EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
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Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries

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Guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.
Abbreviations

CTD Common technical document
ECBS Expert Committee on Biological Standardization
GMP Good manufacturing practice
NCL National control laboratory
NPIPP National pandemic influenza preparedness plan
NRA National regulatory authority
PIP Pandemic Influenza Preparedness framework
PIV Pandemic influenza vaccine
PPIV Pandemic preparedness influenza vaccine
PQ Prequalification
WHO World Health Organization
UN United Nations

1. Introduction
An influenza pandemic occurs when a novel influenza A virus emerges, spreads rapidly around the world and against which most people do not have immunity. A pandemic influenza A virus is significantly different from circulating human influenza A viruses and has the following three characteristics – an ability to infect humans and cause disease, an ability to spread easily from human to human and the absence of immunity against the virus in the population. This may result in several simultaneous epidemics worldwide with high numbers of cases of clinical diseases and deaths, leading to considerable social disruption. New pandemic viruses may be viruses of a new subtype or of a subtype currently circulating in humans but of sufficient antigenic difference for pre-existing immunity in the population to be low or minimal (an example of the latter case is the A(H1N1) pandemic of 2009). Viruses that have caused past pandemics typically originated influenza viruses from animal. Due to urgent public health need, strategies to shorten the time between the emergence of a human pandemic influenza virus and the availability of safe and effective pandemic influenza vaccines are one of the highest priorities in global health security.

WHO’s Guidelines on regulatory preparedness for human pandemic influenza vaccines were adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2007 (1). These guidelines provide national regulatory authorities (NRAs) and vaccine manufacturers with:
• guidance regarding regulatory pathways for approving pandemic influenza vaccines;
• regulatory considerations to take into account in evaluating the quality, safety and efficacy of vaccine candidates; and
• guidance on effective post-marketing surveillance of pandemic vaccines.

The 2007 guidelines (1) apply mainly to countries where influenza vaccine production takes place, but they also contain much information that can be useful for countries where vaccines are not produced (hereafter referred to as non-vaccine-producing countries). However, consultations with stakeholders following the 2009 H1N1 influenza pandemic identified lack of regulatory preparedness as one of the factors that delayed or prevented the deployment of pandemic vaccine in non-vaccine-producing countries. This was especially the case for vaccine destined for donation or deployed by United Nations (UN) agencies in response to the pandemic emergency (2–5).

The present document has been developed in response to requests from non-vaccine-producing countries for guidance on the identification of appropriate regulatory approaches for marketing authorization of pandemic influenza vaccines and on arrangements for lot release of these vaccines in public health emergency conditions. The guidelines were developed in the context of the Pandemic Influenza Preparedness (PIP) Framework’s Partnership Contribution Implementation Plan for regulatory capacity-building and strengthening of pandemic preparedness and response (6).

2. Purpose and scope
This document provides guidance for NRAs of non-vaccine-producing countries on the regulatory oversight of pandemic influenza vaccines for use in public health emergencies. It focuses in particular on the needs of countries which are not producing influenza vaccines including countries supplied with vaccines through UN agencies and countries which procure vaccines by themselves.

The document aims to aid such countries to prepare and put in place, in advance of a pandemic influenza emergency, a regulatory process for pandemic influenza vaccines. This process should enable countries to expedite the provision of marketing authorization and lot release of influenza vaccines in response to a pandemic emergency. It is acknowledged that each country will have national legislation and policies on the regulation of medicines, vaccines and other health products. Some countries may also have regulations in place on accepting donations of vaccines and ancillary products. This document is intended to provide additional and specific guidance to the NRAs of non-vaccine-producing countries when dealing with pandemic influenza emergencies.

This document provides NRAs of non-vaccine-producing countries with general principles in evaluating influenza vaccines and establishing basic emergency procedures for regulating pandemic influenza vaccines. The guidelines emphasize the need to prepare decision-making processes which minimize duplication and make much-needed vaccines available for use without unnecessary delay during pandemic emergencies. The need to
establish appropriate regulatory processes during the inter-pandemic phase is emphasized.

These guidelines apply to all pandemic influenza vaccines. They are intended for NRAs, but will also be of interest to national immunization technical advisory groups (NITAGs), as well as manufacturers and authorities in the private and public sectors which are responsible for planning and managing vaccine deployment and vaccination operations at all levels.

Other relevant WHO guidelines should also be consulted as appropriate.

3. Terminology

The definitions given below apply to the terms as used in this document. The terms may have different meanings in other contexts.

**Alert phase**: the phase during which influenza caused by a new strain is identified in humans. Increased vigilance and careful risk assessment at local, national and global levels are characteristic of this phase (7).

