Guidelines on Regulatory Preparedness for Non-Vaccine Producing Countries in Response to Pandemic Influenza Emergency

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the Guidelines on Regulatory Preparedness for Non-Vaccine Producing Countries in Response to Pandemic Influenza Emergency to a broad audience and to improve transparency of the consultation process.

These Guidelines were developed based on the outcomes and consensus of the WHO working group meeting convened in June 2015 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 3 April 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).

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1. Introduction

This document provides guidance for National Regulatory Authorities (NRAs) of countries where influenza vaccines are not produced (thereafter refer to non-vaccine producing countries). Its aim is to aid such countries to prepare and put in place, in advance of a pandemic influenza emergency, a systematic evaluation and approval process for Pandemic Influenza Vaccines (PIV).

WHO Guidelines on Regulatory Preparedness for Human Pandemic Influenza Vaccines were adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2007 (1). These apply mainly to countries where influenza vaccine production takes place but still have much useful information for non-vaccine producing countries. Other documents may also be of value and should be consulted in preparing for an influenza pandemic (2 - 8). For example, the WHO Pandemic Influenza Preparedness (PIP) framework 2013 (2) considers activities to support the NRAs of non-vaccine producing countries with respect to preparedness planning, strengthened capacity for regulation of all influenza vaccines, and the development of accelerated processes for approval of influenza vaccines, medicines and diagnostics during a public health emergency.

The present document has been developed in response to requests from non-vaccine producing countries for guidance on appropriate regulatory preparedness arrangements for an influenza pandemic emergency. It, and all of the other documents mentioned above, emphasize the importance of avoiding unnecessary duplication as well as unclear and potentially confusing messages during a public health emergency.

It is acknowledged that each country will have national legislation and policies on the regulation of medicines and vaccine deployment. These guidelines are intended to provide additional and specific support to the NRAs of non-vaccine producing countries when dealing with pandemic influenza emergencies. Countries should review the options available to them under such circumstances. Those without appropriate national legislation and policies for regulatory oversight of PIV and other medicines during a public health emergency are strongly encouraged to take corrective action as a matter of urgency.

WHO encourages all regulatory authorities to establish Good regulatory practice, Risk management plans, Crisis management procedures, Information/data management system and Networking/harmonization plans for interacting internationally, and, especially for NRAs of non-vaccine producing countries, plans for reliance on other regulatory systems and/or WHO.

2. Scope

The scope of the document is limited to guidance for non-vaccine producing countries on the
regulatory oversight of pandemic influenza vaccines for use in emergency situations.

The NRAs of non-vaccine producing countries may have more or less capacity to evaluate emergency vaccines but the aim is to help them establish basic emergency procedures for regulating PIV.

The Guidelines are designed to assist NRAs in preparing decision-making processes which minimize duplication and make much needed vaccines available for use without unnecessary delay.

It is recognized that decisions will be difficult but the value of including the opinions and decisions of the stronger or stringent regulatory authorities (SRA) is emphasized.

3. Terminology

**Candidate vaccine:** a prospective influenza A virus vaccine which is in the research and clinical development stages and has not been granted marketing licensure by a regulatory agency.

**None-vaccine producing countries:** refer to a country where influenza 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 (potentially pandemic phases 4 or 5) or during a pandemic (pandemic phase 6).

**Pandemic preparedness vaccines (Mock-up PIVs):** A Mock-up Pandemic Preparedness Vaccine is an influenza vaccine developed and tested in anticipation of a pending influenza pandemic, and manufactured using an Influenza virus strain that is believed to have similar characteristics to the anticipated pandemic virus strain.

**Seasonal influenza vaccine:** a trivalent (or tetravalent) vaccine containing the two influenza A strains and one influenza B virus strain recommended annually by WHO for use in seasonal influenza vaccination.

**WHO prequalification:** the process by which WHO assesses the acceptability of vaccines for purchase by UN agencies. Prequalification ensures that vaccines purchased by UN agencies are consistently safe and effective under conditions of use for national immunization programmes. WHO prequalification provides a single standard against which products from manufacturers can be assessed and so provides a basis upon which emerging suppliers can compete on international markets. Information on WHO prequalified vaccines can be used by countries directly procuring vaccines as an independent verification of quality. A WHO prequalification process already exists for seasonal influenza vaccines, and
processes are being developed for vaccines against novel human influenza viruses and pandemic influenza vaccines (9).

4. General considerations for the regulatory approval of a pandemic vaccine

All countries need to prepare for emergency situations, including an influenza pandemic that may cause extensive sickness and death and lead to considerable societal disruption.

