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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 17 to 21 October 2016

Guidelines on regulatory preparedness for licensing human pandemic influenza vaccines in non-vaccine-producing countries

Proposed new guidelines

NOTE:

These Guidelines were developed based on the outcomes and consensus of the WHO working group meeting and informal consultation convened in June 2015 and April 2016 respectively, with participants from national regulatory authorities, national control laboratories, vaccine manufacturers and academia researchers.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization. Written comments proposing modifications to this text MUST be received by 16 September 2016 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Dianliang Lei at email: **leid@who.int**.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

Contents

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
PSF Product summary file
WHO World Health Organization
UN United Nations

1. Introduction

An influenza pandemic occurs when a novel influenza A virus subtype emerges, spreads rapidly around the world and most people do not have immunity against it. A pandemic influenza A virus is significantly different genetically from circulating human influenza A viruses and has the following three characteristics – an ability to infect humans, an ability to cause disease in humans and an ability to spread easily from human to human. Viruses that have caused past pandemics typically originate from animal influenza viruses. Pandemic influenza is characterized by the fact that there is a very short time interval between the identification of a novel pandemic virus strain and the development, manufacture and licensing of a new vaccine. 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 of the highest priority 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 regulatory delays as one of the factors that caused or exacerbated bottlenecks during 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 pathways for licensing 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 *(6)* 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 that source vaccines for use in their national immunization programmes mainly from UN agencies and countries that procure vaccines using the list of WHO prequalified vaccines as a reference.

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 licensing/approval 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.

The NRAs of some non-vaccine-producing countries may have the capacity to evaluate vaccines for emergency use. This document provides guidance to NRAs with limited experience, and/or fewer resources, in evaluating influenza vaccines and in 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 subtype is identified in humans. Increased vigilance and careful risk assessment at local, national and global levels are characteristic of this phase. If the risk assessments indicate that the new virus is not developing into a pandemic strain, a de-escalation of activities towards those in the inter-pandemic phase may occur *(7)*.

Influenza pandemic: 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)*.

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 (9).

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, 10, 11)*.

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 southern hemisphere) *(1)*.

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)*.

WHO prequalification: the process by which WHO assesses the acceptability of vaccines for purchase by UN agencies of assured quality, safety and efficacy and appropriate for use in national immunization programmes. WHO prequalification (PQ) provides a single standard against which products from manufacturers can be assessed and so provides a basis upon which emerging suppliers can compete in international markets. Information on vaccines prequalified by WHO can be used as an independent verification of quality by countries that procure vaccines directly *(12)*.

4. General considerations for regulatory preparedness for pandemic influenza vaccines

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)*.

A national pandemic influenza preparedness plan (NPIPP) should be developed in the inter-pandemic phase. The plan should acknowledge the roles and responsibilities of the NRA in licensing/authorizing the use, lot release and safety monitoring of medical products used to mitigate an influenza pandemic in the country *(9, 13, 14)*.

The national pandemic influenza preparedness plan should include a defined trigger for implementing national emergency procedures following the declaration of the influenza pandemic phase by the Director-General of WHO *(7, 8)*. A national deployment and vaccination plan for pandemic influenza products – including vaccines, antivirals and diagnostics – should also be developed in the inter-pandemic phase *(15)*. A national policy on using pandemic influenza vaccine and identifying priority groups would facilitate the use of the vaccine (see section 4.1).

Regulatory preparations should 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 *(15)*.

The NRA's powers should be specified in the national law, including provisions for policy, strategic planning and authority to license medicines, vaccines and health products that may be used during a public health emergency.

NRAs should review the options available to them during a public health emergency. 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 *(9, 13)*.

The transparency of the regulatory decision-making process is important. Plans should be developed for communication to the public, health and non-health authorities, international organizations, the media and policy-makers, and should follow *WHO's Good regulatory practices: guideline for national medical products regulatory authorities* (in preparation) *(16)*. Communication and information systems need to be implemented for all stakeholders during the inter-pandemic phase *(15)*.

NRAs together with the national immunization programme should develop post-marketing surveillance plans (including a risk management plan) 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 (17)*.

Those countries without appropriate national legislation and policies for regulatory oversight and use of pandemic influenza vaccines and other medicines during public health emergencies are strongly encouraged to develop both a national pandemic influenza preparedness plan and a national deployment plan for pandemic influenza vaccines that specifies the roles and responsibilities of the NRA *(7, 9, 13, 15)*.

4.1 The national pandemic influenza preparedness plan

The national pandemic influenza preparedness plan should be established and endorsed during the inter-pandemic phase. 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 *(9)*.

In particular, the national pandemic influenza preparedness plan should include recognition of the NRA's responsibilities, namely:

- emergency procedures for use of vaccines and other medicines that will be under the control of the NRA for licensing;
- the need for NRA evaluation and licensing of a pandemic influenza vaccine (and other emergency medicines) that will be included in the national plan.

