Annex 2

Guidelines on regulatory preparedness for human pandemic influenza vaccines ( Adopted 2007)

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Introduction

Strategies to shorten the time between emergence of a human influenza pandemic virus and the availability of safe and effective pandemic influenza vaccines are of the highest priority in global health security. One fundamental component of such a strategy is to promote convergence between national regulatory authorities on regulatory evaluations to assure the quality, safety and efficacy of human vaccines that will be used for pandemic influenza. The World Health Organization (WHO) with support from Health Canada, the United States Food and Drug Administration (US FDA), the Government of Japan and the Government of Spain convened three technical workshops with representatives of national regulatory authorities from a broad range of countries, including vaccine-producing countries and countries that have indicated an interest in exploring influenza vaccine production.

The goal of these workshops was to build a global network of key authorities engaged in and responsible for influenza vaccine regulation and to develop guidelines on regulatory preparedness for pandemic influenza vaccines. These guidelines have been prepared based on discussions at the three workshops and the information available at the time of writing. Although several regulatory dossiers have been evaluated, the scientific knowledge base concerning pandemic influenza vaccines is rapidly evolving. Therefore, the guidelines may be updated as new knowledge and approaches become available. Any revisions to the guidelines will be published on the WHO website (http://www.who.int/biologicals/).

To address the pressing need for a global agreement on information sharing, the World Health Assembly of May 2007 urged Member States and the Director-General to pass a resolution on preparedness for pandemic influenza specifically in the areas of sharing of influenza viruses and other relevant information, access to vaccines, and other benefits. Recognizing the importance of global information sharing related to regulatory preparedness for pandemic influenza vaccines, WHO is investigating different mechanisms to facilitate this process.

General considerations

The guidelines are intended to provide both national regulatory authorities and vaccine manufacturers with the most up-to-date advice concerning regulatory pathways for pandemic influenza vaccines; regulatory considerations to take into account in evaluating the quality, safety and efficacy of vaccine candidates; and requirements for effective postmarketing surveillance of pandemic influenza vaccines.

These guidelines are intended to cover the following scenarios.
Vaccines that are developed during the inter-pandemic period in anticipation of an influenza pandemic. These vaccines contain an influenza A virus subtype not currently circulating in humans. Throughout this document these vaccines are referred to as vaccines against novel human influenza viruses. It is anticipated that the development and regulatory evaluation of these vaccines will facilitate the licensing of pandemic influenza vaccines once a pandemic is declared and the pandemic human influenza A virus strain is identified.

Vaccines that are developed for stockpiling purposes. WHO and some countries are considering establishing stockpiles of vaccines against novel human influenza viruses as part of their plans for pandemic influenza preparedness. Where applicable, special considerations for candidate vaccines intended for stockpiling are noted within the guidelines.

Vaccines that are developed once an influenza pandemic is declared. These vaccines can only be developed once the pandemic human influenza A virus strain is identified. It is expected that the regulatory evaluation of these vaccines will rely largely on information collected during the inter-pandemic period.

Some countries are discussing the use of vaccines against novel human influenza viruses before a pandemic is declared. As the risk–benefit considerations are different in this situation from intended use after a pandemic is declared, special regulatory provisions are outlined in the guidelines. However, the provision of this advice should not be interpreted as any sort of endorsement of, or recommendation for, the use of such a vaccine before a pandemic is declared. Any decisions to recommend the use of human influenza vaccines containing influenza A virus strain(s) with pandemic potential before a pandemic is declared should be in line with national policies and are solely the responsibility of individual governments and their public health authorities.

These guidelines are intended to cover both inactivated influenza vaccines and live attenuated influenza vaccines (LAIV) produced in either embryonated chicken eggs or in cell cultures. The principles outlined in the guidelines will also apply to novel production systems for influenza vaccines currently under development, such as vaccines comprising influenza proteins expressed in various genetically engineered constructs. However, there may be additional quality control and regulatory considerations that need to be taken into account for such vaccine candidates.

**Part A. Definitions**

**A.1 Terminology**

For clarity and consistency of the guidelines, the following terms relating to human influenza vaccine have been used:
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.

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).

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

Vaccines against novel human influenza viruses: a monovalent vaccine containing a human influenza A virus strain that is not in general circulation among human populations, but the virus is considered to pose a threat of infection in humans and to be a potential cause of a pandemic. The term “novel” refers to the human influenza A virus. An H5N1 vaccine is one specific example of a vaccine against novel human influenza viruses, but vaccines based on other influenza A virus subtypes (e.g. H7 or H9) would also apply. There are several potential ways in which such vaccines might be used, including stockpiling, the vaccination of selected individuals to provide direct protection against the specific influenza A virus in non-pandemic situations, or priming human populations in the inter-pandemic period in the situation in which the likelihood of a pandemic related to that specific influenza A virus is considered high. Vaccines against novel human influenza viruses are also referred as “pre-pandemic” and “pandemic-like” vaccines by some regulators and manufacturers.

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.

1 Special considerations for the expedited procedure for evaluating seasonal influenza vaccine (http://www.who.int/immunization_standards/vaccine_quality/final_expedited_procedure_flu_240207.pdf).

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A.2. **Acronyms**

AEFI  adverse event following immunization  
CBER  Center for Biologics Evaluation and Research  
EMEA  European Medicines Agency  
EU  European Union  
GBS  Guillain-Barré Syndrome  
GISN  Global Influenza Surveillance Network  
GMP  good manufacturing practices  
GMT  geometric mean titre  
HA  haemagglutinin  
HI  haemagglutination inhibition  
ICH  International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use  
LAIV  live attenuated influenza vaccines  
LAL  Limulus amoebocyte lysate  
NCL  national control laboratory  
NRA  national regulatory authorities  
PIC/S  Pharmaceutical Inspection Cooperation Scheme  
PSR  periodic safety reports  
QC  quality control  
SRID  single radial immunodiffusion test  
USA  United States of America  
US FDA  United States Food and Drug Administration  
WHO  World Health Organization

A.3  **Background on vaccines against novel human influenza viruses**

A vaccine against a novel human influenza virus is designed to confer protection against an influenza A virus that is not currently circulating in human populations. It contains viral antigens which differ from those used in current or recent seasonal influenza vaccines and to which humans are immunologically naïve. It is anticipated that, in the case of an influenza pandemic, the demand for vaccine will far exceed current supply. Thus, a diversity of technical solutions and manufacturing options, which differ from those used in current or recent seasonal influenza vaccines, are also under intensive investigation.

Current production of vaccines against novel human influenza viruses depends entirely on the manufacturing facilities producing seasonal influenza vaccines. Based on a situational analysis, in 2006, potential vaccine supply in the case of an influenza pandemic will fall short by several billion doses that would be needed to provide protection to the global population. In response to these shortcomings, WHO has developed a Global Action Plan for human pandemic.
influenza vaccines to identify and prioritize practical solutions to fill the anticipated gaps in vaccine supply. The plan aims to promote increased capacity for production of pandemic influenza vaccines to narrow the anticipated gap between potential demand for vaccine and supply during an influenza pandemic. The plan proposes to increase capacity for the production of pandemic influenza vaccine by reaching beyond current seasonal influenza vaccine producers. Consequently, it is anticipated that influenza vaccine will be produced by new influenza vaccine manufacturers over the next few years.

Supported by the laboratories of the WHO Global Influenza Surveillance Network (GISN), manufacturers who intend to produce vaccines against novel human influenza viruses or pandemic influenza vaccines are expected to use vaccine strains that match circulating inter-pandemic or pandemic influenza A variant viruses.

Steps to improve industrial preparedness for an influenza pandemic range from the construction of new production plants meeting higher biosafety standards, through investigation of antigen-sparing technologies (i.e. adjuvants), to the development of candidate vaccine prototype libraries. Some steps taken to develop pandemic influenza vaccines are expected to influence production of seasonal influenza vaccine. Some countries are potentially considering the use of veterinary vaccine production facilities during a pandemic to address their shortage of a human influenza vaccine supply. These new approaches may expedite vaccine production on a larger scale in a pandemic situation, making vaccine potentially available weeks before it could be supplied by conventional manufacture (1).

At a WHO meeting in 2007 (2), 16 manufacturers from 10 countries reported that they were developing prototype vaccines against H5N1 influenza A viruses. Five manufacturers were also involved in the development of vaccines against other avian influenza viruses (H9N2, H5N2, and H5N3). Most manufacturers reported using reference vaccine strains corresponding to viruses provided by WHO Collaborative Centres. More than 40 clinical trials, mostly focusing on healthy adults, had been completed or were in progress. After completing safety analyses in adults, some manufacturers had initiated clinical trials in the elderly and in children. All vaccines tested to date were safe and well tolerated by all age groups. Most of the data obtained were from trials in healthy adults and further studies in children, the elderly and the immunosuppressed were considered necessary.

Most vaccine immunogenicity data have been generated from the use of egg-grown influenza vaccines. Whole virion preparations appear to be more immunogenic than equivalent doses of split vaccine. Split vaccines with alum as adjuvant, in striking contrast to some of the more promising whole virion vaccines with alum as adjuvant, show modest increases in immunogenicity over unadjuvanted vaccines not allowing significant dose sparing. Some split
vaccines formulated with newer adjuvants show encouraging immunogenicity, which would be likely to allow dose sparing. Some studies have demonstrated that vaccination with currently available H5N1 prototype vaccines induced a potentially protective immune response against highly pathogenic strains of H5N1 virus isolated at different times and different geographical locations. Because of the inherent variability in the assay systems used to measure immune responses, it is unwise to directly compare results from different studies.

The cell culture approach does not rely on embryonated chicken eggs for manufacture, thus allowing for faster (but not infinite) scale-up. Provided that the required biosafety levels can be guaranteed, cell cultures offer the potential to work with pandemic influenza A virus strains that would be lethal to eggs without genetic modification. A potential limitation of the cell culture approach is that the process may still require the production of high-yield reassortants. Multiple passage in tissue culture may introduce cell-line-specific mutations in viral genes that can lead to selection of variants with antigenic and structural changes in the HA protein, potentially resulting in less efficacious vaccines. Regulatory issues would include the presence of potential adventitious agents in mammalian cells and unknown side-effects caused by residual host cell and media proteins in combination with new adjuvants (e.g. oil in water emulsions).

Some constraints could be overcome by using recombinant DNA technology to produce HA and NA viral antigens in cell culture. These purified antigens would, in turn, be used as the active ingredients in vaccines against novel human influenza viruses and/or pandemic influenza vaccines. Further information is needed to determine whether the recombinant DNA approach to production of influenza vaccine would meet the challenge of a potential pandemic. Nevertheless, the principles outlined in this document would also apply to such novel vaccine production systems, although additional regulatory considerations may need to be taken into account owing to the recombinant nature of these vaccine candidates.

Based on a WHO situational analysis, live attenuated influenza vaccine (LAIV) technology might be more appropriate for production of pandemic influenza vaccines because it requires less complex downstream processing than that needed for inactivated vaccines. Thus, the WHO Global Action Plan encourages increased production and technology transfer of LAIV.

However, it should be noted that unresolved potential concerns related to public and animal health are associated with live attenuated vaccines against novel human influenza viruses. They relate to whether, even if unlikely, shed vaccine virus containing novel antigens could recombine with circulating influenza viruses to become pathogenic and spread to human or animal populations. This type of environmental concern would not exist during a pandemic.
A.4 Background on seasonal human influenza vaccines

Four types of seasonal inactivated influenza vaccine, defined in the WHO Recommendations for the production and control of influenza vaccine (inactive) (3), are currently available or have been used extensively:

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

Inactivated, adjuvanted whole-virion vaccine against seasonal influenza is used in at least one country (4); however, most countries use split virion or subunit non-adjuvanted inactivated vaccines. Although they are in general less reactogenic, purified influenza virus surface antigens are less immunogenic than purified whole virion vaccines in immunologically naive individuals (e.g. small children and people with no contact with circulating influenza viruses) (5). Individuals with residual immunity display a booster rather than a primary immunization effect post re-vaccination. These observations define the current understanding of split or subunit seasonal influenza vaccines, as they must be given annually to boost the immune system against seasonally circulating virus strains.

All seasonal inactivated influenza vaccines are formulated to meet the WHO requirements of not less than 15 micrograms of haemagglutinin subtype per human dose (3). Currently, most companies produce their vaccine(s) by growing the virus in embryonated chicken eggs. Manufacturers are also developing a number of cell culture-based technologies to produce subunit inactivated seasonal influenza vaccines. The continuous cell lines currently used include Vero cells, which are widely used in the manufacture of other vaccines, the Madin Darby Canine Kidney (MDCK) cell line and others which are less extensively used as a substrate for human vaccine.

At least two countries use live attenuated seasonal influenza vaccines in immunization programmes. There is preliminary evidence that live attenuated seasonal influenza vaccines produced in embryonated chicken eggs might be more efficacious than unadjuvanted and inactivated seasonal influenza vaccines. LAIV have been shown to be more effective in immunologically naive individuals, i.e. children under the age of 2 years with no residual immunity towards influenza virus antigens. Efficacy trials in this age group revealed vaccine efficacy (defined as preventing laboratory-confirmed influenza
infection) exceeding 90% after one dose against influenza virus strains homologous to the vaccine antigens. These findings are in strong contrast to those for use of inactivated seasonal influenza vaccines in this age category (6). Further studies on protection against heterogenous virus and minor variants as well as evidence of induction of herd immunity through childhood vaccination are required. A review of the safety of LAIV in high-risk patients (such as those with asthma, those who are immunocompromised, and the very young and the elderly) would also be beneficial.

**Part B. Regulatory pathways for licensing vaccines against novel human influenza viruses and pandemic influenza vaccines**

**B.1 General remarks**
This section is intended to aid countries in assessing their state of regulatory preparedness for pandemic influenza vaccines, and to identify what may be needed to establish an appropriate regulatory pathway. This section:

- describes possible regulatory pathways to be considered by national regulatory authorities in licensing vaccines against novel human influenza viruses and for licensing pandemic influenza vaccines;
- identifies existing regulatory methods in the process of licensing vaccines against novel human influenza viruses and pandemic influenza vaccines; and
- delineates regulatory areas with potential for international harmonization.

**B.2 Current regulatory approaches**
The regulatory approaches for pandemic influenza vaccines in Australia, Canada, the European Union, Japan and the United States (US) were analysed in detail. These national regulatory authorities have defined regulatory pathways for the licensure of influenza vaccines for use in a pandemic situation. Emergency options have also been identified should a pandemic influenza vaccine be needed before the vaccine has been licensed.

An outline of existing regulatory pathways, including key scientific and administrative elements in the licensing process for pandemic influenza vaccines of the five national regulatory authorities is presented in Appendix 1. This will aid national regulatory authorities in all countries to determine, in advance of a pandemic, the extent of their regulatory capabilities and authority, and to make changes to regulations or pursue mechanisms to obtain or use additional
regulatory authority in an emergency situation, as needed and deemed feasible. Countries without an appropriate regulatory pathway are strongly encouraged to take action as a matter of urgency.

B.2.1 **Commonalities of five selected national regulatory authority pathways**

The following characteristics are common to the five national regulatory authorities studied or are similar with respect to the licensure of a pandemic influenza vaccine:

- All have a clear legal basis and mandate to develop regulatory requirements for these products.
- All have domestic vaccine manufacturers and one or more approved seasonal influenza vaccine(s).
- All have an inspectorate qualified to conduct inspections of good manufacturing practices (GMP), most using the Pharmaceutical Inspection Cooperation Scheme (PIC/S). (The US applied recently for PIC/S membership; Japan is not a PIC/S member.)
- All have outlined regulatory pathways for the licensing of pandemic influenza vaccines thus giving individual companies a predictable environment for planning vaccine development and production.
- All have regulatory provision to request postmarketing surveillance studies if needed.
- All have proposed a flexible approach to the receipt and review of information as part of the licensure of pandemic influenza vaccine.
- All have issued government contracts to manufacturers to produce investigational vaccines and conduct clinical trials. Contracts have been signed at a national level in Europe and the United States.
- All will include review of information on a vaccine against novel human influenza virus as part of the licensure process.
- All will utilize immunogenicity as a likely predictor of efficacy and seek postmarket confirmatory evaluation of effectiveness.
- All agree that wherever possible, the manufacturing, safety, quality and immunogenicity of pandemic vaccines should be evaluated as fully as possible before an influenza pandemic.
- All have identified emergency use options and provisions, including evaluating potential risks and benefits should a pandemic influenza vaccine be needed for use before the licensure process can be completed (e.g. when there are limitations of the data available that would be required to support licensure).
B.2.2 Differing features of five selected national regulatory authority pathways

The similarities and differences in regulatory pathways for human influenza vaccine are presented in these guidelines to provide information to national regulatory authorities and manufacturers and should not be considered as indicating WHO’s endorsement of any specific regulatory pathway.

Europe, the US, Australia and Japan plan to license inactivated vaccines against novel human influenza viruses. Canada has no current plans to license such vaccines; however, data on a vaccine against novel human influenza virus will be required to support licensure of a pandemic influenza vaccine. Modifications of the mechanism of licensure for a vaccine against novel human influenza virus are being explored to facilitate, if necessary, Canada’s contribution to a WHO vaccine stockpile.

There are two regulatory pathways that can be followed depending on the intended use of a vaccine against a novel human influenza virus in Europe. On one pathway, the vaccine against a novel human influenza A virus, although approved via a core pandemic dossier in the interpandemic period, is not intended to be used or marketed before the pandemic is announced. Once pandemic influenza is declared, the matching pandemic influenza A virus strain would be supplanted in the core dossier and undergo fast track approval of a pandemic variation. On the second pathway, where a vaccine for a novel human influenza A virus is intended to be used before the pandemic is declared, special regulatory provisions apply. Refer to the European Medicines Agency (EMEA) Guideline on dossier structure and content of marketing authorization applications for influenza vaccines with avian strains with a pandemic potential for use outside of the core dossier context (EMEA/CPMP/VEG/4717/2003- Rev.1, available at http://www.emea.europa.eu/pdfs/human/vwp/471703enfin.pdf). EMEA guidance regarding licensure of vaccines for novel human influenza viruses is limited to inactivated vaccines. No guidance exists for LAIV.