Pandemic Preparedness Plans should build on the existing infrastructure in a country and include the legally required role of the NRA for licensing (registration) of medicinal products as well as vaccine lot release by NRA (10-12). It is important that NRA powers include provision for policy and strategic planning for emergency use of all medicines including vaccines. There should be a defined trigger for implementing emergency procedures, such as the declaration of an Influenza Pandemic by the Director General of the World Health Organization.

Emergency procedures should include defined processes for ensuring communication and cooperation amongst different branches of the NRA and relevant stakeholders, such as the public health authorities (10, 11). The transparency of the regulatory decision-making process is also critically important.

4.1 The National Pandemic Influenza Preparedness plan

The national pandemic influenza preparedness plan should be established and include:

- definition of public health emergency: Pandemic influenza;
- trigger for emergency use of the plan – WHO pandemic declaration (or alert);
- the need for NRA evaluation and registration of a PIV (and other emergency medicines);
- vaccine lot release procedures for emergency use;
- mechanism for interaction between stakeholders and agencies;
- a regulatory pathway for response to pandemic influenza emergency;
- availability of novel vaccines (e.g. strains, antigen content, adjuvants, live attenuated influenza vaccine (LAIV));
- consideration of limited availability of relevant vaccines and limited choice;
- information sharing with WHO.

4.2 Influenza vaccines – Seasonal and Pandemic
Seasonal influenza vaccines (SIVs) present many production and regulatory challenges due to the need for an annual change in formulation to reflect the current circulating virus strains and very short development timelines. Many countries have established accelerated regulatory procedures for dealing with seasonal influenza vaccines. Provisions should also be in place in non-vaccine producing countries for accelerated regulatory approval of annual influenza virus strain change in a seasonal vaccine formulation. WHO recommendations on annual changes in the vaccine strain composition should be followed (13).

In appropriate circumstances, the annual seasonal vaccine strain change procedure can be adapted to deal with PIV.

Specific provisions can also be made for licensing pandemic preparedness vaccine or mock-up PIVs (MIV) as a precautionary step using the same approach as for SIV.

Mock-up or prototype pandemic influenza vaccines (MIV) are vaccines that have been prepared using strains of influenza that are considered representative of the strains that may cause a future pandemic (such as H5N1, H7N1). These vaccines may be novel in formulation, antigen content and/or adjuvant. Because of the limited immunogenicity of some potential pandemic vaccine candidates and the limited capacity for pandemic vaccine production worldwide, considerable emphasis has been placed on the use of adjuvants both to improve immunogenicity and as a dose sparing measure. Influenza vaccine manufacturers have been encouraged to develop such MIV and conduct suitable nonclinical and clinical testing to demonstrate safety and immunogenicity. Some NRAs will grant a provisional licence to these products so that in a pandemic emergency it may be possible to invoke the national procedure for seasonal strain change to expedite the licensure and availability of these vaccines. WHO pre-qualification of MIVs is encouraged.

Some PIV or MIV may be novel constructs or formulations requiring expert regulatory evaluation. Such evaluations may be assisted by WHO or other more experienced NRAs.

4.3 The National Regulatory Authority contingency plan

The national regulatory authority contingency plan should be established and include:

- NRA contact point – for WHO communications;
- NRA Task Team for PIV (and medicines);
- agreed procedures for facilitating rapid availability of PIVM;
- decide on preferred source on vaccine (together with public health agency);
- agreed system to accelerate the licensure and lot release of pandemic vaccine including reliance on the decisions and expertise of other regulatory authorities (see section 4.4);
- understanding of the provisions of national agency for emergency administration of PIV based on WHO guidelines (1);
• established systems for post-approval surveillance of the PIV in use – special provision in national pharmacovigilance plan;
• an annual review of Task Team appointments and procedures between pandemics;
• a plan to update review of Task Team appointments and procedures when a pandemic alert has been declared by WHO.

4.4 Reliance on the decisions and expertise of other regulatory authorities

In the event of an influenza pandemic NRAs of non-vaccine producing countries are encouraged to plan for reliance on experienced vaccine producing country regulatory systems or WHO. NRAs of vaccine producing countries with considerable experience of seasonal and pandemic influenza vaccines have been called SRAs and recognized by the WHO.

The NRA of the non-vaccine producing country NRA should establish the national system and procedures to:

• accept where possible the regulatory and lot release decisions (see section 6) of the NRA of pandemic vaccine producing countries (The mutual of understanding (MOU) or mutual recognition agreement (MRA) including information sharing agreement between the NRAs is encouraged);
• accept WHO prequalification decisions;
• define the dossier and supporting documents needs for NRA evaluation;
• review Public Assessment Report (PAR) or Summary Basis of decisions for both seasonal and PIV (Recognize that these may not always be available);
• define procedures for appointment of an emergency evaluation team;
• define the extent of the risk-benefit analysis to be undertaken;
• define the emergency risk management system for the approved vaccine “in-use”, including risk management plan/post marketing surveillance system to monitor efficacy and safety.