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:

- suitable regulatory pathways for pandemic influenza vaccines during the emergency;
- appropriate vaccine lot release procedures for emergency use;
- 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 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 licensing of suitable vaccines to the NRA,
  - regular review of task team appointments and procedures in the inter-pandemic phases;
- procedures for interactions (on options for appropriate sources of vaccine) with the public health agency that will procure 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 other regulatory authorities;
- systems for post-marketing surveillance of the pandemic influenza vaccine in use (these may require special provision in the national pharmacovigilance plan).

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. Each non-vaccine-producing country should select and establish links with suitable supporting NRAs during the inter-pandemic period.

The NRA of the non-vaccine-producing country should establish mechanisms and procedures to recognize the licensing decisions of the NRA of the country producing the vaccine, or of other NRAs, when considering the licensing of a pandemic influenza vaccine.

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.

Mechanisms and procedures may include the establishment of a memorandum of understanding or recognition, including an information-sharing agreement, between selected NRAs.

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 licensing of prequalified vaccines *(18)* may be considered. However, this requires advance planning so that agreements are entered into at the earliest opportunity and that the vaccine product is already identified.

It is expected that future pandemic vaccines prequalified by WHO will include an assessment report outlining the basis for prequalification that will be available to countries intending to import, license and use these vaccines.

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

4.4 Influenza seasonal vaccines and pandemic preparedness 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 *(19)*.

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

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

Pandemic preparedness vaccines are vaccines that have been prepared using strains of influenza that are considered of pandemic potential – i.e. H5N1, H7N9. These vaccines may

be novel in formulation, antigen content and/or adjuvant. Influenza vaccine manufacturers have been encouraged to develop pandemic preparedness vaccine and conduct suitable nonclinical and clinical testing to demonstrate safety and immunogenicity.

The rationale for the decision to review pandemic preparedness vaccine should be made publicly available *(10, 11)*.

Some countries may choose to make specific provisions for evaluating pandemic preparedness 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 vaccine has been evaluated and approved (although not licensed 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.

Some pandemic influenza vaccines or pandemic preparedness vaccines may be novel constructs or formulations requiring expert regulatory evaluation. NRAs of non-vaccine-producing countries should 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 pathways

The following elements are necessary to ensure an orderly and legal emergency regulatory licensure or emergency approval and lot release of a pandemic influenza vaccine:

- an NRA;
- a national pandemic preparedness plan that includes:
  - acknowledgement that pandemic vaccines that are used will be licensed by the NRA following appropriate lot release procedures;
- NRA policies and procedures for:
  - NRA evaluation of applications for pandemic influenza vaccine,
  - procedures and criteria for rapid identification of suitable experts for NRA evaluation of pandemic influenza vaccine applications (task team),
  - consideration of a joint review with neighbouring or supporting NRAs;
- a procedure for emergency approval of the NRA's pandemic influenza vaccine recommendations (where higher authority ratification is required);
- a collaborative procedure for expedited licensing of prequalified vaccines, when appropriate;
- a situation analysis of possible approaches for licensing vaccines received through self-procurement, donations and UN supply. The situation should also be recognized whereby a pandemic 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.

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

1. Standard review for full licence that can include fast-track priority review.
2. Abridged fast-track review for emergency licensing.
3. Review of the licensing report/decision issued by another supporting NRA, and based on limited available information.
4. Recognition of the licensing decision of another NRA or WHO prequalification and national licensing without further evaluation.
5. Procedures for licensing of seasonal strain change for influenza vaccines:
    a. a procedure for the evaluation and licensing of seasonal influenza virus strain changes (Appendix 1);
    b. the procedure to be used for pandemic preparedness vaccine evaluation and licensing.
6. A collaborative procedure for expedited licensing of WHO-prequalified vaccines.

5.1 Potential sources of emergency supplies of pandemic influenza vaccine and expected accompanying documentation

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 incomplete.

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. However, in an emergency, the PQ assessment report may not be available.

2) Donation from a company or other source
    - Requirements for strain change of a licensed seasonal influenza vaccine or pandemic preparedness influenza vaccine (if applicable).
    - If the vaccine has been prequalified by WHO, the product summary file (PSF) and assessment report should be provided.
    - If the vaccine has been licensed by a WHO PQ-selected eligible NRA,[1] *(12)* the common technical document (CTD) Module-2 and assessment report, if

[1] In this document, the term eligible NRA refers to a national regulatory authority that exhibits a high level of performance of all WHO recommended regulatory functions *(20),* exercises full regulatory oversight of any given vaccine, and has been selected by the WHO PQ programme for the streamlined PQ process *(12).*

available, should be provided.

- Where the vaccine has been licensed by an NRA other than a WHO PQ-selected eligible NRA, the full dossier for licensure 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 licensure should be provided. 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 (21)* 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 product summary file (PSF) and assessment report should be provided.
- If the vaccine has been licensed by a WHO PQ-selected eligible 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 WHO PQ-selected eligible NRA, the full dossier for licensure 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 licensure should be provided. The procedures and requirements in WHO's *Guidelines on regulatory preparedness for human pandemic vaccines* should be followed *(1)*.