In the US, all submissions for initial licensure of a vaccine against novel human influenza viruses or a pandemic influenza vaccine would be submitted in the form of a Biologics License Application (BLA). This allows for separation of trade names and segregation of reporting of adverse events from those of seasonal influenza vaccines. The amount of data required by FDA from the manufacturer for submission with its application for a licence for a pandemic influenza vaccine would depend on whether the manufacturer already has a licensed influenza vaccine and intends to use the same manufacturing process for its pandemic vaccine.

Japan’s approval of vaccines against novel human influenza viruses intended to be used during both inter-pandemic and pandemic phases is given
based on the quality, nonclinical and clinical data on the potential pandemic influenza vaccine. The application must contain data on the vaccine which is produced with the potential pandemic influenza A virus strain.

Canada has entered into a contract with one domestic supplier to provide enough pandemic influenza vaccine for the entire Canadian population; therefore, regulatory preparedness is based on the concept of a single supplier. The regulatory preparedness of Australia, Japan, the USA and the EMEA is based on several suppliers.

Europe and the USA have numerous guidance documents related to pandemic influenza vaccines. Australia follows many EU and USA guidance documents and Canada has recently developed a guidance document for pandemic influenza vaccine manufacturers. Japan has published a policy document on the H5N1 vaccine regulatory process. In May 2007, the USA issued the following documents: Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines and Guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines. See Appendix 2 for an inventory of guidance documents from selected national regulatory authorities and WHO.

B.3 Towards a harmonized regulatory pathway

A harmonized regulatory process would facilitate (but is not a prerequisite for):

- the availability of pandemic influenza vaccine in a timely manner on a global scale;
- WHO prequalification of pandemic influenza vaccines; and
- the ability to distribute pandemic influenza vaccine between countries.

However, transfer of virus seed strains, particularly wild type virus strains, or bulk materials in and out of some countries could be hampered without the cooperation of internal national regulatory authorities and national security agencies. Dialogue and agreements between interested parties within a country will be essential for international harmonization.

Furthermore, harmonization may allow the establishment of global emergency options and criteria for invoking them in an influenza pandemic situation.

While harmonization may be the ultimate goal, it may not always be fully possible or desirable for all. Individual governments have the responsibility for implementing their own national pandemic influenza preparedness plans. All countries will be constrained somewhat by the existing laws and regulations concerning licensure and use of vaccines within their territory. While it may be possible for some countries to acquire new, additional regulatory capabilities to
address a pandemic, for others this may not be possible or may be possible only once a pandemic has been declared.

The extent to which harmonization is possible depends on the following factors:

**Agreement on core data requirements**

Agreement on core data requirements Recommendations pertaining to core quality, nonclinical, clinical, and postmarketing specifications, as outlined in subsequent sections of this document, are agreed as the international expectations for regulatory evaluations of vaccines against novel human influenza viruses, candidate influenza vaccines intended for stockpiling, and subsequent pandemic influenza vaccines. It is recognized that the pathways for vaccine licensure and use may differ between jurisdictions. National regulatory authorities are encouraged to limit requests for additional data to those that are clearly justified to address safety and/or efficacy concerns unique to that jurisdiction.

**WHO prequalification of vaccines against novel human influenza viruses, pandemic and seasonal influenza vaccines**

In 2007, WHO established a process to prequalify seasonal influenza vaccines which would undoubtedly assist in the evaluation of vaccines against novel human influenza viruses and of pandemic influenza vaccines in due course. While there is no guarantee that any manufacturer will be able to supply vaccine to a non-domestic market, prequalification will enhance the level of regulatory confidence in an influenza vaccine should a pandemic arise and would ultimately enhance vaccine availability. The prequalification process will include specific modifications for vaccines against novel human influenza viruses and pandemic influenza vaccines. This process would be based on the existing WHO “Special considerations for expedited procedure for evaluating seasonal influenza vaccines”.

In addition to aiding developing countries with their pandemic preparedness, prequalification would help national regulatory authorities in acquiring alternative non-domestically produced influenza vaccines in the event of a shortage of vaccine supply. Prequalification would help identify vaccine sources particularly available to developing countries and ensure that only vaccines of assured quality were used. Prequalification would also provide a level of assurance that any vaccine exported from a country, even if

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1 http://www.who.int/immunization_standards/vaccine_quality/final Expedited Procedure Flu_240207.pdf
not manufactured for domestic use, would be of acceptable quality as defined by WHO.

Upon declaration of a pandemic there will be a lag time before any vaccine becomes available. Vaccines against novel human influenza viruses could be the only vaccines available to developing countries, particularly those most affected during the early stages of the pandemic. With various manufacturers proceeding to developing vaccines against novel human influenza viruses with H5N1 strains, potential uses of the vaccine must be maximized in the early stages of a pandemic. Stockpiling vaccines against novel human influenza viruses is an option for preparedness for pandemic influenza; this approach is being pursued or is under consideration by some countries and WHO. Prequalifying bulk producers and “finishers” as well as stockpiling bulk material should also be considered. WHO prequalification of vaccines against novel human influenza viruses could enhance the ability of countries to accept supplies of such vaccines and may expedite the prequalification of pandemic vaccines following identification of the pandemic virus strain.

**Information sharing**

It is imperative that mechanisms be in place for national regulatory authorities and vaccine manufacturers to share data from clinical trials with different vaccine types (e.g. whole virion, split antigen or subunit vaccines and cell culture derived vaccines), formulations (e.g. antigen content, adjuvants) and dosing schedules to establish the most appropriate pandemic vaccine for a particular use (e.g. in a pandemic emergency, for priming vaccination or for stockpiling). This information could be used by other countries or regions in making decisions regarding their pandemic preparedness and vaccine licensure plans.

It should be recognized that vaccine development in the inter-pandemic phase will provide important information for developing countries to use in their pandemic response. As some of these countries are planning to proceed directly to manufacturing pandemic influenza vaccine (without an inter-pandemic step), information sharing between national regulatory authorities and developing countries is essential to maximize successful vaccine production to achieve the best possible vaccine quality, safety and effectiveness throughout the global community.

Although vaccine manufacturers should be prepared to respond to an expectation that information would be shared freely with other key stakeholders (e.g. WHO, national regulatory authorities, national control laboratories and public health authorities), the key areas in which data should be shared could be identified in advance. For example, in a pandemic situation the key strengths would be production capacity, production speed, rapid availability of reagents
and low cost. The key strengths for an inter-pandemic stockpile could be long-term stability and strain cross-protection.

Taking into account national laws and regulations and under clearly defined terms, vaccine manufacturers and national regulatory authorities should work together on defining a process for regulatory information sharing. WHO is investigating various mechanisms to facilitate this process.

**Standard process**

Building on the aforementioned factors necessary for harmonization of regulatory pathways, the skeleton of a standard process for authorization of pandemic influenza vaccine can be developed and is provided as Appendix 3 to this document. It may be that not all steps of the process may be necessary or possible for a particular jurisdiction to follow; however, they can be used as a guide. It is important to highlight steps where the global sharing of information is critical.

**B.4 Criteria for emergency use**

The global regulatory community agrees that as many data as possible should be obtained in the inter-pandemic period with the goal of licensing candidate pandemic influenza vaccines. Since the likelihood, timing and speed of spread of a pandemic cannot be predicted, a high probability exists that all necessary data may not be available. Hence, it will not be possible for the full licensure process requirements to be met before the vaccine is needed. In such instances, some sort of emergency use evaluation and authorization process may be required.

Although it is desirable that internationally accepted emergency use release criteria be established, a number of difficulties exist. Firstly, existing laws and regulations within each jurisdiction will dictate what, if any, emergency options are available. While some national regulatory authorities may have a range of regulatory options for emergency use, those of other countries may be more limited. It is recommended that countries carefully review the options available to them and implement any corrective measures needed as soon as possible.

Secondly, once the need to invoke emergency options is determined, the choice of usable options will depend on availability of data on the vaccine, if any, and the extent of vaccine distribution under such an option. A developing country at the source of an influenza pandemic may need to initiate a large-scale immunization campaign. Other countries may use the emergency option only for certain population groups to be immunized on a priority basis. Therefore, instead of establishing criteria based on population data before using an emergency option, it is the available data which dictate what option for emergency use is most suitable.
In the case that pandemic vaccines are unavailable upon the declaration of a pandemic, the use of cross-protective vaccines against novel human influenza viruses of assured quality and safety, with proven preclinical efficacy and safety, and satisfactory supporting clinical data from manufacturers of prequalified influenza vaccine would be advisable. Vaccines against novel human influenza viruses of assured quality could be the only vaccines available to developing countries, particularly those most affected early in the pandemic. Vaccines against novel human influenza viruses would be used only in case of emergency, i.e. a national disaster, and after approval by the ministry of health, when a specific pandemic vaccine, produced using the same manufacturing process as seasonal influenza vaccines, is not available.

Regulatory pathways for human pandemic influenza vaccines are outlined in Appendix 3. A proposed standard process to guide jurisdictions on the use of an emergency option is provided in Appendix 4 to these guidelines.

Part C. Regulatory considerations for the development and evaluation of vaccines against novel human influenza viruses

C.1 Quality and manufacturing

C.1.1 General manufacturing requirements

The following general requirements should apply to all manufacturers:

- The general manufacturing requirements contained in the WHO Good manufacturing practices for biological products (7) should apply to establishments manufacturing vaccines against novel human influenza viruses.

- Supported by laboratories of the WHO’s GISN, companies that intend to produce vaccines against novel human influenza viruses are expected to use reference vaccine strains that match a wide range of circulating influenza A variant viruses.

- Production and handling of live influenza viruses during the initial stages of manufacture of inactivated vaccines against novel human influenza viruses require an appropriate containment facility (biosafety level) as defined in the WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines (8). Independent evidence that a manufacturer is complying with the appropriate biosafety standard is also required. The responsibility for assessing compliance may differ between jurisdictions. Where applicable, the national regulatory
authority and the agency responsible for biosafety inspections should work together.

- Quality specifications for production and control of egg-grown and tissue culture-grown inactivated vaccines against novel human influenza viruses and pandemic influenza vaccines exist in WHO publications. Current WHO recommendations for the production and control of inactivated influenza vaccines (3) including the specifications for pandemic influenza vaccine should be met. However, if indicated by a risk–benefit analysis of a clinical development programme, some specifications may be modified. For example, the total protein content specification allows up to 100 micrograms of total protein per virus strain per human dose (3). If an unusually high incidence of local and systemic adverse events and/or severe adverse events unknown with other influenza vaccines occurred in a clinical trial of a vaccine against a novel human influenza virus, the vaccine virus concerned may require further purification and more stringent specifications.

- If a cell line is used for manufacturing influenza vaccine, current WHO requirements for the use of animal cells as in vitro substrates for the production of biologicals (9, 10 and subsequent updates) should be met.

- The general requirements on vaccine packaging and labelling contained in the WHO Good manufacturing practices for biological products (7) should apply to establishments manufacturing vaccines against novel human influenza viruses. Specific WHO requirements regarding the information on a standardized label for stockpiled vaccine or surplus vaccines released to international markets are not currently available. National regulatory authorities should require that any manufacturer producing vaccines under contract to them should label vaccines in accordance with the particular requirements of their jurisdiction.

C.1.2 General considerations for novel production systems

If in vivo cell substrates are explored for manufacturing influenza vaccine, the relevant WHO specifications would apply (9, 10). Production of influenza vaccines in cell substrates is a novel technology and the safety and efficacy of vaccine candidates produced in cell substrates has not been fully evaluated. Using influenza vaccines prepared in well-characterized cell substrates by prequalified vaccine manufacturers would be advisable only after data supporting safety, efficacy, and immunogenicity for use in humans become available. The provision of this advice should not be interpreted as any sort of endorsement of,
or recommendation for, the use or development of human influenza vaccines produced in cell substrates.

For more independence from the embryonated chicken egg substrate, production of vaccines against novel human influenza viruses and pandemic influenza vaccines using expression of influenza virus surface proteins in recombinant bacteria, yeast, animal cells, or plants is also under investigation. Although full-scale manufacturing processes are not yet established, the WHO guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology (11), the WHO guidelines for the production and quality control of synthetic peptide vaccines (12), and the WHO guidelines for assuring the quality of DNA vaccines (13) may apply. A WHO informal consultation on the scientific basis for regulatory evaluation of candidate human vaccines from plants (14) also provides relevant guidance.

The following steps and quality control procedures may be crucial in the production of biotechnology-derived influenza vaccines:

- **Fermentation:** definition of optimal harvest time and other harvest parameters; definition of cell density, cell viability, size distribution; performance of haemadsorption assay to monitor haemagglutinin expression.
- **Purification:** detergent extraction of recombinant HA protein; removal of residual DNA, host cell protein, detergents and other trace residuals.
- **Quality control procedures:** determine glycosylation patterns, purity, amino acid sequence and molecular size of recombinant protein.
- **Specifications for purity of recombinant HA which may be expected to be ≥ 95%.
- **Adaptation of tests such as single radial immunodiffusion (SRID) test to determine the specific antigen concentration in the vaccine derived using novel technology.**

### C.1.3 Stability criteria applicable to vaccines against novel human influenza viruses

Independent of virus growth substrate and vaccine production method, shelf-life assigned to vaccine intermediates and products should be justified by data on storage conditions under real time and real temperature as well as under elevated temperatures. Applicable WHO and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) stability guidelines should be followed. Refer to section D.2 for guidance on the stability of vaccines against novel human influenza viruses intended for stockpiling.
C.2 Preclinical and nonclinical evaluation of vaccines against novel human influenza viruses

Preclinical and nonclinical testing are prerequisites to moving candidate human influenza vaccines from the laboratory into the clinic and general principles apply. Preclinical testing includes all aspects of testing, product characterization, proof of concept, protective efficacy studies, and safety testing using appropriate animal models before testing the vaccine in human trials. Nonclinical evaluation refers to all in vivo and in vitro testing performed before and during the clinical development of the vaccine.

Guidance to national regulatory authorities and vaccine manufacturers on the nonclinical evaluation of vaccines as well as the international regulatory expectations in this area published by WHO (15) should be considered. These guidelines should be applied in conjunction with the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (16) pertinent to different stages of vaccine development and for marketing approval. Relevant guidance for national regulatory authorities and manufacturers is also provided in the WHO guidelines on regulation and licensing of biological products in countries with newly developing regulatory authorities (17).

Nonclinical safety testing should normally be performed with the vaccine candidate that contains a variant virus antigenetically and genetically related to the strain intended for the final product. If some or all data were obtained with seasonal influenza vaccine strains or other potential pandemic strains, the applicant should justify the relevance of these data to the final product. If reference is made to the literature as supportive bibliographical data, this literature should be provided and its relevance to the pandemic influenza vaccine candidate should be discussed.

In line with WHO’s policy statement on the use of opened multi-dose vials of vaccine in subsequent immunization sessions, an effective antimicrobial preservative may be used (http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf). The risk of possible microbial contamination during use of opened multi-dose vials of vaccine in subsequent immunization sessions may be assessed. For evaluation of new additives (i.e. excipients and antimicrobial preservatives), the WHO guidelines on clinical evaluation of vaccines: regulatory expectations (16) should be followed.

It may be useful to obtain immunogenicity data from an accepted animal model that responds well to human influenza vaccines (e.g. ferret) before commencing human clinical trials. The investigations should include an evaluation of immune responses according to dose and dose intervals using the vaccine that contains the strain intended for the final product. Immunogenicity studies in relevant animal models may be used to document consistency of production, in particular during the validation phase of the
vaccine manufacturing process. Immunogenicity data on the first three batches should be presented to document consistency of production. The choice of immunogenicity assay(s) needs to be approved by the national regulatory authority; assays need to be appropriately standardized and validated to enable comparison of data between different studies.

For vaccines against novel human influenza viruses, protective efficacy and cross-protection against influenza A viruses with pandemic potential will be very difficult to establish in human clinical trials. Therefore, challenge studies in appropriate animal models (e.g. ferrets or other suitable animals) to support potential vaccine efficacy in humans should normally be conducted using both the original wild type strain from which the vaccine virus was derived and a more antigenically distant wild type variant to the vaccine strain. The challenge virus strains should be chosen to enable an assessment of efficacy against lethal challenge.

If the applicant submits data from challenge studies performed only with other potential pandemic strains, the relevance of the findings to the final product should be justified. It is difficult to provide specifications for such tests until more data become available. Instead, a detailed justification for the definition of the nonclinical end-points selected for the animal studies, e.g. death, weight loss, virus excretion rates, clinical signs such as fever, oculonasal secretions, and others to estimate nonclinical efficacy, should be provided.

For whole virion, split or subunit inactivated human influenza vaccines manufactured by an established production process and formulated similarly to a licensed seasonal influenza vaccine (apart from the strain), nonclinical safety investigations need not be repeated, provided that they have been performed in accordance with relevant WHO requirements (15) and national or regional requirements.

Changes to the dose of whole virion, split or subunit pandemic influenza vaccines derived from a licensed process may not require repetition of the nonclinical safety testing provided that the total HA content per dose does not exceed an amount agreed by the national regulatory authority. The threshold HA content may be based on evidence from seasonal influenza vaccines and the safety of this HA content (plus corresponding impurities) has been confirmed over many years with numerous influenza drift variants. If a candidate vaccine exceeds this threshold, a study on local tolerance to administration of single and repeated doses may be required. Local tolerance may be investigated when the vaccination schedule consists of multiple vaccine doses with total HA antigen content higher than that agreed on by the national regulatory authority. In view of the possible use of vaccines against novel human influenza viruses in pregnant women, reproductive toxicity studies should be performed in animals.

