Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries

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Appendix 1 Checklist of regulatory actions for pandemic influenza preparedness and response

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Guidelines published by the World Health Organization (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
GMP  good manufacturing practice(s)
NCL  national control laboratory
NRA  national regulatory authority
PIP  Pandemic Influenza Preparedness (Framework)
1. Introduction

An influenza pandemic occurs when a novel influenza A virus emerges against which most people do not have immunity, and spreads rapidly around the world. A pandemic influenza A virus is significantly different from normally circulating human influenza A viruses, with a widespread absence of immunity against the virus observed in the population. As with seasonal influenza viruses, pandemic influenza viruses have the ability to spread easily from human to human and cause disease. This may result in several simultaneous epidemics worldwide with high numbers of cases of clinical disease and deaths, leading to considerable social disruption. Pandemic influenza viruses may evolve from subtypes that previously only circulated in animals or from subtypes currently circulating in humans but sufficiently different antigenically for pre-existing immunity in the population to be low or minimal (an example of the latter case is the 2009 H1N1 influenza pandemic). Influenza viruses that have caused past pandemics have typically originated from animals. Owing to the 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.

The WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines (1) were adopted by the WHO Expert Committee on Biological Standardization in 2007. These Guidelines provide national regulatory authorities (NRAs) and vaccine manufacturers with:

- guidance regarding regulatory pathways for approving pandemic influenza vaccines;
- the regulatory considerations to take into account when evaluating the quality, safety and efficacy of candidate vaccines;
- guidance on effective post-marketing surveillance of pandemic influenza vaccines.

The Guidelines apply mainly to countries where influenza vaccine production takes place, but also contain much information that can be useful for countries in which 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 influenza vaccine in non-vaccine-producing countries. This was especially the case for vaccine destined for donation or deployed by United Nations agencies in response to the pandemic emergency (2–4).

The present Guidelines were developed in response to requests from non-vaccine-producing countries for guidance on the identification of
appropriate regulatory approaches to the marketing authorization of pandemic influenza vaccines, and on arrangements for the 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 2013–2016 for regulatory capacity-building and strengthening of pandemic preparedness and response (5).

2. Purpose and scope

These WHO Guidelines provide guidance to NRAs of non-vaccine-producing countries on the regulatory oversight of pandemic influenza vaccines for use in public health emergencies. The document focuses in particular on the needs of countries that are not producing influenza vaccines, including countries supplied with vaccines through United Nations agencies and countries which self-procure vaccines.

This guidance is aimed to aid such countries in preparing and putting in place a regulatory process for pandemic influenza vaccines in advance of a pandemic influenza emergency. Such a 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.

The document specifically provides NRAs of non-vaccine-producing countries with the general principles for evaluating influenza vaccines and establishing basic emergency procedures for regulating pandemic influenza vaccines. A strong emphasis is placed on 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 such appropriate regulatory processes during the interpandemic phase is also emphasized.

These WHO Guidelines apply to all pandemic influenza vaccines. They are intended for use by 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 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 these WHO Guidelines. These 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 (6).

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 almost no one is immune. The Director-General of WHO may, as appropriate, declare a public health emergency of international concern under the International Health Regulations (2005) following the identification and determination of global spread of human influenza caused by a new virus strain (6, 7).

Interpandemic phase: the period between influenza pandemics (6).

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 made available for physicians to prescribe. Also referred to as “licensing” or “registration” in this and other documents (8).

National pandemic influenza preparedness plan: a national plan that aims to set out country-specific priorities and actions, and to identify the major components that must be put in place (for example, coordination, resource identification and allocation, and capacity-building) along with 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 virus strain. Progression from the interpandemic to the alert and pandemic phases may occur quickly or gradually, as indicated by the global risk assessment, principally based on virological, epidemiological and clinical data (6).

