EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 18 to 22 October 2010

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

This document has been prepared for the purpose of inviting comments and suggestions on the proposal contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Comments proposing modification to this text MUST be received by 8 October 2010 and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Ms Emma Uramis Diaz at email: uramisdiazem@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide"(WHO/KMS/WHP/09.1).
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Acronyms

The following acronyms are used in this document.

AEFI: adverse event following immunization
AHU: air-handling unit
AMC: Advance Market Commitment
AR: assessment reports
CHMP: Committee for Medicinal Products for Human Use
CTD: Common Technical Document
EMA: 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
OMCL: Official Medicine Control Laboratories
OOS: out of specification
PSF: product summary file
PSPQ: programmatic suitability of vaccines for prequalification
PSUR: periodic safety updated report
QA: quality assurance
QC: quality control
QS: quality system
QSS: Quality, Safety and Standards (WHO)
SAGE: Strategic Advisory Group of Experts
SOP: standard operating procedure
TSE: transmissible spongiform encephalopathy
TPP: target product profile
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. This service is called prequalification. The purpose of the UN prequalification assessment is to provide assurance that candidate vaccines: (a) meet the WHO recommendations on quality, safety and efficacy, including compliance with WHO recommended Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards; and (b) meet the operational specifications for packaging and presentation of the relevant UN agency. This is to ensure that vaccines provided through the UN for use in national immunization services in different countries are safe and effective, and are suitable for the target populations, at the recommended immunization schedules, and with appropriate concomitant products.

The procedure in place at WHO to assess the acceptability of candidate vaccines for the UN 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). Since then, a number of published revisions to the procedure have been implemented (in 1996, 2002 and 2005). The last revision is published in WHO/IVB/05.19.

The present document is a revision that takes into consideration challenges faced by the vaccines prequalification programme, such as the increasing number of submissions, the increasing diversity and complexity of the products submitted to WHO for evaluation, as well as the on-going maintenance of the prequalified status for those vaccines on the list. The latter includes reassessments and reviews of variations, and investigation of quality and safety concerns reported by field workers, which all translate into a growing workload for WHO.

This document addresses technical, communication and policy aspects of the procedure and is based on the recommendations made by an ad hoc advisory committee of experts on vaccines prequalification convened by WHO in May 2010 and on a series of supporting documents. These can be accessed at: http://www.who.int/immunization_standards/vaccine_quality/pq_consultation_2010/en/index.html

The document proposes an update of the current procedure (WHO/IVB/05.19).

The prequalification (PQ) procedure established by WHO for vaccines has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies and it is based on the following principles:

- Reliance on the national regulatory authority (NRA) of the country of manufacture which is required to be "functional", i.e. meeting the published WHO NRA indicators for prequalification purposes.

General understanding of the product and presentations offered, production process, quality control (QC) methods, quality system (QS) in place and relevance for the target population of available clinical data.

Assurance of production consistency through compliance with GMP requirements and monitoring of continued compliance with specifications through testing of final product characteristics.

WHO can advise United Nations agencies whether vaccines effectively meet WHO-recommended requirements only if the responsible NRA exercises independent and appropriate regulatory oversight of the vaccines in question and if the vaccines have been assessed through the procedure described in this document. 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 the NRA of their application to WHO for the vaccine prequalification by sending to the NRA a copy 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.

The update introduces a procedure for using, in some circumstances, enhanced assistance from eligible National Regulatory Authorities (NRAs) (see section 4).

Under exceptional circumstances, extraordinary and temporary measures may be applied in the situation where the NRA responsible for the regulatory oversight of a product fails to sustain its functionality against WHO standards. This is done only where it is necessary to ensure a global supply of vaccines of assured quality. As recommended by the Strategic Advisory Group of Experts (SAGE), in emergency situations, a process that enables WHO to obtain appropriate regulatory support to maintain the prequalification status of vaccines may be applied. This procedure applies to vaccines for which there is no immediate alternative source thus a removal from the prequalified list would jeopardize the global supply.

As vaccines purchased by United Nations agencies need to meet WHO recommendations or guidelines (whichever are available), novel vaccines for which such recommendations 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. The fact that certain vaccines are not included in the list of prequalified vaccines does not mean that, if evaluated, they would not be found to comply with the required standards.

WHO will define, in consultation with United Nations purchasing agencies, which vaccines are a 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 available 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:

a) The candidate vaccine is on the current list of priority products for UN prequalification.

b) The candidate vaccine meets the mandatory characteristics for programmatic suitability (as defined in the document "Assessing the programmatic suitability of vaccine candidates for WHO prequalification")


Note: WHO encourages manufacturers to discuss with the prequalification secretariat, early in the development process, any concerns over the programmatic suitability characteristics for prequalification.

c) The NRA responsible for the regulatory oversight of the product has been assessed by WHO as "functional" and has been found to meet all the critical indicators defined for prequalification purposes.

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 and the outcome is satisfactory.

d) A marketing authorization (MA) has been granted by the relevant NRA and the post-marketing regulatory oversight is under the responsibility of the NRA of the country of manufacture (or the European Medicines Agency (EMA) in the case of the centralized procedure for MA in Europe) or that of the country of finishing and distribution. Alternatively, if it is intended that the EMA Scientific Opinion1 should serve as a basis to facilitate the MA of the vaccine, the Guideline on Procedural Aspects regarding the Committee for Medicine Products for Human Use (CHMP) should be used in the context of cooperation with WHO for the evaluation of medicinal products intended exclusively for markets “outside the community”.

Note: WHO encourages manufacturers to discuss with the prequalification secretariat, early in the development process, on the product itself and the regulatory requirements.

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1 EMA Scientific Opinion in accordance with Article 58 of Regulation (EC) No726/2004 is exclusively restricted to medicinal product which are not authorized within the European Union. However the issuance of such Scientific Opinion does not prevent the possibility of submitting a future EU Marketing Authorization.
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 audit if applicable. 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.

3.1 Official request and response

An application letter\(^2\) is to be sent to the Coordinator, Quality, Safety and Standards, Department of Immunization, Vaccines and Biologicals (WHO/IVB/QSS) with copies to the vaccines prequalification manager and the relevant NRA, with details of country and sites of manufacture, licensing status and presentations put forward to United Nations agencies for procurement.

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 for evaluation to facilitate planning.

WHO will acknowledge receipt and acceptance of application letter by email with copy to the NRA and will only respond with an official letter in those cases where the vaccine will not be accepted because it is not a priority. In such cases, the applicant, and the NRA will be advised of the rejection of the application within two weeks of receipt of the official request.

3.2 Meetings with manufacturers

If considered necessary or desirable by either party, before the actual evaluation process starts, a discussion may be held between the manufacturer, the responsible NRA (if willing to participate) and WHO. This pre-evaluation meeting should be scheduled as early as possible with a predefined agenda to address questions sent in advance to WHO by the manufacturer.

Such meetings are important to discuss programmatic suitability issues and can be scheduled when requested by the manufacturer.

Additional meetings may be held during the evaluation process as required.

3.3 Product summary file (PSF)

A manufacturer for which the application letter is accepted will prepare and submit one hard copy and five electronic versions (in CD), either in Microsoft Word, or pdf format of a product summary file, fully up to date and written entirely in English following the WHO format provided below:

\(^2\) The application letter's purpose is to communicate to WHO the manufacturer's intention of submitting a vaccine for evaluation.
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. Where PSF cross references to the Common Technical Document format, CTD documentation can be e-copy only. E-copy documents should be searchable text where possible.

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. Two separate deadlines have been set for the submission of applications of seasonal influenza vaccines to WHO, these are 1 July and 1 November of each year.

In each case, applications must arrive at WHO by the submission date to be considered for the following review round. Applications received after the deadline of submissions will not be considered for evaluation until the following review round.