**Influenza pandemic**: An influenza pandemic (or global epidemic) occurs when a novel influenza virus strain appears, which is significantly different from circulating strains and against which no one is immune. The WHO’s Director-General may, as appropriate, declare a public health emergency of international concern under the *International Health Regulations* (2005) upon the identification and determination of global spread of human influenza caused by a new virus subtype (7, 8).

**Inter-pandemic phase**: the period between influenza pandemics (7).

**Marketing authorization**: a formal authorization for a medicine to be marketed. Once an NRA approves a marketing authorization application for a new medicine, the medicine may be marketed and may be available for physicians to prescribe. Also referred to as “licensing” or “registration” in this and other documents (9).

**National pandemic influenza preparedness plan**: a national plan that aims at defining country-specific priorities and actions, identifying the major components that must be put in place (e.g. coordination, resource identification and allocation, capacity-building) and response actions that should be strengthened to respond to a pandemic (10).

**Non-vaccine-producing country**: a country in which vaccines are not produced.

**Pandemic influenza vaccine**: a monovalent vaccine containing the human influenza A virus
strain recommended by WHO for use either when a pandemic is considered by WHO to be imminent or during a pandemic (1).

**Pandemic phase:** the period of global spread of human influenza caused by a new subtype. Movement between the inter-pandemic, alert and pandemic phases may occur quickly or gradually, as indicated by the global risk assessment, principally based on virological, epidemiological and clinical data (7).

**Pandemic preparedness influenza vaccines:** an influenza vaccine developed and tested in anticipation of an influenza pandemic, and manufactured using an influenza virus strain that is believed to have similar characteristics to a potential pandemic virus strain (also referred to as “mock-up pandemic influenza vaccine” or “vaccine against novel human influenza virus” in other documents) (1, 11, 12).

**Risk management plan:** a document submitted as part of the marketing authorization dossier that is evaluated by regulatory authorities before a medicine can be authorised and which is regularly updated as new information becomes available. Risk management plans include information on a medicine’s safety profile and explain the measures that are taken in order to prevent or minimise the medicine’s risks in patients.

**Seasonal influenza vaccine:** a trivalent (or tetravalent) vaccine containing the two influenza A virus strains and one or two influenza B virus strains recommended by WHO at the influenza vaccine composition meetings held annually (once for the northern hemisphere and once for the southern hemisphere) (1).

**Supporting NRA:** an NRA selected by the NRA of receiving country as suitable to support the decisions of licensing PIV. The eligibility of supporting NRAs could be decided after consultation with WHO for guidance.

**Transition phase:** the phase during which, as the assessed global risk of influenza reduces, de-escalation of global actions occurs; the reduction of response activities or movement towards recovery actions by countries may be appropriate, according to their own risk assessments (7).

4. **General considerations for regulatory preparedness for pandemic influenza vaccines**

Countries should have laws requiring all medicinal products including influenza vaccines whether procured or donated in normal or emergency circumstances, to be licensed before being placed on the market.

All countries should prepare for public health emergency situations, including
influenza pandemics that may cause high morbidity and mortality leading to considerable social disruption. WHO has revised and updated its pandemic preparedness guidance to reflect the experience from the 2009 influenza A (H1N1) pandemic and to support further efforts at the national and subnational levels (7). This 2013 update provides for a risk-based approach that enables a more flexible response to different scenarios, reliance on multisectoral participation, and a simplified pandemic-phase structure that includes the inter-pandemic and pandemic (alert and transition) phases (7).

Regulatory preparations for influenza pandemic should also be undertaken in the inter-pandemic phase (7) in order to strengthen legal and regulatory requirements for importing and approving a vaccine in emergency situations, including improved capacity of NRAs and defined regulatory pathways for licensing the use of a new vaccine in emergency conditions (13).

NRAs should review the options available to them during a public health emergency and choose the appropriate procedures to fit the situation. The emergency procedures should include processes for ensuring information management and effective communication and cooperation between different branches of the NRA and relevant stakeholders such as public health authorities (10, 14).

Plans should be developed to address the need for official communication from the NRA relevant to specific audience, such as the public, health care workers, national and subnational authorities as well as international collaborators when needed. Principles set out in WHO’s Good regulatory practices: guideline for national medical products regulatory authorities (in preparation) (15) and other WHO relevant guidelines (16, 17) should be followed. Communication and information sharing systems should be established and need to be implemented for all stakeholders (13).

NRAs together with the national immunization programme and other stakeholders should develop post-marketing surveillance plans (including consideration of a risk management plan which is part of marketing authorization) to monitor the safety and efficacy of pandemic influenza vaccines used during a pandemic emergency. For guidance on safety monitoring and post-marketing surveillance plans, NRAs should refer to WHO’s Guidelines on regulatory preparedness for human pandemic influenza vaccines (1) and Global manual on surveillance of adverse events following immunization (18).

