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WHO Expert Committee on Biological Standardization

Sixty-first report

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization



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Annex 6

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

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This document is intended to be scientific and advisory. Each of the following sections constitutes guidance for manufacturers of biological products. The parts of each section printed in small type are comments for additional guidance intended for manufacturers, which may benefit from these details.

Abbreviations

AEFI	adverse event following immunization
AMC	Advance Market Commitment
CHMP	Committee for Medicinal Products for Human Use
CTD	common technical document
EMA	European Medicines Agency
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practices
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
NRA	national regulatory authority
NCL	national control laboratory
OMCL	official medicine control laboratory
PSF	product summary file
PSPQ SC	Programmatic Suitability of Vaccines for Prequalification (Standing Committee)
PSUR	periodic safety updated report
UNICEF	United Nations Children's Fund
USA	United States of America
VVM	vaccine vial monitor

1. Introduction

The World Health Organization (WHO), through its Department of Immunization, Vaccines and Biologicals, provides advice to the United Nations Children's Fund (UNICEF) and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies. This service is called prequalification. The purpose of the United Nations prequalification assessment is to provide assurance that candidate vaccines: (a) meet WHO recommendations on quality, safety and efficacy, including compliance with WHO's recommended standards for good manufacturing practices (GMP) and good clinical practice

(GCP); and (b) meet the operational packaging and presentation specifications of the relevant United Nations agency. The aim is to ensure that vaccines provided through the United Nations for use in national immunization services in different countries are safe, effective and 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 United Nations was published initially in the thirty-ninth report of the WHO Expert Committee on Biological Standardization (1). Since then, a number of published revisions to the procedure have been implemented (in 1996, 2002 and 2005; 2).¹

The current document is a revision that takes into consideration challenges faced by the vaccines prequalification programme – such as the increasing number of submissions and the increasing diversity and complexity of the products submitted to WHO for evaluation, as well as the ongoing 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 fieldworkers, which equate to 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. The document proposes an update of the current procedure.

The prequalification procedure established by WHO for vaccines has been effective in promoting confidence in the quality of the vaccines shipped to countries through United Nations purchasing agencies. The procedure 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 (3);
- general understanding of the product and presentations offered, the production process, quality control methods, quality system in place, and available clinical data that are relevant to the target population;
- assurance of production consistency through compliance with GMP requirements and monitoring of continued compliance with specifications through testing of final product characteristics.

WHO is able to advise United Nations agencies as to whether vaccines effectively meet the Organization’s recommended requirements only if the

¹ The revisions published in 1996 and 2002 were superseded by those published in 2005 and are therefore not available.

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 on 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.

This update introduces a procedure for using, in certain circumstances, enhanced assistance from eligible NRAs (see section 4).

Under exceptional circumstances, extraordinary temporary measures may be applied in the situation where the NRA responsible for the regulatory oversight of a product fails to sustain its functionality with regard to WHO standards. Such measures are taken only where it is necessary to ensure a global supply of vaccines of assured quality. This procedure is applied to vaccines for which there is no immediate alternative source and where removal from the prequalified list would jeopardize the global supply.

As vaccines purchased by United Nations agencies are required 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 on the list of prequalified vaccines does not mean that, if evaluated, they would be found not to comply with the required standards. The database of prequalified vaccines can be consulted on the WHO web site (4).

WHO will define, in consultation with United Nations purchasing agencies, which vaccines are priorities for prequalification, and will make this information publicly available. Information on priority-setting for WHO vaccine prequalification is available on the WHO web site (5).

This exercise is required in order to focus the use of resources. Priorities are 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 conditions for acceptance of applications are as follows.

- The candidate vaccine is on the current list of priority products for United Nations prequalification.

- 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* (6).

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

- 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.

An applicant should check with the respective NRA whether it has been assessed by WHO. WHO will not be able to process an application until the WHO NRA assessment is conducted and the outcome is satisfactory.

- A marketing authorization 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 marketing authorizations in Europe) or that of the country of finishing and distribution. Alternatively, if it is intended that the EMA “scientific opinion”¹ should serve as a basis to facilitate the marketing authorization of the vaccine, the *Guideline on procedural aspects regarding a CHMP [Committee for Medicinal Products for Human Use] scientific opinion in the context of cooperation with the World Health Organization* (7) should be used.

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

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 Appendix 1) and during

¹ EMA scientific opinion, in accordance with Article 58 of Regulation (EC) No. 726/2004, is restricted exclusively to medicinal products that are not authorized within the European Union. However, the issuing of a scientific opinion does not prevent submission of a future European Union marketing authorization.

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. The steps of the prequalification procedure are shown in Appendix 2.

3.1 Official request and response

An application letter¹ is to be sent to the Coordinator, Quality, Safety and Standards, Department of Essential Medicines and Health Products in WHO, with copies to the vaccines prequalification manager and the relevant NRA, giving details of country and sites of manufacture, licensing status and the presentations put forward to United Nations agencies for procurement.

Application letters can be sent at any time and should provide the expected date of file submission.

To facilitate planning, manufacturers are encouraged to advise WHO as early as possible of their intention to submit a specific vaccine for evaluation.

WHO will acknowledge receipt and acceptance of the application letter by e-mail, with a copy to the NRA, and will respond with an official letter only 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 2 weeks of receipt of the official request.

3.2 Meetings with manufacturers

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

Such meetings are important for discussing 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

A manufacturer whose application letter is accepted will prepare and submit one hard copy and five electronic copies (on CD-ROM), in either Microsoft Word or

¹ The purpose of the application letter is to communicate to WHO the manufacturer's intention of submitting a vaccine for evaluation.

PDF format, of a product summary file (PSF), which should be fully up to date and written entirely in English following the WHO format provided below:

- Chapter 1: General information;
- Chapter 2: Personnel;
- Chapter 3: Premises and equipment;
- Chapter 4: Vaccine composition, presentations and schedules;
- Chapter 5: Production;
- Chapter 6: Quality control;
- Chapter 7: Stability;
- Chapter 8: Clinical experience;
- Chapter 9: Production and distribution data;
- Chapter 10: Update on regulatory actions.

The WHO format is required; however, the common technical document (CTD) format can be accepted so long as (a) a detailed cross-referencing of contents is presented; and (b) those aspects required by WHO but not included in the CTD requirements are presented. Where the PSF cross-references to the CTD format, the documentation may be in electronic form only. Electronic documents should be in searchable text where possible.

The information to be provided in the file is specified in Appendix 1 of this document.

WHO has established three deadlines per year for the submission of PSFs: 31 January, 31 May and 30 September.

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

3.3.1 Screening of the PSF 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 for a subsequent scheduled submission deadline without additional payment. In the 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 in the location 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 WHO prequalification* (6).

At the time of screening, vaccine candidates must be in compliance with the mandatory programmatic characteristics¹ as defined by WHO's Immunization Practices Advisory Committee. If screening reveals that the mandatory characteristics are not met, then the PSF will be rejected. If the prequalification secretariat identifies a deviation from the critical characteristics or a unique, novel and innovative characteristic, as defined by WHO (6), a recommendation from the Programmatic Suitability for Prequalification (PSPQ) Standing Committee is required.

The PSPQ Standing Committee is an advisory body to the prequalification secretariat and the director of the Department of Immunization, Vaccines and Biologicals. The Standing Committee consists of experts on immunization programmes and vaccines regulation. The terms of reference of the PSPQ Standing Committee are available in reference 8.

The Standing Committee will review the documentation exclusively related to the specific problem. During its review and discussion, which will lead to the formulation of recommendations, the PSPQ Standing Committee may engage in confidential discussion with manufacturers and other technical experts 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 3) and a declaration of interests form (see section 16 and Appendix 4) prior to taking up their responsibilities.