**Screening of the product summary file and payment**

Upon receipt, the PSF will be screened for completeness and compliance with the required format and contents. If the PSF is not in compliance with the format and contents, the manufacturer will be informed through an official letter and required to pay the screening fees. An improved PSF may be submitted to meet a subsequent scheduled submission deadline without additional payment. In case of a second (final) rejection, the manufacturer will be informed by official letter and an invoice will be sent requesting payment of the screening fees.

In addition, an assessment of the suitability of the vaccine for the immunization services where it is intended to be used will also be conducted at this stage. The process for review of programmatic suitability of vaccine characteristics is described in the document "Assessing the programmatic suitability of vaccine candidates for prequalification."

At the time of screening, vaccine candidates must be in compliance with the mandatory programmatic characteristics as defined by IPAC. If screening reveals that mandatory characteristics are not met, then the PSF will be rejected. If the PQ Secretariat identifies a deviation from the critical characteristics or a unique, novel and innovative characteristic not otherwise specified as mandatory or critical, is required.

The PSPQ Standing Committee is an advisory body to the PQ Secretariat and the Director IVB constituted of experts on immunization programmes and vaccines regulation. See PSPQ Standing Committee ToR in: http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/index.html

The committee will review the documentation exclusively related to the specific problem. During their review, and discussion leading to the formulation of recommendations, the PSPQ Standing Committee may engage in confidential discussion with manufacturers and additional technical experts that have been approved by WHO and the manufacturer. All members of the PSPQ Standing Committee will be required to sign a confidentiality agreement (see section 15 and Appendix 4) and a declaration of interests form (see section 16 and Appendix 5) prior to taking up their responsibilities for WHO.

Note: Under special circumstances, when there is limited access to a vaccine of public health importance, exceptional considerations will be made regarding suitability of vaccine candidates that are non-compliant with the critical characteristics or that present with unique and innovative characteristics. This decision can be made by the PQ secretariat and will take into consideration the recommendations of the PSPQ Standing Committee as well as public health needs and issues related to access to vaccines.

The screening process will be put on hold while the PSPQ Standing Committee is conducting a review. The duration of the review time by the PSPQ Standing Committee will be not longer than three months. In case of rejection following a recommendation from the PSPQ SC, the reviewers may include a recommendation for resubmission after validation by research of the acceptability of specific vaccine characteristics.

When no review by the PSPQ Standing Committee is required, the manufacturer will be informed within one month after the submission deadline if the PSF is accepted for further review or rejected. 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 proposed for the evaluation, together with a copy of their curricula vitae. At the same

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1 'Mandatory' characteristics are those where compliance is compulsory at the time of application for WHO prequalification and must be unconditionally met prior to evaluation of the PSF. (see PSPQ paper)

2 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 when justification is provided 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
time, 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.

In case of rejection, for any reason, the manufacturer will be informed through an
official letter, an invoice will be sent by WHO requesting payment of the screening
fees, and with the agreement of the manufacturer the PSF will be destroyed at WHO.

**Product summary file evaluation**

The time frame for an initial review of a vaccine PSF will be 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.
There is no further action by WHO (the clock is stopped) until reception of the full
complementary information.

The complementary information must be submitted in one package in one hard copy
and five electronic copies 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.

WHO reserves the right to terminate this procedure for a specific vaccine if the
manufacturer is not able to provide the required response with acceptable action plan
within three months and the actual information within the agreed time period, or if the
information supplied is inadequate.

The time frame for review of complete complementary information will be three
months.

**3.4 Initial testing of vaccine samples**

As soon as the PSF is accepted and when the prequalification procedure described in
section 3 is applied, WHO will request the manufacturer to submit to WHO an
appropriate number of samples (between 25 and 200 depending on the vaccine type
and presentation offered) of three to five final lots, for independent testing. These lots
will have been formulated from consecutive bulk lots (in the case of combination
vaccines, consecutive bulbs will be specified by WHO for one of the components).

The samples shall be accompanied by the respective lot-summary protocols fully
detailed as described in the WHO guideline for independent lot release of vaccines by
regulatory authorities (Ref WHO/BS/10.2128) and the detailed SOP for testing the
product characteristics (relevant tests).

Biological reagents and reference materials for the validation of the tests by WHO
contracted laboratories should be provided by the manufacturer. In some cases,
samples of bulk material may be requested.

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confidentiality agreement (see section 15 and Annex 4) and a declaration of interests form (see section
16 and Annex 5) for that specific evaluation.
WHO will send the vaccine samples to its contracted laboratories for the initial 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 may be performed. If applicable, the relevant method should be transferred from the manufacturer to the contracted laboratory through WHO. The performance of the contracted laboratories for the relevant tests has been evaluated by WHO.

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 United Nations agencies. The expected time frame for testing, from the date of receipt of the samples by WHO to the finalization of testing by WHO, is three months.

To promote the independence and impartiality of the testing, 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. Situations where the manufacturer is asked by WHO to transfer the testing methodology to a National Control Laboratory (NCL) will be the exception to this rule. Upon request, the manufacturer and the relevant NRA will, however, receive a report of the test results.

Generally the selected contracted laboratories do not include the NCL of the NRA in charge of the testing for lot release. Exceptions can be made in the case of streamlined procedure.

### 3.5 WHO site audits

The main objectives of the site audits are to assess if the vaccine complies with WHO recommendations for production and quality control, if it meets the United Nations' tender specifications (which reflect the needs of the immunization programmes at the country level), that the company has an adequate quality system (QS) in place, and that the relevant vaccine/s is/are produced in compliance with WHO-recommended GMP\(^5\). 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 audits are required for those 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 adverse events following immunization (AEFIs) if a quality problem is suspected.

Site audits are part of the standard assessment performed to ensure that vaccine candidates for purchase by UN agencies (or those that are already being purchased) meet (or continue to meet) WHO recommendations and tender specifications.

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\(^5\) In those aspects where GMP requirements are not detailed enough, other international Guidelines shall be followed by the manufacturer and appropriate justification for the choice provided. In such cases, WHO will assess against the standard used.
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 an abbreviated site audit. 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 review of the PSF and testing have been satisfactorily completed, WHO may assemble a team to audit the manufacturing facility. The site audit will take place as soon as possible after satisfactory test results are available, usually within a time frame of two months. Technical staff from the relevant United Nations agency may elect to join the team. 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, quality system and GMP. If additional members or replacement members are needed, the curriculum 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 audit 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 or the NRA for the regulatory oversight of the product will be invited to assign one or two staff members to join the WHO team as observers.

A bilateral consultation meeting will be held between WHO and the NRA, either at the beginning or at the end of the mission. The purpose of this meeting is to discuss regulatory aspects related to the vaccine/s in question and to lay the basis for the letters of agreement. Topics addressed during such consultation meetings relate to commitment for testing and release of vaccine lots for United Nations agencies, need for feedback on findings during inspections, update on safety and efficacy data, variations to the MA/licence that may have been requested, MA/licence renewals, recalls or withdrawal of lots, etc. WHO will establish letters of agreement with all the NRAs responsible for the oversight of prequalified products.

WHO site audits 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.

The findings and recommendations of the team will be discussed with the company on a daily basis as required during the site audit. Where relevant, the team may request the manufacturer to prepare a corrective action plan to address critical recommendations and establish deadlines for receiving responses. The draft report, 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 an opportunity for discussion, questions and clarifications.

The final report providing findings, recommendations and conclusions is prepared by the team and sent to the company within 30 days after completion of the visit with a copy to the NRA. If corrective actions need to be taken by the manufacturer, WHO will postpone its final recommendations to the United Nations agencies involved until such actions are implemented and verified by WHO.

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

3.6 Report and outcome of the assessment

When required, the final decision regarding the acceptability of the product for supply to United Nations agencies may be taken in consultation with an ad hoc committee on vaccines prequalification convened by WHO for this purpose.