Evaluation of a vaccine against a novel human influenza virus in combination with a well-established adjuvanting system will require only local
tolerance studies following administration of single and repeated doses. New adjuvanting systems with which little experience has been gained in relation to human use need to be specifically investigated for their safety profile, separately and in combination with the influenza virus antigen.

Enhancing the immunogenicity of vaccine antigen using adjuvants may carry the risk of increased reactogenicity, thus requiring careful benefit–risk analysis. Considering the expected substantial impact of adjuvants on antigen-sparing, the benefits of using safe adjuvanted vaccines may far outweigh the risks, especially during a pandemic. However, theoretical concerns over the quality of the immune response generated by some adjuvanted influenza vaccines remain.

It has been argued that whole-virion formalin-inactivated alum-adjuvanted pandemic influenza vaccines used in a naïve population (e.g. young children) could trigger a predominantly Th2 cellular immune response making vaccinees more prone to serious influenza disease during a pandemic. This concern is extrapolated from studies on non-human primates with other whole-virion adjuvanted vaccines (Respiratory Syncytial Virus, measles, severe acute respiratory syndrome (SARS)). In these cases, internal proteins e.g. nuclear proteins, are most likely to be responsible for over-stimulation and/or skewing of the cellular immune response. If the nuclear protein was responsible, it could be postulated that the predominantly Th2 cellular response is not only limited to whole-virion influenza vaccines, but also split vaccines. It could be further postulated that adjuvants other than alum (especially adjuvants promoting a Th2 rather than a Th1 response) could cause the same reaction. Therefore, regulatory authorities in at least one region of the world request that manufacturers consider studying this issue, and address it in regulatory submissions. However, the data generated so far in response to this concern are reassuring.

Inactivated influenza vaccines, including vaccines against novel human influenza viruses and pandemic vaccines produced in cell cultures are expected to contain much less process residuals than egg-derived vaccines. This is due to extensive downstream purification. It should be noted that at least one country requires more stringent specifications than WHO, with regard to residual cellular DNA, if continuous cell lines are used.

C.3 Clinical evaluation of vaccines against novel human influenza viruses

In principle, the clinical development of candidate vaccines against novel human influenza viruses should be done in accordance with the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (16) and relevant national or regional recommendations regarding clinical development of vaccines. In the clinical development phase, the applicants are encouraged
to present and discuss with the national regulatory authorities the clinical development plan and any interim results.

The indication to use a vaccine against a novel human influenza virus should strictly reflect the characteristics (e.g. age range and/or immunocompetence) of the population(s) for which sufficient evidence supports that indication. As with all vaccines, variations to the indication extending beyond the population in which dose recommendations were established may be approved if suitable data are provided.

Serological evaluation of vaccines against novel human influenza viruses may follow established criteria for seasonal influenza vaccines. In one region of the world, the serological criteria for assessment of seasonal influenza vaccines include:

- number of seroconversions or significant increase in antihaemagglutinin antibody titre > 40%;
- increase in geometric mean titre (GMT) > 2.5; and
- the proportion of subjects achieving a haemagglutination inhibition (HI) titre ≥ 40 or single radial haemolysis (SRH) titre > 25 mm² should be 70%.

These three parameters are evaluated yearly in human clinical trials due to the annual update of seasonal influenza vaccine strain composition. For a candidate seasonal vaccine in which only one of the three strains in previously registered vaccines is changed, at least one of the serological criteria must be exceeded for the immunogenicity of the new strain(s) to be accepted. For a new candidate seasonal influenza vaccine (e.g. new producer, new production method) all three serological criteria must be met unless specific scientific justification is provided to the contrary.

Failure to meet the three serological criteria may occur if a given study population has a very high residual immunity from pre-vaccination that cannot be further boosted by the candidate influenza vaccine. Seroconversion (increased HI titre > 40% post-vaccination) is assumed to correlate with protection, as it has been associated with a 50% reduction in influenza-like illness in healthy adults after intranasal challenge in the presence of pre-existing immunity against the influenza strains included in the vaccine.

This observed correlation, between HI titre and protection, may not be as strong for vaccines against novel human influenza viruses for which the human population is immunologically naïve. Evidence suggests that there may be different degrees of disease reduction linked to serological performance of

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the vaccine strain. However, the correlation of these two factors is unknown. As a general principle, vaccines used for primary immunization of a previously immunologically naïve population should induce as high an immune response as possible. This principle must be balanced, in the special circumstances of a pandemic vaccine, with the need of antigen-sparing approaches for vaccine formulation to maximize vaccination coverage.

Taking all the above factors into account, vaccines against novel human influenza viruses should induce high GMTs and seroconversion rates, preferably after only two doses. Ideally, the three serological criteria for assessment of seasonal influenza vaccines as defined in guideline CPMP/BWP/214/96 should be exceeded in the target population, with the proportion of subjects achieving an HI titre ≥ 40 being the most important.

Based on current understanding, the public health benefit of an influenza vaccine fulfilling or exceeding these three serological criteria cannot be fully estimated. It is not known whether these are the optimal criteria or whether lower levels of antibody would produce significantly less benefit. Based on the results from studies of seasonal influenza vaccines in animals and humans, the possibility cannot be excluded that there would be little or no public health benefit if some or all of these serological criteria were not fulfilled. Although the ferret model may not always be predictive of human influenza vaccine responses, recent studies suggest that substantial vaccine-induced protection may be achieved against some potentially pandemic H5N1 strains in ferrets with low antibody levels that do not meet the seroconversion criteria. Applicants as well as regulatory and public health agencies should carefully consider the expected public health benefits if a candidate vaccine does not fulfil all the serological criteria specified above. High quality data from immunization and challenge studies in animal models may assist in the decision-making process (28).

In addition to fulfilling the three serological criteria for assessment of influenza vaccines, defining and evaluating neutralizing antibodies could be of primary importance for vaccines against novel human influenza viruses. Neutralizing antibodies should be measured in at least a subset of vaccinated individuals, using standardized procedures and/or international reference standard sera. Additional immunological assessments including cell-mediated immunity and neuraminidase inhibition tests are of unknown relevance to protection. These assessments could be explored in a subset of vaccinees to provide more insight into the overall effects of vaccination.

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To study the need for revaccination, immune responses should be determined at intervals after completion of the primary series in at least a statistically valid subset of the vaccinated population. At the time of initial licensure, these data may be limited (e.g. to 6–12 months and for only a subset of the vaccinated population). Applicants would be expected to have plans in place to follow antibody levels over time and commitments to this effect should be agreed at the time of first approval.

Also at the time of initial licensure, plans should be in place to assess antibody persistence, cross-reactivity to new circulating variant viruses (compared to the vaccine strain) and responses to booster doses in cohorts of vaccinees from each age and risk group for which registration is sought. Plans to assess vaccine effectiveness after exposure to circulating influenza A viruses with pandemic potential should also be prepared (see sections G.3.4 and G.3.5). These plans are important to provide insight as to whether prior vaccination may afford at least some protection against influenza A virus strains that might trigger a pandemic.

The applicant should investigate the immunological response which may include antigenic cross-reactivity elicited by each vaccine against novel human influenza viruses with circulating influenza A viruses having pandemic potential (e.g. drift variants). However, no clinical claims of cross-protection against drift variants should be made without provision of additional evidence (e.g. cross-neutralizing activity of post-vaccination antisera and/or protection demonstrated in animal challenge models). Reporting on antibody boosting effect and persistence of antibody titres would strengthen the application.

Despite the naivety of the population, even a single dose of an inactivated influenza vaccine used before the pandemic is declared might be sufficient to elicit an immune response with public health benefit. Because of the uncertainties, a priming schedule with two (or even more) vaccine doses may be preferred as well as incorporation of an adjuvant. Thus, in addition to the need to determine the optimal dose of the antigens, several potentially feasible vaccination schedules should be explored.

The optimal dose and schedule may depend upon:

- vaccine-specific factors including antigen type and content, and type of adjuvant;
- population-specific factors such as age and immunological naivety to the potential pandemic virus strain(s);
- circumstances of use: for example, a regimen of short duration would be needed to rapidly achieve seroprotection in people who might come into contact with the virus e.g. poultry workers, veterinarians, animal caretakers and human health care providers.
To identify vaccine formulations (e.g. antigen dose and, if needed, amount of adjuvant) and schedules eliciting adequate serological responses, naïve individuals (i.e. HI titre < 1:10) from each specific population group should be studied for each proposed dose and schedule. The number of naïve subjects per dose group should be statistically justified. In the initial dose-finding study, the recommended sample size is at least 50 people.5

Once the applicant considers that the appropriate vaccine formulation and schedule have been identified for healthy adults aged 18–60 years, the safety and immunogenicity of the chosen vaccine candidate should be evaluated in a larger sample of healthy adults aged 18–60 years. The recommended size of the safety database required to detect adverse events following immunization (AEFIs) is shown in Table 1. Depending on the sample size in the initial dose-finding studies, sub-stratification of data by age may be appropriate to obtain more information in under-represented strata. These strata should preferably be predefined in the clinical development programme and should be agreed on by the relevant national regulatory authority. Extension of the population in which use of the vaccine is indicated (e.g. by age group and/or risk factors) might be based on studies completed before or after initial licensure.

Table 1
Size of the safety database required to detect adverse events following immunization (AEFIs) at stated frequency

<table>
<thead>
<tr>
<th>Age group</th>
<th>AEFI frequency and sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults from 18–60 years</td>
<td>≤ 1 in 1000 persons vaccinated (i.e. rare AEFIs) (e.g. a database of approximately 3000 subjects might be sufficient)</td>
</tr>
<tr>
<td>Specified age groups (e.g. infants, children, adolescents, adults over 60 years of age)</td>
<td>&lt; 1 in 100 (i.e. uncommon AEFIs) (e.g. a database of approximately 300 subjects from each specified age group might be sufficient)</td>
</tr>
<tr>
<td>Specified risk groups (e.g. immunocompromised individuals, chronically ill patients)</td>
<td>≤ 1 in 100 (i.e. uncommon AEFIs) (e.g. a database of approximately 300 subjects from each specified risk group might be sufficient)</td>
</tr>
</tbody>
</table>

* Applicants are encouraged to discuss the proposed size of the safety database with the national regulatory authority during the clinical development programme.

The size of safety database for each vaccine would differ depending on the population studied (Table 1). Follow-up of clinical trial participants for the evaluation of safety should continue for at least 6 months and should include specified parameters of adverse event causality, seriousness, expectedness and severity. These data should be submitted as part of the licence application. If any new issues regarding safety arise during the clinical development programme and/or vaccine use, they need to be followed up specifically as part of a risk management plan. Tools should be developed to better interpret rare adverse events occurring within the context of a clinical trial. If the vaccine against novel human influenza virus contains thiomersal as a preservative, relevant WHO and national or regional guidance should be followed.

Whenever the opportunity arises, national regulatory authorities should request further information on safety, immunogenicity and efficacy to expand the safety database on vaccines against novel human influenza viruses. It is particularly recommended to collect additional data in the populations less studied during the pre-authorization clinical trials. A risk management plan should be provided, with the safety information for each major population group that was not studied or was studied only to a limited extent in the pre-authorization phase. During a pandemic influenza event, the effectiveness of prior vaccination in people who do and who do not receive a dose of pandemic vaccine should be estimated through standardized and well-controlled trials.

As is done for seasonal influenza vaccines, the marketing authorization holder might wish to propose replacement of the strain in an approved vaccine. For example, this might occur if sequential studies show low or negligible cross-reactivity and cross-protection to drift variants and/or if expert opinion suggests that the influenza virus subtype most likely to trigger a pandemic has changed. Consequently, two scenarios are possible:

- replacement of the virus strain in the approved vaccine with a different strain of the same subtype (e.g. supplanting the original H5N1 with another H5N1 strain);
- replacement of the HA/NA subtype of virus strain (e.g. supplanting the original H5N1 strain with an H7N7 strain).

These two scenarios may have different regulatory implications and the following general principles apply:

- The market authorization holder would have to submit all manufacturing and quality data related to the new strain.

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- A study in a relevant animal model should be conducted to demonstrate that immune responses to the new vaccine strain are at least as good as those to the original vaccine strain in the licensed product.
- A clinical study should be conducted to demonstrate that immune responses to the new vaccine strain are adequate. If feasible, it is recommended that the new vaccine strain be administered to a cohort that previously received the original vaccine strain in order to assess cross-priming.
- Applicants are encouraged to obtain advice from the national regulatory authority regarding the extent and type of clinical data that would be required for strain change within same subtype.
- It should be expected that changes in virus strain subtype would have more extensive data requirements. Advice from the national regulatory authority should be sought on the regulatory framework and data requirements for such a change.

C.3.1 Special considerations for novel technologies

Clinical evaluation of candidate vaccines against novel human influenza viruses or pandemic influenza vaccines derived using more advanced technologies may differ from the traditional evaluation of inactivated influenza vaccines via HA and HI assays. Ideally, the efficacy of a vaccine derived using new technology would be established initially against seasonal influenza through clinical trials. Preclinical efficacy data on such a vaccine obtained from appropriate animal studies may be useful in supporting the acceptability of a candidate pandemic influenza vaccine derived using new technology.

For inactivated vaccines administered intramuscularly, serological markers such as functional antihaemagglutinin antibody titre and trend have been widely accepted as correlates of protection. For LAIV administered by an alternative route, e.g. intranasally, an initial local response in addition to a systemic immune response may be important. The immunological mode of action of LAIV requires infection of the upper respiratory tract mucosa establishing a robust immune response that protects against infection by circulating wild-type human influenza viruses. Therefore, the use of immunogenicity parameters similar to those applied to inactivated influenza vaccines may be misleading and underestimate the true potential of LAIV. Titres of local immunity, e.g. nasal secretory IgA antibodies, are not currently validated as indicators of mucosal immunity. Thus, the clinical investigation and programme for development of candidate influenza vaccines derived from novel technologies requires careful planning with regard to the choice of endpoints to estimate efficacy.
It should be kept in mind that LAIV cannot be administered concomitantly with neuraminidase inhibitors and/or other antivirals because these medicines would be likely to abolish vaccine efficacy.

C.3.2 Paediatric studies

Data from studies in children are needed for the following reasons:

- The immunological response of children is likely to be different.
- The optimal dose may be different.
- The clinical benefit is likely to be different.
- There may be special safety concerns for children, e.g. for adjuvanted influenza vaccines, or for vaccines that are intended for intranasal administration.
- As in adults, the relevance of immune response criteria to evaluate vaccines against novel human influenza viruses is uncertain.

For the purposes of this document, individuals under 18 years of age are considered children. Within this age band, and to be consistent with ICH-E11 definitions (18), children are divided into the following subgroups:

- preterm newborn infants;
- term newborn infants (0–27 days);
- infants and toddlers (28 days–23 months);
- children (2–11 years);
- adolescents (12 to 16–18 years) (dependent on region).

In most regions of the world, a clinical development programme for a vaccine is generally done in a stepwise fashion, from adults to children. Over the past decade, this development pathway has led to licensure of numerous paediatric vaccines including those against whooping cough, chickenpox, hepatitis A, pneumococcus, influenza, and meningococcus. It is crucial to have safety and immunogenicity data on adults before initiating clinical studies of a vaccine against a novel human influenza virus in children.

Clinical data from adults will provide the basis for selecting an appropriate starting dose and schedule in paediatric populations. Safety data on adults should be obtained from carefully monitored studies with pre-specified safety assessments. The clinical development phases and the size of the safety database on adults needed to support vaccine use in children warrant discussion with the relevant national regulatory authority. Evidence to support clinical trials of a specific manufacturer’s vaccine in paediatric populations should be
derived from clinical data in adults for that specific vaccine and for seasonal influenza vaccine formulations produced by that manufacturer.

Evaluation of immunogenicity and safety in children and adolescents should only be initiated after acceptable data becomes available from studies in healthy adults. Studies in infants and toddlers should only be initiated when data from studies in older children and adolescents are found acceptable. It is possible that the manufacturer will be unable to generate data for all age and risk categories. Under these circumstances, some degree of extrapolation might be allowed (e.g. from healthy adults to older and younger age categories). The appropriateness and extent of any allowed extrapolation should be considered on a case-by-case basis and would depend on total data available. Applicants seeking such extrapolations should ask for advice from the relevant national regulatory authority.

The clinical studies should provide a detailed characterization of the immunological responses to the candidate vaccine against novel human influenza virus containing the virus strain intended for the final product. Data from clinical studies conducted with vaccines that contain other influenza strains may be considered supportive.

The public health benefit of having children participate in clinical trials of vaccines against novel human influenza viruses, as a proxy for pandemic influenza vaccine candidates, may be difficult to predict; especially in geographical areas with no circulating avian influenza viruses. It is crucial to balance the safety benefits against the potential risks. In the recent Southeast Asian experience with avian influenza A (H5N1), those most affected were the young; the virus caused high mortality in infants and children (20). However, the epidemiology of a true pandemic strain may differ from that of a strain with very limited capability for person-to-person transmission.

C.3.2.1 Timing of paediatric studies

As for seasonal influenza vaccine, data on vaccines against novel human influenza viruses would be collected in a stepwise fashion, from adults to children. The quantity of data necessary to support licensure of a particular manufacturer’s candidate influenza vaccine for paediatric use would depend, in part, on the availability of paediatric clinical data for that manufacturer’s seasonal influenza vaccine.

The ethical principles described below (section C.3.2.2) should be carefully considered when making decisions on paediatric trials. These considerations may be viewed from the perspective of pandemic timing and would change as the likelihood of a pandemic increases. The need, timing, and extent of paediatric trials would thus depend on availability of critical information and evidence at specific time-points as well as the need for
additional data. The amount of information accrued would also depend on the predicted starting time of a pandemic. These factors will influence the need for additional data on:

- dose recommendations;
- safety risk–benefit assessment;
- immunological characterizations; and,
- opportunity to obtain efficacy and effectiveness data.

