

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

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DEPARTMENT OF VACCINES AND BIOLOGICALS



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Abbreviations

ATT	Access to Technologies team (WHO)
GMP	good manufacturing practices
NRA	national regulatory authority
PAHO	Pan American Health Organization
PSF	product summary file
UN	United Nations
UNICEF	United Nations Children's Fund
V&B	Department of Vaccines and Biologicals (WHO)
VVM	vaccine vial monitor
WHO	World Health Organization

Introduction

The World Health Organization, through its Department of Vaccines and Biologicals (V&B) provides advice to UNICEF and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies.

The process in place at WHO to assess the acceptability of candidate vaccines for purchase was published initially in the thirty-ninth report of the WHO Expert Committee on Biological Standardization (Technical Report Series 786, Annex 1, 1989). It was further revised and replaced in 1996 by the document *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/VSQ/97.06).

The system in place has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies. In recent years it has been recognized that the system should be expanded to include other vaccines that are or should be used more by countries. This includes vaccines in complex multivalent combinations as well as products used for outbreaks such as cholera and meningitis. It has also been recognized that the system is being used not only by UN agencies, but also by countries looking for guidance on reliable sources of vaccines for purchase.

The present document is a new revision that takes into consideration the above-mentioned considerations, and also includes a new policy governing prequalification of vaccines from manufacturers that perform only bulk filling and formulation activities.

The purpose of the assessment is to verify that the vaccines (a) meet the specifications of the relevant UN agency and (b) are produced and overseen in accord with the principles recommended by WHO, including those for good manufacturing practices (GMP). This is to ensure that vaccines used in national immunization services in different countries are safe and effective and that they meet particular operational specifications for packaging and presentation.

The assessment procedure established by WHO is based on the following principles:

- reliance on the national regulatory authority (NRA) of the country of manufacture;
- general understanding of the product and presentations offered, production process, quality control methods and relevance for the target population of available clinical data;

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- assessment of production consistency through compliance with GMP specifications;
 - random check-testing of vaccines to monitor compliance with tender specifications on a continuing basis;
 - monitoring of complaints from the field.

Since reliance on effective and independent quality assurance by the NRA plays a critical role in the system, WHO recommends that manufacturers (a) inform their NRA of their application for the assessment procedure; (b) at the same time request the NRA to participate in the process; and (c) provide the NRA with the necessary authorization to discuss the relevant files with WHO representatives.

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

It should be noted that other vaccines that have not gone through this process may be as safe and effective as those that have actually been assessed.

Steps of the procedure

WHO requires general information related to the manufacturing company and the product itself. The manufacturer will provide this information through the product file and the site visit. If the manufacturer is not willing to deliver the required information, WHO and the manufacturer will conduct discussions with a view to trying to resolve the situation in a mutually acceptable manner. However, WHO reserves the right to terminate the assessment if at any time it feels that it has not been provided with adequate information to complete the assessment effectively.

1. Product summary file

A manufacturer for which the procedure is initiated will provide WHO a request to Coordinator ATT (WHO/V&B) to start the evaluation process and submit a product summary file (PSF) containing information related to the following aspects:

Chapter 1: General information

Chapter 2: Personnel

Chapter 3: Premises and equipment

Chapter 4: Vaccine composition

Chapter 5: Production

Chapter 6: Quality control

Chapter 7: Stability

Chapter 8: Clinical experience

Chapter 9: Production and distribution data

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

See **Annex 1** for information on the expected contents of each chapter.

The file will be reviewed by experts in the vaccine(s) in question and by experts in clinical trial evaluation selected and appointed by WHO. During the review of the file, emphasis will be placed on assessing the suitability of the vaccine for the immunization services where it is intended to be used, taking into account composition, presentations offered, recommended schedules and clinical data available, labelling (including vaccine vial monitors), information provided on inserts (which should not contradict WHO model inserts), packaging and shipping procedures in accordance with WHO *International guidelines on packaging and shipping of vaccines* (WHO/V&B/01.05).

