirements for immune status for production personnel, and outside contract service personnel entering the manufacturing areas.

Chapter 3: Premises and equipment

These will be examined in depth during the site visit. However, the following preliminary information shall be submitted:

3.1 Provide simple, currently valid, floor plans and text description of manufacturing and QC areas. The floor plans should give an indication of scale, air flow and flows of materials, product, personnel and waste (architectural or engineering drawing are not required), room classification, air handling unit (AHU) identification by room.

3.2 Describe the nature of construction and finishes, of manufacturing and QC areas.

3.3 Describe ventilation systems in the manufacturing and QC areas. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the clean rooms used for the manufacture of sterile products should be included. Description of the environmental monitoring programme is required.

3.4 Provide information on special areas for the handling of highly toxic, hazardous and sensitizing materials.

3.5 Describe water systems (schematic drawings of the systems are desirable showing storage tanks, loops, points of use, and sampling points) including sanitation procedures and schedules. Description of QC testing and schedules is required.

3.6 Describe the maintenance system (description of planned preventive maintenance programmes and recording system).

3.7 List and briefly describe major production and control laboratory equipment.

3.8 For products where a separate facility is required (e.g. tetanus, BCG), describe how separation is achieved.

3.9 Describe qualification and validation procedures, including computerized recording and controller systems. Description of the validation master plan is required.

3.10 Provide a brief description of the procedures for cleaning manufacturing areas and equipment, and for multipurpose areas, the system for cleaning and testing between campaigns.

Chapter 4: Vaccine composition, presentations and schedules

4.1 State the composition of the product.

4.2 Describe the presentations made available to UN agencies, including diluents (if applicable), combination products, forms, dose sizes, type of containers, VVM type used and descriptions of application devices (e.g. syringes) to be delivered with the vaccine, if applicable.

4.3 Give the recommended schedule and route of administration.

4.4 Provide: samples of labels, boxes and package inserts to be used for UN agency supply (in English); samples of vials or ampoules of diluents and its corresponding labelling. French, Spanish, Russian and Portuguese versions need to be made available before supply to UN agencies starts.

4.5 Include a sample of the lot-summary protocol to be provided to UN agencies (to follow the WHO-recommended format).

Chapter 5: Production[1]

5.1 Provide the manufacturing formulae:

a) for the production of each antigen in the vaccine (i.e. fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run);
b) the batching formula for each batch size of final formulated bulk product;
c) the approximate number of vials and doses for each fill size and presentation;
d) the lot numbering system for intermediates and final products.

A copy of the complete master formula (blank batch record) for one batch size would be desirable.

5.2 Provide a description of the manufacturing processes (from master cell bank and virus seeds as applicable) and the characterization of the product together with a detailed flow chart showing:

a) each manufacturing step;
b) location (building/room) of each step, and transfers to other building/sites, if applicable;
c) in-process and quality control tests performed on all intermediates and final products;
d) identification of any processes or tests performed by contract manufacturers or testers;
e) storage times and temperatures of intermediates.

For recombinant vaccines, a description of the construction and characterization of the recombinant vector as well as source of master cell bank/constructs shall be provided. Include details of the manufacture and QC of any adjuvant and diluents.

[1] WHO recommended requirements or guidelines and UN agency tender specifications must be met. For each specific test done, the international standard met should be identified.

5.3 Describe general policy for process validation. List process validation activities performed.

5.4 Summarize arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.

5.5 Summarize arrangements for the handling of rejected materials and products, and procedures for their destruction.

Chapter 6: Quality control

6.1 Starting materials

6.1.1 List control tests performed on raw materials, with appropriate characterization of starting materials:

a) list of raw materials meeting compendia specifications, indicating the pharmacopoeia;

b) list of raw materials meeting in-house specifications including the tests performed and specifications;

c) list of biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product;

d) list of media with ingredients, tests performed and specifications.

6.1.2 List control tests performed on labelling and packaging material(s), including primary and secondary packaging material.