Pandemic preparedness influenza vaccine: 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).
Risk-management plan: a document submitted as part of the marketing authorization dossier that is evaluated by regulatory authorities before a medicine can be authorized 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 minimize any risks associated with the use of the medicine 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 its biannual influenza vaccine composition meetings (once for the northern hemisphere and once for the southern hemisphere) (1).

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

Transition phase: the phase during which the de-escalation of global actions occurs as the assessed global risk of influenza reduces; a corresponding reduction of response activities or movement towards recovery actions by countries may be appropriate, according to their own risk assessments (6).

4. General considerations for regulatory preparedness for pandemic influenza vaccines

Countries should have laws requiring that all medicinal products, including influenza vaccines procured or donated in normal or emergency circumstances, 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. In 2013, WHO revised and updated its pandemic preparedness guidance to reflect experience gained from the 2009 H1N1 influenza pandemic and to support further efforts at national and subnational levels. The updated guidance (6) provides for a risk-based approach that: (a) enables a more flexible response to different scenarios; (b) emphasizes reliance on multisectoral participation; and (c) uses a simplified pandemic phase structure that includes the interpandemic and pandemic (alert and transition) phases.

Regulatory preparations for an influenza pandemic should also be undertaken in the interpandemic phase (6) in order to strengthen the legal and regulatory requirements for importing and approving a vaccine in emergency situations. This would include improving NRA capacity and clearly defining the regulatory pathways for licensing the use of a new vaccine under emergency conditions (12).
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 (9, 13).

Plans should be developed to address the need for official communication from the NRA relevant to specific audiences – such as the public, health-care workers, national and subnational authorities and international collaborators when needed. Principles set out in relevant WHO communication guidelines (14, 15) should be followed. Communication and information-sharing systems should be established and need to be implemented for all stakeholders (12).

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. For guidance on safety monitoring and post-marketing surveillance plans, NRAs should refer to the WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines (1) and the WHO Global manual on surveillance of adverse events following immunization (16).

4.1 Acknowledgement of the role of the NRA 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 (9, 13, 17). The majority of WHO Member States developed and published their national pandemic influenza preparedness plans in 2005 and 2006 and updated them after the 2009 H1N1 influenza pandemic (9).

4.2 Considerations for national regulatory preparedness

During the interpandemic phase the NRA should be responsible for developing the following procedures and plans to support the national pandemic influenza preparedness plan and vaccine deployment plan (12):

- 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 the rapid availability of pandemic influenza vaccines should include:

- an NRA contact point for communications with WHO and other 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:
  (a) include appropriate regulatory and programmatic expertise;
  (b) prepare procedures for evaluation of applications for pandemic influenza vaccine;
  (c) define the dossier and supporting documents needed for NRA evaluation;
  (d) evaluate and recommend marketing authorization of suitable vaccines to the NRA; and
  (e) allow, during the interpandemic phase, for the regular review of task team appointments and procedures;
- procedures for interactions (including discussion of 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 influenza vaccine including recognition of the decisions, or reliance upon the expertise, of supporting NRAs, and the optimizing of available resources in response to the pandemic;
- procedures and requirements for lot release of pandemic influenza vaccines by the NRA during the 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.

A checklist of regulatory actions for pandemic influenza preparedness and response is 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 interpandemic period. Reliance on the decisions or expertise of supporting NRAs is highly encouraged.

The NRA of the non-vaccine-producing country should establish mechanisms and procedures for recognizing 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 during the interpandemic phase of a memorandum of understanding or recognition, including an information-sharing agreement between receiving and selected supporting NRAs in the event of a pandemic.

The assessment reports (summary basis for decision) from other NRAs may provide valuable information and insight into the decision-making processes 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 strongly encouraged.