The reviewers will provide comments on the acceptability of the information provided and will prepare reports to this effect for WHO. This information will be forwarded to the manufacturers.

2. Initial testing of vaccine samples

The manufacturer will include, with the PSF, summary protocols of no fewer than three lots produced from consecutive bulk lots, and will send separately an appropriate number of samples of each of these final lots to WHO. In some cases, samples of bulk material may be requested. WHO will send the vaccine samples to its collaborating laboratories where they will be tested as appropriate, usually for potency and toxicity. If needed, other tests may be performed.

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

3. NRA evaluation

As part of this assessment procedure, WHO will ensure that the NRA of the producing country performs the six essential regulatory functions (as established by WHO) with respect to the vaccine or vaccines to be exported through UN agencies.

For this purpose WHO will perform an assessment of the regulatory functions using a set of established indicators (*Regulation of vaccines: building on existing drug regulatory authorities*, WHO/V&B/99.10).

Furthermore, the WHO team will seek an agreement with the NRA for appropriate lot release of all vaccines to be supplied through UN agencies, and sharing of information in case of serious GMP deviations, adverse events following immunization, or withdrawals due to quality issues.

4. WHO site visits

When the review of the PSF, testing and regulatory assessment have been satisfactorily completed, WHO will assemble a team to visit the manufacturing facility. UNICEF or the Pan American Health Organization (PAHO) may elect to participate in the team if the vaccine in question is under consideration for supply to these agencies. Otherwise the team will be composed of a group of experts, selected and appointed by WHO, in three main areas: production, quality control and GMP. A WHO representative will lead the team and the team members will act, on a temporary basis, as expert advisers to WHO. The team will perform the site visit and report its findings in accordance with the terms outlined in this document. During the closing meeting at the company, the team will brief the company on the main findings and conclusions and will provide the company with a copy of a draft summary report of the site visit. A full detailed report will be sent by WHO to the company at a later date.

The national regulatory authority will be asked to assign a representative to join the WHO team in their visit to the manufacturing facility to review the manufacturing process, in-process testing, personnel qualifications and practices, animal facilities, compliance with GMP, labelling including vaccine vial monitors (VVMs), packaging and shipping procedures, and post-marketing surveillance activities.

5. Report and outcome of the assessment

WHO will write a report of the overall assessment process (including findings, conclusions and recommendations of the site visit) and will send it to the manufacturer with a copy to the NRA.

If minor adjustments need to be made by the manufacturer, WHO will postpone its final recommendations to UNICEF or the other UN agency involved until such adjustments have been incorporated and verified by WHO.

Once WHO considers that the process is complete, and if the outcome is satisfactory, WHO will send a letter to UNICEF or other UN agency involved, advising on (a) compliance of the vaccine with both the requirements recommended by WHO and the specifications of the relevant UN agency, and (b) the role of the NRA in certifying this. This letter will be copied to the manufacturer and the NRA. The vaccine would be then included in the WHO list of pre-qualified vaccines. The current list may be consulted at: <http://www.who.int/vaccines-access/prequalvaccinesproducers.html>. The prequalified status would be valid for a two-year period.

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

There are four basic types of contractual arrangements that may be relevant:

1. *Commodity transaction.* Sale and purchase of bulk vaccine on the open market. Manufacturers and fillers working under this type of arrangement would not be eligible for undergoing the prequalification process for the products in question.
2. *Contract manufacturing.* A contract manufacturer is a facility that is subcontracted by a vaccine manufacturer to do one or more steps of the process. The vaccine manufacturer is responsible for the product and should ensure that all steps of the process are performed in accordance with the licence specifications and in compliance with GMP. A candidate vaccine would be assessed in accordance with the regular procedure as described above.
3. *Partnership/joint venture.* An arrangement between the manufacturer and the finisher, which provides for a stable ongoing supply of bulk to the finisher. This will usually, but not necessarily, include services and mutual monitoring mechanisms as well as the bulk vaccine.
4. *Technology transfer.* Setting up by the manufacturer of a finishing facility, including construction, training of staff, initial activities in assurance of quality and gradual handover to the finisher.