In general, the timing of paediatric studies depends upon several factors\(^7\) including:

- extrapolation of immunogenicity data from adults to children or seeking identical indication for all age bands;
- trial information on relevant clinical outcomes, e.g. effectiveness or immunogenicity, comparability of side-effects and long-term safety;
- nature of disease, e.g. serious and/or life-threatening, urgency of treatment and/or prophylaxis;
- clinical findings in adult populations, e.g. a major safety problem identified in adults; and
- availability of and/or necessity for a paediatric formulation.

The timing of paediatric trials with vaccines against novel human influenza viruses thus depends on the availability of paediatric data from studies of seasonal influenza vaccine, the experience with vaccines against novel human influenza viruses in adults, and the expected need for additional data on children prior to the pandemic. Reactogenicity of the vaccine formulation with vaccines against novel human influenza viruses in adults would be an important determinant of the extent of studies required in children.

There may be national or regional differences with regard to the anticipated timing of paediatric studies with vaccines against novel human influenza viruses. In one country, for example, the law outlines that all sponsors have obligations to study paediatric populations, as appropriate.\(^8\) Some countries with influenza (human and animal) outbreaks have indicated a special interest in conducting paediatric studies with vaccines against novel human influenza viruses. For example, such studies might be conducted in children who are

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at risk for disease caused by avian influenza A (H5N1) virus due to frequent contact with birds. In some countries or regions, it is not anticipated that paediatric trials will be conducted before a pandemic occurs. Consequently, data from bridging studies in adults and/or foreign paediatric populations may be critical bridging adult and/or foreign paediatric data may for regulatory decision-making.\(^9\)

In general, paediatric clinical data on seasonal influenza vaccines would be useful for planning paediatric studies on pandemic influenza vaccine. Critical data would include:

- age-dependent, influenza-associated disease burden: influenza-like illness, serologically confirmed influenza, acute otitis media, complications, and mortality in both healthy children and those with co-morbidity;
- evidence of age- and dose-dependent vaccine efficacy on disease outcomes;
- seroresponse and immunological response characterization using standardized methods, i.e. serological assays, which must be in place before paediatric studies are initiated;
- safety e.g. a system of recording and analysing information on AEFIs (21).

An improved understanding of the efficacy of seasonal influenza vaccine in paediatric populations would be particularly valuable. Available data indicate that the efficacy of inactivated seasonal influenza vaccines in children less than 2 years of age is poor (22). Safety and immunogenicity data on simultaneous administration of seasonal influenza vaccines with other licensed vaccines generally used in childhood immunization programmes would also be useful.

C.3.2.2 Ethical considerations in conducting paediatric studies

Ethical considerations on the conduct of vaccine evaluations as described in the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (16) and the WHO Guidelines for good clinical practices for trial on pharmaceutical products (19) should be met. Vaccine manufacturers are encouraged to submit

\(^9\) A bridging study is: a study performed in a new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data package to the population in the new region (Review of existing documents on planning, performance and assessment of clinical studies on vaccines (WHO/V&B/99.09) (available at: http://whqlibdoc.who.int/hq/1999/WHO_V&B_99.09.pdf)).
paediatric development plans to the national regulatory authorities as early as possible in the vaccine development process.

Since data from clinical trials must support the use of a vaccine against novel human influenza virus in children, the following considerations must be addressed:

- Children represent a vulnerable population with developmental, physiological and psychological differences from adults.
- The clinical trials should be carried out under conditions affording the best possible protection for the subjects.
- Criteria for the protection of children participating in clinical studies should be described.

The scientific conduct of paediatric studies must address issues of protection of human subjects particularly relevant to children, in compliance with applicable national or regional regulations. Decisions on paediatric clinical investigations should follow the framework of institutional review boards or equivalent ethical oversight groups. Ethics committees should take considerable care when reviewing paediatric protocols. Appropriate provisions should be made for soliciting permission from parents or guardians and for obtaining assent from children participating in clinical studies. Ethical considerations include the following (see the ICH E11 guidelines for additional guidance (18)):

- The trial should be explained to the child as his or her age and maturity allows, and assent obtained when this is considered reasonable by consensus between the researchers and parent(s) or guardian(s).
- Risk should be minimized by using trained staff, appropriate study design, and rapid termination, if necessary.
- Distress should be minimized by appropriate measures.
- Financial or other incentives should not be given. Covering reasonable expenses such as travel is allowable.

### C.3.3 Clinical studies in the elderly and specific risk populations

As with children, clinical data on vaccines against novel human influenza viruses cannot be automatically extrapolated from healthy adults to elderly people. Carefully designed studies are also required to adapt dose and vaccination schedules from healthy adults to individual age categories of the elderly. This

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approach is necessary to reduce potential vaccination risks and to optimize its benefits. Other risk categories include individuals with underlying disease or other risk factors that might also affect the clinical performance of the vaccine differently to healthy adults, e.g. co-medication.

Since the elderly would have a significantly increased risk of morbidity and mortality following exposure to a novel human influenza virus, the goal of clinical studies in the elderly and in people who are chronically ill is to maximize efficacy of the vaccine (as expressed by immunogenicity). This might be achieved by increasing the antigen dose or number of doses needed to reach acceptable immune responses. As in paediatric studies, the total number of age and risk strata to investigate might become too high, and clinical trial designs that include different age and risk categories might become too complex.

The recommended size of the safety database required to detect AEFIs in the elderly is provided in Table 1, but details on the design of clinical studies to be performed in specific risk populations are not covered in these guidelines. Due to its potential complexity, the design of such trials should be discussed with the relevant national regulatory authority.

**Part D. Regulatory considerations for stockpiled influenza vaccines**

D.1 General remarks

As part of their pandemic influenza preparedness plans, many countries and WHO are considering establishing stockpiles of vaccines against novel human influenza viruses in anticipation of an influenza pandemic. Any decisions to use such a vaccine before a pandemic is declared should be in line with national policies and are solely the responsibility of individual governments and their public health authorities. While the pathways of intended use for these vaccines may differ between countries, there are general principles that should be considered.

In October 2007, an informal consultation was held in Geneva to develop options for technical specifications for a WHO international H5N1 vaccine stockpile and the recommendations are publicly available.\(^\text{11}\)

D.2 Special considerations for the evaluation of stockpiled vaccines

In addition to the guidelines provided in part C, vaccines against novel human influenza viruses that are intended for stockpiling will need a particularly well-

\(^{11}\) http://who.int/vaccine_research/diseases/influenza/meeting_stockpile_181007/en/index.html
defined stability testing programme to justify the selected design for the stockpile and ensure continued immunogenicity and safety throughout the stockpiling period. Vaccine components including bulk antigen and adjuvant might be stored separately and periodic nonclinical and/or clinical reinvestigation of a stockpiled vaccine might be necessary.

The final stability testing programme should be approved by the relevant national regulatory authority and should include an agreed upon set of stability-indicating parameters, procedures for the continuing collection and sharing of stability data, and criteria for rejecting vaccine(s) from the stockpile.

The continued appropriateness of an H5N1 strain in the stockpiled vaccine to induce immunity against drift variants should be monitored based on recommendations made by WHO. Data to facilitate decision-making on the continued appropriateness of the strain should be defined in advance. One option would be to use sera from clinical trials with the stockpiled vaccines for tests against drift variants. This would require communication and an agreement with the manufacturer to ensure sera are available for this purpose.

Part E. Regulatory considerations for the development and evaluation of pandemic influenza vaccines

E.1 General remarks

This section covers the quality, preclinical, nonclinical and clinical aspects of influenza vaccines to be developed once a pandemic is declared and the pandemic influenza A virus strain identified.

It is expected that the regulatory evaluation of pandemic influenza vaccines will largely rely on information collected in the inter-pandemic period. As many relevant data as possible should be accumulated on the suitability of the manufacturing process as well as on the nonclinical and clinical performance of a vaccine against a novel human influenza virus before a pandemic strikes. The advantage of such an approach is that when the pandemic influenza A virus strain becomes known, the pandemic influenza vaccine may be licensed with minimum additional data. This is assuming that the product attributes and critical quality parameters as well as nonclinical and clinical performance of the vaccine against a novel human influenza A virus would also apply to the pandemic influenza vaccine.

E.2 Quality and manufacturing

The general manufacturing requirements presented in section C.1 apply to the manufacture of pandemic influenza vaccines.
E.2.1 **Stability criteria**

It is anticipated that real-time stability data would be unlikely to be available for the pandemic strain vaccine and that countries would be willing to accept vaccines without such data in the special circumstances of a pandemic. In the urgency of a pandemic situation, it is unlikely that human pandemic influenza vaccines would be stored for long periods. If indicated and if time allows, an appropriate potency-indicating test (e.g. SRID test for antigen content) may be performed before a pandemic vaccine is used.

E.3 **Preclinical and nonclinical evaluation of pandemic influenza vaccines**

Once a pandemic is declared, it would be imperative to produce and use vaccines that are formulated with the antigen to the pandemic strain as quickly as possible. In these special circumstances it is anticipated that few or no preclinical and nonclinical data would be available. If the risk–benefit evaluation warrants such action, countries should be prepared to accept vaccines without these data. As a minimum, data on the approved quality control release tests related to potency and safety should be available. Such a situation would be more likely to be acceptable if experience had been accumulated with vaccines against novel human influenza viruses from the manufacturer concerned.

E.4 **Clinical evaluation of pandemic influenza vaccines**

For a pandemic influenza vaccine, some clinical trial data would be expected to support the appropriate dose and regimen. These trials should also include an assessment of immunogenicity and safety and may build on experience with vaccines against seasonal influenza and/or vaccines against novel human influenza viruses. It is also expected that studies of vaccine effectiveness and safety would be carried out during the pandemic. The general protocols and plans for such clinical studies should be in place as part of a risk management plan prior to the influenza pandemic. Preparation of such plans requires collaboration between all stakeholders (i.e. WHO, public health authorities, national regulatory authorities and industry). See section G for additional guidance.

E.4.1 **Paediatric studies during an influenza pandemic**

Once a pandemic is declared, recommendations for the paediatric dose and schedule would be needed immediately if they are not already in place. Based on current data from studies in healthy adults inoculated with different potential pandemic strains, more than one dose of the pandemic vaccine would be likely to be needed (23–25). As for adults, it is anticipated that children who have not been previously vaccinated will require at least two doses with
a 1-month interval between doses. In the case of seasonal influenza vaccines, seroconversion rates seem to increase with age from < 50% in those aged < 6 years to > 80% in those aged > 10 years, which probably reflects the influence of (natural) priming (26–27).

A two-dose (or more) schedule in immunologically naïve infants and children is probably a reasonable approach for most individuals in a pandemic situation. Also, the seroresponse observed with the investigated dose and schedule in young adults may be extrapolated to children at a comparable stage of immunological development. Thus, when no clinical data on vaccines against novel human influenza viruses in children aged ≥ 6 years exist prior to the pandemic, the dose and schedule used in young adults aged 18–30 years might be extrapolated to the younger group as an emergency measure.

Clinical data on safety and immunogenicity should be obtained for infants and toddlers. However, early in a pandemic, it may be necessary to extrapolate the recommendations for the dose of adult pandemic vaccine and paediatric seasonal vaccine. This implies that recommendations for the paediatric dose of seasonal influenza vaccine need to be well substantiated. Depending on legal constraints, data from paediatric clinical trials using vaccines against novel human influenza viruses might also be obtained prior to the pandemic. Such data should preferably be generated in dose–response studies in appropriately stratified age categories using a step-wise approach (e.g. 6–12 months, 13–36 months, 3–6 years, 6–12 years and > 12 years). With a well-substantiated dose recommendation for the sponsors’ seasonal influenza vaccine formulation (if equivalent) and an accepted dose and schedule recommendation for the vaccine against a novel human influenza virus in young adults, a single-dose paediatric clinical trial might be envisaged. It is recommended that vaccine manufacturers seek advice from the national regulatory authority.

Once a pandemic is declared and the initial cohorts are vaccinated, paediatric dose recommendations must be re-assessed based on data on immunogenicity and initial clinical outcome obtained from active surveillance. If necessary, additional dose–response studies should be performed.

Paediatric safety studies should only be initiated after sufficient clinical data on use of the vaccine against novel influenza virus formulation have been collected and acceptable proof of principle of safety and efficacy i.e. immunogenicity is obtained in healthy adults.

Since an indication for paediatric use is most likely to be sought after initial licensure, data on safety and immunogenicity in children may be submitted as a licence supplement. It is expected that detailed immunological characterization will be performed during clinical trials of vaccines against novel influenza viruses in healthy adults. These data should be used to determine the optimal serological assays and methodologies for use in paediatric studies.
The general protocols and plans for paediatric clinical studies should also form part of a risk management plan that is developed prior to the influenza pandemic. The following specific considerations should be taken into account:

- **Feasibility**: an estimation of the feasibility of conducting paediatric studies during a pandemic.
- **Choice of schedule**: one important issue is whether paediatric studies should address immunogenicity of the predefined schedule for healthy adults or define the optimal schedule for children for each vaccine. The latter is traditionally done during vaccine development. Age-stratified analyses should provide more insight into the role of pre-existing immunity (at whatever age) and immaturity of the immune system in the very young in relation to the chosen vaccination schedule. However, it must be acknowledged that having many different schedules for different subpopulations may create problems for mass vaccination campaigns.

- **Safety assessment**: another issue is how many safety data should be gathered or studied. It is recognized that special safety issues may need to be addressed, e.g., adjuvants. In addition to short-term safety, a plan to assess long-term safety should be considered. Long-term safety refers to a 6-month follow-up period after the last dose.

- **Shedding**: it may be useful to conduct early studies to address the impact of the vaccine on infectivity.

- **Efficacy assessment**: documenting clinical outcomes in a prespecified manner is important. For example, the efficacy of a vaccine in children may differ significantly from the inter-pandemic situation or may differ from efficacy in adults. If possible, case definitions to be used in such evaluations should be defined prospectively.

**Part F. Quality control preparedness**

**F.1 General remarks**

Quality control of pandemic influenza vaccines will be based on the processes and policies for seasonal influenza vaccines. Seasonal influenza vaccines should be produced in compliance with GMP, tested for quality and safety by the vaccine manufacturer, and usually, subjected to independent quality control testing by a national control laboratory. The vaccine may be used only when it has passed the tests at the national control laboratory and has been released by the national control laboratory. In a pandemic situation, vaccine quality control performed by manufacturers and independent assessment by a national control laboratory will also be required. In this situation, tests would be done in
a high-pressure environment with a much higher throughput than normal and in which technical problems connected with the novelty of pandemic vaccines could interfere with efficient testing. In an inter-pandemic situation, vaccine quality control will not be done under emergency conditions, but certain aspects of the technical problems associated with testing will still be relevant.

In view of the likely pandemic emergency, speed would be needed for batch release tests. It may also be necessary for a national control laboratory to perform tests in parallel with vaccine manufacturers and/or to perform only a subset of the tests normally done on seasonal influenza vaccines (e.g. SRID and Limulus amoebocyte lysate (LAL) tests).

It is expected that national control laboratories normally engaged in batch release of seasonal influenza vaccine will also perform batch release of pandemic vaccine. However, this testing capacity may not be sufficient and an assessment of and provision for reserve batch release capacity should be made. It is therefore important to prepare for quality control of pandemic vaccine well before a pandemic starts and for national control laboratories to share their experience in order to minimize disruptions to vaccine supply. Some national control laboratories have already developed procedures for batch release of pandemic vaccine, others have not. Countries where such plans are not in place are strongly encouraged to develop them as soon as possible. Moreover, provisions for batch release of pandemic vaccines should be included in national pandemic influenza preparedness plans. Simulation exercises should be conducted, where possible.

It is also recognized that quality control and batch release procedures are different throughout the world. There are however some common principles to observe. The following assessment and proposals relate mainly to inactivated influenza vaccines, but where appropriate there is also consideration of quality control testing of LAIV.

## F.2 Quality control testing by vaccine manufacturers

### F.2.1 Inactivated vaccines

Current experience with development of inactivated H5N1 influenza vaccines suggests that a pandemic vaccine is likely to contain a reverse genetically-engineered virus and be formulated as a monovalent vaccine with alum or a proprietary adjuvant. Alternatively, the vaccine may be formulated without adjuvant, but the adjuvant may be mixed extemporaneously. This may affect the type of test conducted on the vaccine.

Pandemic influenza vaccines are also likely to be produced in much larger quantities (i.e. more batches) than seasonal vaccines and the pressure for quick release and use of the vaccine will be enormous. Nevertheless, all the normal quality control tests for seasonal influenza vaccines should also be
performed for pandemic influenza vaccines since there is an increased risk of problems when working under extreme time pressure.

Because of technical difficulties or special pandemic circumstances, some quality control tests may need to be modified. In the inter-pandemic period there will not be the high demand for vaccine expected during a pandemic and the technical difficulties described below will still be relevant. Existing WHO recommendations for the production and control of influenza vaccine (inactivated) should be followed.\(^{12}\) National control laboratories and manufacturers should ensure that the following modifications are acceptable for pandemic influenza vaccines:

- **Vaccine reference virus:** A fully characterized reference virus will be provided by a WHO laboratory. This is important to ensure that vaccines derived from reverse genetics have no potentially pathogenic viruses, are safe and have been produced according to accepted quality standards.

- **Identity of seed virus:** For seasonal influenza vaccines, the haemagglutinin and neuraminidase protein (required by the European Pharmacopoeia) in seed viruses are identified by immunological tests. For a pandemic vaccine, it is likely that vaccine production will be under way before immunological reagents are available for identity testing. It is thus recommended that polymerase chain reaction (PCR)-based identity tests are developed and used on vaccine seed viruses. Because of the technical demands of such tests, it may be necessary to perform them at a national control laboratory or a WHO laboratory using primers available from virus surveillance activities or pandemic vaccine development. Confirmation by classical in vitro tests should be provided afterwards.