4.1 Acknowledgement of NRA’s roles in the national pandemic influenza preparedness plan

The national pandemic influenza preparedness plan should be established and endorsed before a pandemic arises and should include acknowledgement of the roles and responsibilities of the NRA in regulatory oversight of vaccines (10, 14, 19). The majority of WHO Member States developed and published their national pandemic influenza
preparedness plans in 2005 and 2006 and updated them after the influenza A(H1N1) 2009 pandemic (10).

4.2 Considerations for national regulatory preparedness

During the inter-pandemic phase, the NRA should be responsible for developing the following procedures to support the national pandemic influenza preparedness plan and vaccine deployment plan (13):

- suitable regulatory pathways for pandemic influenza vaccines during the emergency;
- appropriate vaccine lot release procedures for emergency use; and
- post-marketing safety surveillance plans.

It is recommended that the NRA's preparedness procedures for facilitating rapid availability of pandemic influenza vaccines should include:

- an NRA contact point for communications with WHO and stakeholders on public health/regulatory issues;
- allocation of resources to be used when a pandemic alert has been declared by WHO (Note that the national declaration of a pandemic emergency would be made by the responsible national authority following the declaration by WHO);
- a public risk communications plan summarizing the basis for decision-making;
- procedures for the timely appointment of an emergency evaluation task team for pandemic influenza vaccines (and medicines) that will:
  - include appropriate regulatory and programmatic expertise,
  - prepare procedures for evaluation of applications for pandemic influenza vaccine,
  - define the dossier and supporting documents needed for NRA evaluation,
  - evaluate and recommend marketing authorization of suitable vaccines to the NRA,
  - regular review of task team appointments and procedures in the inter-pandemic phase;
- procedures for interactions (on options for appropriate sources of vaccine) with the public health agencies that will procure, deploy and administer the vaccines;
- a system to accelerate the licensure and lot release of pandemic vaccine, including recognition of the decisions or reliance on the expertise of supporting NRA and optimizing the available resources in response to the pandemic;
- procedures and requirements for lot release of pandemic influenza vaccines by NRA in pandemic phase (or emergency situation).

The following steps should be included in the regulatory preparedness procedures:

- a working procedure for marketing authorization of the seasonal influenza vaccine annual virus strain change (this may be used where the pandemic influenza vaccine involves a strain change from a licensed seasonal influenza vaccine);
• preparation of a template emergency risk–benefit consideration and assessment report;
• a procedure for emergency approval of the NRA recommendation, as appropriate;
• a process to expedite marketing authorization through the WHO collaborative procedure for prequalified vaccines, when appropriate;
• preparation of an outline post-marketing surveillance plan which should include special provisions for post-marketing surveillance of the pandemic influenza vaccine in use.

The checklist of regulatory actions for pandemic preparedness and implementation are provided in Appendix 1.

4.3 Reliance on the decisions and expertise of other regulatory authorities

In the event of a pandemic emergency, the NRA of a non-vaccine-producing country should consider reliance on the product evaluation decisions made by other NRAs in vaccine-producing countries. Non-vaccine-producing countries may select and where possible, establish links with suitable supporting NRAs during the inter-pandemic period. Reliance on the decision or expertise of supporting NRAs is highly encouraged (15).

The NRA of the non-vaccine-producing country should establish mechanisms and procedures to recognize the marketing authorization decisions of the NRA of the country producing the vaccine, or of other supporting NRAs as appropriate, when considering the licensing of a pandemic influenza vaccine. Mechanisms and procedures may include the establishment of a memorandum of understanding or recognition, including an information-sharing agreement between receiving and selected supporting NRAs during the inter-pandemic phase.

The assessment reports (summary basis for decision) from other NRAs may provide valuable information and insight into the decision-making process of these NRAs but may not be readily available in a public health emergency. In this case communication with the relevant NRA regarding the licensure is highly encouraged.

In addition, a procedure for joint review of a pandemic vaccine dossier with neighbouring and supporting NRAs may be considered. This could be facilitated by WHO. The WHO collaborative procedure for marketing authorization of prequalified vaccines (20, 21) could be used as a model.

It should be noted that both joint reviews and WHO collaborative procedure require advance planning so that agreements are entered into effect at the earliest opportunity and that the vaccine product is already identified.

It is expected that future pandemic influenza vaccines prequalified by WHO will include an summary assessment report outlining the basis for prequalification that will be
available to countries intending to import, grant marketing authorization and use these vaccines to mitigate influenza pandemic. Request for more detailed information regarding prequalification of a particular pandemic influenza vaccine should be addressed to the WHO prequalification programme.

