

## **Expedited procedure for evaluating pandemic influenza A (H1N1) 2009 vaccines**

### **Preamble**

On 11 June 2009, WHO declared an influenza pandemic caused by influenza A (H1N1) 2009 virus<sup>1</sup>. On 13 July 2009, WHO made recommendations for the use of pandemic influenza A (H1N1) 2009 vaccines<sup>2</sup>. WHO emphasized the importance of striving to achieve equity among countries concerning access to the pandemic influenza A (H1N1) 2009 vaccine. One way in which WHO will do this is through its prequalification procedure. This document establishes and describes a procedure that provides assurance of the quality, safety and efficacy of pandemic influenza A (H1N1) 2009 vaccines as well as timelines for expeditious evaluation by WHO.

The procedure is stratified depending on whether prior prequalification of seasonal influenza vaccines has been obtained. Where this is the case, the experience and knowledge gained with these prior applications will be used to the utmost. The prequalification procedure for seasonal influenza vaccines is described in the "Special considerations for expedited procedure for evaluating seasonal influenza vaccines"<sup>3</sup>.

The data requirements for products where no seasonal influenza vaccines have been prequalified are incrementally greater, depending on circumstances as described below.

In addition to aiding developing countries to prepare for the pandemic, this prequalification procedure will aid National Regulatory Authorities (NRAs), in the event of a supply shortage, in acquiring vaccines from alternate, non-domestic sources. Prequalification may also be helpful in identifying sources of vaccines that may be available for developing countries in particular and ensure that only vaccines of assured quality are used.

### **Definitions**

**Pandemic influenza vaccine:** refers to a monovalent vaccine containing the strain recommended by WHO for use during a pandemic (pandemic phase 6) or considered by WHO to be of imminent pandemic threat (pandemic phases 4 or 5).

**Programmatic aspects:** considerations relative to the suitability of the vaccine product and vaccine presentation for use in national immunization programmes. Usually related to storage conditions, cold chain volume required, stability profile, inclusion of a vaccine vial monitor, concomitant administration with other vaccines including seasonal influenza vaccines, contraindications, and others.

### **Introduction**

This procedure is intended to cover

(a) inactivated influenza vaccines produced in either embryonated chicken eggs or in cell cultures, including vaccines which are

- a suspension of whole virus particles inactivated by a suitable method;

---

<sup>1</sup> [http://www.who.int/mediacentre/news/statements/2009/h1n1\\_pandemic\\_phase6\\_20090611/en/index.html](http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html)

<sup>2</sup> <http://www.who.int/wer/2009/wer8430.pdf>

<sup>3</sup> [http://www.who.int/immunization\\_standards/vaccine\\_quality/final\\_expedited\\_procedure\\_flu\\_240207.pdf](http://www.who.int/immunization_standards/vaccine_quality/final_expedited_procedure_flu_240207.pdf)

DRAFT DOCUMENT

- a suspension treated so that the virus particles have been partially or completely disrupted by physicochemical means (split vaccine);
- a suspension treated so that the preparation consists predominantly of haemagglutinin and neuraminidase antigens (subunit vaccine);
- a suspension of whole virus particles, split or subunit components formulated with an adjuvant;

and

(b) live attenuated influenza vaccines

This document should be read in conjunction with the WHO guidelines on *Regulatory Preparedness for Human Pandemic Influenza Vaccines* (Version endorsed by the Expert Committee on Biological Standardization, 2007)<sup>4</sup>

---

<sup>4</sup> [http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human\\_pandemic\\_Influenza\\_Vaccines\\_BS2074\\_01Feb08.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf)

**Procedure for the assessment of pandemic influenza A (H1N1) 2009 vaccines**

Applicants for the prequalification of pandemic influenza A (H1N1) 2009 vaccines will be categorized by WHO into one of the four categories described in the table below. The categories are based on whether the applicant has already a prequalified seasonal influenza vaccine, has submitted a dossier for evaluation of a seasonal influenza vaccine, or has other prequalified vaccines; whether the pandemic vaccine is licensed; and, whether the NRA providing regulatory oversight of the vaccine meets the WHO criteria related to prequalification<sup>5</sup>.

Applicants can be moved between categories, if appropriate.

Only vaccines licensed by a regulatory authority found to meet all the critical indicators defined for pre-qualification purposes following a WHO independent assessment will be accepted for submission to the pre-qualification procedure. This regulatory authority will be referred to as the responsible NRA of record.