- **Testing of cell culture-derived vaccines for adventitious agents:** In a pandemic emergency, there will be limited time to perform the in vivo tests for adventitious agents normally required with cell-derived vaccines \((9, 10)\). Manufacturers should perform a risk analysis for use of alternative tests based on the type of cell substrates used (susceptibility to adventitious agents) and the type of vaccine process (capacity to eliminate adventitious agents). In vivo testing could be substituted by validated PCR techniques only for well-characterized cell substrates used for influenza vaccine production. In vivo testing for influenza vaccines produced in novel primary, continuous and/or

diploid cell substrates would still need to be performed according to standard requirements (9, 10). In one part of the world, PCR tests are allowed provided a comparison of in vivo and validated PCR tests is performed to substantiate the approach.

- **Vaccine potency test:** Vaccine potency is normally assessed by the SRID test. This test requires strain-specific antigen and antisera reagents which normally require 3 months to prepare and calibrate. There might be different pandemic vaccine scenarios. First, specific antigen and antisera may not be available at the start of vaccine quality control testing. Second, these reagents may be available, but they may not be useful to test final product owing to the presence of certain adjuvants (e.g. alum). Third, the reagents may be available and the vaccine is formulated without adjuvant.

In the absence of strain-specific antiserum, the use of alternative potency tests such as protein and/or sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) assays or mouse immunogenicity tests is recommended. However, it should be noted that immunogenicity studies are difficult to validate, time consuming and often unreliable. These surrogate potency tests should be validated by vaccine manufacturers and the relevant national control laboratories and acceptance criteria should be defined before the pandemic.

When SRID reagents are available, they should be used to test bulk vaccine (also named monovalent pooled harvest\(^\text{13}\) in one region of the world). Blending of vaccine into final formulation should be based on a potency agreed between the manufacturer and the national control laboratory.

SRID potency tests should also be done on final product if possible, but if there are difficulties (i.e. due to presence of alum), it is recommended that alternative, validated potency tests (see section F.3.7, tests of adjuvanted vaccine) be used.

- **Endotoxin test:** If national regulations require an endotoxin test for batch release (required by the European Pharmacopoeia), the LAL assay should be evaluated by manufacturers and national control laboratories for possible interference by the adjuvant. If interference is likely, the LAL test should be done on the bulk vaccine before adding adjuvant.

\(^{13}\) Monovalent pooled harvest is a more accurate name for the pandemic influenza vaccine bulk. Bulk also can be used for a monovalent vaccine, but bulk is used for seasonal influenza vaccines to describe the three strains pooled together.
F.2.2  Live attenuated influenza vaccines

In the event that a LAIV is used as a pandemic vaccine, there would be similar concerns about rapid vaccine production and testing to those previously described for inactivated vaccines. However, there are some issues concerning tests for identity, attenuation phenotype and infectivity that also merit special attention with LAIV.

- A reference virus, fully characterized by a WHO Collaborating Laboratory should be used for generation of seed viruses. If a highly pathogenic avian virus is chosen, the virus must be rendered nonpathogenic by removal of known molecular markers of pathogenicity.
- It may not be possible to perform immunological tests for identity of the HA and NA proteins in the seed virus as described for inactivated vaccines. It is recommended that PCR-based tests are used.
- The seed virus should be tested for molecular markers of attenuation and identity of the virus gene segments using methods approved by the national control laboratory.
- Tests for adventitious agents and mycoplasma on seed and vaccine viruses should be conducted.
- Attenuation phenotype and attenuation stability of the virus should be established by testing in an animal model(s) approved by the national control laboratory.

F.3  National control laboratory batch release procedures

F.3.1  Flexibility in batch release testing by national control laboratories

Batch release of influenza vaccines by national control laboratories is essentially a repetition of the important quality control tests performed by a vaccine manufacturer. In a pandemic emergency, each national control laboratory should agree on procedures to ensure confidence as to quality and safety of vaccines without compromising rapid clinical availability of vaccines. It may therefore be necessary to introduce some flexibility into batch release procedures. For example, the scope of testing by national control laboratories could be reduced to include only key tests (see section F.3.2) and/or testing could be done jointly by the vaccine manufacturer and the national control laboratory.

F.3.2  Batch release procedures for inactivated influenza vaccines

There are technical and logistic issues for pandemic influenza vaccines which could affect the batch release process of national control laboratories. Although there are significant differences between batch release procedures around the world, there is consensus on the key issues in vaccine testing by national control
laboratories for a pandemic emergency. Most of the procedures described below refer to vaccine batch release during a pandemic situation. During the inter-pandemic situation, emergency procedures need not be applied, but the technical difficulties in testing described in sections i and ii should be addressed. First priority should be given to review of the manufacturers’ protocols and should always be part of the batch release by the national control laboratory.

1. First priority: protocol review

A protocol summarizing a manufacturer’s quality control test results should be submitted to the national control laboratory, preferably by electronic submission. The protocol should be based on the model supplied by WHO (3) but should also comply with national regulations.

2. The second priority, if time and resources allow, would be a protocol review plus the following tests or activities:

i. Vaccine potency test

In the countries where this is done, the national control laboratory should perform potency tests on bulk vaccine (before adding adjuvant) in parallel with tests required by manufacturers to release batches. Alternative, a validated potency test should be performed on adjuvanted final product.

The national control laboratory should perform SRID tests when reagents are available. In special pandemic circumstances, greater interchangeability of reagents may be required than when testing seasonal influenza vaccines. When SRID reagents are not available, an agreed surrogate potency test should be performed. If in a pandemic situation, national control laboratories will not perform potency tests on final product, manufacturers should formulate vaccine based on a potency agreed between the manufacturer and the national control laboratory. Manufacturers should formulate vaccine based on a potency value agreed between the manufacturer and the national control laboratory. This agreement would enable the formulation of the final lot of vaccine based on the potency of bulk vaccine with the required degree of confidence.

If tests on final product are required by a national control laboratory (e.g. for assessment of vaccine stability), it is recommended that a subset of batches be tested for antigen content using a validated potency test (see section F.3.7, tests of adjuvanted vaccines). Immunogenicity using an appropriate animal model might be considered; however these studies are difficult to validate, time consuming and often unreliable.
ii. Endotoxin test

If required by national regulations for batch release, the LAL test should be evaluated by vaccine manufacturers and national control laboratories for possible interference from adjuvant. If interference is detected, the LAL test would be done on the bulk vaccine before adding the adjuvant.

iii. Trend analysis

In situations where there is extreme urgency for vaccine production and quality control testing, there is the potential for mistakes which could affect vaccine safety and/or efficacy. Particular consideration should be given to monitoring the manufacturers’ and/or national control laboratory’s quality control data to reveal any trends towards non-compliance (e.g. coefficient of variation, stability). Where applicable, it may be desirable to establish a link between the national control laboratory and the national inspectorate to ensure compliance with good manufacturing practices during upstream production.

F.3.3 Batch release procedures for live attenuated influenza vaccines

For LAIV products, consideration should be given to performing an assessment of the attenuation of the vaccine by testing in suitable animal models, by testing for any in vitro markers of attenuation or by performing a general safety test. Review of the manufacturer’s test results is also critical for the assessment of the suitability of the vaccine lot for release.

F.3.4 Mutual recognition of batch release

When pandemic vaccine bulks or final lots are shipped from the country of origin to another country, it is proposed that the national control laboratories of both countries work towards recognizing mutual batch release. This would avoid duplication of the same batch release process by two or more national control laboratories. It is recognized that national control laboratories will require time, evidence and support to develop mutual confidence in the results of another national control laboratory. It is proposed that WHO coordinates a process for the purpose of evidence-based mutual recognition of batch release data.

F.3.5 Number of batch release tests needed

It is difficult for any national control laboratory to estimate its capacity for pandemic vaccine batch release when it is not clear how many batches will be submitted. Similarly, it is difficult to estimate the number of pandemic vaccine
SRID reagents needed globally in the absence of this information. Vaccine manufacturers should provide estimates of the likely number of pandemic vaccine batches and the number of SRID tests required. This information should be provided to the relevant national control laboratory and to WHO as appropriate.

F.3.6 Provision of reagents for SRID tests

SRID reagents for batch release of seasonal influenza vaccines are normally supplied by one of four laboratories that are part of the WHO network. The reagents are developed and calibrated jointly by collaborative study among the four laboratories; this process normally takes about 3 months. In a pandemic, these procedures may not be able to ensure a speedy and adequate supply of reagents.

- **International collaboration:** In an an emergency, there may be transport and import restrictions. The aforementioned laboratories normally involved in producing SRID reagents may find it difficult to exchange reagents for cross-calibration. These laboratories should be prepared to take responsibility for performing calibration of new pandemic vaccine viruses either alone or using locally-developed networks which may include vaccine manufacturers and/or other national control laboratories.

- **Supply of SRID antigen:** One of the manufacturers usually supplies the regulatory authorities with one of their first batches of antigen in a new vaccine campaign for use as the SRID antigen. In a pandemic situation, vaccine manufacturers would be under enormous pressure to meet orders in time and may find it difficult to supply the SRID antigen. National control laboratories and manufacturers should ensure that there are secured contractual arrangements in place (preferably with a back-up) for supply of antigen for quality control purposes.

- **SRID libraries:** When a new candidate H5N1 vaccine virus strain is developed through WHO processes, there is a need for matching SRID reagents. A SRID antigen must be antigenically homologous to the vaccine antigen; therefore, it can only be produced when the identity of the candidate pandemic vaccine virus is known. However, production of SRID antiserum requires approximately 3 months for preparation. There is evidence that sheep antisera are cross-reactive between antigenic drift variants, so that antiserum prepared against one H5N1 virus may be usable in SRID tests of another H5N1 virus.
WHO should play a coordinating role between vaccine manufacturers and the four laboratories normally involved with reagent production to ensure that reagents are available for each candidate H5N1 vaccine strain. SRID reagents are also being developed for other virus strains recognized by WHO as priority pandemic subtypes (i.e. H7, H2 and H9). National reference laboratories and manufacturers should ensure that the reagents from a library are acceptable for quality control purposes. One criterion for acceptability may be that the reagents are evaluated among the four laboratories involved in SRID reagent preparation.

F.3.7 Tests of adjuvanted vaccines

It is known that alum interferes with the SRID potency test and may interfere with the LAL endotoxin test. However, in one region of the world, alum used in the formulation of vaccines for novel influenza viruses from two manufacturers does not interfere with the LAL test. During development of pandemic influenza vaccines, there should be an evaluation of interference in key quality control tests. Methods to elute vaccine antigen from alum or other adjuvants should be evaluated and information shared between vaccine manufacturers and national control laboratories. If alternative tests for antigen content (e.g. protein and/or SDS PAGE) are developed by vaccine manufacturers, information should be shared with the relevant national control laboratory in preparation for batch release testing.

F.3.8 Risk assessment

Each NCL should carry out a risk assessment to ensure that batch release of pandemic vaccine is not compromised by problems which could have been prevented. Questions that should be addressed include:

- Are there sufficient personnel trained in batch release of influenza vaccine to cope with the increased amount of testing? Should staff be required to work in shifts? (Back-up staff should be trained if necessary.)
- Is there need for a back-up national control laboratory?
- Will batch release personnel be immunized against infection during an influenza pandemic? Consideration should be given to use of antivirals, candidate pandemic vaccines, and quarantine procedures.
- Will the national control laboratory's essential services be maintained during a pandemic when there may be high numbers of staff absences? Services could include utilities (e.g. gas, electricity and water), information technology and communications support, laboratory supplies and essential vaccine testing programmes.
- Is there a press policy? There will be heightened press interest in vaccine testing activities during a pandemic and batch release staff need to be protected from this.
- Will there be transport restrictions (including on import or export) on SRID reagents and vaccines? A mechanism is needed to avoid such restrictions.
- Has an assessment been performed to ensure that all foreseeable risks to the supply of SRID reagents have been mitigated? Topics to be addressed should include
  - large-scale supply of antigen;
  - availability of freeze-drying facilities;
  - availability of sheep;
  - ordering and shipment of reagents; and
  - information exchange with other collaborating centres and vaccine manufacturers.
- Are there adequate storage facilities at the national control laboratories to handle the anticipated surge in samples for testing?

**Part G. Postmarketing surveillance**

**G.1 General remarks**

It is quite likely that limited immunogenicity and safety data, and no efficacy data will be available when human pandemic influenza vaccines are first administered after a pandemic is declared. Furthermore, the vaccines may be of different strain composition to that in vaccines against novel human influenza viruses studied before the pandemic.

Clinical trials with vaccines against novel human influenza viruses during the inter-pandemic phase will mainly detect common AEFIs, and will probably not address rare adverse events, potential safety issues within subgroups, or potential vaccine–drug interactions. Safety experience with seasonal influenza vaccines may have only limited relevance due to the changes in vaccine strain composition and manufacturing procedures made to produce pandemic influenza vaccines. In consequence, the risks and benefits of pandemic influenza vaccines will need to be studied postmarketing.

Because of the likely extreme conditions of a pandemic, clear postmarketing surveillance objectives to evaluate effectiveness and safety of a pandemic influenza vaccine need to be agreed upon in advance. Protocols should be developed to ensure that effectiveness and safety of the pandemic vaccine are adequately documented, analysed and assessed during use in
the field. Preparedness plans for postmarketing surveillance should enable authorities to quickly and adequately assess vaccine safety, immunogenicity and effectiveness, thereby allowing them to make evidence-based decisions concerning any necessary changes in vaccination programmes (e.g. virus drift). Important aspects of study protocols need to be agreed upon in advance, and functionality of protocols and systems should be tested in the inter-pandemic period. Sponsors should seek approval by ethics committees and/or institutional review boards and by national regulatory authorities (if necessary) in advance. A need for flexibility, constant real-time review, and adaptability to changing plans and study designs of postmarketing surveillance will arise. Therefore, it is important to determine feasible and realistic conditions for postmarketing surveillance in different scenarios.

Setting up a postmarketing surveillance plan to respond to an influenza pandemic would facilitate an appropriate response to public concerns and maintain the public’s confidence in the vaccination programme. The sharing of postmarketing information (e.g. safety signals) is important, especially for those countries that do not conduct routine postmarketing surveillance. Such postmarketing preparedness requires collaboration between all stakeholders, WHO, public health authorities, national regulatory authorities and industry.

G.2 Postmarketing considerations for vaccines against novel human influenza viruses

With limited knowledge on immunogenicity and safety of vaccines against novel human influenza viruses and no knowledge of their efficacy regarding cross-protection with a pandemic strain, some governments might plan to stockpile vaccines against novel human influenza viruses and immunize certain at-risk populations (i.e. poultry culling crews, veterinarians, influenza laboratory workers and health care providers) before a pandemic is declared. Some countries may also opt to use these vaccines for pandemic preparedness in WHO Phases 4 and 5 (i.e. if a vaccine strain was considered a close enough match to a virus transmissible between humans).

Using vaccines against novel human influenza viruses in the inter-pandemic period would provide an important opportunity to collect data on safety and immunogenicity. To expand the safety and immunogenicity databases, it is advisable to plan the collection of information from observational studies or vaccination registries when the opportunity arises. As a prerequisite, data collection should allow for well-designed and pre-planned analysis. These data should also be assessed for implications on surveillance activities during the pandemic and for the need for any modification of postmarketing surveillance plans.

Ideally, vaccine immunogenicity and safety should be determined in cohorts of vaccinees from different age and risk groups; however, the choice
of population to study depends on the immunization strategy. Determining immunogenicity and safety before the pandemic in all age groups, pregnant women, and representative numbers of patients with comorbidities is unlikely to be practical and may even be unfeasible.

When feasible, the following parameters may be considered:

**Immunogenicity**

- assessment of antibody persistence (study of antibody kinetics);
- induction of immunity to other influenza strains (cross-reaction and cross-protection studies);
- response to booster doses.

Plans should consider a selection of tests to be performed at specific time points. It might not be necessary to perform a full characterization of the immune response every time. However, HI titres should be measured at each time point for each vaccine formulation. In the absence of internationally validated and harmonized assays, inconsistent data should be interpreted with caution. Testing of cell-mediated immunity and neutralization assays should also be performed using standardized methods, when these are available.

The frequency of testing might be higher at the start of using vaccines against novel human influenza viruses in order to define antibody kinetics. A sufficient volume of serum should be stored under appropriate conditions in order to allow re-testing with novel methods as they are developed. It is important to identify the period over which boosting can be effective for both homologous and heterologous strain vaccines, if available.

**Efficacy**

The effectiveness of vaccines against novel human influenza viruses administered in the inter-pandemic period can only be studied during exposure of the population to the pandemic virus (i.e. during the influenza pandemic). Nevertheless, a strategy to follow up vaccinees who come into contact with an avian (i.e. non-pandemic) influenza virus (e.g. poultry workers, cullers, veterinarians and diagnostics laboratory workers) in the inter-pandemic phase should be developed beforehand. Follow-up strategies will depend on how the vaccine is used in countries and may vary between countries. As a general principle, follow-up strategies should be based on the best available information and this requires collaboration of all stakeholders (i.e. national regulatory authorities, health authorities, vaccine manufacturers and health care professionals). At a minimum, disease signs and seroconversion should be investigated in these populations. If available, pre-exposure titres should also
be assessed if seroconversion originated from vaccine virus or from exposure to the wild type virus. Plans should also address monitoring the effectiveness of inter-pandemic priming in the pandemic phase.

**Safety**

In principle, all options to demonstrate vaccine safety should be explored and implemented in the inter-pandemic period as the opportunity will no longer be available once pandemic Phase 6 is declared. These options may include enhanced passive surveillance, active surveillance and, if feasible, safety studies. Procedures described in the routine pharmacovigilance system should apply.

Adverse events of special interest are also considered important and should be specifically monitored by documenting cases reported by health care professionals. Case definitions from the Brighton Collaboration should be used if possible (29). Background data for these adverse events of special interest are important for the interpretation of reporting rates.

In the case of priming large parts of the population with vaccines against novel human influenza viruses within a short time, health care professionals should be encouraged to prioritize reports of the following adverse events:

- fatal or life-threatening adverse reactions;
- serious unexpected adverse reactions; and
- AEFIs.