The NRAs of some vaccine producing countries with considerable experience in the evaluation of seasonal and pandemic influenza vaccines supported WHO in expediting the prequalification of pandemic influenza vaccines during the 2009 pandemic and are encouraged to support the NRAs of non-vaccine-producing countries in regulatory decision-making and marketing authorization of pandemic influenza vaccines.

4.4 Seasonal influenza vaccines and pandemic preparedness influenza vaccines

Seasonal influenza vaccines present many production and regulatory challenges similar to those of pandemic influenza vaccines due to the need for an annual change in formulation to reflect currently circulating virus strains, and very short development timelines. Many countries have established accelerated regulatory procedures for licensing seasonal influenza vaccines. Some non-vaccine-producing countries may also have provisions in place for accelerated regulatory approval of annual influenza virus strain change in a seasonal vaccine formulation.

WHO’s recommendations on annual changes in the vaccine strain composition should be followed (http://www.who.int/influenza/vaccines/virus/recommendations/en/) (9).

In appropriate circumstances, the NRA may decide that the procedure for annual seasonal vaccine strain change can be adapted to authorize pandemic influenza vaccines. Circumstances under which the strain change procedure can be adapted to license pandemic influenza vaccines are as follows:

- The candidate monovalent pandemic vaccine has a quantity of antigen content of single component similar to that of a licensed tri- or tetravalent seasonal influenza vaccine containing same subtype;
- The excipients in the candidate vaccine are the same as those in the licensed vaccine; and
- The manufacturing technology (e.g. eggs, inactivant, purification process) and controls are the same as those of the licensed vaccine.

Pandemic preparedness influenza vaccines are vaccines that have been prepared using strains of influenza viruses that are considered of pandemic potential – i.e. H5N1, H7N9. These vaccines may be novel in formulation, antigen content and/or adjuvant. Influenza vaccines manufacturers have been encouraged to develop pandemic preparedness influenza vaccines and conduct suitable nonclinical and clinical testing to demonstrate their safety and immunogenicity.

The rationale for the decision to review pandemic preparedness influenza vaccines should be made publicly available (11, 12).
Some countries may choose to make specific provisions for evaluating pandemic preparedness influenza vaccine as a precautionary step so that the strain-change policy and procedures used for seasonal influenza vaccine can be adapted for suitable pandemic vaccine applications. Once the pandemic preparedness influenza vaccine has been evaluated and approved (although not marketed for sale), the change to an appropriate pandemic virus strain – when identified and formulated into a pandemic vaccine – can be approved using similar criteria to those used for an annual seasonal vaccine strain change. This procedure may be implemented in those countries with adequate regulatory expertise and resources.

Some pandemic influenza vaccines or pandemic preparedness influenza vaccines may be novel constructs or formulations requiring expert regulatory evaluation. NRAs of non-vaccine-producing countries may request assistance in such evaluations by WHO or by other NRAs more experienced in the regulation of seasonal and pandemic influenza vaccines (see section 4.3).

5. Regulatory evaluation processes

The following elements are necessary to ensure an orderly and legal regulatory marketing authorization or emergency approval and lot release of a pandemic influenza vaccine in emergency situation in a minimum possible time:

- an NRA or a regulatory system;
- a national pandemic preparedness plan that includes:
  - acknowledgement that pandemic vaccines that are used shall be formally licensed or grant emergency approval by the NRA and released onto the market;
- NRA policies and procedures for:
  - NRA evaluation of applications for pandemic influenza vaccine,
  - procedures and criteria for rapid identification of suitable experts for regulatory evaluation of pandemic influenza vaccine applications (task team),
  - consideration of a joint review with neighbouring or supporting NRAs,
  - recognition of marketing authorization decision of other NRAs and WHO prequalification decision;
- a procedure for emergency approval of the NRA’s pandemic influenza vaccine recommendations (where higher authority ratification is required);
- a collaborative procedure for expedited marketing authorization of prequalified vaccines, when appropriate;
- a situation analysis of possible procedures for marketing authorization of vaccines received through self-procurement, donations and/or UN supply. The situation should also be recognized whereby a pandemic influenza preparedness vaccine has been evaluated and approved during the inter-pandemic period and where the application
can subsequently be approved for pandemic use on the basis of the national seasonal influenza vaccine strain-change procedure.

- recognition of lot release certificate of other responsible NRAs;
- plan for post-marketing surveillance of the pandemic influenza vaccine in use.

Depending on the pandemic phase and the source of the vaccine, the following regulatory approaches could be followed by a NRA (details see section 5.2):

1. Full review: A standard review process to authorize a product licensure that can include fast-track priority review.
2. Fast-track review of basic documentation: a fast-track review process, and review based on basic available information for emergency authorization.
3. Reliance: a process to review the marketing authorization report/decision issued by another supporting NRA or WHO prequalification (21).
4. Recognition: recognition of the marketing authorization decision of another NRA or WHO prequalification without further evaluation.
5. Strain change procedure: a procedure for authorizing seasonal strain change for influenza vaccines:
   a. a procedure for the evaluation and approval of seasonal influenza virus strain changes (Appendix 2);
   b. the procedure to be used for pandemic preparedness influenza vaccine evaluation and marketing authorization.