Under special circumstances, when there is limited access to a vaccine of public health importance, exceptional consideration will be given regarding the 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 prequalification secretariat and will take into account the recommendations of the PSPQ Standing Committee, public health needs and availability of alternative products.

The screening process will be put on hold while the PSPQ Standing Committee conducts the review. The duration of the review by the PSPQ Standing Committee will be no longer than 3 months. In case of rejection following a recommendation from the PSPQ Standing Committee, the reviewers may include a recommendation for resubmission after validation by research of the acceptability of specific vaccine characteristics.

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 reference 6).

When no review by the PSPQ Standing Committee is required, the manufacturer will be informed within 1 month from 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 experts¹ proposed for the evaluation, together with a copy of their curricula vitae. At the same 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 the acceptability of the proposed experts within 2 weeks. Payment of the fees without any further communication will be considered as *de facto* agreement to 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, and an invoice will be sent by WHO requesting payment of the screening fees. With the agreement of the manufacturer, the PSF will be destroyed by WHO.

3.3.2 PSF evaluation

The time frame for an initial review of a vaccine PSF will be 3 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. WHO takes no further action until the full complementary information is received.

The complementary information must be submitted in a single package containing 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 addressed 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 an acceptable action plan within 3 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 3 months.

¹ NRA staff, independent consultants or staff from consulting companies may be appointed as external experts, depending on the specific needs. The manufacturer has the right to reject one or more team members if 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 confidentiality agreement (see section 15 and Appendix 3) and a declaration of interests form (see section 16 and Appendix 4) for that specific evaluation.

3.4 Initial testing of vaccine samples

As soon as the PSF is accepted and when the prequalification procedure described in section 3.3 is applied, WHO will request the manufacturer to submit 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 bulks will be specified by WHO for one of the components).

The samples should be accompanied by the respective lot summary protocols, fully detailed as described in the WHO Guidelines for independent lot release of vaccines by regulatory authorities (9) and the detailed standard operating procedure 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.

WHO will send the vaccine samples to the 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 in conducting the relevant tests is 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 must be representative samples of the product that is intended for marketing 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 3 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 of where the testing is 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.

In general 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 a streamlined procedure.

3.5 WHO site audits

The main objectives of site audits are to assess whether the vaccine complies with WHO recommendations for production and quality control, whether

it meets the United Nations' specifications for tender (which reflect the needs of the immunization programmes at country level), whether the company has an adequate quality system in place, and whether the vaccine is produced in compliance with WHO-recommended GMP.¹ Other important aspects of the assessment include, but are not limited to, labelling, packaging, whether a post-marketing surveillance system is in place, vaccine vial monitor (VVM) implementation when required, and a stability programme.

Site audits are required for those manufacturers applying for the prequalification of new products to be evaluated for purchase by United Nations 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 United Nations agencies (or those that are already being purchased) meet (or continue to meet) WHO recommendations and tender specifications. As far as possible, site audits 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 under evaluation that have not been addressed by the NRA that did the inspection, including all those aspects that are specific to the United Nations 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, and usually within 2 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 experts who 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 curricula vitae of the proposed new members will be submitted to the company for clearance. The team will cover the range of expertise required to assess the vaccine in question from the different perspectives. A WHO staff member will lead the audit team and the members will act, on a temporary basis,

¹ With regard to aspects for which GMP requirements are not sufficiently detailed, other international guidelines should be followed by the manufacturer and appropriate justification for the choice provided. In such cases, WHO will assess against the standard used.

as expert advisers to WHO. In some circumstances, 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 with 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 matters related to the vaccine 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, the need for feedback on findings during inspections, updates on safety and efficacy data, variations to the marketing authorization/licence that may have been requested, marketing authorization/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 of 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, the follow-up assessments should be performed within no more than 6 months. The outcome of the follow-up assessment may have an impact on the final decision about 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 the main findings, recommendations and closing remarks, is prepared by the WHO team and left with the manufacturer. The findings and recommendations will also be reported to company and NRA representatives during the closing meeting, thus providing an opportunity for discussion, questions and clarifications.

The final report with findings, recommendations and conclusions is prepared by the team and sent to the company, with a copy to the NRA, within 30 days of completion of the visit. If corrective actions need to be taken by the manufacturer, WHO will postpone its final recommendations to the concerned United Nations agencies until such corrections 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 on the acceptability of the product for supply to United Nations agencies may be taken in consultation with an ad hoc committee on vaccine prequalification convened by WHO for this purpose.

Once WHO considers that the process is complete, and if the outcome is satisfactory, the Organization will send a letter to the United Nations agencies and to the GAVI Alliance in the case of Advance Market Commitment- (AMC-)¹ eligible products advising on: (a) the 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, the management of WHO's Department of Immunization, Vaccines and Biologicals, and the approved VVM manufacturer.

For AMC-eligible products, WHO will send a report to the GAVI Alliance and the AMC's Independent Assessment Committee, providing the rationale for confirming or otherwise that the vaccine meets the target product profile.

The vaccine will be included in the WHO list of prequalified vaccines immediately after the letter is sent to the United Nations agencies. A page providing the basis for the acceptance of the prequalification of the specific vaccine will also be included in the list. The current list may be consulted on the WHO web site (4). In the event of disagreement between the manufacturer and WHO, a standard operating procedure for the handling of such disagreements will be followed, in order to discuss and resolve the issue.

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.

Communications, at any time, with the experts involved in a vaccine evaluation should be conducted through the WHO focal person in charge of the product.

4. Considerations for streamlining the prequalification procedure on the basis of 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 on effective regulatory oversight by the responsible NRA has the potential to play a critical role in facilitating the prequalification

¹ 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.

procedure. It is considered that the experience in the context of pandemic influenza can be extrapolated to other vaccines.

The proposed procedure envisages enhanced reliance on the oversight carried out by the responsible NRA, when the authority 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 additional performance indicators to supplement 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, in order to ensure standards for quality, safety and efficacy at least equivalent to those recommended by WHO (such as those published in the WHO Technical Report Series) (10).¹

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;
 - the extent of the 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, thus 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 vaccines that have been

¹ And subsequent updates to reference 10 published after every meeting of the WHO Expert Committee on Biological Standardization.

licensed by selected NRAs that 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 outlines the shared understanding of roles, responsibilities and commitments of each party. Provisions for confidentiality will be 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, and nonclinical 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 this with a short audit focused on aspects related to United Nations tender specifications, instead of conducting a full site audit.

4.2.1 Review of NRA assessment reports instead of the PSF

In this case, WHO recognizes the assessment of the marketing authorization/licence dossier performed by 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 on the basis of the information provided by the NRA responsible for the marketing authorization/licensing of the vaccine submitted for prequalification. If there are questions related to issues not addressed in the NRA reports, WHO will contact the manufacturer directly and copy the NRA on such exchanges of additional information.

Typically, the responsible NRA does not focus its review either on aspects that are specific to the national immunization schedules of countries that receive the vaccines through the United Nations, or on the programme needs stated in United Nations specifications. These elements must be assessed by WHO, except

in the case of the EMA scientific opinion procedure (Article 58 of Regulation (EC) No. 726/2004).

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

- mandatory and critical characteristics from the programmatic point of view;
- eligibility, when required, for the AMC through review of the proposed product characteristics against the target product profile criteria;
- confirmation that the vaccine meets WHO recommendations;
- stability data to ensure that the vaccine meets the needs of immunization programmes in developing countries (particularly those with weak cold-chain systems), and assignment of a VVM category;
- clinical data to ensure that the vaccine is suitable for the target population;
- recommended immunization schedules to ensure compatibility with those of national immunization programmes;
- suitability of samples, labels, inserts and packaging to meet the United Nations agencies' tender requirements;
- packaging for international shipment and its validation.