Health care professionals should also be encouraged to report at least a minimum set of data to properly evaluate the suspected adverse events and reports. Co-medication is another important item to record and report.

For those countries with adequate electronic tools, it is recommended that an ad-hoc reporting system (e.g. electronic reporting) be instated for the duration of the vaccination campaign. Additional ad-hoc safety reports may be of importance. The format and periodicity of reporting may be the same as for pandemic vaccines. If a safety signal were to arise, reactive hypothesis testing studies might be warranted.

G.3 **Postmarketing considerations for pandemic influenza vaccines**

G.3.1 **Implementation of postmarketing surveillance**

Pharmacovigilance and epidemiological surveillance systems will most probably be weakened during a pandemic possibly resulting in limited numbers of personnel available in industry, regulatory agencies and public health agencies. A pandemic situation will require a prioritization of activities (i.e. pharmacovigilance and effectiveness) with simplification and
harmonization measures that replace excessively time-consuming and non-urgent activities. To avoid duplication of work, stakeholders should clarify responsibilities beforehand.

Some countries already have or are in the process of establishing or enhancing surveillance systems for seasonal influenza vaccines. Some systems may also meet the postmarketing surveillance needs of pandemic influenza vaccines. It is strongly recommended that methods, tools and systems to investigate safety and effectiveness of pandemic vaccines be implemented in the inter-pandemic phase. Countries are advised to pilot regulatory preparedness during the seasonal vaccination programme to ensure that pandemic vaccine postmarketing surveillance systems provide robust and reliable information. Critical assessment of the strengths and limitations of the postmarketing systems would then help with meeting public health needs during the pandemic. Alternatively, systems may be tested with other vaccines. However, it is essential that the pilot testing of regulatory preparedness covers all age groups (children, adults and the elderly) as pandemic influenza vaccines might target the whole population.

The mechanisms for sharing data on the effectiveness, efficacy and safety of seasonal influenza vaccines among different countries should be used as a pilot test of regulatory preparedness concerning exchange of information once the pandemic is declared.

Uncertainties regarding the use of the pandemic influenza vaccines have to be acknowledged and include:

- availability of pandemic influenza vaccines;
- differing strategies concerning the use of vaccines against novel human influenza viruses in the inter-pandemic and early pandemic periods;
- prioritization of the targeted populations in the early pandemic period (e.g. first responders and specific risk groups) and follow-up approach;
- different settings for vaccine distribution and immunization e.g. workplace, community centres or general practitioners;
- different types of vaccines used in different countries (information on safety and effectiveness should be available on all vaccines);
- differences in health system organization;
- availability of data sources and surveillance systems in place for seasonal influenza illness and seasonal influenza vaccine (safety and effectiveness and efficacy);
- study protocols already in place for investigating safety of pandemic influenza vaccine in some countries;
availability of large electronic databases and pre-existing methods of data collection.

It is unlikely that a single postmarketing surveillance method will be suitable in all situations of influenza vaccine use in different countries. Although data collection methods may differ between countries, the following common principles apply:

- rapid generation of data on effectiveness and safety as a basis for operational decisions and model predictions;
- comprehensive analysis of safety and efficacy data by subgroups, e.g. children stratified by age categories, adults, the elderly, pregnant women, patients with chronic disease and immunocompromised patients;
- postmarketing surveillance protocols and detailed workplans should be agreed upon beforehand;
- use of common terminology for consistent communication across regulatory bodies worldwide;
- data collection that allows for:
  - estimation of incidence;
  - comparison and differentiation between vaccines, events associated with influenza vaccine and those associated with other vaccines;
  - assessment of causality for adverse events conducted at the earliest feasible time;
  - evaluation of possible virus drift over time and impact on vaccine effectiveness in the different target groups;
  - comparison of effectiveness among different pandemic vaccines if more than one vaccine is used in a country.

For continuous and balanced assessment of benefit and risk, provisions should be made to have, in at least one place per country, access to the entire body of information on safety and effectiveness of influenza vaccines. Furthermore, provision should be made for the international exchange of such data and the associated risk–benefit assessments.

National public health authorities, WHO, national regulatory authorities and vaccine manufacturers need to assess their capacities in anticipation of a pandemic crisis. The probability of having to handle large datasets within a short time is high during a pandemic. The availability of resources in the case of a pandemic should be critically evaluated. Provisions should be made to make...
available the necessary resources in terms of personnel, technical equipment and tools to collect, manage and assess the data needed to respond to public needs.

G.3.2 Pharmacovigilance activities
The data available on the safety of pandemic influenza vaccines will inevitably be limited at the time of first administration. In addition, long-term safety studies of pandemic vaccines will not be feasible and will probably not be relevant during a pandemic. Monitoring for delayed adverse events after the pandemic using routine pharmacovigilance (i.e. spontaneous reporting of AEFI’s and periodic safety reports (PSRs)) may be supplemented, if necessary, by ad hoc epidemiological studies. Therefore, preparedness plans should consider:

- routine pharmacovigilance activities (spontaneous reporting, PSR, and data management);
- additional pharmacovigilance studies (monitoring system for severe AEFIs, and epidemiological studies with feasibility analysis); and
- procedures for information-sharing.

G.3.2.1 Routine pharmacovigilance
G.3.2.1.1 Spontaneous reporting
The potential disruption to postal services and limited availability of health care professionals during a pandemic require the development and/or strengthening of alternative channels for reporting adverse reactions i.e. fax, telephone or electronic transmission. The functionality and validity of these systems should be tested before the pandemic. Due to potential postal backlogs, consideration should be given to discouraging postal reporting to avoid loss of data at critical times. Back-up strategies for transmission of safety information need to be developed to ensure the preparedness of the system (i.e. if mail and/or electronic transmission fail, the telephone might work).

Simplified reporting forms for health care professionals and consumers should be developed to enhance compliance in a crisis. Forms should focus on fields of information absolutely necessary for evaluation, which would include patient identifier, age, adverse event, time-to-onset, outcome, vaccine, batch, vaccine dose, concurrent use of other vaccines and medicines, concomitant diseases and risk factors. It is strongly recommended to validate the relevance of selected fields to the medical assessment applied to seasonal influenza vaccines in the inter-pandemic period. Such experience should be communicated to WHO to facilitate development of further guidance. Each country should ideally have at least one national centre to which manufacturers and health care providers could report. Consumer reporting, where acceptable, should also be used.
All serious and medically-significant AEFIs (e.g. febrile convulsions, Bell’s palsy and Guillain-Barré Syndrome (GBS)) may be reported to the relevant national centre and from national centres to regional or global databases (i.e. WHO Vigibase and rapid reporting system, and the EMEA EudraVigilance). These events should ideally be reported within fewer than 15 days for quantitative detection of previously unrecognized adverse events associated with the use of the different pandemic influenza vaccines.

Countries that do not have a database available for registration and querying of AEFIs may explore the implementation and use of the WHO Vigibase to meet national pharmacovigilance needs. Countries interested in obtaining a national licence for the WHO Vigibase are advised to contact the Uppsala Data Monitoring Centre (WHO Programme for International Drug Monitoring and the Uppsala Data Monitoring Centre) using the following weblink: http://www.who-umc.org/DynPage.aspx. In the absence of a national pharmacovigilance centre, expanded programmes on immunization are also encouraged to submit data on AEFIs.

As a minimum requirement, frequent exchanges (e.g. every 2–3 days within the first few weeks post-vaccination and weekly thereafter) of line-listings (according to the relevant Council for International Organizations of Medical Sciences form at http://www.cioms.ch/cioms.pdf) might be acceptable where no database of AEFIs is accessible.

A list of specific potential adverse events of particular interest should be drawn up for “active” reporting (e.g. convulsions, anaphylaxis, neuritis, Bell’s palsy, GBS, oculorespiratory syndrome, or arthritis or arthralgia). Case definitions (e.g. for each high priority reaction) should be developed with corresponding WHO Adverse Reaction Terminology (http://www.umc-products.com/DynPage.aspx?id=73589&mn1=1107&mn2=1664) or standard MedDRA queries (SMQs) (http://apps.who.int/bookorders/WHP/detart1.jsp?sesslan=1&codlan=1&codcol=84&codcch=25# and http://www.ich.org/LOB/media/MEDIA5261.pdf). Case definitions published by the Brighton Collaboration may be helpful to identify key elements including data collection and data analysis (30). A number of new case definitions will be published soon or are under development, such as that for GBS. Harmonization of reporting rules, language and dictionaries across countries may be considered. Vaccine failure should not be prioritized, as there are likely to be many suspected cases and there will be other, more robust means to assess vaccine effectiveness.

Data management should allow for retrieval and analysis by age, number of doses received, different vaccines and underlying diseases. The safety profile of a vaccine may vary among different batches, therefore retrieval of data on different batches is necessary. Rapid transmission of information on safety is essential. Information on AEFIs should be communicated by vaccine
manufacturers to national regulatory authorities ideally within 15 days. National regulatory authorities may consider working with the media on information campaigns to educate the public on identifying reportable adverse reactions.

G.3.2.1.2 Periodic safety reports

Periodic safety reports (PSR) by manufacturers may provide an opportunity for aggregated summary safety data. These reports should be product-specific, and simple to prepare and assess. The periodic safety reports should be more than a duplication of case data on AEFIs and should involve some degree of signal analysis. The frequency and the content of the report including reporting formats and tabulations must be agreed upon beforehand. The report should be as simple as possible. The events do not need to be validated during the pandemic period and the capacity to produce and review the reports needs to be considered.

More frequent submission of PSRs may be important in the first 4–6 weeks after the start of vaccination and they may be submitted less frequently thereafter. The PSR may contain information on the number of the different types of AEFIs in the reporting period: fatal AEFIs, life-threatening AEFIs, AEFIs of interest (e.g. allergic reactions requiring immediate resuscitation and serious neurological adverse events), special populations and unexpected AEFIs. The AEFIs may be presented according to the strength of the signal or according to system organ classes. Any meaningful disproportion between batches should be evaluated and discussed. Non-serious AEFIs are considered to be of less importance and should not be included in the report. An electronic spreadsheet may present tables of AEFIs with a unique case identifier and a limited number of fields. Data on vaccine distribution by batch and country (period covered by PSR and cumulatively since vaccine launch) should be provided. Vaccine manufacturers should be prepared to submit an ad hoc PSR in the event of a signal.

At an agreed time after the pandemic period, an ‘ad-hoc’ PSR update in a recommended format (29, 30) should be prepared with a summary of all safety data covering the period since the last report. The aggregated summary reports are expected to help national regulatory authorities to compare vaccines for possible differences in safety profiles.

G.3.2.1.3 Signal detection

A large amount of safety information is expected to be generated during pandemic vaccination. Signal detection, even by crude inspection of single cases or line-listings, might not be adequate. Depending on the number of reports, quantitative, automated numerator-based and data-mining methods (e.g. proportional reporting ratios or Bayesian methods) may also be used for detection of adverse event signals.
Existing tools should be used and ideally adapted for issues relating to influenza vaccine. It is noted that quantitative signal detection methods for drugs may not apply for pandemic influenza vaccines. Vaccines require special consideration when applying data-mining tools to reduce background noise and to make appropriate comparisons. Comparisons should be made in groups with similar likelihood of experiencing similar adverse events. It may be necessary to stratify by age, seriousness of event, gender and dose. Since it is very likely that concomitant diseases such as sudden infant death syndrome, myocardial infarction, seizures and others will be reported, the analysis may be based on a comparison with other vaccines and not with drugs.

Data-mining tools may support the detection of unexpected AEFIs, whereas comparisons of reporting frequencies of AEFIs of interest (e.g. reporting rate after seasonal influenza vaccines) might provide an important signal with regard to possible increase of the incidence of certain expected AEFIs. It is acknowledged that one tool might not be sufficient to address all questions. The use of several tools or methods in parallel may be considered.

Specific computerized methods of signal detection should be tested in the inter-pandemic phase with suspected AEFIs reported for seasonal influenza vaccines or other vaccines used in the same target population. This process will aid in assessing the strengths and limitations of the method and avoiding possible misinterpretations or false alarms.

G.3.2.1.4 Programmatic errors
Improper handling of vaccines before, or during, immunization sessions may lead to infections, bacterial contamination and abscess formation, especially if multidose container vaccines without preservative are used. The general guidance of WHO (15) should be followed in this respect.

G.3.3 Additional pharmacovigilance activities
Postmarketing surveillance should address safety issues specific to pandemic influenza vaccines. Non-serious adverse events are generally of less importance in a pandemic situation. Safety parameters based on biological plausibility of the occurrence of certain adverse events should be investigated in detail. Targeted monitoring may be required for certain types of reactions (i.e. GBS and Bell's palsy), which can be anticipated for pandemic vaccines on the basis of their relationship to currently licensed or tested influenza vaccines. Safety parameters should be appropriate for the specific pandemic vaccine (e.g. cell-culture based vaccines, whole virion vaccines or adjuvanted vaccines).

G.3.3.1 Methodological considerations
Protocols for postmarketing safety studies should be developed in advance. The key issues to be addressed are:
target population to be studied;
- sample size;
- outcomes to be studied;
- analysis and control groups;
- data sharing; and
- follow-up of signals detected.

Depending on resources and pre-existing systems, different methods may be appropriate. Possible designs may include:

- establishment of web-based procedures for active follow-up of vaccinees;
- recruitment of subjects immunized with seasonal trivalent influenza vaccine during the interpandemic period, which would also allow a comparison of the safety of interpandemic and pandemic influenza vaccines;
- standardized case definitions and ascertainment of outcomes; and
- development of study databases in the inter-pandemic phase.

Procedures should be in place to collect data on a continuous basis (e.g. through a web-based system). Automated procedures to detect predefined adverse events may help to identify potential safety issues as quickly as possible. Statistical analysis may be performed at defined times or based on certain triggering events. Ideally, decision thresholds should be specified in a statistical plan beforehand.

G.3.3.2 Analysis

Possible questions to be answered by safety studies might be:

- whether the overall safety profile of the pandemic vaccine is acceptable in the pandemic situation (aiming to extend the safety database);
- whether the safety profile of the pandemic vaccine is comparable with the historical data on inter-pandemic vaccines; or
- whether it is comparable with the clinical phase 1–3 data on a vaccine against a novel human influenza virus.

Possible methods for analysing data on safety of an influenza vaccine include:

- relative risk (and confidence intervals) with stratification by age and other relevant risk factors;
G.3.3.3 Target population
The target population for a postmarketing study should include groups not covered in the clinical trials conducted in the inter-pandemic phase. Subgroups (e.g. first responders such as health care professionals and their family members) likely to receive early vaccination may be selected for participation in postmarketing studies. Other groups that might be vulnerable to influenza and AEFIs (e.g. elderly people, children and pregnant women) need to be included in postmarketing surveillance. Studies might also be conducted in children's homes, kindergartens and schools. Adequate sample size for analyses of important subgroups should be justified and documented by calculations of statistical power.

G.3.3.4 Randomized clinical trials
As randomized clinical trials provide the highest level of evidence, this design might be envisaged in the first pandemic wave when enough vaccine for the entire population is not yet available. In this situation, it might be ethically acceptable, in some countries, to allocate non-eligible subpopulations (i.e. low risk groups who will receive late vaccination) to both the vaccine-receiving and non-receiving groups. If there is insufficient vaccine for all eligible people, it might also be ethically acceptable to randomize them. Effectiveness and immunogenicity of pandemic-specific strains may also be studied in randomized clinical trials. The study protocol should be agreed upon in the inter-pandemic phase. However, it should be acknowledged that such studies may be very difficult to conduct under pandemic conditions.

Randomized clinical trials may also be conducted in a situation where the human pandemic influenza vaccine is intended for use in the inter-pandemic phase in special risk groups i.e. poultry workers, cullers, first responders and their families.

G.3.3.5 Prospective cohort study with a comparison group unexposed to vaccine
A prospective cohort study design may also be feasible in some countries to assess risks associated with the use of pandemic vaccines during a pandemic. It might be possible to identify a cohort of people who will receive vaccination very early (e.g. high-risk groups or first responders) and a cohort who will receive vaccination later.

- historical comparison; and
- observed versus expected analyses.

Pooling of data might increase the power of statistical analyses especially for analysis at the risk-subgroup level.
The same holds true for situations where the strain in a vaccine against a novel human influenza virus is antigenically close to the pandemic strain, and vaccine stockpiles would be used in certain target groups in the very early pandemic phase when pandemic vaccine would not yet be available.

G.3.3.6  Prospective (observational) cohort study design without control group

Observational studies provide a simple methodology to demonstrate that the safety profile of the pandemic vaccine is acceptable under real-life conditions. The safety of the pandemic vaccine would be investigated in a predefined number of vaccinees (e.g. a few thousand) who will receive vaccination in the early pandemic phase. In this study design, comparison incidence rates might be obtained from the medical literature or from historical data.

G.3.3.7  Case–control study design

Case–control studies are useful for rare adverse reactions to the vaccine and may be useful in investigating particular serious and rare AEFIs, such as GBS, although such studies may not be the method of choice to provide rapid information during the pandemic. Nested case–control analyses may be useful, if large population-based databases including vaccinated and non-exposed (infected) subjects can be identified.

G.3.3.8  Use of large computerized database

Systems allowing automated data extraction (safety and efficacy) might exist or be set up in some countries. Systems requiring specific conditions that probably do not exist in many countries include the electronic network and legal framework to extract patient-based information from electronic systems and allow its use by health care professionals. If such systems exist or are currently being developed, it might be useful to test them in the inter-pandemic period. These databases might also be useful for evaluation of delayed AEFIs and of the effectiveness of pandemic-specific strains.

G.3.4  Immunogenicity, efficacy and effectiveness

Disease incidence during an influenza pandemic cannot be anticipated. Unlike for other diseases, measuring vaccine effectiveness as “the protection rate conferred by vaccination in a certain population” will be impossible and the true impact of the vaccination on a population cannot be determined. However, an estimation of protection in individuals may be made.