Contractual arrangements of type 3 and 4 above would enable the finisher to undergo the prequalification process, in which case the following criteria would be followed:

1. The assessment evaluation will be product specific just as it is for vaccines produced by one company from seed.
2. The bulk material should be already prequalified by WHO for the UN market under the procedure described above (items 1 to 5).
3. There must be a long-term contract between the bulk manufacturer and the finishing company. The terms of the contract, regardless for which vaccine, should include the criteria described in the document *Guidelines for bulk procurement of oral polio vaccine*, Task Force on Situation Analysis, 29-30 November 1993 (CVI/TFSA/94.4) and should define the liabilities. This contract must be submitted to WHO for review as part of the assessment procedure.
4. The finisher should have authorization from the company producing the bulk to export the final product. A proper assessment of this authorization should be undertaken by the UN purchasing agencies before commitment to purchase. In the case that the bulk antigen A is used for combination with other antigens B and C, proper authorization by the bulk producer of antigen A for combination (and possible limitations for distribution of the combined vaccines) is required, as well as clear demonstration of efficacy and safety of the intended combined vaccine.
5. Each product for which the antigen(s) come(s) from a different manufacturer of bulk is considered as a unique product and will be prequalified separately.
6. The vaccine production process should be overseen by an independent regulatory authority, the options being:
 - a) The national regulatory authority of the country where the bulk is produced (in the case of the bulk), and the national regulatory authority of the finishing country (in the case of the final product). In this option, both authorities must demonstrate to WHO the required technical expertise and the fields of responsibility of each manufacturer, and each NRA must be precisely defined.
 - b) The national regulatory authority of the country where the final product is manufactured oversees the process from seed to finished product. In this case, this authority must demonstrate to WHO the appropriate expertise for this purpose.
7. The product summary file should be submitted to WHO by the finisher, providing details of all the information required in a regular PSF (Annex 1) in relation to the company, general information on bulk material (confidential information is not required), product specifications and detailed information related to all steps to be performed by the finisher.
8. A sample of not fewer than three consecutive lots should be submitted to WHO for independent testing of consistency of final product characteristics (actual number to be decided on a case-by-case basis). Lot summary protocols for these lots should be submitted together with the samples.

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9. A full assessment by WHO of the national regulatory authority(ies) that take(s) the responsibility for the oversight of concerned product(s) should take place.
 10. A joint technical audit of the finisher's facilities should be carried out by WHO and the regulatory authority that takes responsibility for the oversight of the product.
 11. If both the bulk manufacturer and the finisher are seeking prequalification at the same time, technical audits will take place for both the bulk manufacturer and the finisher. In both cases the relevant regulatory authority will be involved.
 12. It is desirable, although not imperative, to state on the vaccine box labels the source of the bulk material.
 13. The prequalification status will last for a maximum of two years or as long as the contract between the bulk manufacturer and the finishing company remains active.

7. Supply

All lots shipped in response to orders placed by a UN agency must have been released beforehand by the NRA. Lot-release certificates will be kept by the manufacturer (Annex 2) and sent, on request, to the UNICEF Supply Division or to the Department of Vaccines and Biologicals, Coordinator, Access to Technologies team, World Health Organization, Geneva (WHO/V&B/ATT). In addition, a suitable number of samples of each lot of vaccine supplied will be retained by the manufacturer, to be provided to WHO/V&B/ATT for testing on request.

The manufacturer should inform WHO/V&B/ATT of any changes notified to the NRA in the formulation, in methods of manufacturing, in facilities, or in any other aspects which might (a) result in a change of safety and/or efficacy of the vaccine or (b) change the basis of the regulatory approval by the NRA. Such changes may necessitate a further assessment by WHO to assure continued compliance with WHO-recommended requirements.