5.1 Expected basic documentation according to the sources of pandemic influenza vaccine

Non-vaccine-producing countries can access pandemic influenza vaccine from different sources, including a UN agency, a donation from a company or other source, or self-procurement. In general, full dossiers are required for evaluation of the quality, safety and efficacy of vaccines; however, in an emergency situation the accompanying documentation dossier may be provided in sections as it becomes available.

Under these circumstances, at least the following documents should be made available for evaluation to ensure the quality, safety and efficacy of vaccines from each source:

1) UN agency supply (WHO-prequalified vaccines)
   - Evidence/certificate of WHO-prequalification with assessment report (20, 21).

2) Donation from a company or other source
   - Requirements for strain change of an licensed seasonal influenza vaccine or pandemic preparedness influenza vaccine (if applicable).
   - If the vaccine has been prequalified by WHO, the common technical document (CTD) Module-2 and Prequalification assessment report should be provided.
• If the vaccine has been licensed by a supporting NRA, the CTD Module-2 and assessment report by the NRA should be provided.
• Where the vaccine has been licensed by an NRA other than a supporting NRA, the full dossier for marketing authorization and the assessment report by the NRA, if available, should be provided.
• In the case of a vaccine that has not previously been licensed, a full dossier for marketing authorization should be provided by the manufacturer. The procedures and requirements in WHO’s Guidelines on regulatory preparedness for human pandemic vaccines should be followed (1).

National guidelines on donations of medicines should be followed. If these do not exist, the recommendations in WHO’s Guidelines for medicine donations (22) should be followed.

3) National procurement
• Information on strain change of licensed seasonal or pandemic preparedness influenza vaccine should be provided (if applicable).
• If the vaccine has been WHO-prequalified, the CTD Module-2 and Prequalification assessment report should be provided.
• If the vaccine has been licensed by a supporting NRA, the CTD Module-2 and assessment report, if available, should be provided.
• Where the vaccine has been licensed by an NRA other than a supporting NRA, the full dossier for marketing authorization and the assessment report by the NRA, if available, should be provided.
• In the case of a vaccine that has not previously been licensed, a full dossier for marketing authorization should be provided. The procedures and requirements in WHO’s Guidelines on regulatory preparedness for human pandemic vaccines should be followed (1). Seeking support from NRA of producing country is high encouraged.

5.2 Possible regulatory review processes in a pandemic emergency
Even in the midst of pandemic emergency, the NRA should conduct an appropriate review of the documentation submitted that covers the components set out below, and should document the extent of evidence that is available and on which the recommendation to authorize/approve/reject has been based.

In a pandemic emergency, it is possible that not all documentation for a vaccine will be available at the time of application, and many NRAs have accepted that applicants will submit the evidence as it becomes available. This approach is generally known as a “rolling review” (23). It would be expected that the sections on manufacturing, specifications and
controls would be available, together with evidence of consistency of manufacture. For nonclinical safety studies, preliminary results should be available. Results of stability studies would be delayed as would any results from clinical studies.

Where possible, the NRA could make arrangements for joint review of pandemic vaccine dossiers with neighbouring and/or supporting NRAs. The possible parties involved in such an arrangement should establish this agreement during the inter-pandemic phase.

Depending on the different pandemic phase and the source of the vaccine, review activities may include one or more of the following procedures (summarized in Table 1 as well):

1. Full review
   This is the standard process of review full dossier in a fast-track review process (as normally conducted in that country) for vaccines that are new applications or previously licensed by NRAs other than a supporting NRA.
   Available documentation: The documentation should be complete, as legally required in each country.
   Applicability: This procedure would apply to licensed vaccines in inter-pandemic pandemic phase.
   This would require evaluation of the documentation of product quality and the evidence of nonclinical and clinical studies to show safety and efficacy in the target population. The documentation should be as legally required in each country.
   In inter-pandemic phase the NRA of non-vaccine-producing countries may conduct full review dossier of pandemic preparedness influenza vaccine to be familiar with the characteristics of pandemic influenza preparedness vaccine.

2. Fast track review of basic documentation
   This is a fast-track review process and marketing authorization is based on the information available at the time. In the event that a fast-track review is deemed appropriate (as defined in the approved NRA pandemic emergency procedures), the following documents from the manufacturer and the responsible NRA/WHO should be reviewed. The full application dossier may be provided when available.
   Available documentation:
   - assessment reports of NRA;
   - evidence of quality (certificate of analysis or lot release) and good manufacturing practices (GMP) compliance (GMP certificate);
   - CTD Module-2 quality, nonclinical and clinical overviews (if available)

   Applicability: This procedure would apply in a pandemic alert phase, and transition phase for a pandemic influenza vaccine is licensed by a NRA other than supporting NRA.