In addition to existing surveillance systems to monitor the onset and evolution of the pandemic, Public health authorities may consider the installation of enhanced surveillance tools to analyse the “effectiveness” of vaccination campaigns. Protocols should be developed in the inter-pandemic
phase. The study design may need to be reviewed in light of the anticipated epidemiological features of the pandemic. The methods to be used will depend on the existing vaccination strategy and tools. For example, if the entire population was vaccinated, non-vaccinated groups would not be available for comparison cohort studies (although data from the pre-vaccination period would be useful). The analysis of data from electronic registries or linked databases may be feasible only in a few countries. Different methods and strategies may be used in different countries. A number of examples are provided in section G.3.5 and its subsections.

G.3.5 Study design

Vaccine effectiveness may be estimated from observational cohort studies that describe disease occurrence prevented in the target population over time. Alternatively, vaccine effectiveness may be estimated during a phased introduction of the vaccine into the target population, in which the non-eligible groups (first wave) might form the strata for randomization. Without a randomization step, considerable biases may be introduced. A prospective cohort design might also be conducted ensuring that an adequate mix of individuals reflects the target populations to be vaccinated. If plans to prioritize vaccination in the first wave (e.g. first responders will receive vaccination early) exist, identification of the cohorts and a detailed study plan should be possible in the inter-pandemic phase.

Continuous assessment of vaccine effectiveness throughout the whole pandemic is essential to detect possible virus drift and to enable public health authorities to modify, if necessary, the vaccination programme. The extension of the follow-up period for a subset of the cohort members may address this objective. Possible virus drift can also be investigated by identification and follow-up of cohorts of subjects successively immunized with the pandemic vaccines. Another option is sentinel reporting of clinical disease throughout the whole pandemic. Clinical data should be linked with laboratory surveillance data.

Some countries might choose a stepped wedge design for postmarketing surveillance of the effectiveness of a vaccination programme. This method is particularly suitable when the vaccine is introduced in phases, group by group, until the entire target population is covered; the groups form the unit for randomization (31). As subjects with a higher risk for infection and/or severe disease may receive vaccination first, the introduction of bias should be carefully considered.

Case–control studies are particularly useful for diseases with low incidence or small isolated outbreaks and therefore might not be ideal to measure the effectiveness of pandemic influenza vaccines.

In order to make appropriate decisions, real-time data should ideally be collected, evaluated and analysed by national regulatory authorities and/
or public health authorities. Any hold-up in this process may cause delays in decision-making with serious implications for public health.

G.3.5.1 End-points
Laboratory confirmation of influenza virus may not be feasible as the primary end-point for postmarketing surveillance of effectiveness in the entire population, but only for a defined subset of the population. Laboratory surveillance may provide important information concerning possible virus drift variance and subsequent loss of effectiveness of available vaccines.

In most instances, the evaluation of protective effectiveness will focus on the ability of the vaccine to prevent clinical disease, such as influenza-like illness, most likely without laboratory confirmation. However, the positive predictive value of clinical disease should be high in a pandemic. It may also be appropriate for the primary analysis to focus on overall mortality from pneumonia and clinical mortality from influenza. As influenza vaccines may prevent severe complications rather than mild disease, special attention should be given to severity of disease and influenza-related complications.

G.3.5.2 Conduct of studies
Analysis of all cases of influenza should be provided regardless of time since vaccination. All vaccine failures (as defined) and any other breakthrough cases should be investigated in detail.

Case-definitions should be used for diagnosis of primary end-point(s) (e.g. WHO definition of clinical disease, definition of need for hospitalization and categories for severe disease) and should be specified in the protocol. It is critical that the same case-detection methodology be applied in the vaccinated and unvaccinated groups and throughout the duration of the study. It is crucial that the individuals most likely to initiate possible case-detection have clear instructions related to criteria for contacting designated healthcare professionals, telephone contacts, and on initial and further investigations once a case is confirmed.

In studies where influenza detection assays are used, procedures should be in place to ensure that these assays are sensitive and validated.

G.3.6 Postmarketing surveillance in different target groups
In a pandemic situation, it is very likely that health authorities may have to make recommendations on the use of the vaccine in population groups not previously studied in clinical trials. Postmarketing surveillance of safety and effectiveness in particular target groups is recommended to enable national regulatory authorities and health authorities to review the appropriateness of public health decisions.
G.3.6.1 Age
Immunological responses to vaccines depend on the independent and coordinated function of innate and adaptive immune responses which differ between infants and adults. These age differences in immune response might translate into differences in the efficacy and safety of certain types of pandemic influenza vaccine. Targeted surveillance of effectiveness and safety in different age categories is thus warranted.

G.3.6.2 Pregnant women
Based on morbidity from seasonal influenza, pregnant women are considered to constitute a risk group for influenza-related complications and public health authorities might therefore recommend vaccination of pregnant women. On the other hand, pregnant women are unlikely to be included in clinical trials with vaccines against novel human influenza viruses. Although inactivated vaccines are considered to cause no harm when administered to pregnant women, the knowledge concerning reproductive toxicity of inactivated vaccines against pandemic influenza (as they will be new vaccines perhaps in new formulations) in humans will be limited.

LAIVs are usually not recommended during pregnancy, but there might be circumstances where these vaccines are used in pregnant women during a pandemic. Women who are immunized with LAIV shortly before or during pregnancy should be monitored and data should be collected on outcomes.

It is not known whether conclusions from animal studies conducted during nonclinical evaluations of candidate influenza vaccines will apply to humans. As a consequence there will be very limited or no data available regarding safety and efficacy of pandemic influenza vaccines in pregnancy prior to their use.

Continuous evaluation of risks and benefits of pandemic influenza vaccines should be established in pregnant women. As a first step, more information may be gathered on seasonal influenza vaccines. In this respect, the capability of existing pregnancy registries or currently running epidemiological studies should be evaluated. Studies on vaccines against pandemic human influenza should be designed to identify spontaneous abortions, stillbirth, congenital malformations and any adverse reactions in the neonate that are classified as serious.

G.3.6.3 Other target groups
Effectiveness and safety should, ideally, also be established in chronically ill and immunocompromised patients in whom the risk–benefit balance might deviate from that in the healthy population.
G.3.7  **Considerations for specific types of pandemic influenza vaccines**

The potential difference in safety and efficacy (effectiveness) profiles of different types of human pandemic influenza vaccines (e.g. live attenuated, inactivated whole virion, cell-culture based, and subunit vaccines with and without adjuvants, preservatives and excipients) have to be considered. Safety concerns associated with different types of vaccines should be addressed in the postmarketing surveillance.

G.3.7.1  **Live attenuated influenza vaccines**

Live attenuated influenza vaccines may cause vaccine-associated disease of less severity, if any, in vaccine recipients than would result from being naturally infected. However, some LAIV are linked to rare but serious syndromes closely resembling wild-type disease, probably associated with individual host factors of increased susceptibility. If a live attenuated human pandemic influenza vaccine is deployed when the wild-type virus is circulating, some individuals may be vaccinated at a time when they are incubating the wild-type strain. Validated and standardized assays should be developed and implemented prior to the use of such vaccines to differentiate between vaccine virus and wild-type virus and allow these cases to be properly assessed.

In addition, reversion to virulence after reassortment between vaccine and wild-type virus in the human host has been a particular concern with the use of LAIV. In addition to extensive testing pre-licensure, careful postmarketing investigation of cases indicating a possible reversion to virulence is essential.

G.3.7.2  **Immunological adjuvants**

Postmarketing surveillance will depend on the type of adjuvant and the results of the nonclinical and clinical investigation of the pandemic influenza vaccine. New adjuvants that stimulate a specific immune response will justify attention to specific issues such as auto-immune diseases that are potentially rare and adverse events that can occur a long time after immunization. Enhanced surveillance in certain subgroups such as infants may be necessary. Synergistic immune mediated reactions of adjuvant and the biologically active antigen have to be considered.

G.3.8  **Risk–benefit assessment**

In contrast to other biologicals and medicines used to treat clinical disease, vaccines differ in safety considerations. Vaccines are a preventive measure mainly given to healthy individuals. In consequence, a very high standard of safety is usually expected for vaccines used in non-epidemic situations. However, in a pandemic situation the risk–benefit balance shifts towards the benefit. As a rapid
health benefit is expected to become evident for the individual vaccinee, a certain probability of adverse event(s) might be acceptable to the individual even if the incidence of the adverse event(s) is higher than for seasonal influenza vaccines.

The risk–benefit balance for pandemic influenza vaccines depends not only on the efficacy and safety of the vaccines but also on the incidence of infectious disease in the target population, the proportion of infected persons with clinical disease, the severity of clinical disease, the identification of high-risk groups and the risk of transmission. The risk–benefit assessment may differ between the various target populations.

The benefit of a pandemic influenza vaccine for an individual may decline as vaccine coverage rises, the disease incidence decreases, and herd immunity is acquired. Despite a decrease in disease incidence, the public health benefit of vaccination might remain high if the probability of disease re-emergence increases when vaccine coverage in the population becomes too low. Thus, the risk–benefit balance of using a pandemic influenza vaccine has both public and individual health aspects.

In all circumstances, any safety concern arising from the use of a pandemic influenza vaccine will concern a very large number of actual and potential vaccinees. Therefore, safety issues need to be evaluated promptly.

G.3.9 Responsibilities of key stakeholders

Key stakeholders in the process of postmarketing surveillance include:

- vaccinees;
- health professionals;
- vaccine manufacturer(s) and associations;
- national regulatory authorities;
- public health authorities;
- immunization delivery programmes (such as the Expanded Programmes on Immunization);
- governments; and
- the media.

Depending on their area of responsibility, stakeholders have differing roles that contribute, through properly communicated and coordinated risk reduction strategies, to the safest and most effective use of products. It is important that all stakeholders agree beforehand on the principles of exchange of information on vaccine safety during a pandemic. All possible efforts should be made to coordinate information exchange and mutual recognition of study results to avoid duplication of work and enable evidence-based decision-making.
Regulatory authorities in vaccine-receiving countries may accept vaccine qualification from producing countries. In such cases, vaccine manufacturers may not be requested to repeat suitable safety and efficacy studies performed in a producing country with functional regulatory oversight.

**G.3.10 Principles of communication**

It is essential to ensure that the public be provided with a consistent and balanced message. Communications should be a collaborative undertaking that involves input from industry, regulators and public health organizations.

A multi-layered communication initiative to provide a broad overview of the regulatory processes of vaccine development, licensing and marketing as well as detailed information on pandemic influenza vaccines is envisaged. Such an initiative should meet the needs of interested stakeholders including lawyers, the media, industry, health professionals, and, most importantly, the public. It may be helpful to utilize experienced (external) risk communication advisers to provide balanced information on real and perceived concerns.

Also vital is a clear explanation of what is known about the safety and efficacy of the pandemic vaccine when it is first used and what processes are in place for gathering the outstanding data without causing panic. An essential part of the latter would be to give clear instructions for reporting suspected adverse events related to the vaccine.

Communication might differ depending on the vaccine type (e.g. whole virion, cell culture or adjuvanted vaccine) and how the vaccine is used. Thus, transparency of information and definition of stakeholders’ roles and responsibilities are essential.

It is recommended that authorities agree upon development of a common system for rapid exchange of information on serious concerns regarding the safety and effectiveness of pandemic influenza vaccine with possible public health impact. This may include any measures that lead to a change in vaccination strategies.

WHO would provide a forum for data exchange concerning safety, efficacy and effectiveness of pandemic influenza vaccine. It is recommended that influenza pharmacovigilance experts from vaccination programme authorities participate in the network. Its functionality should be tested by using pharmacovigilance data on seasonal influenza vaccine. Pharmacovigilance institutions should routinely exchange data on vaccine safety, efficacy and effectiveness and send rapid alerts in the case of risk signals. The trigger for sending rapid alert information as well as general principles and conditions of data exchange should be defined by participating countries in cooperation with WHO.

Postmarketing surveillance data should be made available to WHO in order to contribute to strategic decisions about global control of influenza.
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The final draft (WHO/BS/07.2074) was prepared by the drafting groups, Dr C. Alfonso, Dr D. Wood and Ms Stephanie Hardy, taking into account comments made by the Expert Committee on Biological Standardization at its meeting from 8–12 October 2007 and recommendations from a WHO consultation on the technical specifications for a WHO international H5N1 vaccine stockpile in October 2007.

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References


Appendix 1

Overview of five selected national regulatory authority pathways to licensure of pandemic influenza vaccine

Note: the information presented in the appendices is current as of 26 November 2007. Please refer to the relevant national regulatory authority websites for the most up-to-date information. The website links are provided in Table A.1.

Table A.1
Websites for national regulatory authorities

<table>
<thead>
<tr>
<th>Country</th>
<th>National regulatory authority</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Therapeutic Goods Administration</td>
<td><a href="http://www.tga.gov.au">www.tga.gov.au</a></td>
</tr>
<tr>
<td>Canada</td>
<td>Health Canada</td>
<td><a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a></td>
</tr>
<tr>
<td>European Union</td>
<td>European Medicines Agency</td>
<td><a href="http://www.emea.europa.eu">www.emea.europa.eu</a></td>
</tr>
<tr>
<td>Japan</td>
<td>The Ministry of Health, Labour and Welfare</td>
<td><a href="http://www.mhlw.go.jp">www.mhlw.go.jp</a></td>
</tr>
<tr>
<td>United States of America</td>
<td>US Food and Drug Administration</td>
<td><a href="http://www.fda.gov">www.fda.gov</a></td>
</tr>
</tbody>
</table>

See Table A.2 for a tabular summary of the information presented in this section.

Australia

Regulatory authority

Influenza vaccines are regulated by the Department of Health and Aging, Therapeutic Goods Administration, Drug Safety and Evaluation Branch, pursuant to the Therapeutic Goods Act, 1989 and the Therapeutic Goods Regulations, 1990. In December 2003, the Australian and New Zealand Governments signed a treaty to establish a single, bi-national agency to regulate therapeutic products, including medical devices and prescription, over-the-counter and complementary medicines. This single agency, which will replace the Australian Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), will be accountable to both the Australian and New Zealand governments. The agency is expected to
commence operation during 2007–2008. It is expected that the same regulation in force in Australia will also apply to New Zealand as per the amended law.

**Submission type and application**

New influenza vaccines require a Category 1 Application. Annual strain changes for licensed influenza vaccines require a Category 3 Application – *Changes to the quality information requiring prior approval.*

**Timelines**

For review of Category 3 submission – 45 working days after receipt of the application.

**Annual influenza vaccine licensure**

In the case of a new influenza vaccine, TGA requires a full submission including quality data, preclinical data and clinical data. Data expectations would accord with general Committee for Proprietary Medicinal Products (CPMP) guidance on new vaccines. Annual strain changes require an application with quality data consistent with CPMP/BWP/214/96 – *Note for guidance on harmonisation of requirements for influenza vaccines.* Because of the production time frames, if the strains differ from those used in the northern hemisphere winter there may not be a clinical efficacy study submitted with the quality data.

**Proposed pandemic regulatory pathway**

TGA accepts the guidelines of the European Medicines Agency (EMEA) on pandemic vaccine licensing. As with the EMEA, licensure of a pandemic influenza vaccine will be based on approval of a core dossier for an inter-pandemic vaccine with quality, safety and efficacy data for the inter-pandemic vaccine to be provided and authorized during the inter-pandemic period.

Vaccine manufacturing companies are encouraged to submit applications for authorization of new methods of manufacture for pandemic influenza virus vaccines. Upon the declaration of a pandemic, the TGA will register the pandemic vaccine based on an approved inter-pandemic vaccine. The manufacturer would then proceed to produce vaccine as per the Core Pandemic Dossier, but using the actual pandemic strain. Quality data and technical data would be submitted in parallel with pandemic vaccine production as a pandemic variation to the TGA for rapid approval and release.

The TGA and the WHO Collaborating Centre for Reference and Research on Influenza will cooperate with the manufacturers in providing laboratory reagents for standardization of inactivated vaccine and reference strains for antigenic analysis.
Special requirements regarding quality and manufacturing data
Pre-pandemic influenza vaccines containing ingredients of human or animal origin should be evaluated for freedom from transmissible spongiform encephalopathy agents.

Special clinical data requirements
To support confidence in decisions to register pre-pandemic influenza vaccines, human immunogenicity and safety studies covering all age groups (especially children) and patients with some disease states are required.

Canada
Regulatory authority
Influenza vaccines are regulated by Health Canada’s Biologics and Genetic Therapies Directorate (BGTD) within the Health Products and Food Branch pursuant to various provisions of the Food and Drugs Act and Regulations (FDA & R).

Submission type and application
New vaccines are authorized for marketing in Canada following the review of a New Drug Submission (NDS) by BGTD. An NDS must include a complete dataset in support of the safety, efficacy and quality of the vaccine as well as product-specific information on the facility that describes the method of manufacture of the vaccine in significant detail. Furthermore, an on-site evaluation is completed to assess the production process and the facility as this has an impact on the safety and efficacy of the product. The manufacturer must also provide samples of at least three and preferably five batches or “lots” of the vaccine for testing in the laboratories of BGTD.

Annual influenza vaccine licensure
Although the regulatory requirements for new vaccines are clear, influenza vaccines have been marketed in Canada for over 50 years and their approval predates some of the regulations being applied to new vaccines. In addition, the need to reproduce the vaccine each year with the new circulating strains has necessitated a special approach to the regulation of these vaccines. Changes to the vaccines to reflect the year to year strain variation were originally approved through the filing of an amendment to the existing licence, in which manufacturers would submit for review only their revised labelling material once the strains which would be included that year were known. There was no requirement for the submission of any clinical data for the vaccine with the new strains.
During the 2000–2001 influenza season, an increased number of adverse events associated with influenza vaccine, described as oculorespiratory syndrome (ORS) were observed. These adverse events led to a re-evaluation of the requirements for the annual approval. Since 2000–2001, manufacturers have been required to submit clinical trial data for their products, to assess the tolerance and efficacy of the vaccine in two groups of healthy volunteers aged between 18 and 60 years and over 60 years, as per the CPMP guidelines.