5.2 Possible regulatory review activities in a pandemic situation

Even in the most critical pandemic situation, 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 license/approve/reject has been based.

In a pandemic situation, 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 known as a "rolling review" *(22)*. 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 urgency of the pandemic status and the source of the vaccine, review activities may include one or more of the following procedures (Table 1):

1. Full dossier review 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 WHO PQ-selected eligible NRA.

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.

2. Abridged review

This would apply in a pandemic alert phase, pandemic phase and transition phase.

In the event that a fast-track abridged evaluation 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:

- assessment reports;
- evidence of quality and good manufacturing practices (GMP) compliance (certificate of analysis or lot release);
- CTD Module-2 quality, nonclinical and clinical overviews (if available)
  - summaries of nonclinical and clinical evidence in support of safety and efficacy,
  - WHO PQ product summary file (PSF).

3. 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 licensing, this process would require the following elements:

- certificate of the responsible NRA's licensing decision;
- assessment reports of the responsible NRA;
- acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine.

4. Recognition of the WHO PQ decision or the decision of another competent NRA

Where it has been agreed (as defined in the approved NRA pandemic emergency procedures) that the decision of another supporting NRA can be used as the basis for a recommendation for licensing, this approach would require:

- a certificate of the responsible NRA's licensing decision;
- acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine.

5. Procedure for a strain change from a licensed seasonal vaccine

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

- 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.

6. Expedited licensure through WHO collaborative procedure for prequalified vaccines may be used for suitable pandemic vaccines *(18)*

This procedure requires advance planning and ratification of agreements for information-sharing. Therefore if, in an emergency, time does not allow for this to occur prior to the decision to use the vaccine:

- The WHO PQ assessment report should be provided (if available).
- The conditions and limitations on the use of the vaccine should be accepted.

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: Possible regulatory actions relative to the status of the vaccine and the continuum of pandemic phases* (decision tree)

Status of vaccine	Inter-pandemic phase	Alert phase	Pandemic phase	Transition phase
PPIV	Full review	Abridged review	Abridged review (if applicable)	(not applicable)
Strain change for a PPIV	Strain change	Strain change	Strain change (if applicable)	Strain change
Eligible NRA-licensed PIV	(not applicable)	Recognition	Recognition	Recognition
Other NRA-licensed PIV	(not applicable)	Abridged review	Recognition	Abridged review
WHO-prequalified PIV	(not applicable)	Recognition	Recognition	Recognition

Note:

PIV: Pandemic influenza vaccine
PIV may continue to be used after the pandemic.
PPIV: Pandemic preparedness influenza vaccine for current pandemic.
Eligible NRA: WHO PQ programme-selected eligible NRA *(12)* OR an NRA selected by another NRA as suitable to support decisions.

Other NRAs: NRAs not selected by the WHO PQ programme.
*Pandemic status**:** As defined by WHO (see section 3 Terminology) *(7, 8)*.

Final review

Except for procedure No. 6 (expedited licensure through WHO collaborative procedure for prequalified vaccines), and before a regulatory decision to recommend approval of a pandemic influenza vaccine is taken, a final evaluation of the available documentation should be conducted to ensure that the pandemic influenza vaccine is suitable for use in the country.

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

The NRA should ensure that the following apply:

- An adequate document package is provided. A post-licensure commitment by the manufacturer to provide outstanding information should be considered.
- There is a national 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 (NPIPP).
- The vaccine is compatible with the national environment (i.e. disease background).

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

An assessment report should be produced by the NRA.

5.3 Steps required in the regulatory preparedness procedures

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

- preparation of a risk–benefit consideration and assessment report;
- a procedure for emergency approval of the NRA recommendation, as appropriate;
- a procedure for licensing of the seasonal influenza vaccine annual virus strain change where the pandemic influenza vaccine involves a strain change from a licensed seasonal influenza vaccine influenza vaccine;
- a process to expedite licensure through the WHO collaborative procedure for prequalified vaccines, when appropriate;
- preparation of a post-marketing surveillance plan.

5.4 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 incomplete clinical data or quality data (e.g. stability) and abridged evaluation of the available evidence. Therefore, the approval may include one or more special 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.

5.5 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 (17)*. The risk management plan for pandemic should be developed 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

Non-vaccine-producing countries should consider the establishment of a lot release system and access to control laboratories, as recommended in WHO guidelines on regulatory functions for licensed vaccines *(18, 21, 23–25)*.

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 national control laboratory (NCL) in accordance with WHO's *Guidelines for independent lot release of vaccines by regulatory authorities (14)*. 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 *(14)*.

For self-procured, but not WHO-prequalified, pandemic influenza vaccines, the procuring NRA/NCL 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. In such circumstances, 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. 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) license 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 licensed 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.

8. Authors and acknowledgements

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10. Appendix 1. 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.