5. Regulatory pathways

The following components need to be in place to ensure an orderly and legal emergency regulatory approval and lot release of a PIV:

• a legally constituted NRA;
• a procedure for the evaluation and approval of seasonal influenza virus strain changes (Appendix 2);
• integration into a National Pandemic Preparedness Plan (Appendix 1) that includes:
  o provision for NRA licensing of emergency medicines and vaccine lot release for emergency use;
  o procedures for NRA evaluation of applications for PIV;
Identified suitable experts for NRA evaluation of PIV applications;
- Consideration of joint review with other competent/stringent NRAs.
  - a procedure for emergency approval of NRA PIV recommendations;
  - a situation analysis of different possible approaches for licensing vaccines received through self-procurement, donations and UN supply. The condition should also be recognized where a MIV has been evaluated and approved during the inter-pandemic period, and where the application can subsequently be approved based on the national Seasonal Influenza vaccine strain change procedure.

5.1 Potential Sources of emergency supplies of PIV and expected accompanying documentation

Non-vaccine producing countries could get PIV from different sources and the accompanying documentation required for evaluation to ensure the quality, safety and efficacy for each source as following:

1) UN Agency supply

The following documents should be available: Evidence/certificate of WHO pre-qualification with PAR. However, in an emergency PAR may not be available. The information on strain change of prequalified seasonal influenza vaccine or MIV.

2) Donation from a company or other source

The following data package should be provided: Requirements for strain change of a licensed seasonal influenza vaccine or MIV (see Appendix 2); In the case of the vaccine is WHO prequalified, the Product Summary File (PSF) should be provided. In the case of the vaccine is licensed by a SRA, common technical document (CTD) Module-2 and PAR if available should be provided. In the case of the vaccine is licensed by a non-SRA, full dossier for licensure and PAR should be provided. In the case of the vaccine is not licensed before, full dossier for licensure should be provided.

3) National procurement

The following data package should be provided: information on strain change of licensed seasonal or pre-pandemic vaccine (See Appendix 2). In the case of the vaccine is WHO prequalified, the PSF and PAR should be provided. In the case of the vaccine is licensed by a SRA, CTD Module-2 and PAR if available should be provided. In the case of the vaccine is licensed by a non-SRA, full dossier for licensure and PAR should be provided. In the case of the vaccine is not licensed
before, full dossier for licensure should be provided.

5.2 Possible Regulatory Review Activities in Pandemic situation

Even in the most critical pandemic situation, the NRA will be expected to conduct an appropriate expedited review of the documentation submitted (see section 5.1) that covers the components set out below, and to document the extent of evidence that is available on which to base the decision-recommendation.

Depending on the urgency of the pandemic status and the source of the vaccine, these activities may include one or more of the following procedures:

1. full review (as normally conducted in that country);
2. abridged review (See section 5.3);
3. review of the decision of other competent NRA;
4. recognition of decision of other competent NRA;
5. procedure for a strain change from licensed seasonal vaccine;
6. expedited licensure through WHO collaborative procedure for prequalified vaccines.

Except for procedure No.6 expedited licensure through WHO collaborative procedure for prequalified vaccines, and before a regulatory decision to accept a PIV is taken (based on the table below, a Final evaluation of the available documentation should be conducted to ensure that the PIV is suitable for use in the country. This review can be conducted in a single day, with a risk-benefit consideration and recommendation for approval.

This evaluation may need to work with minimal and incomplete documents, and this should be acknowledged in the recommendation.

A public assessment report should be produced.

<table>
<thead>
<tr>
<th>Status of vaccine</th>
<th>Inter-Pandemic</th>
<th>Pandemic alert</th>
<th>Pandemic other</th>
<th>Pandemic crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>New PIV vaccine</td>
<td>1: Full</td>
<td>1: Full</td>
<td>2: Abridged</td>
<td>Accept</td>
</tr>
<tr>
<td>Strain change - PPIV</td>
<td>2: Pandemic change</td>
<td>5: Accept</td>
<td>2: Accept</td>
<td>Accept</td>
</tr>
<tr>
<td>Non-SRA licensed PIV</td>
<td>3: Full</td>
<td>2: Abridged</td>
<td>2: Accept</td>
<td>Accept</td>
</tr>
<tr>
<td>SRA licensed PIV</td>
<td>5: Abridged</td>
<td>4: Accept</td>
<td>2: Accept</td>
<td>Accept</td>
</tr>
<tr>
<td>WHO prequalified PIV</td>
<td>6: Expedited</td>
<td>5: Accept</td>
<td>2: Accept</td>
<td>Accept</td>
</tr>
</tbody>
</table>

Possible Regulatory actions relative to pandemic status

Pandemic Status:
Inter-Pandemic: As defined by WHO
Pandemic Alert: As defined by WHO
Pandemic Other: Pandemic declared but not yet affecting your country
Pandemic Crisis: Pandemic infections in your country.