<b>Category</b>	<b>Criteria</b>	<b>WHO assessment approach</b>	<b>Time for process at WHO</b>
<b>I</b>	Seasonal influenza vaccine is prequalified by WHO  Pandemic influenza A (H1N1) 2009 vaccine is licensed by NRA of record	Review of programmatic aspects	1 working day from the time of reception of the documentation
<b>II</b>	Seasonal influenza vaccine has not been prequalified by WHO  Seasonal and pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record  Other vaccines from same company are prequalified	Review of NRA assessment reports  Review of NRA test results, or independent testing of samples  Site visit may be waived on the basis of availability of GMP inspection reports  Review of programmatic aspects	10 working days (if site visit is waived)  20 working days (if site visit is needed) from the time of reception of the documentation

<sup>5</sup> [http://www.who.int/immunization\\_standards/vaccine\\_quality/pq\\_system/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/index.html)

DRAFT DOCUMENT

<p><b>III a)</b></p>	<p>Seasonal influenza vaccine has not been prequalified by WHO, but manufacturer <u>has experience</u> in the production of flu vaccines</p> <p>Seasonal and pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record</p> <p>No other vaccine from same company is prequalified</p> <p>NRA meets WHO criteria</p>	<p>Full assessment process to be conducted on fast track basis, in consultation with NRA and based on a site visit</p>	<p>Full assessment process to be conducted on fast track basis, 20 working days from the time of reception of the documentation</p>
<p><b>III b)</b></p>	<p>Seasonal influenza vaccine has not been prequalified by WHO and manufacturer has <u>no prior experience</u> in the production of flu vaccines</p> <p>Pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record</p> <p>No other vaccine from same company is prequalified</p> <p>NRA meets WHO criteria</p>	<p>Full assessment process to be conducted on fast track basis.</p>	<p>6 months from the time of reception of the documentation (excluding time taken by manufacturer to respond to queries)</p>
<p><b>IV</b></p>	<p>NRA does not meet WHO criteria</p>	<p>Not acceptable for prequalification evaluation</p>	

## DRAFT DOCUMENT

The procedure will involve:

### Category I

Review of Product Summary File (PSF) and testing of samples will be waived.

1. The manufacturer submits a summary of product characteristics including the following information
  - a. General information: name of the vaccine, name and address of the manufacturer and manufacturing site, name, address of the regulatory authority responsible for the oversight of the vaccine (NRA of record)
  - b. Pharmaceutical information: composition, pharmaceutical forms (nature and contents of container, shelf life, storage conditions, special precautions for preparation, disposal and other handling, others)
  - c. Production and quality control (QC): outline of the production process including strain specific production details (including rationalization for the similarity between already prequalified seasonal influenza vaccine(s) and the submitted pandemic influenza vaccine) and QC methods and specifications for intermediates and final product
  - d. Vaccine vial monitors (VVM): stability data to justify proposed shelf life and the selection of a certain VVM category
  - e. Copy of the proposed labels and inserts and secondary and tertiary packaging information
  - f. Indications: target population, immunization schedule (number of total doses; need for booster dose, variation for pediatric dose), injection method, injection site
  - g. Contraindications and undesirable effects
  - h. Copy of the file submitted to the NRA of record for licensure of the pandemic vaccine for filing purposes
  - i. Plans and protocols for clinical studies in different age groups
2. The manufacturer makes the following post-prequalification commitments (including proposed deadlines for a, b, d):
  - a. to provide additional clinical data
  - b. to provide stability data
  - c. to allow a site visit if deemed necessary by WHO
  - d. to provide information on serious Adverse Events Following Immunization (AEFI)

### Category II

The applicant shall provide WHO with a copy of the file submitted to the NRA. The manufacturer ensures that the data required under category I are included in this submission, and also makes the same post-prequalification commitments as in category I.

The applicant shall grant permission to the NRA of record to disclose the NRA's assessment reports to WHO and to disclose results of tests conducted for lot release. In addition, the applicant will submit to WHO a copy of the NRA assessment reports (including inspection

## DRAFT DOCUMENT

reports if such inspections have been conducted). WHO will make use of test data obtained by the NRA of record for lot release purposes to assess consistency of final product characteristics. If other NRAs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available. On the basis of available data, WHO will decide whether independent testing needs to be conducted. A consultation meeting with the NRA to discuss the evaluation process can be scheduled.