6.1.3 Describe qualification criteria for suppliers of raw material and relevant certificates.

6.2 Intermediate products (as appropriate)

6.2.1 List routine tests performed and specifications for intermediates. Include copies of standard operational procedures (SOPs) for critical QC tests (uncontrolled copies or concise description of the method and retest criteria are acceptable).

6.2.2 List assay validation activities performed.

6.3 Finished products

6.3.1 List routine tests performed and specifications for final product. Include copies of the SOPs for critical QC tests (uncontrolled copies or concise description of the method and re-test criteria are acceptable).

6.3.2 List assay validation activities performed.

6.3.3 List final lots internally rejected in the previous two years and reasons for rejection.

Chapter 7: Stability

7.1 Provide information on stability tests on intermediates:

a) assigned shelf-life and storage conditions;
b) QC methods and specifications, and rationale for the choice of tests for determining stability;
c) identification of the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production;

Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as "pass" or "fail".

7.2 Provide information on stability testing of the finished product:

a) assigned shelf-life and storage conditions;
b) QC methods and specifications and rationale for the choice of tests for determining stability;
c) identification of the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production.

Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as "pass" or "fail".

7.3 Provide information on stability testing of diluents and reconstituted vaccine in case of lyophilized vaccines.

7.4 Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g. combination vaccine) and diluents, as appropriate.

Chapter 8: Clinical experience

Note 1: Clinical studies are expected to have been designed and conducted to meet WHO and international GCP principles. Applicants should consult the following three documents in the WHO technical Report Series (TRS).

1) WHO TRS 924 (2004). *Annex 1: WHO guidelines on clinical evaluation of vaccines: Regulatory expectations.*
2) WHO TRS (in press): *WHO guidelines on non-clinical evaluation of vaccines* (in final draft).
3) WHO TRS 850 (1995). *Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*.

Other guidance documents such as International Conference on Harmonization (ICH) guidelines are also relevant.

Note 2: For vaccines whose licence was originally obtained some years ago, it is possible that many or all of the clinical trials may not have been performed or monitored to current international standards. For these vaccines all sections should be completed but additional emphasis should be given to information provided in sections 8.1.1, 8.1.5, 8.2.1 and 8.2.2 in order to sufficiently establish a history of safe and effective use.

Note 3: In some cases, where the information received regarding the sections detailed below is not enough or not clear enough, or requires further scrutiny, WHO may request the applicant to submit the raw data.

8.1 Clinical trials information

8.1.1 Applicant's sponsored clinical trial overview

The sponsor should provide a list of all clinical trials performed in all countries that are relevant to the application for WHO prequalification. These should include all studies sponsored by the applicant both before and at any time after initial licensure, whether or not submitted previously to the NRA(s) where the product is licensed. For each study on the list, the following information is required:

- the type of study
- the rationale for its conduct
- the location(s) of study sites
- the dates of the study
- numbers and ages of subjects
- statement of final conclusions on safety and immunogenicity
- date of protocol approval by the NRA, if this was done
- level of compliance with GCP including ethics approvals

All publications and abstracts about these trials should accompany the submission in section 8.1.1.

In addition, the applicant should list any trials that are known to be currently ongoing with details of the study plan and expected date of results.

8.1.2 Other trials with the applicant's product

In addition, the applicant should make every effort to provide a list of all trials relevant to the application that were not sponsored by the applicant but in which the product was evaluated.

This list should be compiled from publications identified using an extensive literature search (details of which should be provided) and, in the case of co-licensure agreements, from any other company that holds a licence for or a right to market the same product.

8.1.3 Clinical summary

Provide a detailed summary and interpretation of the safety and efficacy data obtained from the pre-licensure clinical studies and all studies performed in the post-licensure period that support the current prescribing information. The summary should pay particular attention to any data that are relevant to the use of the product worldwide at WHO recommended schedules. In the absence of such data, the summary should provide a preclinical and/or clinical justification for the extrapolation of the existing data to the likely circumstances of use after prequalification, should the vaccine be prequalified. This summary should complement, and not replace, the summary written by an independent clinical expert described in 8.1.5.

8.1.4 Assessment reports (AR)

Whenever possible the applicant should provide the clinical sections of the NRA assessment reports from the country of origin and/or country where initially licensed. Assessment reports for both initial licensure and for any subsequent variations to the licence for changes relevant to clinical data are requested.