8. Reassessments

Reassessments will be done in the following situations:

1. At regular intervals, usually every two years.
2. If vaccine fails to meet WHO-recommended requirements and/or the specifications of the offer to bid.
3. If no supply to the UN has taken place for a period equal to, or greater than, two years.
4. In case of a suspension of production.
5. If and when, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made.

Routine reassessments performed regularly as defined in item (i) above, require:

- Submission of an updated PSF providing information on changes introduced since the previous assessment evaluation (Annex 1).
- Testing of samples.
- Consultation with the NRA on outstanding issues with the vaccine(s) supplied to UN agencies.
- A site visit of the manufacturing facilities, ideally with participation of representatives of the local NRA. The purpose of the visit will be primarily to verify that the vaccine continues to meet WHO-recommended requirements and the specifications of the relevant UN agency, and that it complies with GMP standards. Furthermore, these site visits provide an opportunity for the manufacturer and the team members to discuss any changes which may be foreseen in production and/or quality control methods, as well as any new specifications and/or issues regarding introduction of new policies or strategies proposed by WHO.

The site visit may be waived on a case-by-case basis if the criteria shown in Annex 3 are met. However, a WHO site visit has to take place at a minimum once every five years, regardless of the criteria in Annex 3.

The characteristics of the reassessment will vary depending on the actual circumstances and, for items (ii) to (v) above, may require special provisions, such as submission of specific documents, records, testing of samples and site visit.

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

Random samples of lots will be selected, at regular intervals, for independent testing of final product characteristics. On request, each manufacturer and the relevant NRA will receive a report of the test results. Manufacturers will in any case be contacted for follow-up actions in case of failure to meet specifications. Upon request of WHO, the manufacturer or NRA, as appropriate, will provide WHO with lot summary protocols and information on lot release for review.

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

10. Monitoring of complaints from the field

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

In the case of vaccines purchased through other UN agencies, the information should be communicated through the relevant purchasing agency to WHO, so that the investigation process can be started.

After investigation, WHO will provide UNICEF or the other UN agency involved with a written report of the problem and include recommendations for action, if any. WHO will then be available as a technical resource while UNICEF or the other UN agency implements the recommendations.

WHO will make a copy of its report available to the manufacturer and the NRA.

11. Recommendations for action

In the event of the situations described in points 9 and 10 above and depending on the nature of the failure to meet the established criteria, WHO may include a recommendation that manufacturers' lots of vaccines are more closely monitored during a probationary period, or that purchase of the vaccine be suspended pending investigation and resolution of the problem, or if a formal reassessment is required, until this has been completed. WHO will generally route communications relating to problems in the field or failure to meet established criteria through the NRA.

12. Costs

The cost of the activities required to assess the acceptability in principle of candidate vaccines for purchase are covered by the manufacturers. The current cost of initial evaluation of a candidate vaccine valid until the year 2004, is US\$ 17 000 (regardless of whether the vaccine is a monovalent or a combined vaccine). The evaluation of a vaccine will be started only after payment of this fee and receipt by WHO of the product summary file. The cost of activities required to keep the WHO list updated (reassessment evaluations) is charged to the manufacturers on the basis of an annual fee which varies according to the antigens contained in the vaccine as shown in table 1:

**Table 1: Annual fee for reassessment purposes
excluding site visits and extra activities**

Vaccine group	Type of vaccine	Reassessment fee
Monovalent vaccines	Tetanus toxoid, BCG, yellow fever, hepatitis B (HepB), <i>Haemophilus influenzae</i> type b (Hib), measles, rubella, mumps, rabies, meningococcal types A, B or C, etc	Each US\$ 2500/year
Two component vaccines	Diphtheria-tetanus toxoids, measles-rubella combined, meningococcal A+C or B+C, Hib-HepB combined, etc.	Each US\$ 4000/year
Three component vaccines	Diphtheria-tetanus-pertussis (DTP) combined, measles-mumps-rubella combined, oral polio, inactivated polio (IPV), etc	Each US\$ 6000/year
Four component vaccines	DTP-Hib combined, DTP- HepB, combined etc	Each US\$ 7500/year
Five/six component vaccines	DTP-HepB-Hib (fully combined), DTP-IPV, etc	Each US\$ 9000/year

These fees will be valid for an initial period of five years (2000–2004), after which they may be adjusted to reflect increases in the cost of the reassessment process.