Once WHO considers that the process is complete, and if the outcome is satisfactory, WHO sends a letter to the United Nations agencies and also to the Global Alliance for Vaccines and Immunization (GAVI) Alliance for Advance Market Commitment (AMC) eligible products advising on (a) compliance of the vaccine with both the WHO requirements and the specifications of the relevant United Nations agency, and (b) the role of the NRA in certifying this. This letter will be copied to the manufacturer, the NRA/NCL responsible for lot release, the relevant WHO Regional and Country Offices, IVB department management and the approved VVM manufacturer.

For AMC eligible products, WHO will send to the GAVI Alliance and the AMCs Independent Assessment Committee (IAC) a report providing the rationale for confirming or otherwise that the vaccine meets the Target Product Profile (TPP).

The vaccine will be included in the WHO list of prequalified vaccines immediately after the letter to United Nations agencies is sent. A page providing the basis for the acceptance of the prequalification of the specific vaccine will also be included in the list of prequalified vaccines. The current list may be consulted at:


In the event of any disagreement between the manufacturer and WHO, an SOP for the handling of such disagreements will be followed to discuss and resolve the issue.

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6 An AMC is a legally-binding agreement for an amount of funds to subsidize the purchase, at a given price, of an as yet unavailable vaccine against a specific disease causing high morbidity and mortality in developing countries. The establishment of AMCs should encourage the development of future generations of vaccines and in particular accelerate the development and availability of priority new vaccines to developing countries.
The prequalified status of a vaccine is valid until a new reassessment is scheduled by WHO. (see section 9).

WHO reserves the right to revoke the prequalification status if fraud by the manufacturer becomes evident.

For details on notification of changes or introduced variations, see section 7

Obligations after prequalification is granted.

Note: Communications, at any time, with the experts involved in a vaccine evaluation should be done through the WHO focal person in charge of the product.
4 Considerations for streamlining the prequalification procedure based on enhanced assistance by NRAs

4.1 Procedure for selecting eligible NRAs

Experience gained with the evaluation of influenza H1N1 (2009) pandemic vaccines showed that reliance upon effective regulatory oversight by the responsible NRA has the potential to play a critical role in facilitating the prequalification procedure. It is considered that the experience in the pandemic influenza context can be extrapolated to other vaccines.

The proposed procedure envisages enhanced reliance on the oversight performed by the responsible NRA, when the NRA exhibits a high level of performance of WHO’s six recommended regulatory functions and exercises full regulatory oversight of any given vaccine.

Full implementation of such an approach will require the development of a revised NRA assessment tool with the additional performance indicators to supplement the existing indicators. During the development and operational implementation of a revised tool able to distinguish levels of functionality (maturity levels), an interim selection process will be implemented with a limited number of NRAs with established regulatory capacity to ensure standards for quality, safety and efficacy at least equivalent to those recommended by WHO (eg Technical Report Series).

The interim process to be used for selection of NRAs will be:

- Acceptance of NRAs that have provided enhanced support to WHO for pandemic H1N1 (2009) influenza vaccines
- Case by case analysis of feasibility for other potential NRAs based on:
  - Review of the established procedures and practices for marketing authorization/licensing of vaccines,
  - Review and approval of variations/changes,
  - Extent of the actual ongoing regulatory oversight exercised for the vaccine of interest,
  - Willingness of the agency to collaborate with WHO in the evaluation and ongoing regulatory oversight of the vaccine of interest.

Once the performance indicators have been developed, and the NRA assessment tool is revised, allowing the establishment of functionality levels, a stepwise expansion to include additional authorities can be carried out.

4.2 Streamlined procedure for vaccines with marketing authorization/ licensing granted, by eligible NRAs

As an alternative to the WHO vaccine prequalification procedure described in section 3, the streamlined option can be applied to vaccine applications submitted for evaluation by those selected NRAs who are eligible and willing to share regulatory information with WHO through a collaboration agreement;

WHO will explicitly request the assistance of the NRA responsible for the regulatory oversight of the candidate vaccine, and will engage in discussions for the
establishment of a formal collaboration agreement that will outline the shared
understanding of roles and responsibilities, and commitments of each party.
Provisions for confidentiality will be also included.
The scope of this agreement can be determined by both parties and could include one
or more of the following (each subject to agreement by the manufacturer):
- Sharing of NRA reports relevant to product quality, non-clinical and clinical
evaluation
- Sharing of NRA/ NCL test results (including the raw data)
- Sharing of inspection reports
Once the collaboration agreement is formally established, depending on its nature and
scope, WHO may decide on a product by product basis to do one or more of the
following:
- review the NRA assessment reports instead of reviewing the PSF;
- review NRA/NCL testing results and their trending, if applicable, instead of
independently testing the final product characteristics;
- review the NRA inspection reports and supplement with a short audit focused
on aspects related to United Nations' tender specifications instead of
conducting a full site audit.

**Review NRA assessment reports instead of the PSF**
In this instance WHO recognizes the assessment of the MA/licence dossier performed
by the selected NRAs responsible for the regulatory oversight of the candidate
vaccine as the basis for the decision on prequalification. WHO will review the NRA
assessment and inspection reports instead of reviewing the PSF and may follow-up on
queries, based on the available information provided by the responsible NRA for the
MA/licensing of the vaccine submitted for PQ. In case of additional questions related
to issues not addressed in the NRA reports, WHO will contact the manufacturer
directly and copy the NRA of such exchanges of additional information.

Typically, the responsible NRA would neither focus its review on aspects that are
specific to the national immunization schedules of countries that receive their
vaccines through the UN nor on the programme needs stated in the UN specifications.
These are to be assessed by WHO. In this respect the EMA Scientific Opinion
procedure (Article 58 of Regulation (EC) No. 726/2004) represents the exception

In view of the above, a review by WHO of the following aspects would remain
essential:

a) Review of mandatory and critical characteristics from the programmatic point
of view.
b) Eligibility, when required, for the AMC through review of the proposed
product characteristics against the target product profile criteria.
c) Confirmation that the vaccine meets WHO recommendations.
d) Review of stability data to ensure it meets the needs of immunization
programmes in developing countries (particularly those with weak cold chain
systems) and assignment of a VVM category.

e) Review of clinical data to ensure that are applicable to the target population.

f) Review of recommended immunization schedules to ensure compatibility with those existing in national immunization programmes.

g) Review of the suitability of samples, labels, inserts and packaging to meet the United Nations agencies tender requirements.

h) Review of packaging for international shipment and its validation.

The applicant must provide a copy of the file submitted to the NRA and relevant sections of the PSF to cover information required in items a to h above to WHO for its perusal.

For those NRAs that do not require renewal of the licence on a regular basis, the NRA should have an alternative mechanism in place to conduct an ongoing monitoring of the quality, safety and efficacy of the vaccines over which they exercise the regulatory oversight. Updated information on these vaccines should be conveyed to WHO by the NRA at defined intervals. This information may be used in the reassessment procedure.

**Review of NRA testing results and their trend, if applicable, instead of independently testing consistency of final product characteristics**

Vaccines submitted for the initial evaluation for prequalification are categorized by WHO into one out of four categories described in table 1 (see Annex 2). Vaccines that meet the criteria described under categories I to III may be evaluated applying the streamlined procedure.

In this case, WHO will recognize the lot release testing performed by the selected NRA/NCL responsible for the regulatory oversight of the candidate vaccine. WHO will review the available information e.g. testing results, raw data, trends -if applicable-, and control charts. Based on the information provided by the NRA/NCL responsible for the lot release and testing of the vaccine submitted for prequalification, WHO will consider whether additional independent testing by WHO contracted laboratories is required or if this information can be accepted by WHO for prequalification purposes.