The applicant must provide WHO with a copy of the file submitted to the NRA and relevant sections of the PSF to cover information required on the items listed above.

An NRA that does not require renewal of the licence on a regular basis should have an alternative mechanism in place to conduct ongoing monitoring of the quality, safety and efficacy of the vaccines over which it exercises 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.

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

Vaccines submitted for the initial evaluation for prequalification are categorized by WHO into one of the four categories described in Appendix 5. Vaccines that meet the criteria described under categories I to III in Appendix 5 may be evaluated by 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). On the basis of 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 whether the information supplied can be accepted by WHO for prequalification purposes.

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

4.2.3 **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 procedure 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 United Nations 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, AEFIs reported, or other matters that could affect the normal supply of vaccine to United Nations agencies.

4.2.4 **Other considerations**

The implementation of the streamlined prequalification procedure described above requires an eligible authority and the willingness of this authority to engage in a 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 in making its reports

available in English. Specificities of the collaboration (nature and extent) should be defined on a case-by-case basis and should be 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. In these cases, the report of the assessment is performed in accordance with the standard prequalification procedure (see section 3).

4.3 Vaccines with positive scientific opinion issued by the EMA

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

All vaccine applications submitted for evaluation under Article 58, and intended for immediate prequalification after a positive scientific opinion, will be assessed through a streamlined procedure (see Appendix 6), in such a way that the time elapsed between the 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 in special circumstances. This procedure is applicable to licensed vaccines (marketing authorization available) that are part of routine immunization programmes, or those that are used only in an emergency response; it is not applicable in the case of novel vaccines not yet introduced or recently introduced into 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 shortage¹ of a vaccine that puts at risk the global supply of routine immunization programmes and/or an eradication effort;
- an emergency situation (i.e. an outbreak or epidemic of a disease for which no prequalified vaccine is available, or where availability is insufficient and an additional source of the same vaccine is required);

¹ As agreed with United Nations purchasing agencies and other partners.

- exceptional situations such as:
 - declaration of a pandemic of a disease for which production capacity needs to be established;
 - need for alternatives 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 submission to the NRA for marketing authorization purposes upon:

- special request from the manufacturer; and
- endorsement by senior management of WHO.

In 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. As in the streamlined approach described under section 4, consideration should be given to review of information provided by the relevant regulatory authority with the manufacturer's permission (including inspection reports), and to the results of tests performed by the relevant NRA/NCL to facilitate the evaluation process.

6. Special considerations for accepting submissions of vaccines manufactured at multiple sites or in different countries

It is a precondition of any submission of vaccines for prequalification evaluation that the NRA responsible for the regulatory oversight of the product must 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 over time.

Owing to the increasing diversity and complexity of the vaccines that can be manufactured at multiple sites, including different countries, WHO has to ensure that the regulatory oversight is fully exercised and that responsibilities are clearly defined at all stages of production by the relevant functional NRAs. Certain criteria will be applied, as described here.

The assessment evaluation will be product-specific, as for vaccines produced by one company at a single site or in one country.

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

If the formulation process used by the manufacturer of finished product of a vaccine (company A) is different from that used by the manufacturer of the vaccine from seed (company B) (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 manufacturer of the finished product has authorization from the vaccine manufacturer producing the bulk to export the final product. In a 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 on distribution of the combination vaccines) is required.

There must be a long-term contract between manufacturers, although a minimum of two 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 from 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 will need to exercise full regulatory oversight of the product. This means that this NRA is responsible for technical, nonclinical and clinical review, and for regulatory inspections of the facilities in each country performing manufacturing operations. This NRA would also grant the marketing authorization, perform lot release, including testing as necessary, as well as post-marketing surveillance.

For finished product manufacturers of OPV vaccines to be eligible for the prequalification process, as an exception the bulk material must have been evaluated as part of a vaccine already prequalified by WHO for the United Nations market.

In 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 in order to ensure the ongoing regulatory oversight of vaccines:

- responsibility for overseeing manufacturing of different production steps should be shared between the relevant NRAs (functionality being a condition), with relevant agreements in place, and marketing authorization/licensing and release should be under the responsibility of the NRA of the country where the vaccine is distributed;
- consideration may be given to use of 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;
- use of a production site in a country in which the NRA has not been assessed as functional requires that the NRA in the country of manufacture of the final product takes full responsibility for the oversight of the product. If this does not apply and/or Article 58 of Regulation (EC) No. 726/2004 cannot be used for any reason, this production 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 normally be 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 acceptability.

WHO encourages early discussions with manufacturers and their respective NRAs if they plan to embark on a project involving multiple sites or countries in the production process, in order 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 Nations agency must have been released by the NRA in advance of shipping. Copies 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 Essential Medicines and Health Products, WHO, Geneva. In addition, a suitable number of samples (defined during the assessment process) of each vaccine lot supplied to the United Nations agencies will be retained by the manufacturer, in order to be made available to WHO on request, for testing.

The manufacturer must inform WHO of all changes/variations that must be notified or submitted to the NRA regarding the formulation, presentation, methods of manufacture or quality control, specifications, facilities, or any other aspects that might (a) result in a change of safety and/or efficacy of the vaccine; or (b) change the basis of the regulatory approval of the NRA.

If the regulations of the manufacturing country do not require approval by the NRA of changes/variations that fall under (a) and (b) above, WHO must 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) will be sufficient.

When such reliance is not established, changes/variations that fall under (a) and (b) above must be accepted by WHO before United Nations 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 United Nations tender requirements, manufacturers must comply with the revised United Nations 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 the case of noncompliance with post-prequalification commitments and/or in the 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 on a product, since initial prequalification). Table A6.1 is provided as guidance.

Table A6.1
Summary of changes/variations to the product report

Description of variation	PSF chapter/section	CTD cross-reference (where appropriate)	Responsible NRA ^a		WHO prior acceptance date (where required); or WHO notification date (as applicable) ^c
			Prior approval date	Date of acknowledgement of notifiable change ^b or not applicable to national registration [✓ if required]	

^a For the columns under the heading "Responsible NRA", one of the three choices will be relevant and the manufacturer should provide the requested information in the relevant column.

^b Provide the date of the NRA letter acknowledging the notification, or indicate if the NRA has not responded and hence give the date the change was implemented under national law.

^c See "Points to consider" in reference 11.

- B. The manufacturer should provide testing results from the ongoing stability programme since the previous annual report (or, for the first annual report on a product, since initial prequalification).
- Production and distribution data should include a summary table showing the quantity of batches and doses of finished product distributed since the previous annual report. The table should include product used domestically and product exported. The batches supplied to United Nations agencies should be indicated. If more than one presentation is manufactured, these should be listed separately.
- C. The manufacturer should provide details of GMP inspections (in which the prequalified product was within the scope of inspection) performed since the previous annual report.
- D. A summary update on implementation of post-prequalification commitments should be provided by the manufacturer if these are indicated in the approval letter or reassessment report. These may be, for instance:
- 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 that might affect the international supply of this vaccine, both in terms of volume and/or lead times.
- E. The periodic safety update report should be provided (electronic data only).

Following review of the annual report, WHO may request supporting data.

The deadline for submission of the first annual report should be one year after the date of prequalification, with subsequent submissions each year on the same date. The manufacturer may provide the latest annual report submitted to the NRA provided that this contains the relevant information. The established deadlines for submission of PSFs will apply (31 January, 31 May and 30 September).

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 the responsible NRA;
- prior experience with the manufacturer and the specific product;
- variations to the product indicated in annual reports since the previous assessment;
- interruptions to production and/or supply to United Nations 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 United Nations 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 6–12 months prior to the time of the proposed assessment. 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 that 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 file that was submitted initially. Only sections indicated as changed will be evaluated. Changes made that are not indicated in the change control section will not be considered as approved.

