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



**GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
VACCINE SUPPLY AND QUALITY**



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Copies may be requested from:
World Health Organization
Global Programme for Vaccines and Immunization
CH-1211 Geneva 27, Switzerland
• Fax: +22 791 4193/4192 • E-mail: gpv@who.ch •

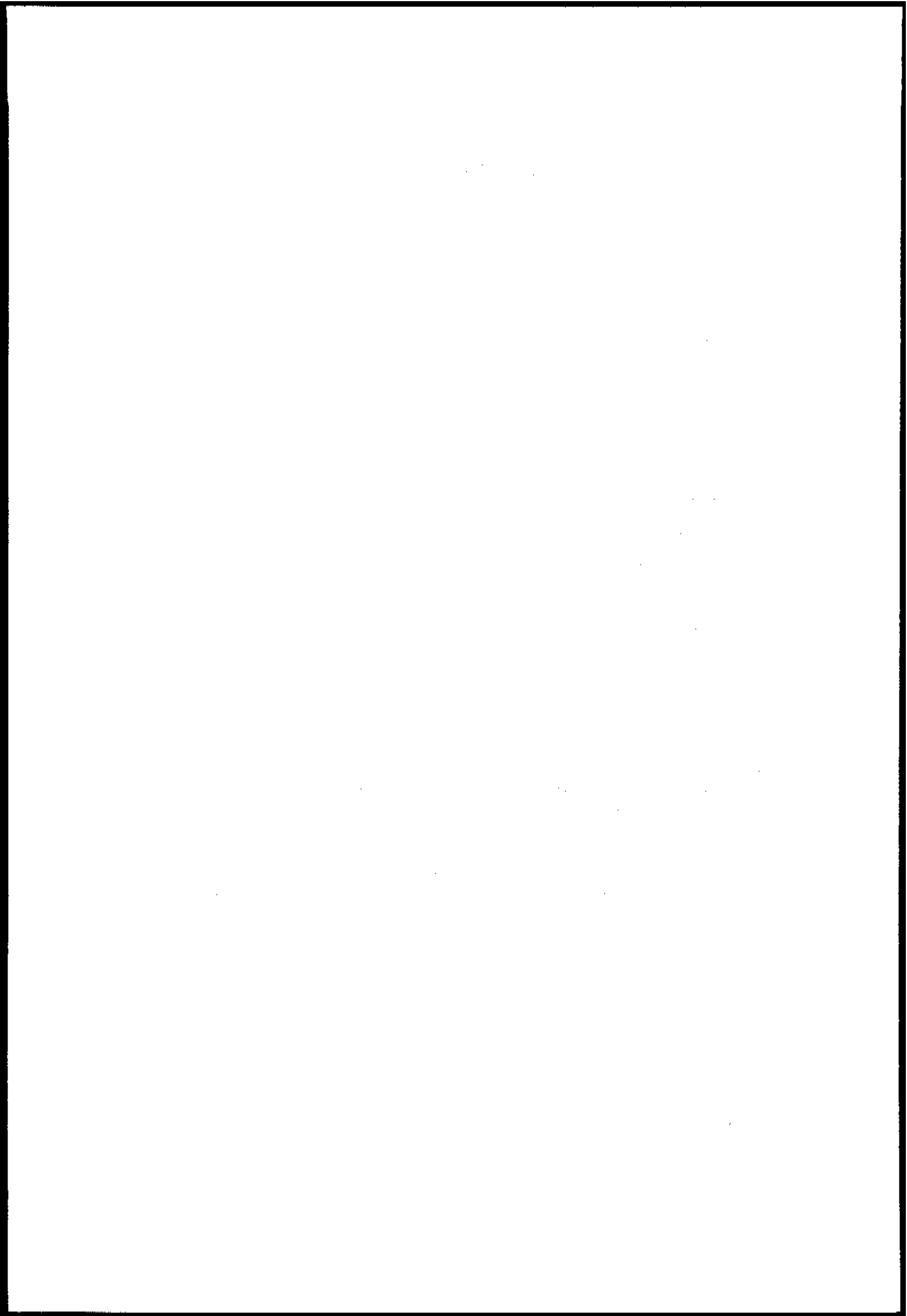
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Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

Introduction

The World Health Organization, through its Global Programme for Vaccines and Immunization (GPVI), will provide advice to UNICEF and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by UN agencies.