8.1.5 Clinical expert report

Provide an independent clinical expert report on the clinical studies if justification is being made for submitting clinical data that do not fully meet the provisions of 8.1.3. That is, if the application for prequalification is based on the extrapolation of the existing clinical data to the likely circumstances of use after prequalification. Also, wherever the data are old or there is a doubt regarding the ethical or regulatory oversight of the trial, the report should discuss the degree of compliance with WHO GCP recommendations and current guidance regarding preclinical and clinical trials with vaccines.

8.1.6 Preclinical studies sponsored by the applicant

Provide a simple list of all preclinical studies that were sponsored by the applicant in support of use in clinical trials in humans, or for significant changes to manufacture or use. Include in the list any important conclusions. For preclinical studies performed after initial licensure, indicate the reasons for these studies. Any other particularly relevant reports regarding safety aspects, whether or not generated by the applicant, should be provided.

8.2 Documentation of safety

Safety data should be submitted both in the case of the initial application for prequalification evaluation and for reassessment purposes.

8.2.1 Initial evaluation of vaccines that have been in the market for a long time or reassessment of already prequalified vaccines

Provide an outline of the applicant's procedures for the collection, onward notification and assessment of adverse events.

Provide a listing of all reported AEFIs for the vaccine in question in the last five years or since the last WHO reassessment. As far as is possible from the reports received, applicants should list the type of reaction, lot number, date and place of immunization, patients' initials and age and, for immunization series, the dose number. A judgment of serious/non-serious and whether or not the event was expected (in the light of the prescribing information) should be provided where this was possible from the information. An assessment of the relationship to the vaccine made by a clinician and, where relevant, by the applicant company, or its independent clinical expert, should be included.

In cases where ICH periodic safety updated reports (PSURs) are available, these can be submitted. Information regarding other geographical areas shall be added to that provided in the PSURs.

8.2.2 Recently licensed vaccines

In the case of vaccines that have been recently licensed, provide information on any ongoing phase IV studies or on any active monitoring of the safety profile that is taking place.

8.2.3 Documentation of serious adverse events

For serious adverse events reported in the last five years, or as long as the vaccine has been marketed (when shorter than five years), provide fullest possible description of each case, including any information there may be on investigations, actions, patient treatment and outcome.

Chapter 9: Production and distribution data

9.1 Provide information on the quantity of finished product distributed domestically and exported in the previous three years. List the different presentations separately, and indicate whether the list gives the numbers of vials or the numbers of doses distributed.

9.2 Provide a list of countries where the product is licensed (marketing authorization) and supplied.

9.3 Summarize the arrangements and recording system for distribution, including the release process performed by the manufacturer and the NRA.

9.4 Summarize the packaging procedures for international shipments (including box sizes, packing volumes, etc.). Provide the validation protocols and reports of the shipping boxes used for UN supply. Recommendations provided in the most recent version of the WHO *Guidelines on the international packaging and shipping of vaccines* shall be followed.

9.5 Describe the arrangements for handling complaints and product recalls. Include description of the recall investigation system, procedures for corrective actions, and description of regulatory requirements in case of recalls.

9.6 List the quantity of finished product supplied to UN agencies on a per annum basis. List the different presentations separately, and indicate whether the list gives the number of vials or the number of doses distributed.

9.7 Give the quantity of bulk vaccine destined for UN agencies, supplied to contract fillers/packagers for finalization (list individually).

Chapter 10: Update of regulatory authority actions relevant to the product

10.1 Provide a copy of regulatory documentation:

a) marketing authorizations for all formulations;
b) information on refusals, withdrawals, or suspensions including those that are manufacturer initiated;
c) GMP certificate or equivalent.

In addition, if the manufacturer wishes to provide reports of inspections from NRAs or other regulatory authorities, including any follow-up actions, such reports may be useful upon WHO review as they can allow for streamlining of the site visit accordingly.