In addition, a procedure for joint review of a pandemic influenza 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 (18, 19) could be used as a model.
It should be noted that both joint reviews and the WHO collaborative procedure require advance planning so that agreements are brought 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 a summary assessment report outlining the basis for prequalification that will be available to countries intending to import, grant marketing authorization for and use these vaccines to mitigate an influenza pandemic. Requests 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 H1N1 influenza 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 changes in a seasonal vaccine formulation. In all cases, the WHO recommendations on seasonal influenza vaccine strain composition\(^1\) should be followed (8).

In appropriate circumstances, the NRA may decide that the procedure for an annual seasonal vaccine strain change can be adapted to authorize pandemic influenza vaccines. The combination of circumstances under which the strain-change procedure can be adapted to license pandemic influenza vaccines are:

- the candidate monovalent pandemic influenza vaccine has an antigen content similar to that of the corresponding single component in a licensed trivalent or tetravalent seasonal influenza vaccine containing the same subtype; and

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the excipients in the candidate vaccine are the same as those in the licensed vaccine; and

the manufacturing technology (for example, 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 to have pandemic potential. These vaccines may be novel in formulation, antigen content and/or adjuvant. Influenza vaccine manufacturers have been encouraged to develop pandemic preparedness influenza vaccines and to 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 (10, 11).

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 influenza 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 influenza vaccine – can be approved using similar criteria to those used for an annual seasonal vaccine strain change. This procedure may be implemented in 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 from WHO or other NRAs more experienced in the regulation of both seasonal and pandemic influenza vaccines (see section 4.3 above).

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 an emergency situation in the shortest possible time:

- an NRA or a regulatory system;
- a national pandemic preparedness plan that acknowledges that pandemic influenza vaccines that are used shall be formally licensed or granted emergency approval by the NRA and released onto the market;
NRA policies and procedures for:
(a) NRA evaluation of pandemic influenza vaccine applications;
(b) procedures and criteria for rapid identification of suitable experts for regulatory evaluation of pandemic influenza vaccine applications (task team);
(c) consideration of a joint review with neighbouring or supporting NRAs; and
(d) recognition of the marketing authorization decisions of other NRAs and the 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 United Nations supply. The situation should also be recognized whereby a pandemic preparedness influenza vaccine has been evaluated and approved during the interpandemic 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 an NRA (see section 5.2 below):

- Full review – a standard review process to authorize a product licensure that can include fast-track review.
- Fast-track review of basic documentation – a fast-track review process based on basic available information for emergency authorization.
- Reliance – a process to review the marketing authorization report/decision issued by a supporting NRA or WHO prequalification (19).
- Recognition – recognition of the marketing authorization decision of another NRA or WHO prequalification without further evaluation.
Strain-change procedure: a procedure for authorizing a seasonal strain change for influenza vaccines:

(a) a procedure for the evaluation and approval of seasonal influenza virus strain changes in an approved seasonal influenza vaccine (see Appendix 2);
(b) the approved procedure to be used for pandemic preparedness influenza vaccine evaluation and marketing authorization following inclusion of the identified pandemic virus strain.

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

Non-vaccine-producing countries can access pandemic influenza vaccine from different sources, including a United Nations agency, a donation from a company or other source, or through national 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:

United Nations agency supply (WHO-prequalified vaccines)

- Evidence/certificate of WHO prequalification with assessment report (18, 19).

Donation from a company or other source

- Information on strain change of a 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, 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 by
the manufacturer. The procedures and requirements in the WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines should be followed (1).

National guidelines on donations of medicines should be followed. If these do not exist the recommendations in the WHO Guidelines for medicine donations (20) should be followed.

**National self-procurement**

- Information on strain change of a licensed seasonal influenza vaccine or pandemic preparedness influenza vaccine (if applicable) should be provided.
- If the vaccine has been prequalified by WHO 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 by the NRA, 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 by the manufacturer. The procedures and requirements in the WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines should be followed (1). Seeking support from the NRA of the producing country is strongly encouraged.