5.3 Components of an Abridged Evaluation

In the event that an expedited abridged evaluation is deemed appropriate (as defined in the approved NRA pandemic emergency procedures), the following documents from the manufacturer and the SRA/WHO should be reviewed:

- public assessment reports;
- evidence of quality and GMP compliance – Certificate of analysis or lot release;
- CTD Module 2 Quality, Nonclinical and clinical overviews (if available);
- nonclinical and clinical evidence to support for safety and efficacy.

The results of the evaluation at each step should be recorded and used to support the recommendation.

5.4 Components of a Final Evaluation

The NRA should ensure that the following issues are acceptable:

- there is a Responsible national agency for supply of product;
- an applicant or State body – a defined responsible legal entity;
- packaging, label and package insert are nationally acceptable;
- vaccine is compatible with PIP national plan for administration (EPI);
- vaccine is compatible with national environment (disease background).

5.5 Steps as required in the National Preparedness Plan

The following steps should be followed in the national preparedness plan:

- prepare a post-marketing surveillance plan
- prepare a risk-benefit consideration and National PAR
- recommend emergency approval – as appropriate.
- where the PIV is a strain change from a licensed SIV or MIV, the procedures for SIV annual virus strain change can be applied (Appendix 2).
- the expedited licensure through WHO collaborative procedure for prequalified vaccines can be used when appropriate.
- a positive recommendation following an abridged evaluation may support an
Emergency. Approval by the national decision making body. The decision to approve the vaccine would be taken as defined in the NRA Pandemic Preparedness Plan.

5.6 Emergency Approval

During the pandemic period emergency approval may be used. Approval is based on limited evidence and abridged evaluation. Therefore, the approval may include one or more special conditions for use as following: e.g. limited to pandemic period, limited to use by certain agencies or may be limited to certain listed high-risk groups.

6. Quality Control Preparedness

For the non-vaccine producing countries establishment of lot release system and the access to control laboratories should be considered as recommended in WHO guidelines on regulatory functions for vaccines (4, 14, 15). The vaccine received by procuring countries are 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 according to the WHO Guidelines for independent lot release of vaccines by regulatory authorities (12). It is recommended that for vaccines supplied through United Nations agencies, further release by the NRA/NCL of receiving countries is not recommended because such products are prequalified by WHO and released by the responsible NRA/NCL. For self-procured vaccines, the procuring NRA/NCL may conduct lot release through reviewing of the summary protocol. Laboratory testing by the NRA/NCL of receiving country may not be necessary. Recognition of lot release certificate of the responsible NRA/NCL of producing country is recommended by WHO (12).

In defined exceptional circumstances such as a public health emergency, exemption from lot release could be allowed. The permitted circumstances and the procedures to be followed to ensure quality in the absence of lot release should be covered by legal provisions and clearly defined in national pandemic influenza preparedness plans.

Each NRA/NCL should carry out a risk assessment to ensure that lot release of pandemic vaccine is not compromised by problems which could have been prevented.

The use of vaccine should be not be delayed in any case.

7. References


5. Sarah Ramirez: 2015: Expert review and analysis of available resources relevant to PIP Regulatory Capacity Building Output 1 “Develop guidelines on regulatory preparedness for non-vaccine producing1 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”.


8. Authors and acknowledgements

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9. Appendix 1
Example of the contents of a National Pandemic Preparedness Plan
To be developed…….

10. Appendix 2
Example of Procedures for evaluation of Seasonal Influenza Vaccine annual virus strain change

Information and documentation 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) the source, history and master/working seed characterization of each strain included;
5) egg/cell culture: Safety specifications and tests (Declaration if unchanged);
6) final product release Specifications and results. This must include Endotoxin release limit;
7) retrospective data about the "efficacy or performance" of influenza vaccines (preceding year/season);
8) stability data (accelerated or from the most recent, or most similar batch of approved vaccine);
9) copy of the approved Package insert;
10) 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 (Southern or Northern hemisphere) for the year/season must be included.
11) copy of the approved Patient information Leaflet;
12) copy of the proposed Patient information Leaflet indicating:
   i) the year/season for which the vaccine will be used;
   ii) WHO recommended strains.
13) 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;
14) international core Data Sheet or SMPC.