3. Reliance
   This is a process of review of the decision of other competent NRAs with which there has been agreement for support. Where it has been agreed (as defined in the approved NRA
pandemic emergency procedures) that the decision of another NRA can be considered, and used as the basis of a recommendation for marketing authorization, this process would require the following elements.

Available documentation:
- certificate of the responsible NRA’s marketing authorization decision;
- assessment reports of the responsible NRA;
- acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine.

Applicability: This procedure would apply in a pandemic alert phase, pandemic phase and transition phase for a pandemic influenza vaccine is licensed by a NRA other than supporting NRA.

4. Recognition

This is a process of recognizing of the WHO PQ decision or the decision of supporting NRA. Where it has been agreed (as defined in the approved NRA pandemic emergency procedures) that the decision of a supporting NRA can be used as the basis for a recommendation for marketing authorization, this approach would require the following documents:
- a certificate of the responsible NRA’s marketing authorization decision or WHO-prequalification assessment report;
- acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine.

Applicability: This procedure would apply in a pandemic alert phase, pandemic phase and transition phase for a pandemic influenza vaccine that is licensed by a supporting NRA or prequalified by WHO. It may also apply in a pandemic phase for a pandemic influenza vaccine that is licensed by a NRA other than supporting NRA.

5. Strain change procedure

This is a procedure for a strain change for an licensed seasonal vaccine. Where it has been agreed (as defined in the approved NRA pandemic emergency procedures) that the dossier of a pandemic preparedness influenza vaccine may be evaluated, following the criteria set out for an annual strain change, as applicable for pandemic use.

Available documentation:
- The documentation required would be as for an annual strain change;
- The approved conditions and limitations on the use of the vaccine should be accepted.

Applicability: This procedure would apply in all pandemic phases for a pandemic influenza vaccine that is licensed by a strain change approach from pandemic preparedness influenza vaccine or seasonal influenza vaccine by the NRA of producing country.
Apart from the regulatory procedures for marketing authorization of pandemic influenza vaccines there is expedited licensure through WHO collaborative procedure for prequalified vaccines (20) may be used for suitable pandemic vaccines as appropriate. The agreement among WHO, receiving NRA and manufacturer for information-sharing could be signed in the inter-pandemic phase. Therefore if, in an emergency, time does not allow for this to occur prior to the decision to use the vaccine. For this procedure WHO prequalification assessment report should be provided to the receiving NRA. The full dossier in the format of CTD could be provided to the NRA as well.

It would be expected that, following the pandemic phase, the full dossier as required by the relevant non-vaccine-producing country would be completed and submitted for evaluation.

Table 1: Illustrative chart of regulatory approaches relative to the status of the vaccine and the continuum of pandemic phases*

<table>
<thead>
<tr>
<th>Licensed vaccines from any sources</th>
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<tbody>
<tr>
<td>Prequalified</td>
</tr>
<tr>
<td>Recognition procedures in all phases</td>
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</tbody>
</table>

Note:

Supporting NRA: an NRA selected by the NRA of receiving country as suitable to support the decisions of licensing of PIV. The eligibility of supporting NRAs could be decided after consultation with WHO for guidance.

Other NRAs: NRAs not deemed as supporting NRA by the NRA of receiving country.

*Pandemic status: Inter-pandemic phase, alert phase, pandemic phase and transition phase as defined by WHO (see section 3 Terminology).
If a pandemic influenza vaccine is licensed by a strain change approach from a pandemic preparedness influenza vaccines or a seasonal influenza vaccine the receiving country NRA could choose strain change approach or the other appropriate approaches based on the source of vaccine.

If the vaccine has not been licensed by any NRAs the recommendation set out in Guidelines on regulatory preparedness for human pandemic influenza vaccines should be applied (1).

**Final evaluation**

Before a regulatory decision to recommend marketing authorization of a pandemic influenza vaccine is taken, a final evaluation of the available documentation should be conducted to ensure that the pandemic influenza vaccine presentation is suitable for use in the country (24, 25).

Provided the procedures are in place (see section 5.3), this final evaluation can be conducted rapidly (e.g. in as little as one day, depending on circumstances and marketing authorization status of the pandemic influenza vaccine), with a risk–benefit consideration and recommendation for marketing authorization.

The NRA should ensure that the following apply:

- An adequate document package is provided. A post-marketing commitment by the manufacturer to provide outstanding information should be considered.
- There is a local agency responsible for supply of the product (i.e. an “applicant” or state body that is a defined responsible legal entity).
- Packaging, label and package insert are nationally acceptable.
- The vaccine is compatible with the national pandemic influenza preparedness plan.
- The vaccine indicated for circulating strain(s).