### 5.2 Possible regulatory review processes in a pandemic emergency

Even in the midst of a 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 the available evidence on which the recommendation to authorize, approve or reject had 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” (21). 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. The results of stability studies would be delayed as would any results from clinical studies.
Where possible the NRA could make arrangements for the joint review of pandemic influenza vaccine dossiers with neighbouring and/or supporting NRAs. The possible parties involved in such an arrangement should establish this agreement during the interpandemic phase.

Depending on the pandemic phase and the source of the vaccine, review activities may include one or more of the following procedures (see also Fig A7.1):

- full review;
- fast-track review of basic documentation;
- reliance;
- recognition;
- strain-change procedure.

5.2.1 Full review

This is the standard process of review of the 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 the interpandemic phase.

This would require evaluation of the documentation of product quality and of the results of nonclinical and clinical studies to demonstrate safety and efficacy in the target population. The documentation should be as legally required in each country.

During the interpandemic phase the NRA of a non-vaccine-producing country may conduct a full pandemic preparedness influenza vaccine dossier review to ensure familiarity with the characteristics of such vaccines.

5.2.2 Fast-track review of basic documentation

This is a fast-track review process in which marketing authorization is based upon 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 and/or WHO should be reviewed. The full application dossier may be provided when available.

- *Available documentation:*
  a) assessment reports of the responsible NRA;
b) evidence of quality (certificate of analysis or lot release) and good manufacturing practices (GMP) compliance (GMP certificate);

c) CTD Module-2 quality, nonclinical and clinical overviews (if available).

**Applicability:** this procedure would apply during the pandemic alert phase and transition phase for a pandemic influenza vaccine licensed by an NRA other than a supporting NRA.

### 5.2.3 Reliance

This is the process of reviewing the decisions of other competent NRAs with which there has been an 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 approach would involve acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine, and would require the following *available documentation*:

- certificate of the responsible NRA’s marketing authorization decision;
- assessment reports of the responsible NRA.

**Applicability:** this procedure would apply during the pandemic alert phase, pandemic phase and transition phase for a pandemic influenza vaccine licensed by an NRA other than a supporting NRA.

### 5.2.4 Recognition

This is the process of recognizing the WHO prequalification decision or the decision of a 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 involve acceptance on the basis of the already agreed conditions and limitations on the use of the vaccine, and would require the following *available documentation*:

- certificate of the responsible NRA’s marketing authorization decision or WHO prequalification assessment report.

**Applicability:** this procedure would apply during the pandemic alert phase, pandemic phase and transition phase for a pandemic influenza vaccine licensed by a supporting NRA or prequalified by WHO. It may also apply during the pandemic phase for a pandemic influenza vaccine licensed by an NRA other than a supporting NRA.
5.2.5 **Strain-change procedure**

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

- Available documentation: as for an annual strain change.

The approved conditions and limitations on the use of the vaccine should be accepted.

**Applicability:** this procedure would only apply to a pandemic influenza vaccine licensed by a strain-change approach from a pandemic preparedness influenza vaccine or seasonal influenza vaccine by the NRA of the producing country.

If a pandemic influenza vaccine is licensed by a strain-change approach from a pandemic preparedness influenza vaccine or seasonal influenza vaccine then a receiving country NRA could use the strain-change procedure (or other appropriate approach based on the source of vaccine).

If a vaccine has not been licensed by any NRA then the guidance provided in the WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines should be followed (1).

5.3 **WHO collaborative procedure for prequalified vaccines**

Apart from the regulatory procedures for marketing authorization of pandemic influenza vaccines, expedited licensure through the WHO collaborative procedure for prequalified vaccines (18) may also be used for suitable pandemic influenza vaccines as appropriate. An information-sharing agreement between WHO, the receiving NRA and the manufacturer should be signed in the interpandemic phase – particularly given that, during an emergency, time may not allow for this step to occur prior to the decision to use the vaccine. For this procedure the WHO prequalification assessment report should be provided to the receiving NRA. The full dossier in the format of the CTD could also be provided to the NRA.