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

Consideration of the need for and scope of a site audit at the time of reassessment will take into account the demonstrated history of regulatory inspection of the facility by the NRA (including 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, the vaccine 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

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 United Nations agencies will be requested from the manufacturer. The manufacturer will provide lot summary protocols and the NRA/NCL release certificate as appropriate, for review. Manufacturers should commit to keeping an adequate number of retention samples for this testing programme.

Manufacturers will, in any case, be contacted for follow-up actions if they fail 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

11.1 Vaccine quality complaints

In the 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, the testing results and related data.

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

11.2 AEFIs

In the case of serious AEFIs, or whenever WHO considers necessary, the Organization will conduct an investigation according to established procedure (12). 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 requested from the NRA/NCL exercising

the regulatory oversight of the vaccine when AEFIs are investigated. Further testing would be resource-intensive and may not yield useful data. Therefore, the testing of a vaccine lot/batch will 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 will indicate whether testing is required and, if so, which type of test(s).

Depending on the tests to be performed, the number of unopened containers required for testing (sampled from the field and from the manufacturer) needs to be calculated so that the sample is representative and allows definitive conclusions to be drawn about the relevant lot. In the event that testing is needed, WHO will contact one of the WHO-contracted laboratories that can perform the test and subsequently inform the national authorities of the number of vaccine vials to be sent to WHO, as well as of other logistical 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 both of the following:

- the manufacturers' lots of vaccines should be more closely monitored through additional testing, visits 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;
- purchase of the vaccine by United Nations agencies should be suspended pending investigation and resolution of the problem.

Failures relating to gaps in the manufacturing and/or quality system of the manufacturer may require a complete reassessment of the vaccine.

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

13. Handling out-of-specification/inconsistent results between laboratories

Owing to the increased complexity of the vaccines and new combinations currently available or in the pipeline for prequalification, challenges may be posed by the diversity of the methods applied for the quality control of vaccines,

as well as by the evaluation of results obtained through independent testing of such vaccines by WHO-contracted laboratories.

In the case of inconsistent results from two WHO-contracted laboratories, WHO may require testing of the vaccine by a third laboratory.

WHO may convene an ad hoc committee of experts to assess the combined results and make a recommendation to the Organization. Representatives from the WHO laboratories may take part in this committee. The recommendation from the committee will be 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 United Nations agency purchase is covered by the manufacturers. It involves a screening fee and an evaluation fee. Both are paid after the screening of the PSF 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 are charged on a cost-recovery basis. The evaluation of a vaccine commences only after payment of the fee and receipt by WHO of the PSF.

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 out-of-specification results), is charged to the manufacturers, as an annual fee at the beginning of each calendar year. The expenses related to reassessment site audits are charged on a cost-recovery basis. 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 regularly.

Fees (screening, initial evaluation of candidate vaccines, and annual maintenance) are kept on a separate list available on the WHO web site, along with other information and guidance documents for vaccine manufacturers (11).

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 United Nations agencies may include confidential information. However, if, in the opinion of the manufacturer, any information submitted to WHO and its expert team members in the course of the (re)assessment procedure includes confidential

information, the manufacturer must advise WHO of this in writing prior to, or at the same time as, the disclosure, duly identifying the confidential information in question. Notwithstanding the above, 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 out here.

WHO will treat any information contained in the PSF (see Appendix 1) and information disclosed during site audits as confidential and proprietary to the manufacturer. In this connection, WHO will take all reasonable measures to ensure that (a) the confidential information is not used for any other purpose than the (re)assessment procedure described in this document; and (b) the confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use.

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:

- was known to them prior to any disclosure by the manufacturer; or
- was in the public domain at the time of disclosure by the manufacturer; or
- has become part of the public domain through no fault of WHO and/or any of its expert team members; or
- 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 Appendix 3, prior to taking up their responsibilities for WHO.

16. 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, which is attached as Appendix 4. In addition, the confidentiality agreement referred to in section 15 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 that:

- 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
- 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 will provide the curricula vitae of the experts. The manufacturer will then have the opportunity to express possible concerns regarding any of the expert team members. 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.

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and Dr D. Wood, World Health Organization, Geneva, Switzerland, taking into account the recommendations from the ad hoc committee members and posted on the WHO biologicals web site for public consultation.

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

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Appendix 1

The PSF

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

The PSF 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, telephone, fax and 24-hour telephone numbers, and the principal contacts of the company) and its relation to other sites where steps of the process or testing activities (for both the active biological components and diluent) may be conducted.
- 1.2 List pharmaceutical and non-pharmaceutical manufacturing activities carried out at the site, as licensed by the NRA. 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 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 the 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 company responsible for manufacture.
- 1.7 Give a short description of the internal audit system and the programme for qualifying suppliers of raw materials.
- 1.8 List the 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 (heads of production, quality assurance, quality control, warehousing and engineering).
- 2.2 Provide curricula vitae 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) of production personnel, and for 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 must be submitted.

- 3.1 Provide simple, currently valid, floor plans and text descriptions of manufacturing and quality control areas. The floor plans should give an indication of scale, air flow and flows of materials, product, personnel and waste (architectural or engineering drawings are not required), room classification, and air handling unit identification by room.
- 3.2 Describe the nature of construction and finishes of manufacturing and quality control areas.
- 3.3 Describe ventilation systems in the manufacturing and quality control 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. A description of the environmental monitoring programme is required.

- 3.4 Provide information on special areas for the handling of highly toxic, hazardous and sensitizing materials.
- 3.5 Describe water systems (schematic drawings of the systems are desirable, showing storage tanks, loops, points of use and sampling points), including sanitation procedures and schedules. A description of quality control testing and schedules is required.
- 3.6 Describe the maintenance system (planned preventive maintenance programmes and recording system).
- 3.7 Complete a table (as in the example shown), briefly describing major production and control laboratory equipment used for the production of the vaccine (including diluent).

Room ID	Major equipment in room	Clean room class

- 3.8 For products where a separate facility is required (e.g. tetanus, bacille Calmette–Guérin vaccine [BCG]), describe how separation is achieved.
- 3.9 Describe qualification and validation procedures, including computerized recording and controller systems. A description of the validation master plan is required.
- 3.10 Provide a brief description of the procedures for cleaning manufacturing areas and equipment. For multipurpose areas, briefly describe 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 United Nations agencies, including diluents (if applicable), combination products, forms, dose sizes, type of containers, VVM type used, and descriptions of application devices (e.g. autodisable 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 United Nations agency supply (in English). French, Portuguese, Russian and Spanish versions need

to be made available before supply to United Nations agencies starts. Include the calculated volume per dose in cm³ of the secondary packaging.

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

Chapter 5: Production¹

- 5.1 Provide the following:

- the manufacturing formulae 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);
- the batching formula for each batch size of final formulated bulk product;
- the approximate number of vials and doses for each fill size and presentation;
- 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 of the master cell banks/virus seeds. Detailed flowcharts should be provided to indicate:

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

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

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

¹ WHO recommendations or guidelines and United Nations agencies' tender specifications must be met. For each specific test done, the international standard met should be identified.

- 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 the control tests performed on raw materials, with appropriate characterization of starting materials, namely:
 - list of raw materials meeting compendial specifications, indicating the pharmacopoeia;
 - list of raw materials meeting in-house specifications, including the tests performed and specifications;
 - list of biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies and human diseases (HIV, hepatitis, etc.) in the final product;
 - list of media with ingredients, tests performed and specifications.
- 6.1.2 List the control tests performed on labelling and packaging material(s), including primary and secondary packaging material.
- 6.1.3 Describe the qualification criteria for suppliers of raw material and relevant certificates.