The purpose of this assessment is to verify that the vaccines (a) meet the specifications of the relevant UN agency and (b) the requirements recommended by WHO, including those for good manufacturing practices (GMP). This is to ensure that vaccines used in national immunization programmes 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 Control Authority (NCA) of the country of manufacture;
- General understanding of the production process and quality control methods;
- Assessment of production consistency through compliance with GMP specifications;
- Random check-testing of vaccines to monitor compliance with specifications on a continuing basis;
- Monitoring of complaints from the field.

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

WHO can only advise UNICEF and other UN agencies whether vaccines effectively meet WHO recommended requirements if the vaccines have been assessed through this procedure. *Other vaccines that have not gone through this process may, however, 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 in part in the Product File and also during the site visit. If the manufacturer is not willing to deliver the required information, WHO and the manufacturer will conduct discussions with a view to trying to resolve the situation in a mutually acceptable manner. However, WHO reserves the right to terminate the assessment if at any time it feels that it has not been provided with adequate information to complete the assessment effectively.

1. *Product File*

A manufacturer for which the procedure is initiated will provide WHO with a Product File containing information related to the following aspects:

- 1) Composition of the vaccine (formulation).
- 2) Layout of the production facilities.
- 3) Organizational chart of the company.
- 4) Copy of the relevant national requirements for production.
- 5) Staffing of production, quality control and quality assurance units, plus information on the staffs' professional qualifications.
- 6) Copy of the original regulatory approval by the NCA of the country of origin.
- 7) List of countries where the vaccine is registered and is currently distributed by the applicant or any other authorized entity.
- 8) Clinical data showing the safety and efficacy of the vaccine in the target population, at the dosage and schedules intended to be used in national immunization programmes.
- 9) Additional data on reactogenicity or lack of efficacy detected through post-marketing surveillance.
- 10) Flowchart of the production process with a detailed description of the relevant steps involved. For recombinant vaccines, an adequate description of the construction of the recombinant vector should be provided.
- 11) Detailed description of the quality control methods used (a) during the production and (b) applied to the final product; this should include an adequate characterization of starting materials and gene products (if applicable).
- 12) Quality specifications set at different stages of the production process and for the final product.

2. *Initial testing of vaccine samples*

The manufacturer will include, with the Product File, summary protocols of five lots produced from five consecutive bulk lots, and will send separately twenty

multidose vials or ampoules of each of these final lots to WHO. WHO will send the vaccine samples to one of its collaborating laboratories where they will be tested for potency and toxicity; in special cases other tests may be performed.

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

3. WHO site visits

When the review of the Product File and the testing has been satisfactorily completed, WHO will put together a team to visit the manufacturing facility. UNICEF may elect to participate in the team if the vaccine in question is under consideration for supply to UNICEF. Otherwise the team will be composed of a group of experts, selected by WHO, in three main areas: **production, quality control and GMP**. A WHO staff member 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.

It is preferable for the visit to start at the National Control Authority/Laboratory for discussions on the procedures in place for regulatory approval, lot release, testing and inspection of vaccine manufacturers, as well as the post-marketing surveillance system. Although the laboratory facilities of the NCA may be visited, staff discussions will be of primary importance.

A representative of the National Control Authority involved in control and release of the vaccine would be normally expected to accompany the team to the manufacturing facility to review the manufacturing process, in-process testing, personnel qualifications and practices, animal facilities, compliance with GMP, packaging and shipping processes, and post-marketing surveillance activities.

4. Report and outcome of the assessment

The team will write a report, describing its findings and conclusions and giving its recommendations to the manufacturer and the NCA.

If any 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 is satisfied that the process is complete, it will send a letter to UNICEF or the other UN agency involved, advising on (a) whether or not it finds the vaccine to meet both the WHO recommended requirements and the specifications of the relevant UN agency, and (b) the role of the NCA in certifying this.

WHO will send a copy of the letter to the manufacturer and the NCA.