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.
Fig. A7.1
Illustrative chart of regulatory approaches relative to the status of the vaccine and the continuum of pandemic phases

Licensed vaccines from any source

Prequalified
Licensed by supporting NRA\(^b\)
Licensed by other NRA\(^c\)

Recognition procedure in all phases
Recognition procedure in all phases
Recognition in the pandemic phase OR Reliance or Fast-track procedure in the alert or transition phases

\(^a\) Interpandemic phase, alert phase, pandemic phase or transition phase as defined by WHO (see section 3, Terminology above).
\(^b\) Any NRA selected by the NRA of the receiving country as suitable in supporting pandemic influenza vaccine licensing decisions; the eligibility of supporting NRAs could be decided upon after consultation with WHO.
\(^c\) Any NRA not designated as a "supporting NRA" by the NRA of the receiving country.

5.4 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 (22, 23).

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

The NRA should ensure that the following conditions are met:

- An adequate document package is provided. A post-marketing commitment by the manufacturer to provide any outstanding information should be considered.
There is a local agency responsible for supply of the product (that is, 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 is indicated for the circulating strain(s).

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

An evaluation report should be produced by the NRA.

### 5.5 Emergency approval

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

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

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

### 5.6 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 the WHO *Guidelines on regulatory preparedness for human pandemic influenza vaccines* (1) and the WHO *Global manual on surveillance of adverse events following immunization* (16). The risk-management plan for pandemic influenza 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 the implementation of a pandemic influenza vaccination campaign.
6. Quality control preparedness

Lot release and quality control of pandemic influenza vaccines by the NRAs and/or national control laboratories (NCLs) of non-vaccine-producing countries should follow the guidance set out in relevant WHO documents (17, 18, 20, 22–24).

Vaccines received by procuring countries should be produced in compliance with GMP, and tested for quality and safety by the vaccine manufacturer. Typically, such vaccines should also be subjected to independent quality control testing and released by the responsible NRA/NCL in accordance with the WHO Guidelines for independent lot release of vaccines by regulatory authorities (17). For vaccines supplied through United Nations agencies it is recommended that 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 normally 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 (17).

For self-procured non-WHO-prequalified pandemic influenza vaccines the NRA/NCL of the 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 the WHO 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.

Authors and acknowledgements

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The scientific basis for the development of these WHO Guidelines was discussed at a working group meeting held in Tunis, Tunisia, 9–10 June 2015 and attended by: Dr M.E.M. Ahmed, National Medicines & Poisons Board, Sudan; Mr S. Dorji, Drug Regulatory Authority of the Royal Government of
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References


Appendix 1

Checklist of regulatory actions for pandemic influenza preparedness and response

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 interpandemic phase.

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

3. In the interpandemic phase (provisionally) grant marketing authorization to 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 or rejection that includes the assessment report; and
   (f) alert the national control laboratory regarding potential vaccines that may be granted marketing authorization 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 national regulatory authority/national control laboratory 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 post-marketing surveillance plan;
(e) continue to update the data packages from the vaccine supplier(s); and
(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 influenza vaccine(s) if appropriate;
   (d) review the activities of the pandemic task team and propose improvements; and
   (e) review the reports from the pandemic surveillance plan.
Appendix 2

Examples of information and documentation that may be required for the evaluation of a seasonal influenza vaccine annual virus strain change

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 or cell culture: safety specifications and tests (declaration if unchanged).
7. Qualification of potency test (single radial immunodiffusion – SRID) reagents.
8. Final product release specifications and results (this must include endotoxin release limit).
9. Retrospective data on the “efficacy or performance” of influenza vaccines (preceding year or 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:
   (a) the year/season for which the vaccine will be used;
   (b) WHO-recommended strains; and
   (c) 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:
   (a) the year/season for which the vaccine will be used; and
   (b) WHO-recommended strains.

15. All labels and inner and outer containers 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 summary of product characteristics.