6.2 *Intermediate products* (as appropriate)

- 6.2.1 List the routine tests performed and specifications for intermediates. Include copies of standard operating procedures for critical quality-control tests (uncontrolled copies or concise descriptions of the method and re-test criteria are acceptable).
- 6.2.2 List the assay validation activities performed.

6.3 *Finished product* (including diluent)

- 6.3.1 List the routine tests performed and specifications for the final product. Concise descriptions of the method and retest criteria are acceptable but full standard operating procedures in English should be made available on request.

- 6.3.2 List the assay validation activities performed.
- 6.3.3 List the final lots internally rejected in the previous 2 years and the reasons for rejection.

Chapter 7: Stability

Stability studies are expected to have been designed and conducted to meet WHO guidance (1).

7.1 Provide information on stability tests on intermediates, namely:

- information on containers for intermediate products;
- assigned shelf-life and storage conditions;
- quality control methods and specifications, and rationale for the choice of tests for determining stability;
- 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, namely:

- assigned shelf-life and storage conditions;
- quality control methods and specifications, and rationale for the choice of tests for determining stability profile;
- 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 data on final product stability at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the choice of VVM for use with the product (2).

7.3 Provide information on stability testing of diluents and reconstituted vaccine in the 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 documents and any related updates in the WHO Technical Report Series:

- Guidelines on clinical evaluation of vaccines: regulatory expectations (3)
- WHO Guidelines on nonclinical evaluation of vaccines (4)
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (5).

Other guidance documents are:

- *Clinical considerations for evaluation of vaccines for prequalification* (6)
- *ICH guidelines* (7).

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 establish sufficiently a history of safe and effective use.

Note 3: In some cases, where the information received regarding the sections detailed below is not sufficient, is 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 the date of protocol approval by the ethics committee and the NRA;

- evidence of 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, in a tabulation or brief summary, the following information should be provided:

- the type of study;
- the rationale for its conduct;
- the location(s) of study sites;
- the dates of the study;
- the numbers and ages of subjects;
- a statement of final conclusions on safety and immunogenicity.

Copies of all publications and abstracts relating to 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 a 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, where 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 (e.g. 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. 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*

Whenever possible, the applicant should provide the clinical sections of the NRA assessment reports from the country of origin and/or country where the vaccine is initially licensed. Assessment reports for both initial licensure and 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 *Post-marketing pharmacovigilance*

Provide an outline of the post-marketing pharmacovigilance plan for the product.

8.3.2 *Initial evaluation of vaccines that have been on 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 5 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 judgement of seriousness and whether or not the event was expected (in the light of the prescribing information) should be provided where this is 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 following the ICH format, from all geographical areas where the vaccine is used, or the absence of such information should be defended.

8.3.3 *Recently licensed vaccines*

In the case of vaccines that have recently been 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 5 years, or as long as the vaccine has been marketed (when shorter than 5 years), provide the fullest possible description of each case, including any information there may be on investigations, actions, patient treatment and outcome. This information should 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 3 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 United Nations supply. Recommendations provided in the most recent version of the WHO *Guidelines on the international packaging and shipping of vaccines* shall be followed (8).
- 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 the regulatory requirements in case of recalls. Include provisions for informing WHO and the United Nations agencies.
- 9.6 Give the quantity of bulk vaccine destined for United Nations agencies that has been supplied to contract fillers/packagegers for finalization (list individually).

Chapter 10: Update on regulatory actions

10.1 Provide a copy of regulatory documentation, namely:

- marketing authorizations for all formulations;
- information on refusals, withdrawals or suspensions, including those initiated by the manufacturer;
- the 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 the initial licensure was granted.

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

10.7 List inspections conducted by NRAs within the previous 2 years, including the scope of each inspection.

10.8 List inspections conducted by foreign authorities within the previous 2 years, including the scope of each inspection.

References

1. *Guidelines on stability evaluation of vaccines*. Geneva, World Health Organization, 2006 (WHO/BS/06.2049; http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049.Stability.final.09_Nov_06.pdf, accessed 20 February 2013).
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5. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *WHO Expert Committee on the Use of Essential Drugs. Sixth report*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850; http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf, accessed 20 February 2013), Annex 3.
6. *Clinical considerations for evaluation of vaccines for prequalification*. Geneva, World Health Organization, 2010 (http://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf, accessed 20 February 2013).
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8. *Guidelines on the international packaging and shipping of vaccines*. Geneva, World Health Organization, 2005 (WHO/IVB/05.23; http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.23_eng.pdf, accessed 20 February 2013).