When the NRA/NCL responsible for the regulatory oversight does not perform the critical tests, either for novel or traditional vaccines, testing by WHO contracted laboratories needs to be conducted before the prequalification is granted.

**Review of NRA inspection reports supplemented with a short audit focused on aspects related to United Nations' tender specifications instead of conducting a full site audit**

This is based on WHO's recognition of the inspections conducted by the selected NRAs responsible for the regulatory oversight of the candidate vaccine. The WHO site audit as part of the initial evaluation, follow-up to corrective actions taken by the manufacturer following WHO recommendations, or reassessment, will be replaced by a review of inspection reports from the responsible NRA and a short audit by WHO that will include verification of specific items relevant to UN tender specifications.
If the review of inspection reports conducted by the responsible NRA is considered sufficient to ensure that vaccine candidates (or those already being purchased) meet or continue to meet the WHO requirements and specific conditions required for purchase by United Nations agencies this information can be accepted by WHO for prequalification purposes.

WHO will include, as part of the agreement with the relevant NRA an 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 AEFIIs reported or other matters that could affect the normal supply of vaccine to United Nations agencies.

**Other considerations**

The implementation of the streamlined prequalification procedure as described above requires an eligible authority and the willingness of this authority to engage in the collaborative effort. Special attention should be given to authorities from countries where English is not the mother tongue. In such cases, engagement in this exercise would imply additional workload for the NRA to make their reports available in English. Specificities of the collaboration (nature and extent) should be defined on a case by case basis and reflected in the agreement.

Vaccines that are produced for export-only purposes require special consideration and are not eligible for evaluation through the streamlined procedure described in section 4.2.

The report of the assessment is performed as per the standard prequalification procedure. (see section 3).

**4.3 Vaccines with positive scientific opinion issued by EMA**

WHO is involved at different stages of the process of evaluation of vaccines by EMA/CHMP under Article 58 (Regulation EC No. 726/2004). In this context, EMA/CHMP issues a scientific opinion based on evidence of quality, safety and efficacy, taking into consideration the benefit/risk assessment for the intended population, which is consistent with the WHO's focus on developing countries.

All vaccine applications submitted for evaluation by EMA under Article 58, and intended for immediate prequalification after a positive Scientific Opinion, will be assessed through a streamlined procedure (see Annex 3) in such a way that the time elapsed between a positive scientific opinion and prequalification will be minimized.
5 Special considerations for fast-track procedure

The implementation of a fast-track procedure may be required under special circumstances. This procedure is applicable to licensed vaccines (marketing authorization available) 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 recently introduced into the routine immunization programmes.

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

- An acute shortage\(^7\) of a vaccine that puts at risk the global supply of routine immunization programmes and/or an eradication effort.
- An emergency situation, i.e. outbreak or epidemic 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.

Exceptional situations such as:

- Declaration of a pandemic of a disease for which production capacity needs to be established.
- Need of alternative to existing vaccines to be used during an eradication effort.

Any of the above exceptional situations may lead to acceptance of vaccines for evaluation in parallel to the submission to the NRA for marketing authorization purposes upon:

- a) special request from the manufacturer, and
- b) endorsement by senior management at WHO

In those cases where the fast-track procedure is followed, the established deadlines for submission of PSFs do not apply. In addition, the site audit will take place (in parallel with quality control tests of samples) while the results of tests are pending.

There should be maximum flexibility in this process. For example, review of the dossier and testing of samples will be concomitantly performed and the site audit will be conducted as soon as the dossier review is completed. Similarly to the streamlined approach described under section 4, consideration should be given to reviewing information provided by the relevant regulatory authority with the manufacturer’s permission (including inspection reports), and to results of tests performed by the relevant NRA/NCL to facilitate the evaluation process.

\(^7\) As agreed with UN purchasing agencies and other partners.
6 Special considerations for accepting submissions of vaccines manufactured in multiple sites or countries

It is a pre-condition to any submission of vaccines for prequalification evaluation that the NRA responsible for the regulatory oversight of the product be assessed by a WHO team with respect to its compliance with the six critical functions identified by WHO. The functionality status of the NRA also needs to be sustained with time.

Due to the increasing diversity and complexity of the vaccines that can be manufactured in multiple sites including different countries, WHO has to ensure that the regulatory oversight is fully exercised and responsibilities are clearly defined at all steps of production by the relevant functional NRAs.

The following criteria will be followed:

The assessment evaluation will be product specific, just as it is for vaccines produced by one company in a single site and/or country.

If a company formulates and/or fills from bulks purchased from different sources each of these final products is considered as a unique product and will be prequalified separately.

If the formulation process used by a manufacturer of finished product of a vaccine is different from that used by the manufacturer of the vaccine from seed (e.g. different formulation procedures, different stabilizers, different adjuvants, different preservatives and/or different excipients), these vaccines will be considered unique products and may require preclinical and clinical evaluation.

Evidence will be required by WHO that the finished product manufacturer has authorization from the vaccine manufacturer producing the bulk to export the final product. 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 combination vaccines) is required.

There must be a long-term contract between manufacturers although a minimum of 2 years can be acceptable, if justified. The technical terms and the duration of the contract must be submitted to WHO for review as part of the assessment procedure and whenever necessary additional information can be requested to the manufacturers.

For a manufacturer, with subsidiaries in different parts of the world that perform different manufacturing steps, and if the bulk is not part of a licensed final product in the country of manufacture, the NRA of the country where the finished product is manufactured would need to exercise full regulatory oversight of the product. This means this NRA is responsible for technical, non-clinical and clinical review, and regulatory inspections of the facilities in each country performing manufacturing operations. This NRA would also grant the marketing authorization, perform lot release, testing as necessary as well as post marketing surveillance.
For finished product manufacturers of OPV vaccines to be eligible for the prequalification process, the bulk material must have been evaluated as part of a vaccine already prequalified by WHO for the UN market.

In those cases where the vaccine manufacture is conducted in more than one country which may not be fully covered by the above provisions, the following aspects should be considered to ensure the ongoing regulatory oversight of vaccines:

a) Responsibility for overseeing manufacturing of different production steps should be shared between the relevant authorities (functionality being a condition) with relevant agreements in place and MA/licensing and release is under the responsibility of the authority from where the vaccine is distributed.

b) Consideration may be given to use article 58 of Regulation (EC) No 726/2004 if the applicant is based in the European Economic Area (EEA), or has a contact point within the EEA.

c) Use of a production site in a country where the NRA has not been assessed as functional requires that the NRA in country of manufacture of the final product takes full responsibility for the oversight of the product.

d) If c) does not apply and/or article 58 of Regulation (EC) No 726/2004 alternative pathway can not be used for any reason, this site becomes unacceptable for a product to be evaluated for purchase through United Nations agencies.

The use of a totally unrelated (third party) NRA for the oversight of the product (outside of the option of article 58 of Regulation (EC) No 726/2004) would not be normally acceptable. However, if an agreement between NRAs is established for a specific product, giving the third party authority full regulatory responsibility that includes lot release for United Nations purposes, regular inspections, monitoring of variations, and post-marketing surveillance, then WHO would review the terms of agreement between the NRAs and make a case-by-case decision on it's acceptability.

WHO encourages the early discussions with the manufacturers and their respective NRAs should they plan to embark in a project where multiple sites or countries are involved in the production process, to discuss the proposed scheme and allocation of responsibilities to the NRAs.
7 Obligations after prequalification is granted

All lots of prequalified vaccine shipped in response to orders placed by a United Nation agency must have been released by the NRA in advance of shipping. A copy of the lot release certificates will be kept by the manufacturer and sent, on request, to the United Nations agencies or to the Coordinator, Quality, Safety and Standards, Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva (WHO/IVB/QSS). 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/QSS on request for testing.

The manufacturer shall inform WHO/IVB/QSS of 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.

If the manufacturing country regulations do not require approval by the NRA of changes/variations 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 United Nations agencies.