10.2 Provide a list of lots rejected by the NRA, if applicable.

10.3 Describe restrictions on distribution or recalls, including manufacturer-initiated recalls.

10.4 Name clinical trial suspensions, including manufacturer-initiated suspensions.

10.5 Describe dosage or schedule modifications.

10.6 Provide information on changes in target populations or indications.

10.7 List inspections conducted by NRAs within the previous two years, including the scope of each inspection.

10.8 List inspections conducted by foreign authorities within the previous two years, including the scope of each inspection.

Annex 2:
Confidentiality agreement

Provisions for team members participating in WHO missions to assess/ reassess the acceptability, in principle, of vaccines for purchase by United Nations agencies

In the course of discharging your functions as an expert adviser under this Agreement, you will gain access to certain information, which is proprietary to WHO or to the manufacturer(s) of the vaccine(s) which need(s) to be assessed for purchase by UN agencies. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid manufacturer(s). In this connection, you agree to:

1) not use the Information for any other purpose than discharging your obligations under this Agreement; and

2) not disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

1) was known to you prior to any disclosure by WHO and/or the manufacturer(s); or

2) was in the public domain at the time of disclosure by WHO and/or the manufacturer(s); or

3) has become part of the public domain through no fault of your own; or

4) has become available to you from a third party not in breach of any legal obligations of confidentiality to WHO and/or the manufacturer(s).

You also undertake not to communicate the deliberations and findings of the team(s) of experts in which you will participate, as well as any resulting recommendations and/or decisions of WHO, to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities hereunder exclusively in your capacity as an expert adviser to WHO. By signing this Agreement, you furthermore confirm that you have no financial interest and/or other relationship with a party, which:

1) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

2) may have a vested interest in the outcome of the assessment of the vaccine(s), in which you will participate, including but not limited to parties, such as the manufacturer(s) of the vaccine(s) that is (are) being assessed or manufacturers of competing vaccines.

In this regard, it should be noted that the manufacturer(s) of the vaccine(s) under evaluation have the right to object to your participation in the team(s) of experts which will evaluate (its) (their) vaccine(s). If such objection cannot be resolved in consultation with the manufacturer(s), WHO shall be entitled to terminate this Agreement or cancel part of the activities to be undertaken by you hereunder. The travel and per diem allowances payable to you under this Agreement will in such event be adjusted accordingly.

I hereby agree to the conditions and provisions contained in this document.

Signed: _____

Name (typewritten): _____

Institute: _____

Place: _____

Date: _____

Annex 3:
Declaration of interests for WHO experts

Title of meeting or work to be performed, including description of subject matter, substance (compounds and organisms), technology or process to be considered: *Provisions for team members participating in WHO missions to re/assess the acceptability, in principle, of vaccines for purchase by United Nations agencies.*

Public health considerations have a primary importance in all WHO technical work. Measures need to be taken to ensure that the best possible assessment of scientific evidence is achieved in an independent atmosphere free of either direct or indirect pressures. Thus, to assure the technical integrity and impartiality of WHO's work, it is necessary to avoid situations in which financial or other interests might affect the outcome of that work.

Each expert is therefore asked to declare any interests that could constitute a real, potential or apparent conflict of interest, with respect to his/her involvement in the meeting or work, between (1) commercial entities and the participant personally, and (2) commercial entities and the administrative unit with which the participant has an employment relationship. "Commercial entity" refers to any company, association (e.g. trade association), organization or any other entity of any nature whatsoever, with commercial interests.

In addition, as a result of WHO's strong stance against tobacco use, it is considered relevant for the Organization to know whether experts working with it have, or have had, any relationship with any part of what may be called "the tobacco industry". Nevertheless, declaration of such an interest would not necessarily be considered a reason to disqualify an expert.

What is a conflict of interest?

Conflict of interest means that the expert or his/her partner ("partner" includes a spouse or other person with whom s/he has a similar close personal relationship), or the administrative unit with which the expert has an employment relationship, has a financial or other interest that could unduly influence the expert's position with respect to the subject matter being considered. An apparent conflict of interest exists when an interest would not necessarily influence the expert but could result in the expert's objectivity being questioned by others. A potential conflict of interest exists when any reasonable person could be uncertain whether or not an interest should be reported.