The reassessment fees are charged to the manufacturers at the beginning of every calendar year. The reassessment process will not be initiated until the corresponding fees are paid to WHO. Failure to pay could ultimately lead to withdrawal of the vaccines from the list.

Site visits to manufacturing facilities as part of the reassessment process will be waived if certain criteria are met (Annex 3). In all cases where site visits are not waived and in cases where site visits and other additional activities and resources are required for special reasons (e.g. failure to meet the criteria), these will be charged separately on a cost recovery basis.

13. Confidentiality

Information to which WHO requires access for the purpose of assessing or reassessing the acceptability in principle of a vaccine for purchase by UN agencies, will not, as a general rule, include confidential information. However, if, in the opinion of the manufacturer, any information to be submitted to WHO and its expert team members in the course of the (re)assessment procedure includes confidential information, the manufacturer must advise WHO thereof in writing, prior to or at the same time as the disclosure, duly identifying the confidential information in question. Notwithstanding the foregoing, WHO and its expert team members will treat all information submitted to them during site visits as confidential, in accordance with the terms set forth below.

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

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

- 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.

14. No conflict of interest

The team for site visits referred to in point 4 above, includes experts in the field of production, quality control and GMP. These experts are selected by WHO and act as WHO temporary advisers or consultants. Prior to formalizing arrangements with such experts, WHO will require them to complete the WHO declaration of interests form. In addition, the agreement between WHO and such experts will include similar obligations of confidentiality and non-use as contained in point 12 above, as well as a conflict of interest undertaking. Through this conflict of interest undertaking, the aforesaid experts agree to discharge their functions exclusively as advisers to WHO. They also confirm that they have no financial interest and/or other relationship with a party, which:

1. 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
2. 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.

At the manufacturer’s request, WHO will advise the manufacturer in advance of the composition of the team performing the site visit, and provide *curricula vitae* of the temporary expert advisers included in the team. The manufacturer will then have the opportunity to express possible concerns regarding any of the expert team members to WHO prior to the site visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may reject an expert team member, within, at the latest, 10 days of receipt of the proposed team composition.

Annex 1:

The product summary file

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

For initial product *assessments*, a product summary file should be submitted for each vaccine to be assessed. For combination vaccines, information should be submitted on each of the component vaccines and on the combination itself.

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

Chapter 1: General information

- 1.1 Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understanding the manufacturing process. Name and address of the site, including telephone, fax and 24-hour telephone numbers.
- 1.2 Pharmaceutical and non-pharmaceutical manufacturing activities carried out on the site as licensed by the national regulatory authority.
- 1.3 Short description of the site (size, location and immediate environment and other manufacturing activities on the site).
- 1.4 Number of employees engaged in the production, quality control, storage and distribution.
- 1.5 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis. In case of contract manufacturing of part of the process, information on the way in which GMP compliance of the contract acceptor is assessed.
- 1.6 Short description of the quality management system of the firm responsible for manufacture.
- 1.7 Short description of the internal audit system.

Chapter 2: Personnel

- 2.1 Organizational chart showing the relationships between different areas including quality assurance, production and quality control, with identification by name of key personnel.
- 2.2 Qualifications, experience and responsibilities of key personnel.

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- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
 - 2.4 Health requirements for personnel engaged in production, particularly relating to requirements for immune status for production personnel.