The applicant shall allow a WHO site visit, which will be scheduled immediately. Site visit may be waived on the basis of availability of GMP inspection reports.

### **Category III**

The applicant shall provide WHO with a Product Summary File (PSF). The required PSF format is described in the “Guideline for the preparation of the product summary file for vaccine prequalification, WHO/IVB/06.16<sup>6</sup>”. Information for pandemic influenza virus vaccines are provided in the annex to this procedure.

The manufacturer ensures that the data required under category I are included in this submission, and also makes the same post-prequalification commitments as in category I.

For category III a) an assessment process will be conducted on fast track basis, in consultation with the NRA and on the basis of available reports and including a site visit.

The applicant can discuss with WHO whether to submit the same file as submitted to the NRA instead of a PSF.

Testing of samples may be waived, provided that the applicant grants permission to the NRA(s) to disclose all results of testing of batches. If other NRAs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available. On the basis of available data, WHO will decide whether independent testing needs to be conducted, and whether this can be done as a post-prequalification monitoring exercise.

The applicant shall allow a WHO site visit, which will be scheduled immediately.

For category III b) an assessment process will be conducted on fast track basis: full review of information by WHO assigned experts will be conducted both for technical and clinical sections of the PSF, independent testing and a site visit will be conducted

### **Category IV**

The application will not be accepted.

### **Notes applicable to categories I, II, and III a) and b)**

In the context of the evaluation by WHO, the manufacturer is expected to give authorization to the NRA to share with WHO information relevant to the quality, safety, and efficacy of the vaccine.

For a pandemic influenza vaccine, some clinical trial data would be expected to support the appropriate dose and regimen. These clinical trials should also include an assessment of immunogenicity and safety, and may be built on experience with seasonal influenza vaccines

---

<sup>6</sup> <http://www.who.int/vaccines-documents/DocsPDF07/870.pdf>

## DRAFT DOCUMENT

and/ or vaccines against novel human influenza viruses. Dose-response relationships may differ in younger and elderly individuals and should be explored in an age-specific manner. These studies may be reported as part of the post-prequalification commitment.

A fee will be charged for this procedure that will reflect the cost of the evaluation to be made. This fee may be different from the fee established already for other vaccines (see item 16 of the Procedure for assessing the acceptability of vaccines for purchase by United Nations agencies, WHO/IVB/05.19)<sup>7</sup>.

### Fees:

Category I: US \$ 10,000

Category II: US \$ 20,000

Category III a) and b) US \$ 30,000

Site visits for categories II and III will be charged on cost recovery basis

---

<sup>7</sup> [http://whqlibdoc.who.int/hq/2006/WHO\\_IVB\\_05.19\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_IVB_05.19_eng.pdf)

**Annex I Product Summary File Format for pandemic influenza A (H1N1) 2009 vaccines, and other vaccines against novel human influenza viruses**

The Product Summary File (PSF) for pandemic influenza A (H1N1) 2009 vaccines and other vaccines against novel human influenza viruses shall meet the description in the “Guideline for the preparation of the product summary file for vaccine prequalification, WHO/IVB/06.16<sup>6</sup>” with the following modifications.

The information in the PSF shall at least reflect the recommendations of the WHO Guideline: Regulatory Preparedness for Human Pandemic Influenza Vaccines<sup>4</sup>

Chapter 8 Clinical experience

For a pandemic influenza A (H1N1) 2009 vaccine, clinical trial data should be provided as it becomes available.

Information on cross-reactivity with circulating wild-type variants of the same subtype shall be provided, where relevant, and regularly updated by the applicant.

The applicant is expected to include a Clinical Expert Report (8.1.5) addressing the possible use during a pandemic discussing the value of demonstrated cross-reactivity.

The applicant shall provide a risk assessment of the production, quality control, and storage of seed material, bulks and final product. The assignment of the containment level (BSL classification) for production and QC shall be provided and justified. Evidence of compliance with the "WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines" (TRS 941 Annex 5) standards shall be provided<sup>8</sup>.

An outline of the precautions taken to protect the staff and the environment shall be provided.

---

<sup>8</sup> <http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Annex%205%20human%20pandemic%20influenza.pdf>