This evaluation may need to be based on minimal and incomplete documentation, and this should be acknowledged in the recommendation.

An evaluation report should be produced by the NRA.

**5.3 Emergency approval**

In some countries the NRA may have authority to approve the use of a medicine or vaccine without reference to another authority, while in other countries a final approval or directive is required. Thus there is reference to a “recommendation” as well as an “approval” process.

During the pandemic period, emergency approval procedures may be used. Approval may be based on limited clinical data or quality data (e.g. stability) and expedited evaluation of the available evidence. Therefore, the approval may include one or more special
Post ECBS version
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conditions for use. These may include post-marketing safety reporting conditions and
limitations such as:

- use only during the pandemic period;
- use by certain agencies;
- use in certain listed high-risk groups;
- post-marketing safety reporting conditions.

5.4 Post-marketing risk management and surveillance

Each country should include post-marketing surveillance of adverse events in the pandemic
vaccine deployment plan. This should follow recommendations in WHO’s Guidelines on
regulatory preparedness for human pandemic influenza vaccines (1) and WHO’s Global
manual on surveillance of adverse events following immunization (18). The risk management
plan for pandemic should be monitored by the NRA and national immunization programme
with input from the vaccine manufacturer.

National systems for post-marketing surveillance and reporting of adverse events
following immunization should not be compromised by implementation of a pandemic
influenza campaign.

6. Quality control preparedness

Lot release and quality control of pandemic influenza vaccines by the NRA/NCL of non-
vaccine-producing countries should following the recommendations set out in relevant WHO
guidelines (19, 20, 22, 24–26).

Vaccines received by procuring countries should be produced in compliance with
GMP, tested for quality and safety by the vaccine manufacturer and, usually, subjected to
independent quality control testing and released by the responsible NCL in accordance with
WHO’s Guidelines for independent lot release of vaccines by regulatory authorities (19). It
is recommended that, for vaccines supplied through UN agencies, further release by the
NRA/NCL of receiving countries should not be performed because such products are
prequalified by WHO and released by the responsible NRA/NCL. Likewise, self-procured
WHO-prequalified vaccines are released by the responsible NRA/NCL and, if so, should not
be subjected to further lot release by the importing country in the event of an influenza
pandemic. Recognition of the lot release certificate of the responsible NRA/NCL of the
producing country is recommended by WHO (19).

For self-procured none WHO-prequalified pandemic influenza vaccines, the
NRA/NCL of procuring country may, in the event of an influenza pandemic emergency,
conduct lot release through review of the summary lot protocol. Further laboratory testing by
the NRA/NCL of the receiving country may not be necessary, based on risk assessment. Part
F of WHO’s Guidelines on regulatory preparedness for human pandemic influenza vaccines
(1) should be consulted.
The procedures adopted should ensure the deployment of vaccines without undue delay.

7. **Authors and acknowledgements**

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The scientific basis for development of these guidelines was discussed at the meeting of the working group held in Tunis, Tunisia, on 9–10 June 2015 attended by Dr C.P. Alfonso, World Health Organization, Geneva, Switzerland; Dr M.E.M. Ahmed, National Medicines & Poisons Board, Khartoum, Sudan; Ms D. Decina, World Health Organization, Geneva, Switzerland; Dr R.O.A. Dehaghi, World Health Organization, Geneva, Switzerland; Mr S. Dorji, Drug Regulatory Authority of the Royal Government of Bhutan, Thimphu, Bhutan; Dr M. Eisenhawer, World Health Organization Regional Office for South-East Asia, New Delhi, India; Dr L. Elmgren, Health Canada, Ottawa, Canada; Dr O.G. Engelhardt, National Institute for Biological Standards and Control, Potters Bar, United Kingdom; Dr E. Griffiths, Consultant, Kingston upon Thames, United Kingdom; Ms L. Hedman, World Health Organization, Geneva, Switzerland; Mr S. Hiem, Registration Bureau of Department of Drugs and Food, Phnom Penh, Cambodia; Mrs T. Jivapainsarnpong, Institute of Biological Products, Ministry of Public Health, Bangkok, Thailand; Dr H. Langar, World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt; Ms M.L.L. Mendez, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico DF, Mexico; Dr D. Lei, World Health Organization, Geneva, Switzerland; Dr I.B. Mansour, Laboratoire National Contrôle Médicaments, Tunis, Tunisia; Ms E. Nantongo, National Drug Authority, Kampala, Uganda; Dr L. Oueslati, Laboratoire National Contrôle Médicaments, Tunis, Tunisia; Dr P. Palihawadana, Ministry of Healthcare and Indigenous Medicine, Colombo, Sri Lanka; Dr M. Pfleiderer, Paul Ehrlich Institute, Langen, Germany; Mr A.R.A. Rauf, Drug Regulatory Authority of Pakistan, Islamabad, Pakistan; Ms J. Rodgers, Food and Drugs Authority Ghana, Accra, Ghana; Ms C.A. Rodriguez Hernandez, World Health Organization, Geneva, Switzerland; Dr S. Sebai, Laboratoire National Contrôle Médicaments, Tunis, Tunisia; Dr S.F. Shah, Consultant, World Health Organization Regional Office for the Western Pacific, Manila, Philippines; Dr J. Southern, Adviser to Medicines Control Council of South Africa, Cape Town, South Africa; Dr I. Tebib, Laboratoire National Contrôle Médicaments, Tunis, Tunisia; Ms E. Yonis, Food, Medicines
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The document WHO/BS/2016.2289, incorporating comments received from regulators and industry following public consultation on the WHO Biologicals website, was
8. References