Chapter 3: Premises and equipment

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

- 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawing are not required).
- 3.2 Nature of construction and finishes.
- 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the clean-rooms used for the manufacture of sterile products should be included.
- 3.4 Special areas for the handling of highly toxic, hazardous and sensitizing materials.
- 3.5 Brief description of water systems (schematic drawings of the systems are desirable) including sanitation.
- 3.6 Maintenance (description of planned preventive maintenance programmes and recording system).
- 3.7 Brief description of major production and control laboratories equipment (a list is not required).
- 3.8 For products where separate facility is required (e.g. tetanus, BCG) describe how separation is achieved. For multipurpose areas, describe cleaning system between campaigns.
- 3.9 Description of qualification and validation procedures, including computerized recording and controller systems.
- 3.10 Availability of written specification and procedures for cleaning manufacturing areas and equipment.

Chapter 4: Vaccine composition, presentations and schedules

- 4.1 Formulation of the product.
- 4.2 Brief description of the presentations made available to UN agencies, including diluent (if applicable), combination products, forms, dose sizes, type of containers, VVM type used and descriptions of application devices (e.g. syringes) to be delivered with the vaccine, if applicable.
- 4.3 Recommended schedule and route of administration.
- 4.4 Samples of labels, boxes and package inserts to be used for UN agencies' supply. Samples of vials or ampoules of diluent and its corresponding labelling.
- 4.5 Sample of lot summary protocol to be provided to UN agencies (to follow the WHO-recommended format).

Chapter 5: Production*

- 5.1 Manufacturing formula (including details of batch size).
- 5.2 Description of the manufacturing processes and the characterization of the product together with a flow-chart showing the control tests performed on intermediate and final products and an identification of any processes or tests performed by contract manufacturers or testers. For recombinant vaccines, a description of the construction and characterization of the recombinant vector should be provided.
- 5.3 Brief description of general policy for process validation. List of the process validation activities performed.
- 5.4 Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
- 5.5 Arrangements for the handling and procedures for destruction of rejected materials and products.

Chapter 6: Quality control*

- 6.1 Starting materials.
 - 6.1.1 Control tests performed on raw materials, with appropriate characterization of starting materials.
 - 6.1.2 Control tests performed on labelling and packaging material(s).
- 6.2 Intermediate products (as appropriate).
 - 6.2.1 Specifications and routine tests performed.
 - 6.2.2 List of test validation activities performed.
- 6.3 Finished products.
 - 6.3.1 Specifications and routine tests performed.
 - 6.3.2 List of test validation activities performed.

Chapter 7: Stability

- 7.1 Stability tests on intermediates, assigned shelf life and storage conditions.
- 7.2 Stability tests on the finished product, assigned shelf life and storage conditions.
- 7.3 Description of 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.

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

Chapter 8: Clinical experience

- 8.1 Clinical trial results to show the safety and efficacy of the vaccine in the target population, at the dosage and schedules intended to be used in national immunization services. This data has to be relevant to the developing country public sector target population at the recommended schedules.
- 8.2 Published reports in scientific and medical literature summarizing efficacy or safety studies (other than 8.1).
- 8.3 Additional reports of clinical experience or toxicity studies pertinent to safety (for example, epidemiological studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the manufacturer.
- 8.4 Summary of available post-marketing reporting of adverse events.

Chapter 9: Production and distribution data

- 9.1 The quantity of finished product distributed domestically and exported in the previous three years.
- 9.2 Arrangements and recording system for distribution.
- 9.3 Arrangements for the handling of complaints and product recalls (only for reassessment purposes).
- 9.4 The quantity of finished product (differentiating combination products) supplied to UN agencies on a per annum basis.
- 9.5 The quantity of bulk vaccine destined for UN agencies, supplied to contract fillers/packagegers for finalization (list individually).

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

- 10.1 Copy of marketing authorizations, information on refusals, withdrawals, or suspensions including those that are manufacturer initiated.
- 10.2 Restrictions on distribution or recalls, including manufacturer-initiated recalls.
- 10.3 Clinical trial suspensions, including manufacturer-initiated suspensions.
- 10.4 Dosage or schedule modifications.
- 10.5 Changes in target populations or indications.
- 10.6 Reports of inspections conducted by national authorities within the previous two years.
- 10.7 Inspections conducted by foreign authorities within the previous two years.