When WHO relies on the oversight of changes/variations by the responsible NRA, an annual summary of changes/variations (see section 8) would be sufficient.

When such reliance is not established, changes/variations that fall under categories (a) and (b) stated above must be approved by WHO before implementation for UN supply. All other changes/variations can be reported to WHO on an annual basis as detailed in Section 8.

If the labelling specifications are changed or model inserts are updated as part of UN tender requirements manufacturers shall comply with the revised UN tender specifications. The updated versions of labels and package inserts must be reviewed by WHO before implementation.

WHO reserves the right to take appropriate measures including "suspension of supply, initiating a reassessment or withdrawal from the list " in case of non compliance with post prequalification commitments and/or in case of misconduct.
8 Annual Reporting

The following information should be provided in an annual report for each prequalified vaccine:

A. The manufacturer should provide a summary of changes/variations to the product(s) that have been implemented since the previous annual report (or for the first annual report for a product, since initial prequalification). The table below is provided as guidance.

<table>
<thead>
<tr>
<th>Description of variation</th>
<th>PSF Ch/section</th>
<th>CTD X-ref (where appropriate)</th>
<th>Responsible NRA</th>
<th>Prior approval date</th>
<th>Date of acknowledgement of notifiable change†</th>
<th>Self-assessable under national law or not applicable to national registration [☑ if required]</th>
<th>WHO prior approval date (where required) Or WHO notification date (as applicable)‡</th>
</tr>
</thead>
</table>

For responsible NRA columns: manufacturer should complete one out of the three columns which are relevant to change.

† Provide the date of the NRA letter acknowledging the notification or indicate if NRA has not responded and hence give date change implemented under national law.
‡ Ref to Points to consider "Variations to the vaccine prequalification file (in preparation)

B. The manufacturer should provide testing results from the ongoing stability programme since the previous annual report (or for the first annual report for a product, since initial prequalification).

C. Production and distribution data

- Summary table showing the quantity of batches and doses of finished product distributed since the previous annual report. This should include product used domestically and product exported. The batches which have been supplied to UN agencies should be indicated.
- If more than one presentation is manufactured, these should be listed separately.

D. GMP inspections (in which the PQ product was within the scope of inspection) performed since the previous annual report.

E. A summary update on implementation of post-PQ commitments from the manufacturer when these are indicated in the approval letter or reassessment report such as:

- reports of serious adverse events following immunization;
- reports of quality complaints and/or recalls from the field for batches of the prequalified vaccine;
- notification of any problem/constraint in production or quality control which might affect the international supply of this vaccine, both in volume and/or lead times.
F. Periodic Safety Update Report (electronic data only)

Following review of the annual report, WHO may request supporting data. The timing for submission of annual reports should be established as the first submission deadline one year after the date of prequalification. The manufacturer may provide the latest annual report submitted to the NRA provided it contains the relevant information. The same established deadlines for PSFs submission will apply:

31 January, 31 May and 30 September and for seasonal influenza vaccines: 1 July and 1 November.

9 Reassessments

Prequalification status is maintained until action is taken by WHO to revoke it. However, periodic reassessment by WHO is required. The frequency, scope and need for reassessment will be based on quality risk management principles.

The following aspects will be taken into consideration by WHO:

- stringency of oversight exercised by responsible NRA;
- prior experience with manufacturer and specific product;
- variations to the product indicated in annual reports since previous assessment;
- interruptions to production and/or supply to UN agencies;
- reported quality complaints and AEFIs;
- any failure to meet the WHO recommendations and/or the specifications of the offer to bid;
- results from targeted testing of batches supplied to UN agencies.

The above list is indicative but not exhaustive.

A letter to the manufacturer requesting submission of an updated PSF for reassessment should be made six months to one year prior to the proposed assessment time. Unless a paper copy is requested by WHO, the updated PSF should be in electronic form only. The updated PSF should contain a change control section which indicates the sections which have been changed from the previously submitted PSF. Items indicated in the change control section will be compared with summary tables of variations that have been submitted annually. The changed sections will also be compared to the initially submitted file. Only sections indicated as changed will be evaluated. If any changes are made that are not indicated in the change control section, they will not be considered as approved.

Testing of samples at reassessment is required only when there is insufficient evidence of continued compliance with specifications from the WHO annual targeted testing programme of batches supplied to UN agencies.

The need for and scope of a site audit at time of reassessment will take into consideration the demonstrated history of regulatory inspection of the facility by the NRA (including supply of reports of GMP inspections by the NRA).
If, as a result of the reassessment, it is found that a vaccine no longer complies with the WHO-recommended standards, such vaccines will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to removal from the list.

10 Monitoring continued compliance with specifications through targeted testing programme

Samples of lots supplied through United Nations agencies will be selected, at least once a year, for testing of final product characteristics by WHO contracted laboratories. An appropriate number of samples (between 25 and 200 depending on the vaccine type and presentation offered) of three to five lots selected by WHO from a list of products supplied to UN agencies will be requested from the manufacturer. The manufacturer will provide lot summary protocols and the NRA/NCL release certificate as appropriate; will provide information on lot release for review. Manufacturers should commit to keep adequate number of retention samples for this testing programme.

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, WHO will investigate the problem and provide the United Nations agency with written information, copied to the manufacturer and the NRA, on the actions that need to be taken.

11 Monitoring vaccine quality complaints or AEFIs from the field

Vaccine quality complaints

In case of vaccine quality complaints, WHO will conduct an investigation and may perform independent testing after review of the relevant documentation including review of the temperature monitoring devices, review of the testing results and related data.

In case of complaints from the NCLs in the receiving countries, review of the testing results and related documentation (i.e. validation reports, SOPs and control charts) from the laboratory that puts forward the complaint is needed for WHO review before arbitration testing is commissioned.

Adverse Events following immunization (AEFIs)

In case of serious AEFIs or whenever WHO considers necessary, WHO will conduct an investigation according to established procedure. The review of the batch records by the manufacturer and the NRA exercising the regulatory oversight of the vaccine allows for detection of any potential deviation during the manufacturing process that may impact on the quality of the vaccine.

The targeted testing programme performed by WHO on a continuous basis supports the continued compliance of the vaccine with the established quality specifications. In addition, testing results gathered during the lot release process by the NRA/NCL are
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requested from the NRA/NCL exercising the regulatory oversight of the vaccine when
the AEFIs are investigated. Further testing would be resource intensive and may not
yield useful data.

Therefore, the testing of a vaccine lot/batch would be recommended only if the
clinical and/or epidemiological information about the AEFI case(s) indicates a
potential vaccine quality problem and after review of the relevant manufacturing and
control documentation. The investigation of AEFI cases would indicate if testing is
required and in such case which specific type of test(s) is needed.

Depending on the tests to be performed, the number of unopened containers (sampled
from the field and from the manufacturer) required for testing needs to be calculated,
so that it is powered enough to draw definitive conclusions about the relevant lot. In
the event that testing is needed, WHO would contact one of the WHO contracted
laboratories that could perform the test and subsequently inform the national
authorities of the number of vaccine vials to be sent to WHO as well as other logistic
arrangements.

12 Recommendations for action in cases of non
compliance

In the event of situations as described in sections 10 and 11 above and depending on
the nature of the non compliance, WHO may recommend one or more of the
following:

- The manufacturers’ lots of vaccines be more closely monitored through
  additional testing, visit to the manufacturing facilities together with the NRA
  responsible for the regulatory oversight of the product and/or review by WHO
  of the corrective/preventive actions during a probationary period that will
depend on the failure.
- Purchase of the vaccine by UN agencies be suspended pending investigation
  and resolution of the problem.

The failures related to gaps in the manufacturing and/or quality system in place by the
manufacturer may require a complete reassessment of the vaccine.