Different ***types of financial or other interests***, whether personal or with the administrative unit with which the expert has an employment relationship, can be envisaged; and the following list, which is not exhaustive, is provided for your guidance. For example, the following types of situations should be declared:

1) a current proprietary interest in a substance, technology or process (e.g. ownership of a patent), to be considered in – or otherwise related to the subject-matter of – the meeting or work;

2) a current financial interest, e.g. shares or bonds, in a commercial entity with an interest in the subject matter of the meeting or work (except share holdings through general mutual funds or similar arrangements where the expert has no control over the selection of shares);

3) an employment, consultancy, directorship, or other position during the past 4 years, whether or not paid, in any commercial entity which has an interest in the subject matter of the meeting/work, or an ongoing negotiation concerning prospective employment or other association with such commercial entity;

4) performance of any paid work or research during the past 4 years commissioned by a commercial entity with interests in the subject matter of the meetings or work;

5) payment or other support covering a period within the past 4 years, or an expectation of support for the future, from a commercial entity with an interest in the subject matter of the meetings or work, even if it does not convey any benefit to the expert personally but benefits his/her position or administrative unit, e.g. a grant or fellowship or other payment, e.g. for the purpose of financing a post or consultancy.

With respect to the above, an interest in a competing substance, technology or process, or an interest in or association with, work for or support by a commercial entity having a direct competitive interest must similarly be disclosed.

How to complete this Declaration: Please complete this Declaration and submit it to the Secretariat. Any financial or other interests that could constitute a real, potential or apparent conflict of interest should be declared (1) with respect to yourself or partner, as well as (2) with respect to the administrative unit with which you have an employment relationship. Only the name of the commercial entity and the nature of the interest are required to be disclosed, no amounts need to be specified (though they may be, if you consider this information to be relevant to assessing the interest). With respect to items 1 and 2 in the list above, the interest should only be declared if it is current. With respect to items 3, 4 and 5, any interest during the past 4 years should be declared. If the interest is no longer current, please state the year when it ceased. With respect to item 5, the interest ceases when a financed post or fellowship is no longer occupied, or when support for an activity ceases.

Assessment and outcome: The information submitted by you will be used to assess whether the declared interests constitute an appreciable real, potential or apparent conflict of interest. Such conflict of interest will, depending on the situation, result in (i) being asked not to take part in the portion of the discussion or work affecting that interest, (ii) being asked not to take part in the meeting or work altogether, or (iii) if deemed by WHO to be appropriate to the particular circumstances, and with your agreement, your taking part in the meeting or work and your interest being publicly disclosed.

Information disclosed on this Form may be made available to persons outside of WHO only when the objectivity of the meeting or work has been questioned such that the Director-General considers disclosure to be in the best interests of the Organization, and then only after consultation with you.

Declaration: **Have you or your partner any financial or other interest in the subject matter of the meeting or work in which you will be involved, which may be considered as constituting a real, potential or apparent conflict of interest?**

Yes: ☐ No: ☐ If "yes", please give details in the box below.

Do you have, or have you had during the past 4 years, an employment or other professional relationship with any entity directly involved in the production, manufacture, distribution or sale of tobacco or any tobacco products, or directly representing the interests of any such entity?

Yes: ☐ No: ☐ If "yes", please give details in the box below.

Type of interest, e.g. patent, shares, employment, association, payment (including details on any compound, work, etc.)	Name of commercial entity	Belongs to you, partner or unit?	Current interest? (or year ceased)

Is there anything else that could affect your objectivity or independence in the meeting or work, or the perception by others of your objectivity and independence?

_____

_____

I hereby declare that the disclosed information is correct and that no other situation of real, potential or apparent conflict of interest is known to me. I undertake to inform you of any change in these circumstances, including if an issue arises during the course of the meeting or work itself.

_____	_____
Signature	Date
_____	_____
Name	Institution

The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested (Initiative for Vaccine Research).

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards (Quality Assurance and Safety of Biologicals).

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented (Vaccine Assessment and Monitoring).

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies (Access to Technologies).

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives (Expanded Programme on Immunization).

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World Health Organization