Annex 2:

Model certificate for the release of vaccines acquired by UN agencies

(Revised 1988)

(To be completed by the national control authority of the country where the vaccines have been manufactured, and to be sent by the vaccine manufacturer to UNICEF.)

The following lots of¹ vaccine produced by² in³, whose numbers appear on the labels of the final containers, meet all national requirements.⁴ Part A⁵ of Requirements for Biological Substances No.⁶ (Requirements for¹, published in 19..... [if applicable, revised 19....., addendum 19.....]) and Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, published in 1959; revised 19.....).⁷

Lot No.	Expiry date	Lot No.	Expiry date
.....
.....
.....
.....

As a minimum, this certificate is based on examination of the manufacturing protocol. The Director of the National Control Laboratory (or Authority as appropriate)⁸

Name (typed)

Signature

Date

¹ Indicate type of vaccine (measles, oral poliomyelitis, tetanus, diphtheria-tetanus, diphtheria-pertussis-tetanus, BCG).
² Name of manufacturer.
³ Country.
⁴ If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the national control authority.
⁵ With the exception of the provisions on shipping, which the national control authority may not be in a position to control.
⁶ Indicate the reference number of the relevant Requirements for Biological Substances published by WHO.
⁷ These requirements were revised in 1965; a further revision is in preparation for consideration by the WHO Expert Committee on Biological Standardization in 1989.
⁸ Or his or her representative.

Annex 3:

Criteria for waiving a site visit during the WHO re-assessment procedure for vaccines supplied to UN agencies

All the following criteria should be met.

1. A GMP inspection relevant to the product(s) has been conducted within the previous five years, by a competent authority, either national or foreign, and a copy of the inspection report in English has been made available to WHO.
2. A site visit has been conducted by WHO within the last five years.
3. There have been no significant changes or additions to the approved processes and procedures listed in the national authorization of the manufacturing and testing facilities.
4. There have been no significant changes in the product indications, patient groups, or consumer warnings as compared to those mentioned in the regulatory approval of the country of manufacture.
5. There have been no recalls of the product(s) and there have been no withdrawals or cancellations of registration licences related to quality issues since the previous reassessment evaluation.
6. Significant changes to the product or its manufacturing processes or facilities (which can potentially have effects on the product's quality, safety or efficacy) have been notified to WHO (with adequate information to justify the change), before the changed product has been supplied to UN Agencies, *and* WHO has not found that these changes require a reassessment with a site visit.
7. No confirmed incidents related to non-compliance with quality specifications of tenders have been received by WHO with regard to the product(s) since the previous reassessment evaluation.
8. No significant complaints from the field or reports of adverse events following immunization (AEFI) attributable to quality of the product(s) have been received and confirmed by WHO.
9. Post-market surveillance or studies conducted by or otherwise obtained by the manufacturer or the national regulatory authority in regard of the product(s) have shown no significant increase in expected or unexpected adverse events in an established or new patient group.
10. It is assured that the national regulatory authority will continue to function well through open and timely communication with WHO on issues of vaccine quality impacting the UN market (e.g. changes to the license, reports of AEFI, withdrawals, changes in indications, major GMP non-compliance, etc.).

Annex 4:

Provisions for team members participating in WHO missions to assess acceptability, in principle, of vaccines for purchase by UN agencies

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

1. not use the Information for any other purpose than discharging your obligations under this Agreement; and
2. not disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

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

1. was known to you prior to any disclosure by WHO and/or the manufacturer(s); or
2. was in the public domain at the time of disclosure by WHO and/or the manufacturer(s); or
3. has become part of the public domain through no fault of your own; or
4. has become available to you from a third party not in breach of any legal obligations of confidentiality to WHO and/or the manufacturer(s).

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

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

1. may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or
2. may have a vested interest in the outcome of the assessment of the vaccine(s), in which you will participate, including but not limited to parties, such as the manufacturer(s) of the vaccine(s) that is (are) being assessed or manufacturers of competing vaccines.

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

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

Signed:.....

Name (typewritten):

Institute:.....

Place:

Date:.....