Appendix 2

Flowcharts of WHO prequalification for vaccines

Figure 1
Overall process

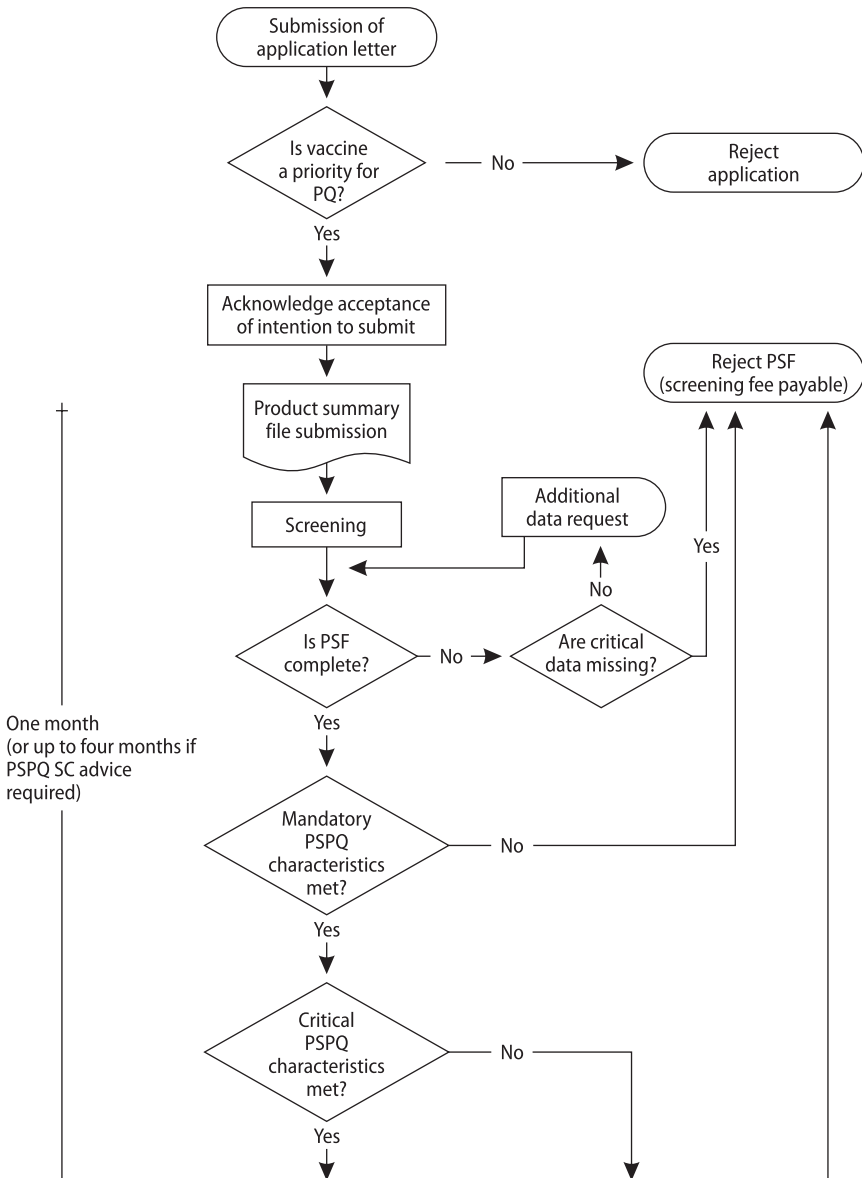
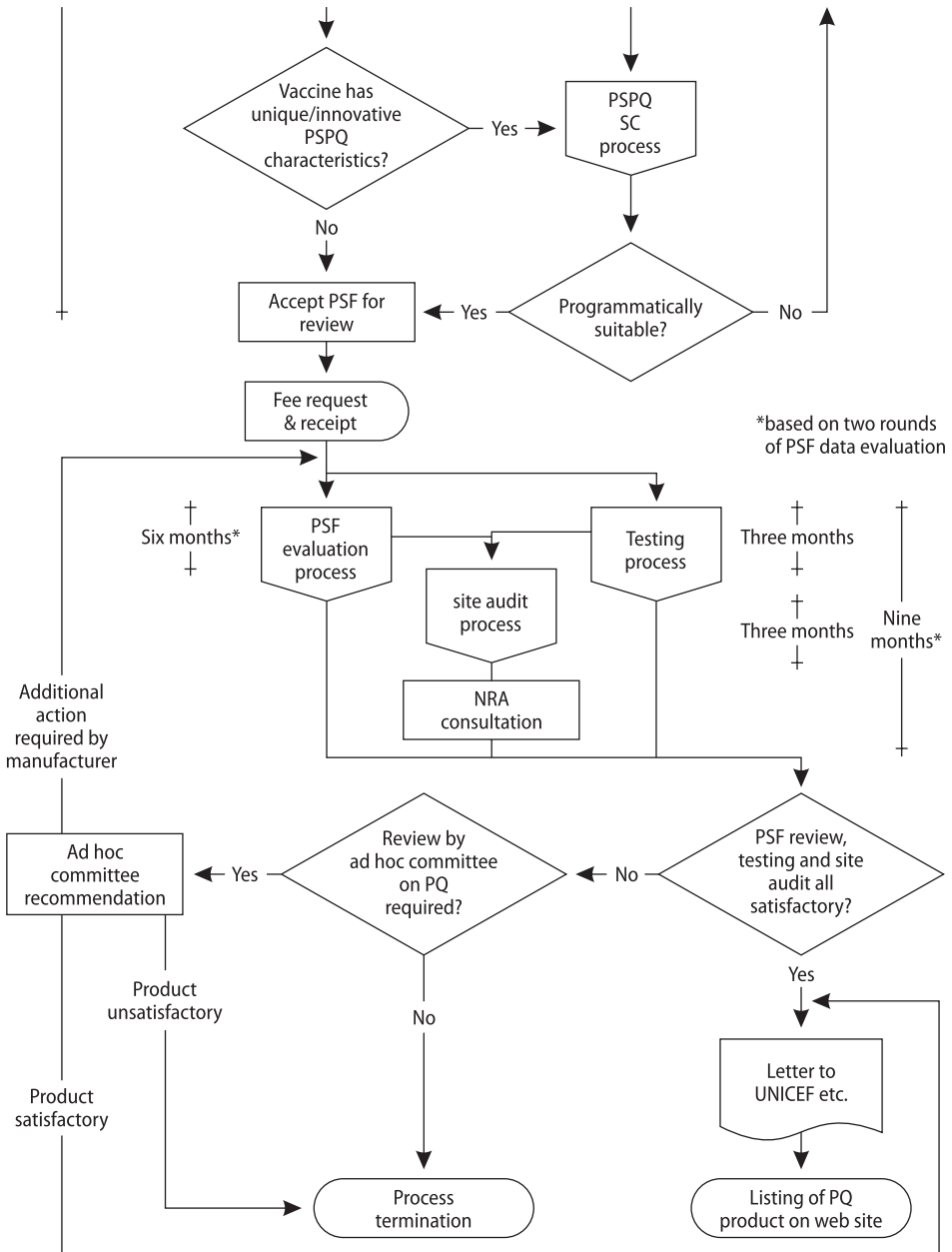



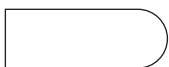
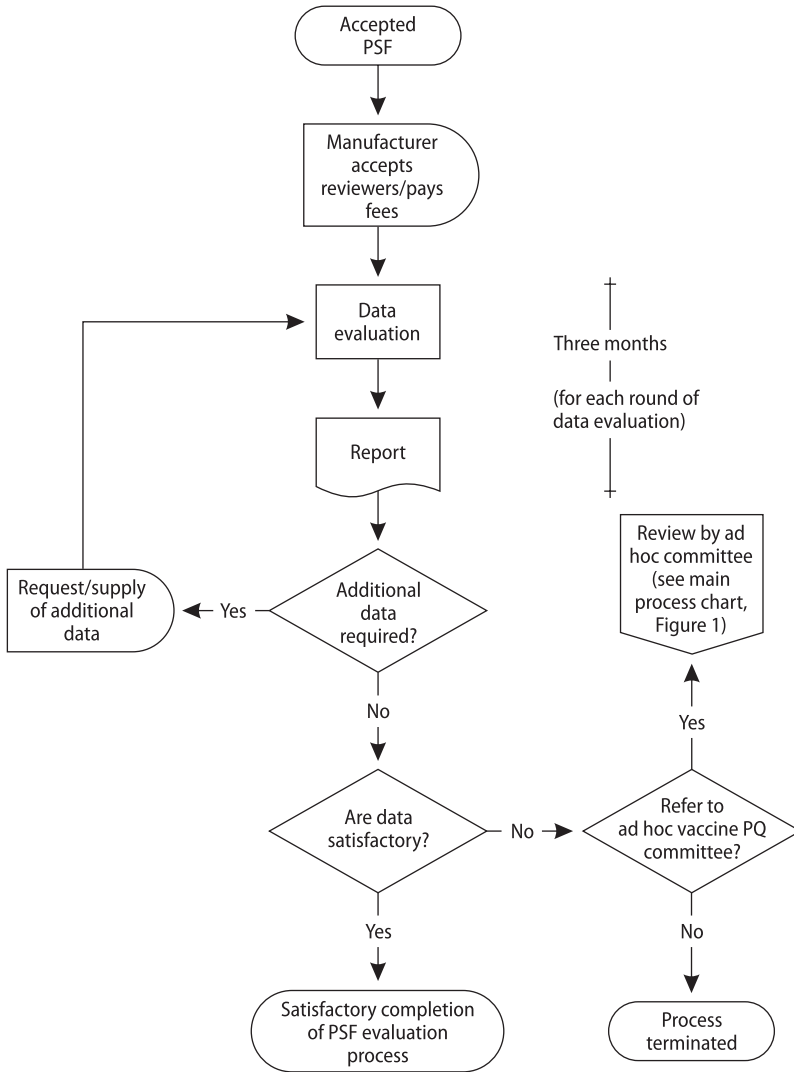
Figure 1 continued



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

PQ, prequalification; PSPQ, Programmatic suitability for prequalification; SC, Standing Committee.