WHO will inform the relevant NRA responsible for the regulatory oversight about
problems in the field or failure to meet established criteria.

13 Handling of Out-of-specification (OOS)/inconsistent
results between laboratories

1. Due to the increased complexity of the vaccines and new combinations
   currently available or in the pipeline for prequalification, the diversity
   of the methods applied for the quality control of the vaccines as well as
   the evaluation of results obtained through independent testing of such
   vaccines by WHO contracted laboratories, may pose challenges.

2. In the case of inconsistent results by two WHO contracted laboratories,
   WHO may require testing of the vaccine by a third laboratory.
3. WHO may convene an ad hoc committee of experts to assess the combined results and make a recommendation to WHO. Representatives from the WHO laboratories may take part in this committee. Recommendation from the committee will be then considered as final by the Prequalification Secretariat.

14 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.

The expenses related to the site audit will be charged on a cost recovery basis.

The evaluation of a vaccine will commence only after payment of the fee and receipt by WHO of the product summary file.

The cost of activities required to keep the WHO list updated or maintenance fee (i.e. review of annual reports, reassessments, handling of complaints and resolution of OOS results) is charged to the manufacturers on the basis of an annual fee. The expenses related to reassessment site audits are charged on a cost recovery basis. The maintenance fees will be 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 audits 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. Fees will be updated on a regular basis.

Fees (screening, initial evaluation of candidate vaccines and annual maintenance fee) are kept on a separate list available on the website.


15 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 audits 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 audits 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.

In connection with the above, WHO requires all experts to sign the confidentiality agreement attached as Annex 4, prior to taking up their responsibilities for WHO.

16 No conflict of interest

The team of experts selected for a specific evaluation process includes experts in the fields of production, quality control/quality assurance, quality system, 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 also require them to complete the WHO declaration of interests form attached as Annex 5. In addition, the confidentiality agreement referred to in section 15 above contains a conflict of interest undertaking, pursuant to which the 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 experts 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.
The proposals for the revision of the "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies" were prepared by:

**Working group 1: Programmatic suitability of vaccines for WHO prequalification (PSPQ) membership** - Robin Biellik, Independent, Switzerland; Maria Cortes, PAHO Vaccine Quality Issues, U.S.A.; Nora Dellepiane, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Rudi Eggers, WHO, Immunization, Vaccines and Biologicals, Expanded Programme on Immunization; Mauricio Landaverde, PAHO Immunization Services, U.S.A.; Chris Nelson, Independent (Working Group Chair), U.S.A.; Ann Ottosen, UNICEF Supply Division, Denmark; Monica Pereira, PAHO Revolving Fund, U.S.A.; Piyanit Tharmaphornpilas, Department of Disease Control, Ministry of Public Health, Thailand; Emma Uramis, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland.

**Working group 2: Comparison of prequalification programmes membership** - Drew Meek, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Anita Sands, WHO, Essential Health Technologies, Diagnostics and Laboratory Technology, Switzerland; Morteza Zaim, WHO, HIV/AIDS, TB, Malaria and Control of Neglected Tropical Diseases, Switzerland; André Van Zyl, WHO, Essential Medicines and Pharmaceutical Policies, Quality Assurance and Safety: Medicines, Switzerland.

**Working group 3: Revised approaches to testing final product characteristics membership** - Teeranart Jivapaisarnpong, Department of Medical Sciences, Ministry of Public Health, Thailand; Carmen Rodriguez, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Ute Roskopf, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Lorenzo Teselin, Scientific Institute of Public Health, Belgium; Wilma Vergeer, National Control Laboratory, South Africa; Geneviève Waeterloos, Scientific Institute of Public Health, Belgium.

**Working group 4: Streamlining the prequalification procedures for products with EMA/CHMP positive scientific opinion membership** - David Cockburn, Inspection sector, European Medicines Agency (EMA); Emer Cooke, Directorate, International Liaison Officer, European Medicines Agency (EMA); Liliana Chocarro, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Marie-Hélène Pinheiro, European Medicines Agency, United Kingdom; Lembit Rago, WHO, Essential Medicines and Pharmaceutical Policies, Quality and Safety: Medicines; Carmen Rodriguez, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Alessandro Spina - Legal sector, European Medicines Agency (EMA)

**Working group 5: WHO assessment of vaccines regulatory system: Proposal for establishment of maturity level concept membership** - Norman Baylor, Center for Biologics Evaluation and Research, US Food and Drug Administration (USFDA), U.S.A.; Lahouari Belgharbi, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland (working group Chair); Pierre Henry Bertoye, Agence Française de Sécurité Sanitaire de Produits de Santé (AFSSAPS); Faten Fathalla and/or Heba Wali, Egyptian National Regulatory Authority (ENRA), Egypt; Stephane Guichard, WHO, Regional Office in Southeast Asia, India; Teeranart Jivapaisarnpong, Department of Medical Sciences, Ministry of Public Health, (MoPH) Thailand; Youssou Ndøo, Health Manager of Public Market Central Department, Ministry of Finance and Economy, Senegal; Jose Peña,
The proposals were discussed at the "Informal consultation with the ad hoc committee on vaccines prequalification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by UN agencies" and recommendations were received from the Ad-hoc Committee Members (WHO Temporary Advisers) - Laura Gomes Castanheira, ANVISA, Brazil; Patrice Chagnaud, Agence Française de Sécurité Sanitaire de Produits de Santé (AFSSAPS), France; Xingyu Chen, Department of International Cooperation, State Food and Drug Administration (SFDA), People's Republic of China; Emer Cooke, European Medicines Agency, United Kingdom; Roland Dobbeltaer, Vaccine Quality and Regulatory Expert, Belgium; Rolando Domínguez Morales, Department for Biologics and Vaccines, Centro Control Estatal de la Calidad de los Medicamentos (CECMED), National Regulatory Authority, Cuba; Martin Eisenhawer, Swiss Agency for Therapeutic Products Inspectorates, Switzerland; Ian Feavers, National Institute for Biological Standards and Control (NIBSC), United Kingdom; Morag Ferguson, Independent, United Kingdom; Teeranart Jivapaisarnpong, Department of Medical Sciences, Ministry of Public Health, Thailand; Jeewon Joung, National Institute of Food and Drug Safety Evaluation, Korea Food and Drug Administration (KFDA), Republic of Korea; Ria Nibbeling, Centre for Biological Medicines and Medical Technology (BMT), National Institute of Public Health and Environment Protection (RIVM), The Netherlands; Marie-Hélène Pinheiro, European Medicines Agency, United Kingdom; Helen Rees, Reproductive Health and HIV Research Unit,
The first draft of the revised procedure was prepared by the drafting group:

Emma Uramis, Consultant, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland; Nora Dellepiane, Drew Meek, Carmen Rodriguez, Sergio Nishioka, Liliana Chocarro, Ute Rosskopf, all from WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland and David Wood, Coordinator, WHO, Immunization, Vaccines and Biologicals Department, Quality, Safety and Standards, Switzerland taking into account the recommendations from the Ad-hoc Committee Members and posted on the WHO biologicals web site for public consultation.

Based on comments received from regulators, vaccine manufacturers and other experts the WHO/BS/10.2155 document was prepared by the drafting group and posted on the WHO biologicals web site for public consultation.