2. Ramirez S. Expert review and analysis of available resources relevant to PIP Regulatory Capacity Building Output 1 – “Develop guidelines on regulatory preparedness for non-vaccine producing countries that enables them to expedite approval of influenza vaccines used in national immunization programs and/or deployed by United Nations agencies in response to a pandemic emergency”. Internal report. Geneva: World Health Organization; 2015.


9. Appendix 1. Checklist of regulatory actions for pandemic preparedness and implementation

It is important to ensure that regulatory legislation is in place to enable the various approaches listed below to be applied as needed in preparation for, or during, a pandemic.

1. Prepare regulatory preparedness procedures compatible with the national pandemic influenza preparedness plan during the inter-pandemic phase.

2. Appoint and maintain a pandemic task team (with staff, training, budget and annual review).

3. In the inter-pandemic phase to (provisionally) marketing authorize pandemic preparedness influenza vaccines.

4. Liaise with other national agencies on pandemic preparedness procedures.

5. Develop memoranda of understanding with potential supporting NRAs.

6. In the pandemic alert phase (or earlier, if possible):
   a. Determine which vaccines may be sourced by national agencies.
   b. Request data packages from potential vaccine suppliers.
   c. Decide on appropriate evaluation procedures and evaluators.
   d. Prepare a format for an assessment report and post-marketing surveillance plan.
   e. Make a recommendation for licensure/rejection that includes the assessment report.
   f. Alert the NCL regarding potential vaccines that may be marketing authorized and imported.

7. In the pandemic phase:
   a. Complete the activities from the alert phase.
   b. Conduct vaccine lot release procedures or, where appropriate, recognize the lot release certificate issued by the NRA/NCL of the producing country.
   c. Where possible, keep records of the vaccine lot deployment (consider that there may be more than one vaccine approved for use).
   d. Implement the national surveillance plan.
   e. Continue to update the data packages from the vaccine supplier.
   f. Conduct regular reviews of activities and optimize where possible.

8. In the pandemic transition phase:
a. Complete the data package for the emergency-approved vaccine/s.
b. Collate and analyse the data from post-marketing surveillance activities.
c. Withdraw the licence of the emergency-approved pandemic vaccine if appropriate.
d. Review the activities of the pandemic task team and propose improvements.
e. Review the reports from the pandemic surveillance plan.
10. Appendix 2. Example of procedures for evaluation of seasonal influenza vaccine annual virus strain change

Example of information and documentation that may be required:

1) WHO-recommended strain list for the relevant hemisphere.
2) Manufacturer's choice of strains for inclusion.
3) Details of manufacturing procedure (declaration if unchanged).
4) Validation of the inactivation and fragmentation.
5) Source, history and master/working seed characterization of each strain included.
6) Egg/ cell culture: safety specifications and tests (declaration if unchanged).
7) Qualification of potency test (SRID) reagents.
8) Final product release specifications and results (this must include endotoxin release limit).
9) Retrospective data about the "efficacy or performance" of influenza vaccines (preceding year/season).
10) Stability data (accelerated or from the most recent, or most similar, batch of approved vaccine).
11) Copy of the approved package insert.
12) Copy of the proposed package insert, indicating:
   i) the year/season for which the vaccine will be used;
   ii) WHO recommended strains;
   iii) a statement that the vaccine complies with WHO recommendations (southern or northern hemisphere) for the year/season.
13) Copy of the approved patient information leaflet.
14) Copy of the proposed patient information leaflet, indicating:
   i) the year/season for which the vaccine will be used;
   ii) WHO recommended strains.
15) All labels, immediate and outer container, must prominently indicate the year/season for which the vaccine will be used, and a facsimile must be submitted as proof.
16) International core data sheet or SMPC.