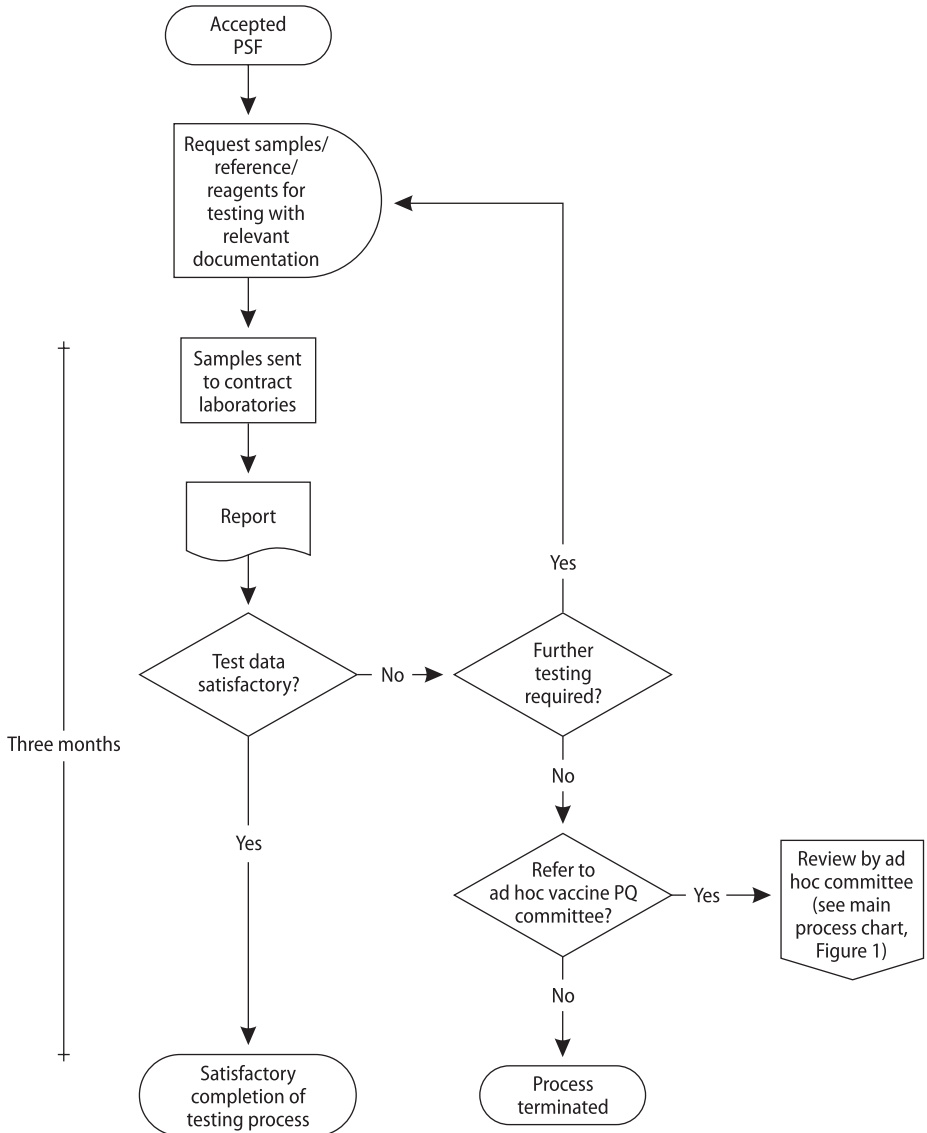
Figure 2
Product summary file evaluation



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

PQ, prequalification.

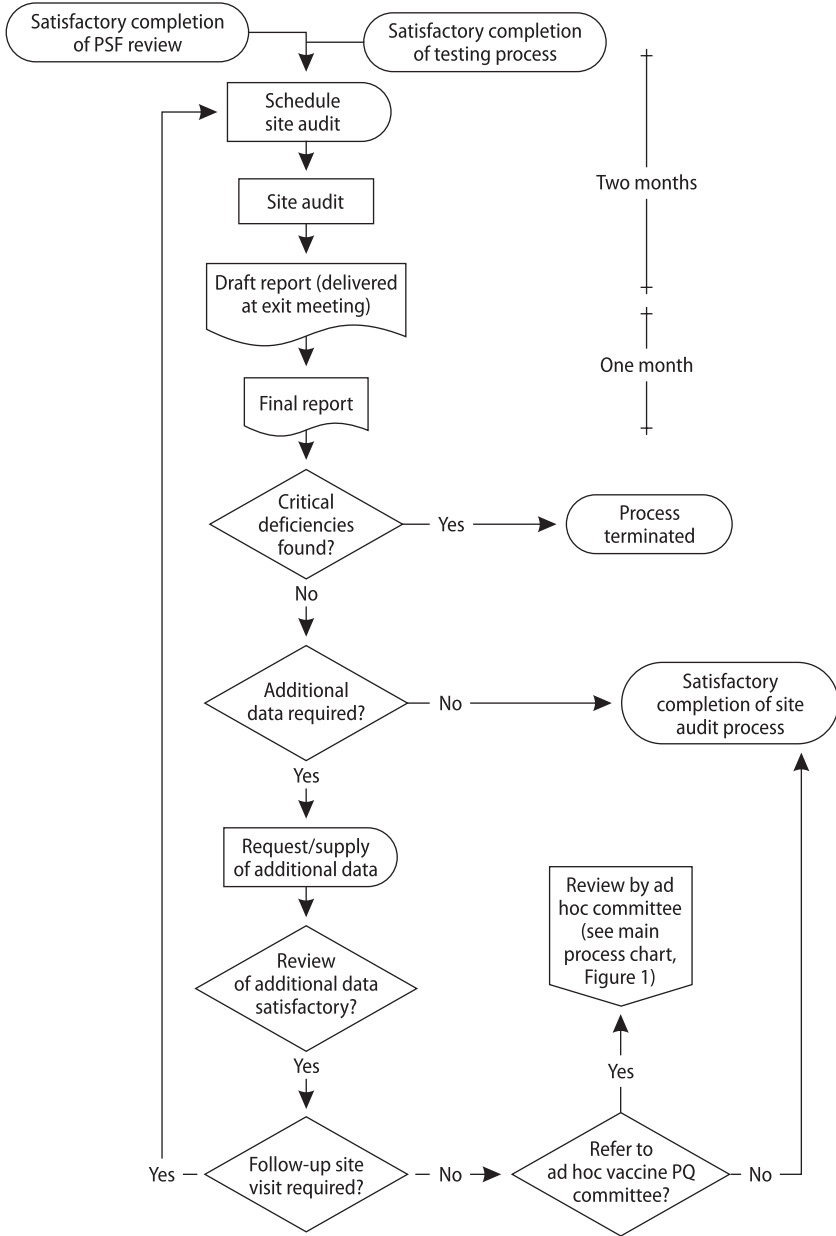
Figure 3
Testing process



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

PQ, prequalification.

Figure 4
Site audit



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

PQ, prequalification.

Appendix 3

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 that is proprietary to WHO or to the manufacturer(s) of the vaccine(s) that need(s) to be assessed for purchase by United Nations 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 that:

- (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 that 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: _____

Appendix 4

Declaration of interests for WHO experts

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 that 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 that 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 the 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, time frame 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: _____

E-mail: _____

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):

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 adviser **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 speaker's 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.*

Nos. 1–4; 7 Type of interest, question number and category (e.g. Intellectual Property 4.a copyrights) <i>and</i> basic descriptive details	Name of company, organization, or institution	Belongs to you, a family member, employer, research unit or other?	Amount of income or value of interest (if not disclosed, is assumed to be significant)	Current interest (or year ceased)

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 _____

Appendix 5

Testing approach for initial evaluation for prequalification

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post-prequalification
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	<ul style="list-style-type: none"> Review of United Nations 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 at least three lots formulated from consecutive bulk lots Review of the trends of the testing results of both NCL and manufacturer (if applicable) Review of the control chart of the reference used in manufacturer's and NCL's assays Review of the method validation of the manufacturer and the NCL may be required 	<ul style="list-style-type: none"> Detailed standard operating procedures 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 	<ul style="list-style-type: none"> Commitment from the manufacturer to keep retention samples for WHO-contracted laboratories Testing of the vaccine through the targeted testing programme