This final document was prepared based on comments received from regulators, vaccine manufacturers, other experts, and members and participants of Experts Committee on Biological Standardization meeting 2010.
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Agence Française de Sécurité Sanitaire de Produits de Santé (AFSSAPS), France; BioManguinhos, Oswaldo Cruz Foundation, Brazil; CBER, US Food and Drug Administration (FDA), U.S.A.; Rolando Domínguez Morales, Department for Biologicals and Vaccines, Centro Control Estatal de la Calidad de los Medicamentos (CECMED), National Regulatory Authority, Cuba; European Medicines Agency, United Kingdom; Martin Eisenhawer, Swiss Agency for Therapeutic Products Inspectorates, Switzerland; Ian Feavers, National Institute for Biological Standards and Control (NIBSC), United Kingdom; Morag Ferguson, Independent, United Kingdom; GlaxoSmithKline Biologicals, Belgium; International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Switzerland; Victor Maqueda, Independent, Argentina; John McEwen, Therapeutic Goods Administration (TGA), Australia; Julie Milstien, University of Maryland, U.S.A.; Agency of Food and Drug Control (NADFC), Indonesia; National Regulatory Authority, Iran; Chris Nelson, Independent, U.S.A.; Panacea Biotec Limited, India; Serum Institute of India, India; UNICEF Supply Division, Denmark.  

Second draft -  
Agence Française de Sécurité Sanitaire de Produits de Santé (AFSSAPS), France; BioFarma, Indonesia; Biologicals E. Limited, India; BioManguinhos, Oswaldo Cruz Foundation, Brazil; Crucell, Switzerland; Federal State Unitary Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Federation; GAVI Alliance, Switzerland; GlaxoSmithKline Biologicals, Belgium; GreenCross Corporation, Republic of Korea; Japan BCG Laboratory, Japan; Houda Langar, WHO Regional Office in the Eastern Mediterranean; Novartis, Italy; Panacea Biotec Limited, India; Dina Pfeifer, WHO Regional Office in Europe, Denmark; Sanofi Pasteur, France; Serum Institute of India, India; UNICEF Supply Division, Denmark.
Appendix 1 The product summary file

The product summary file (PSF) is a 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 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 (for both the active and diluent) 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 buildings on the site(s) or provide 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 assurance, 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 qualifying suppliers of raw materials.

1.8 List manufacturers supplying biological raw materials and adjuvants

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 and Engineering).
2.2 Provide CVs for heads of production, quality assurance and quality control indicating educational and experience qualifications.

2.3 Outline arrangements for basic and continuing training and how records are maintained.

2.4 Describe requirements for personnel engaged in production, particularly relating to requirements for monitoring of health status (including 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 audit. 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.

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 Complete a table, briefly describing major production and control laboratory equipment used for the production of the vaccine (including diluent).

<table>
<thead>
<tr>
<th>Room ID</th>
<th>Major equipment in room</th>
<th>Clean room class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (including diluents).

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. auto disable syringes) to be delivered with the vaccine, if applicable.

4.3 Give the recommended schedule and route of administration.

4.4 For both the final product and diluent, provide samples of primary container, labels, boxes and package inserts to be used for UN agency supply (in English). French, Spanish, Russian and Portuguese versions need to be made available before supply to UN agencies starts. Include the calculated volume per dose in cm\(^3\) of the secondary packaging.

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

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.

5.2 Provide a description of the manufacturing processes and the characterization of the product. This should include history or the master cell banks/virus seeds.

Detailed flow charts should be provided to indicate:

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.

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;

\(^8\)WHO recommendations or guidelines and UN agencies tender specifications must be met. For each specific test done the international standard met should be identified.
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 product (including diluent)

6.3.1 List routine tests performed and specifications for final product. Concise description of the method and re-test criteria are acceptable but full SOPs in English should be made available on request.

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

Stability studies are expected to have been designed and conducted to meet WHO guidance WHO/BS/06.2049 Guideline on stability evaluation of vaccines or any update.


7.1 Provide information on stability tests on intermediates:

a) information on containers for intermediate products;
b) assigned shelf-life and storage conditions;
c) QC methods and specifications, and rationale for the choice of tests for determining stability;
d) 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 For each presentation 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 profile;
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”.

In addition to final product stability data at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the
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 or any update in the WHO Technical Report Series (TRS):


Other guidance documents:

Points to consider for applicants - Clinical Considerations for Evaluation of vaccines for Prequalification


International Conference on Harmonization (ICH) guidelines.

Note 2: For vaccines whose licence was originally obtained many years before the application for WHO prequalification, it is possible that many or all of the clinical trials may not have been conducted 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 8.2.1, 8.2.5, 8.3.1 and 8.3.2 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 The applicant should provide a tabulated summary of the clinical development programme, in one or more tables, in which critical parameters that may have changed during the clinical development should be mentioned.

8.2 Clinical trials information

8.2.1 Overview of clinical trials sponsored by the applicant

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:

- Final approved protocol, which should indicate date of protocol approval by the Ethics Committee and the NRA.
- Evidence for registration in a clinical trial registry that is included in the WHO International Clinical Trials Registry platform.
- Indication of whether the study complied with GCP.
- For each such study, provide in a tabulation or a brief summary, the following information:
WHO/BS/10.2155

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- 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

Copies of all publications and abstracts about these trials should accompany the submission in section 8.2.1.

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

8.2.2 Other studies with the applicant’s product

The applicant should make every effort to provide a list of all trials and, when applicable, observational studies, 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.

8.2.3 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 in WHO recommended schedules, for instance co-administration of other vaccines. 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 8.2.5.

8.2.4 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.

8.2.5 Clinical expert report

Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided). If the application for prequalification is based on the extrapolation of the existing clinical data to the likely circumstances of use after prequalification and if 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.

8.2.6 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.

8.3 Documentation of safety

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

8.3.1 Provide an outline of the post marketing pharmacovigilance plan for the product

8.3.2 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 seriousness 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.

Whenever periodic safety updated reports (PSURs) are available, these shall be submitted. The PSURs should include information from all geographical areas where the vaccine is used or the absence of such information defended and should follow the ICH format.

8.3.3 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.

8.3.4 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. This information shall be provided as part of the PSUR.

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. When the product is a combination vaccine, information should also be provided on the history of distribution of component vaccine(s), when applicable.

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. Include provisions to inform WHO/UN.

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

Chapter 10: Update of regulatory actions

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.

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 since initial licensure granted.

10.6 Provide information on changes in target populations or indications since initial licensure granted.

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.
### Appendix 2 Testing approach for initial evaluation for PQ

#### Table 1:

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>WHO requirements/testing approach</th>
<th>Requirements from the manufacturer before PQ is granted</th>
<th>Requirements post PQ</th>
</tr>
</thead>
</table>
| I        | Novel vaccine or new combination released by a competent NRA/NCL responsible for the regulatory oversight. NCL is performing the critical tests on a regular basis | - Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF)  
- Review of the testing results by the manufacturer and the NCL (raw data) of minimum 3 lots formulated from consecutive bulk lots  
- Review of the trends of the testing results of both NCL and manufacturer (if applicable)  
- Review the control chart of the reference used in manufacturer's and NCL's assays.  
- Review of the method validation of manufacturer and NCL may be required | - Detailed SOP for testing the product characteristics (relevant tests)  
- Biological reagents and reference materials for the validation of the tests by WHO contracted laboratories  
- Transfer of the relevant method by the manufacturer to the relevant laboratories through WHO | - Commitment from the manufacturer to keep retention samples for testing by WHO contracted laboratories  
- Testing of the vaccine through the targeted testing programme |
| II       | Novel vaccine released by a competent NRA/NCL responsible for the regulatory oversight Validation of the critical tests is in progress. | - Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF)  
- Review of the testing results by the manufacturer (raw data) of minimum 3 lots formulated from consecutive bulk lots  
- Review of the trends of the testing results of the manufacturer (if applicable)  
- Agreement with the NCL to validate the tests during the PQ evaluation  
- Review of the method validation of manufacturer and the control chart of the reference used in manufacturer's assays may be required  
- Agreement to perform and provide results to WHO before PQ is granted | | |
### Table 1 (continued):