5. *Supply*

All lots shipped in response to orders placed by a UN agency must have been released beforehand by the NCA. Lot-release certificates will be kept by the manufacturer and sent, on request, to the UNICEF Supply Division or to the Chief, Vaccine Supply and Quality Unit, Global Programme for Vaccines and Immunization, World Health Organization, Geneva (VSQ/GPV/WHO). In addition, at least twenty samples of each lot of vaccine supplied will be retained by the manufacturer, to be provided to VSQ/ GPV/WHO for testing on request.

The manufacturer should inform VSQ/GPV/WHO of any changes notified to the NCA 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 NCA. Such changes may necessitate a further assessment by WHO to assure continued compliance with WHO recommended requirements.

6. *Reassessments*

Reassessments will be done in the following situations:

- (i) Before every new agreement for purchase.
- (ii) If vaccine fails to meet WHO recommended requirements and/or the specifications of the offer to bid.
- (iii) If suspension of supply for a period is equal to, or greater than, two years.
- (iv) In case of a suspension of production.
- (v) If, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made.

Reassessments before every new agreement for purchase, item (i) above, require a joint site visit, which may also include a visit to the NCA/NCL, by a WHO team and a representative of the NCA; UNICEF may elect to be represented in the team if it is considering purchase of the vaccine in question. 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 characteristics of the reassessment will vary depending on the actual circumstances and, for items (ii) to (v) above, may require provision of special written information (amendments made to the original regulatory approval, Standard Operating Procedures, validation data, etc.), testing of samples (from lots derived from consecutive bulk lots to verify consistency of production), a site visit and possibly a review of product samples and circulars.

7. *Random testing of samples*

Random samples of lots will be selected, every six months, for independent testing of final product characteristics. Lot summary protocols and information on lot release will be provided by the manufacturer or NCA as appropriate, for review by WHO upon request.

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

8. *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. Information communicated by any other route should also be relayed immediately to WHO, through the UNICEF Supply Division in Copenhagen, to allow for the investigation procedure to begin.

In the case of vaccines purchased through other UN agencies, the information should be communicated through the relevant Supply Division 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 NCA/NCL.

9. *Recommendations for action*

In the event of the situations described in points 7 and 8 above, 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 kept pending until formal reassessment has been completed. Depending on the nature of the failure to meet the established criteria, WHO may recommend a suspension of purchase pending investigation and resolution of the problem. WHO will generally route communications relating to problems in the field or failure to meet established criteria through the NCA.

10. *Costs*

Any costs incurred by the manufacturer in the assessment or reassessment of a vaccine, as described in this document, will be borne exclusively by the manufacturer. Moreover, the manufacturer will cover any costs borne by WHO in respect of reassessments or site visits related to problems in meeting specifications, or as a follow-up on implementation of recommendations made during a previous assessment.

11. 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 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.

12. No conflict of interest

The team for site visits referred to in point 3 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. In this connection, the agreement between WHO and such experts will include similar obligations of confidentiality and non-use as contained in point 11 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:

- (i) 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

-
- (ii) may have a vested interest in the outcome of the (re)assessment procedure, including, but not limited to, parties such as the manufacturer 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, ten days of receipt of the proposed team composition.

Annex 1

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

In the course of discharging your functions as an expert adviser under this Agreement, you will gain access to certain information, which is proprietary to WHO or to the manufacturers of the vaccine(s) which need 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:

- (a) not use the Information for any other purpose than discharging your obligations under this Agreement; and
- (b) 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:

- (i) was known to you prior to any disclosure by WHO and/or the manufacturer(s); or
- (ii) was in the public domain at the time of disclosure by WHO and/or the manufacturer(s); or
- (iii) has become part of the public domain through no fault of your own; or
- (iv) 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:

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

(ii) may have a vested interest in the outcome of the assessment of the vaccine(s), in which you will participate.

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

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

Signed: _____

Name (typewritten): _____

Institute: _____

Place: _____

Date: _____

Annex 2

Model certificate for the release of vaccines acquired by United Nations 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

<i>Lot No.</i>	<i>Expiry date</i>	<i>Lot No.</i>	<i>Expiry date</i>
.....
.....
.....

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.