Table continued

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post-prequalification
II	Novel vaccine released by a competent NRA/NCL responsible for the regulatory oversight; Validation of the critical tests is in progress	<ul style="list-style-type: none"> • Review of United Nations 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 at least three 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 prequalification evaluation • Review of the method validation of the manufacturer and the control chart of the reference used in the manufacturer's assays may be required • Agreement to perform and provide results to WHO before prequalification is granted 	<ul style="list-style-type: none"> • Detailed standard operating procedures 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 	<ul style="list-style-type: none"> • Commitment from the manufacturer to keep retention samples for testing by WHO-contracted laboratories • Testing of the vaccine through the targeted testing programme

Table continued

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post-prequalification
III	Traditional vaccine released by a competent NRA/NCL responsible for the regulatory oversight; NCL is performing the critical tests on a regular basis	<ul style="list-style-type: none"> • Review of United Nations 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 at least three lots formulated from consecutive bulk lots • Review of the trends of the testing results of both the NCL and the manufacturer • Review the control chart of the reference used in the manufacturer's and the NCL's assays 	<ul style="list-style-type: none"> • Detailed standard operating procedures for testing the product characteristics (relevant tests) • Biological reagents and reference materials for the tests by WHO-contracted laboratories 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Review of United Nations 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 prequalification is granted • Agreement with the NCL to validate the tests 	<ul style="list-style-type: none"> • Detailed standard operating procedures for testing the product characteristics (relevant tests) 	

Table continued

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post-prequalification
IV	<ul style="list-style-type: none"> • Review of the testing results by the manufacturer (raw data) of at least three lots formulated from consecutive bulks lots • Review of the control chart of the reference used in the manufacturer's assays • For novel vaccines, review of the method of validation of the manufacturer 	<ul style="list-style-type: none"> • 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 6

Prequalification procedure for vaccines evaluated by the EMA under Article 58 of Regulation (EC) No. 726/2004

Background

WHO provides a service to UNICEF and other United Nations 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 United Nations agency, and are produced and overseen in accordance with the principles and specifications recommended by WHO for GMP, and for 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 those with a legal presence in the European Community) intended for exclusive use in markets outside the European Community, the EMA established a mechanism (Article 58 of Regulation (EC) No. 726/2004) whereby the EMA may give a scientific opinion, in the context of cooperation with WHO.

WHO recognizes that the evaluation by EMA under Article 58 is conducted 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). WHO provides input at different stages of the process, including 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

The applicant must submit the following:

- (1) An application letter is to be sent to the Coordinator, Quality, Safety and Standards, Department of Essential Medicines and Health Products at WHO, with a copy to the vaccines prequalification manager and the EMA, with details of the country and sites of manufacture and presentations offered.

Application letters can be sent at any time after the submission of the dossier to the 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 the EMA will share 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) An electronic copy of the dossier submitted to the EMA for evaluation under Article 58.
- (4) Technical information relevant to United Nations specifications, including information relevant to the programmatic suitability of the vaccine.
- (5) Notification about the official medical control laboratory (OMCL) selected for any testing required by the EMA for evaluation under Article 58 or for prequalification by WHO.
- (6) Fees (see section 14).

The evaluation process

WHO will base the evaluation on the following:

- the EMA Article 58 scientific opinion and its annexed assessment report from EMA/CHMP;
- a certificate of analysis of consistency lots by a qualified (OMCL) laboratory;
- reports from relevant inspections (GMP, GCP and good laboratory practice) jointly agreed by WHO and the EMA and performed during the EMA/CHMP evaluation procedure for Article 58 scientific opinion.

Although the EMA/CHMP procedure under Article 58 of Regulation (EC) No. 726/2004 is done by rapporteur/co-rapporteur, in collaboration with WHO and its experts/expert groups, with the evaluation ensuring that the clinical data provided by the applicant is relevant to the United Nations target population at the intended schedules, other programmatic aspects reflected in the tender specifications of the United Nations 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 number of reviews by WHO will remain essential, namely:

- confirmation that the vaccine meets the WHO recommendations and United Nations tender specifications;
- review of stability data to ensure they meet the needs of immunization programmes in developing countries (particularly those with weak cold-chain systems) and to assign a VVM category;*
- review of recommended immunization schedules to ensure compatibility with those existing in national immunization programmes and non-interference with co-administered vaccines;*
- review of samples, labels, inserts and packaging to suit the United Nations agency tender requirements;*
- review of mandatory, critical and innovative product characteristics from the programmatic point of view;*
- review of packaging for international shipment and its validation;
- 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: The items marked * 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 should indicate specifically where these have been addressed in EMA/CHMP Article 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 United Nations agencies, advising on the compliance of the vaccine with both the WHO recommendations and the specifications of the relevant United Nations 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_vaccine_list_en/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 United Nations

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 United Nations agencies;
- monitoring of continued compliance with specifications;
- follow-up of complaints and reports of AEFI.

The above list is indicative but not exhaustive.

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

These activities will be conducted, whenever applicable, in collaboration with the EMA within the context of Article 58 of Regulation (EC) No. 726/2004.

Annex 7

Biological substances: International Standards and Reference Reagents

A list of International Standards and Reference Reagents for biological substances was issued in WHO Technical Report Series, No. 897, 2000 (Annex 4) and an updated version is available on the Internet at <http://www.who.int/biologicals>. Copies of the list may be obtained from appointed sales agents for WHO publications or from WHO Press, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int; web site: <http://www.who.int/bookorders>).

At its meeting in October 2010, the Expert Committee made the following changes to the previous list.

The Transfusion-relevant bacterial strain repository is held and distributed by the Paul-Ehrlich-Institute, 63225 Langen, Germany. The Second International Standard for vancomycin is held and distributed by the European Directorate for the Quality of Medicines & Healthcare (EDQM), Council of Europe, 7 Allée Kastner, CS 30026, F-67081 Strasbourg, France. The other substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts, EN6 3QG, England.

Additions

Preparation	Activity	Status
Antibiotics		
Vancomycin	109 700 IU per vial	Second International Standard
Blood products and related substances		
Preparations of four bacterial strains (<i>Staphylococcus epidermidis</i> , <i>Klebsiella pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Escherichia coli</i>)	No assigned values	Transfusion-relevant bacterial strain repository
Antithrombin, plasma	Antithrombin function 0.95 IU/ampoule; antithrombin antigen 0.96 IU/ampoule	Third International Standard

Preparation	Activity	Status
C1 inhibitor, plasma	0.89 IU per ampoule	First International Standard
C1 inhibitor, concentrate	9.6 IU per ampoule	First International Standard
Factors II, VII, IX, X, plasma	Factor II: 0.89 IU/ampoule; factor VII: 0.99 IU/ampoule; factor IX: 0.86 IU/ampoule; factor X: 0.89 IU/ampoule	Fourth International Standard
von Willebrand factor, concentrate	VWF:Ag 10.7 IU/ampoule; VWF:RCo 9.2 IU/ampoule; VWF:CB 10.3 IU/ampoule	Second International Standard
Cytokines, growth factors and endocrinological substances, and related substances		
Follicle-stimulating hormone, human, recombinant, for bioassay	126 IU/ampoule	Second International Standard
Granulocyte colony-stimulating factor	95 000 IU/ampoule	Second International Standard
Sex hormone-binding globulin	180 IU/ampoule	Second International Standard
Thyroid-stimulating antibody	113 mIU/ampoule	Second International Standard
Diagnostic reagents		
Human cytomegalovirus for nucleic acid amplification technique-based assays	5 million IU/ml	First International Standard
<i>RHD/SRY</i> plasma DNA	No assigned value	First Reference Reagent
Vaccines and related substances		
Antibody to influenza A/California/7/2009 (H1N1) virus	1300 IU/ampoule	First International Standard
BCG vaccine, Russian BCG-I substrain	3.39 million cfu per ampoule; 7.5 ng ATP per ampoule	First Reference Reagent
Tetanus vaccine	490 IU/ampoule	Fourth International Standard