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>WHO requirements/testing approach</th>
<th>Requirements from the manufacturer before PQ is granted</th>
<th>Requirements post_PQ</th>
</tr>
</thead>
</table>
| III      | Traditional vaccine released by a competent NRA/NCL responsible for the regulatory oversight. NCL is performing the critical tests on a regular basis | • Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF)  
• Review of the testing results by the manufacturer and the NCL (raw data) of minimum 3 lots formulated from consecutive bulk lots  
• Review of the trends of the testing results of both NCL and manufacturer  
• Review the control chart of the reference used in manufacturer’s and NCL’s assays | • Detailed SOP for testing the product characteristics (relevant tests)  
• Biological reagents and reference materials for the tests by WHO contracted laboratories | • Commitment from the manufacturer to keep retention samples for testing by WHO contracted laboratories  
• Testing of the vaccine through the targeted testing programme |
| IV       | Novel or traditional vaccine NRA/NCL responsible for the regulatory oversight does not perform the critical tests | • Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF)  
• Testing by WHO contracted laboratories before the PQ is granted  
• Agreement with the NCL to validate the tests  
• Review of the testing results by the manufacturer (raw data) of minimum 3 lots formulated from consecutive bulk lots  
• Review the control chart of the reference used in manufacturer’s assays  
• For novel vaccines, review of the method validation of manufacturer | • Detailed SOP for testing the product characteristics (relevant tests)  
• Biological reagents and reference materials for the validation of the tests by WHO contracted laboratories  
• Transfer of the relevant method (if applicable) by the manufacturer to the relevant laboratories through WHO |
Appendix 3 Prequalification procedure for vaccines evaluated by EMA under Article 58 of Regulation (EC) No 726/2004

Background
WHO provides a service to UNICEF and other UN agencies that purchase vaccines, to determine the acceptability in principle of vaccines from different sources for supply to these agencies.

The purpose of the prequalification assessment is to verify that the vaccines meet the specifications of the relevant UN agency, and are produced and overseen in accordance with the principles and specifications recommended by WHO for good manufacturing practice (GMP), 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.

For vaccines (and all medicines) manufactured by European manufacturers (or at least with a legal presence in the European Community) intended for exclusive use in markets outside the European Community, EMA established a mechanism (Article 58 of Regulation (EC) No 726/2004) whereby the European Medicines Agency (EMA) may give a scientific opinion, in the context of cooperation with the World Health Organization (WHO).

WHO recognizes that the evaluation by EMA under “Article 58” is done according to the principles applied by the prequalification process, in terms of assurance of quality, safety and efficacy for the intended population (i.e. developing countries). WHO provides input at different stages of the process, including the determination of eligibility of the product for evaluation under Article 58 and involvement in the assessment of the dossier.

Therefore, in order to align the EMA evaluation under Article 58 and the WHO evaluation for prequalification purposes, a simplified procedure has been developed.

Application process to WHO/QSS
The applicant must submit the following:
1) An application letter is to be sent to the Coordinator, Quality, Safety and Standards, Department of Immunization, Vaccines and Biologicals (WHO/IVB/QSS) with a copy to the vaccines prequalification manager and EMA, with details of country and sites of manufacture and presentations offered.

Note: Application letters can be sent at any time after the submission of the dossier to EMA. Manufacturers are encouraged to advise WHO as early as possible of their intention to submit a specific vaccine application to facilitate planning.
2) A statement that the applicant acknowledges and agrees to the fact that EMA will share with WHO the report of the CHMP evaluators, inspection reports (manufacturing facilities and clinical trial sites), and test results if available with the WHO Prequalification team, as well as mutual immediate notification of quality or safety concerns of the product.
3) Electronic copy of the dossier submitted to EMA for evaluation under “Article 58”.
4) Technical information relevant to UN specifications, including information relevant to the programmatic suitability of the vaccine.
5) Notification about the OMCL laboratory selected for any testing required by EMA for evaluation under article 58 or for prequalification by WHO/QSS.
6) Fees (see section 14)
The evaluation process

WHO will base the evaluation on the following:

a) EMA “Art. 58” Scientific Opinion and its annexed Assessment report from EMA/CHMP
b) Certificate of analysis of consistency lots by a qualified (OMCL) laboratory
c) Reports from relevant inspections (GMP, GLP and GCP) jointly agreed upon betweenWHO/QSS and EMA and performed during the EMA/CHMP “Article 58” Scientific Opinion evaluation procedure.

Although the EMA/CHMP procedure under Article 58 of Regulation (EC) No 726/2004, is done by rapporteur/co-rapporteur in collaboration with WHO/QSS and its experts/expert groups and the evaluation ensuring that the clinical data provided by the applicant is relevant to the UN target population at the intended schedules, other programmatic aspects reflected in the tender specifications of the UN purchasing agencies will not be part of the review process under “Article 58” evaluation and will therefore remain to be reviewed by WHO during the streamlined prequalification evaluation.

In view of the above, a review by WHO of the aspects listed below would remain essential:

a) Confirmation that the vaccine meets the WHO recommendations and UN tender specifications;
b) Review of stability data to ensure it meets the needs of immunization programmes in developing countries (particularly those with weak cold chain systems) and to assign a VVM category;
c) Review of recommended immunization schedules to ensure compatibility with those existing in national immunization programmes and non interference with co-administered vaccines;
d) Review of samples, labels, inserts and packaging to suit the UN Agency tender requirements;
e) Review of mandatory, critical and innovative product characteristics from the programmatic point of view;
f) Review of packaging for international shipment and its validation;
g) If applicable, recommendation that the vaccine would be eligible for the AMC through review of the proposed product characteristics against the target product profile criteria.

Note: items b, c, d, and e are expected to be included in the EMA/CHMP evaluation done in collaboration with WHO under Article 58 of Regulation (EC) No 726/2004. If such assessment and supportive data are available, the applicant should state so and indicate specifically where this have been addressed in EMA/CHMP Art. 58 Scientific Opinion documents.

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 the compliance of the vaccine with both the WHO recommendations and the specifications of the relevant UN agency. The vaccine will then be included in the WHO list of prequalified vaccines immediately after the letter to United nations agencies is sent. The current list may be consulted at: http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html

The prequalified status of a vaccine is valid until revoked by WHO.
Assurance of continued acceptability

After the prequalification of the product has been granted, follow up activities to ensure continued acceptability of the vaccine for supply through UN agencies will be performed according to the general prequalification procedure, as follows:

- reassessments
- evaluation of variations submitted by the applicant
- targeted testing of lots supplied to UN agencies
- monitoring of continued compliance with specifications
- follow up of complaints and reports of adverse events following immunization (AEFIs).

The above list is indicative but not exhaustive.

Failure from manufacturers to submit variations through EMA may lead to withdrawal of the scientific opinion and the prequalification status.

Note: These activities will be done, whenever applicable, in collaboration with EMA within the context/basis of Article 58 of Regulation (EC) No 726/2004.
Appendix 4 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: ___________________________________________________
WHO's work on global health issues requires the assistance of external experts who may have interests related to their expertise. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a potential conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be disclosed to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be published in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may...
decide that you be totally recused from the meeting or work concerned, after consulting with you.

**Name:**

**Institution:**

**Email:**

**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 by the organizer of the activity):

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**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 and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with 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 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment Yes/No

1b Consulting, including service as a technical or other advisor Yes/No

**RESEARCH SUPPORT**

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding Yes/No

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc. Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work? Yes/No

**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? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes/No

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships,
controlling interest in a company) Yes/No

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

4a Patents, trademarks, or copyrights (including pending applications) Yes/No

4b Proprietary know-how in a substance, technology or process Yes/No

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

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? Yes/No

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? Yes/No

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that 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 personal, professional, financial or business competitive advantage? Yes/No

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, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes/No

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? Yes/No

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? Yes/No

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

7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work)

Within the past 4 years, have you had employment or received research support or other funding from, 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? Yes/No

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 describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.
CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

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, I will promptly notify the responsible staff of WHO and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: ________________ Signature_______________________________