Consequently influenza vaccines for annual administration now require an initial NDS authorization, with yearly updates of information on annual strain variation. Health Canada addresses the regulatory review and authorization of the necessary strain variations of annual influenza vaccines with a modified submission process. Manufacturers are required to submit supportive information for the strain change, particularly:

- data to support the quality of production of the vaccine, as it relates to the new strain, plus any improvements or alterations to the production process;
- data from two small clinical studies (generally of approximately 50 patients each, in patients in the age groups 18–60 years and more than 60 years), to assess the tolerability and immunogenicity of the vaccine; and
- revised labelling material (inner and outer labels, and a revised product monograph or direction leaflet).

**Proposed pandemic regulatory pathway**

The unknown factors surrounding a pandemic vaccine, including whether changes will be needed to the manufacturing process currently used, increase the likelihood that a pandemic vaccine will differ significantly from a seasonal influenza vaccine. Therefore, the regulatory process for approval of a pandemic vaccine, while in many respects similar to that for the seasonal influenza vaccine, will be that of an NDS and not of an amendment to an existing licence for a seasonal influenza vaccine.

The Public Health Agency of Canada has entered into a contract with a domestic supplier to provide enough pandemic vaccine for the entire Canadian population; hence regulatory preparedness is based on the concept of a single supplier. The contract includes provisions for the production and testing of a pre-pandemic vaccine in clinical trials. Therefore the licensure of a pandemic vaccine will follow the filing of an NDS containing composite information on the pre-pandemic vaccine supplemented with additional information on the actual pandemic vaccine once the pandemic has been declared, filed in a rolling fashion as data become available. It is anticipated that most of the substantive
information will be provided for the pre-pandemic vaccine, which will be considered representative of both the type and the manufacturing process for the pandemic influenza vaccine. Some comparisons may also be anticipated for the determinants of safety, efficacy and immunogenicity of the pandemic influenza vaccine. While, at present, the intent is to authorize for use only the pandemic vaccine, some consideration is being given to the regulatory requirements necessary for stockpiling the pre-pandemic vaccine, for potential delivery in mass immunization programmes.

Before a pandemic occurs, protocols must be in place both to investigate immunological responses to the pandemic vaccine to support authorization and to study the level of clinical protection during an actual pandemic as part of postmarket commitments.

Clinical trial applications to be used for proposals for trials to be conducted with the actual pandemic strain should be developed and filed for review during the inter-pandemic phase and should be updated as needed in the light of developing knowledge. This will provide for protocols which can be implemented immediately upon declaration of the pandemic.

Estimation of vaccine effectiveness may need to be done by studying predetermined target populations during the pandemic. These effectiveness studies should be addressed as part of the NDS filing as conditional postmarket commitments.

Health Canada is committed to working with the contract manufacturer to expedite the regulatory authorization, the release of the product lots and the availability of an adequate, safe and effective vaccine against pandemic influenza, in order to protect the health, safety and security of all residents of Canada. In December 2006, Health Canada issued specific guidance to the contract manufacturer on the manufacturing and clinical information required to support licensure, as well the review and regulatory authorization process that Health Canada will follow.

**Special requirements regarding quality and manufacturing data**

- The manufacturing process review for regulatory authorization of seasonal influenza vaccine including advance on-site evaluation(s) of the production facilities, will be the basis of the expedited assessment of the chemistry and manufacturing of the pandemic influenza vaccine.

- The relevant information relating to the seasonal influenza production lots, with the addition of specific data regarding the pre-pandemic vaccine, monovalent bulks and drug product is considered supportive and may be cross-referenced.
Protocols, including a certificate of analysis, identifying pass or fail specification limits and controls as well as specific batch information, are expected to be provided for the manufactured lots of:

- the inter-pandemic vaccine used in clinical trials;
- the pandemic vaccine used in clinical trials; and
- the pandemic vaccine intended for mass immunization.

Both the prototype (mock) and the pandemic influenza vaccines are subject to the lot release requirements of the Food and drug regulations, Section C.04.015, as provided in the document Guidance for sponsors – lot release program for Schedule D (biologic) drugs (2005). In situations of pandemic emergency, targeted or sentinel testing of commercial lots will be performed. Additionally, testing may be performed on the bulk production batch(es).

Any changes to the physical entity of the drug substance, its derivation, or analytical methods for identity and characterization, and any changes to the drug substance or drug product manufacturing processes, or specification controls, for the designated pandemic influenza vaccine, should be submitted to Health Canada for comparative review and assessment.

Product-specific facility information, for the production of the inter-pandemic and pandemic influenza virus vaccines, for clinical trial and marketed lots.

Stability data and protocol for stability testing of pandemic vaccine.

Viral safety data.

Special requirements regarding clinical data

Preclinical and clinical data on safety and immunogenicity obtained with the inter-pandemic vaccine. If the pandemic virus strain differs from the prototype strain, an indication of the immunogenicity of the pandemic influenza vaccine will be required.

The results of preclinical and clinical studies of the inter-pandemic vaccine(s) should aid in determination of the:

- safety of the adjuvant used in the formulation of the vaccine;
- formulation of a vaccine appropriate for immunization of a naive population; and
- the requirements to assess the safety and efficacy of the pandemic vaccine during clinical trials.
A complete plan to evaluate the vaccine safety and efficacy during clinical trials including anticipated timelines for generating the necessary data during the pandemic period and for providing these data for regulatory review. The plan would be prepared during the inter-pandemic period.

Any available data on clinical safety and efficacy of the pandemic vaccine.

Accelerated approval options and emergency use provisions

An NOC shall be issued only if complete data on quality, safety, efficacy and effectiveness are provided, and an acceptable risk–benefit profile, in full compliance with the FDA & R, can be demonstrated. If sufficient data on the pandemic influenza vaccine(s) are not provided, or are not available for evaluation at the time of the pandemic, an NOC may not be issued. However, in the event that the Minister of Health believes that immediate action is required in the interests of public health, a Decision for Release under one of the following mechanisms may be made.

Extraordinary use new drug regulations

An extraordinary use new drug (EUND) is a drug that would be used to treat, mitigate or prevent a life-threatening or serious health condition in humans, which results from exposure to a chemical, biological, radiological or nuclear substance in an emergency situation (e.g. an outbreak of pandemic influenza, an attack with chemical or biological weapons, a chemical spill or a natural disaster). The Food and Drug Regulations currently require manufacturers to establish the safety and clinical effectiveness of new drugs, for the defined purpose and under the recommended conditions of use. An EUND, however, is intended to treat a condition that does not lend itself, ethically or logistically, to study through a traditional clinical trial in humans prior to approval. In some instances, intentional exposure of study subjects to the causative agents of these conditions would not be ethical. In the case of pandemic influenza, there would be insufficient time to allow for full clinical testing of vaccines against the pandemic virus. Under the current regulations, the absence of data on safety and clinical efficacy limits Health Canada’s ability to grant market authorization to an EUND. At the same time, it is recognized that access to these drugs is essential for emergency preparedness to address potential threats to the Canadian population.

Health Canada is in the process of implementing a regulatory amendment that would enable market authorization of EUNDS based on in vitro and animal studies and clinical data for safety. The proposed regulatory
amendment will outline an application process separate from the New Drug Submission process. The labelling requirements will call for clear indication that the drug was approved based on limited clinical data and that efficacy in humans has not been established, and there will be a requirement for the manufacturer to provide data on clinical safety and efficacy in humans, if it becomes available, or to conduct postmarket studies. Manufacturers will be asked to provide updated safety information, to be submitted as part of the existing annual drug notification process, and current requirements regarding record keeping, reporting of adverse drug reactions, recall, drug identification number (DIN), establishment licensing and good manufacturing practice remain in place. It is anticipated that these new regulations will be in place in 2008.

**Special Access Programme**

The Special Access Programme (SAP) enables access on a case by case basis to products not currently approved for sale in Canada. Access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable or unavailable. A variation of this tool is the Block SAP, which would enable emergency “block” (large quantity) release of a product in the case that Canada has a public health crisis and does not have an approved product. Release would be to the Surgeon General of the Department of National Defence, the Federal, Provincial and Territorial senior medical officer or medical officer designated by the Surgeon General.

The SAP is a possible short-term solution to vaccinating front-line workers or where additional time is needed to complete the regulatory review of an NDS.

**Interim orders**

The *Public Safety Act, 2002*, provides the Minister of Health the authority to make an interim order under the *Food and Drugs Act* in a situation where immediate action is required. An interim order is a regulation that is issued by the Minister in a situation that presents a significant risk, direct or indirect, to human health, public safety, security, or the environment and is intended to address circumstances where there is no time to make a regulation as the law would normally require.

Health Canada has identified a library of interim orders which could be used to allow for the licensure of a pandemic vaccine in an emergency situation (i.e. where vaccine is required before standard regulatory requirements for licensure have been met).
Clinical trials

In the context of pandemic influenza, a clinical trial could be used in Canada to immunize certain risk groups while, at the same time, accumulating clinical data to support approval and broader use of the vaccine.

European Union


Submission type and application

The marketing authorization for a new medicinal product is granted through three procedures: centralized, decentralized and mutual recognition. Under the first procedure, applications are submitted directly to the EMEA to be evaluated by the Committee for Human Medicinal Products (CHMP). In accordance with article 3 of Regulation (EC) No. 726/2004, for some applications the centralized procedure is mandatory:

- medicines developed by means of biotechnology;
- orphan medicinal products; and
- medicinal products containing a new active substance and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, and, from May 2008 onwards, also autoimmune disease and other autoimmune disorders and viral disease.

Other medicinal products containing a new active substance, or for which the applicant shows that the product constitutes a significant technical, scientific or therapeutic innovation, or that the granting of a centralized authorization is in the interest of patents at Community level, may be granted access to the centralized procedure.

The centralized procedure will either be mandatory for pandemic influenza vaccines (if the strain is made using reverse genetics technology) or optional (on the basis of community interest). The CHMP appoints two Rapporteurs from the EU Member States, who will perform the assessment on its behalf. CHMP will then consider the completed scientific assessment and deliver a favourable or unfavourable opinion. The time limit for the evaluation procedure is 210 days. The EMEA then forwards its opinion to the European
Commission (within 15 days) which makes a final decision on granting of the European Community marketing authorization. A European Community authorization is valid throughout the European Union and is usually given for five years. Once renewed, the marketing authorization will be valid for an unlimited period (unless on grounds related to pharmacovigilance, an additional 5-year renewal is required). Applications for renewal must be made to the EMEA 6 months before the end of this 5-year period.

Under the mutual recognition procedure, the applicants seek to have an existing authorization recognized by one or more other Member States selected by applicant. The applicant must submit identical applications to the relevant Member States and all Member States must be notified of them. When one Member State decides to evaluate the medicinal product, it becomes a Reference Member State (RMS) and it should notify this decision to the other Member States. This procedure is completed within 90 days. In the case of a new product, the applicant has first to submit the application in one of the EU Member States for authorization. This Member State will become the Reference Member State. Only after this has been done can the 90-day mutual recognition procedure start.

Annual influenza vaccine licensure
Currently, all seasonal influenza vaccines in Europe are authorized through the mutual recognition procedure. A special fast-track type II variation procedure is in place for the annual strain change. The fast-track procedure consists of two steps. The first concerns the assessment of the administrative and quality data (summary of product characteristics (SPC), patient leaflet, labelling and the chemical, pharmaceutical and biological documentation). The second step is the assessment of the clinical data. Results of clinical studies are required according to the Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/ 214/96). A similar fast-track variation procedure exists in the centralized system.

Proposed pandemic regulatory pathway
The perspective of the EMEA is that a pandemic vaccine will differ significantly from an annual vaccine. The EMEA strategy relies on the evaluation of a pre-pandemic vaccine core dossier during the inter-pandemic period where quality, nonclinical testing and clinical data will be evaluated. Once the pandemic strikes, manufacturers will have to submit a type II variation to introduce information on the actual pandemic strain. The aim of the core dossier process is to provide a fast-track authorization of pandemic influenza vaccines as new (full) marketing authorizations, not as a variation to seasonal vaccine. Most scientific aspects as well as product information (doctor and patient leaflets) can be considered before a pandemic and can be approved during the interpandemic period.
In 2005, EMEA published the guidance *Core summary of product characteristics (SPC) for pandemic influenza vaccines*. The aim of this guidance is to standardize SPCs for all inactivated vaccines against pandemic influenza, thereby facilitating the submission of core dossiers. Following these guidelines, product information will be approved as part of the core dossier authorization and only minimal changes would be needed as part of the approval of the pandemic variation (only information related to the pandemic strain). The pre-pandemic vaccine will be produced (ideally) in the same way as intended for production of the pandemic vaccine (either cell culture or egg-derived, whole virion or split or subunit vaccine) and with the same antigen content and adjuvant system (if used) as the future pandemic vaccine.

Preclinical testing to establish safety and immunogenicity and clinical trials with the pre-pandemic vaccine to verify safety and efficacy and to establish a dose and dosing schedule will be required.

**Special requirements regarding quality and manufacturing data**

The required data on vaccine quality and manufacturing shall include:

- development and testing of vaccine reference virus;
- production process for vaccine seed lots including testing for freedom from extraneous agents;
- process of vaccine production;
- formulation, and testing for antimicrobial preservative in the case of multi-dose vials;
- vaccine standardization, including the development of alternative tests;
- adjuvant;
- stability of vaccine including the protocol for testing stability of the pandemic vaccine.

**Special requirements regarding clinical data**

The required data on clinical evaluation of the vaccine shall include:

- immunogenicity studies in animal models e.g. chickens, mice and ferrets;
- nonclinical evaluation of vaccine safety, the extent of which will depend on the composition of the pandemic vaccine. For an entirely new vaccine composition, the complete programme for nonclinical evaluation of pandemic vaccine is required;
for novel adjuvants with which there has been no experience in humans, the safety profile of adjuvant alone and in combination with influenza virus antigen should be investigated;

- challenge experiments using mice, ferrets and other animals should be performed unless the applicant provides justification for not performing such experiments;

- the results of immunogenicity studies in healthy adults from various age groups and from children to be gathered post-authorization;

- if results from protective efficacy trials are not available, the characterization of immunological response to pre-pandemic vaccine should be provided;

- all serological criteria for evaluation of annual influenza vaccines should be met:
  - neutralizing antibodies should be determined;
  - formulation, dose-finding studies and vaccination schedules should be used;
  - evaluation of safety and immunogenicity to be made through:
    - a larger study, based on the results of dose-finding study;
    - establishing a safety database (size of study should be sufficient to detect adverse events at a frequency of 1%);
    - safety follow-up for at least 6 months;

- post-authorization commitments would include:
  - protocol for evaluation of immunogenicity, effectiveness and safety of pandemic vaccine;
  - data in children.

**Accelerated approval and emergency use provisions**

In the event that a pandemic vaccine would be needed to protect the European Community before a core dossier approval could be issued, the EMEA has options in place for an emergency authorization. An emergency use authorization would rely on the concept of a very close interaction between the manufacturer and the EMEA after the announcement of the pandemic and the first batches of vaccine being produced. During this period the manufacturer will be submitting data packages (including on manufacturing, on testing, any preclinical data, and relevant clinical data from pandemic-like strains). This information would be evaluated in a rolling review process, before the formal submission of the application for the pandemic vaccine. (Note that a similar
Rolling review process is in place for the fast-track evaluation of the type II variation to introduce the information on the actual pandemic strain into the mock-up vaccine licence.

Once the application is submitted (i.e. once the first batches of pandemic vaccines have been manufactured), Europe has two pieces of legislation already in place which could be used alone or in combination to approve pandemic vaccines on the basis of a very limited data package and very shortly after the vaccines become available:

- The accelerated review process (maximum 150 days, can be shortened with the agreement of the CHMP; art 14(9) of Regulation (EC) No 726/2000).
- Conditional marketing authorizations (Commission Regulation (EC) No 507/2006), which allow, in the case of medicinal products to be used in emergency situations in response to public health threats, for authorization on the basis of a limited data package. In emergency situations such a conditional marketing authorization may be granted even if comprehensive clinical, nonclinical and quality data are not available at the time of submission. Such marketing authorizations are linked to strict commitments to provide the missing clinical and nonclinical information within a defined period.

Japan

Regulatory authority

The Pharmaceuticals and Medical Devices Agency (PMDA) reviews pharmaceuticals and medical devices, based on the Pharmaceutical Affairs Law (Law 145, 1960 revised 2002). The Ministry of Health, Labour and Welfare (MHLW) has the authority to approve pharmaceuticals and medical devices based on the findings of the PMDA’s review. The PMDA also gives guidance and advice on clinical trials. The responsibility for research and development of vaccines including pandemic influenza vaccine resides with the National Institute of Infectious Diseases (NIID).

Submission type and application

A manufacturer will file an NDA for examination and approval of all new drugs including vaccines. The MHLW will execute a drug approval upon receipt of the advice from the Pharmaceutical and Food Sanitation Council in the NDA review process, based on demonstrated quality, safety and effectiveness of the product reviewed through the PMDA’s scientific review process.
Annual influenza vaccine

The NIID reviews the strains used for vaccine production every year prior to manufacturing, on the basis of data on circulating wild-type strains. Upon the advice of the NIID, the MHLW notifies relevant manufacturers as to which strains are to be used for vaccine production. The MHLW and the PMDA do not usually require any specific clinical data for this strain replacement process. Manufacturers submit for review their revised labelling materials for the strains used.

Timelines

NDA standard review period: 12 months, priority review for 6 months following immunization.

Proposed pandemic regulatory pathway

The MHLW and PMDA request a manufacturer who is producing vaccine against novel human influenza viruses (pre-pandemic and pandemic type) to file an NDA pursuant to the Pharmaceutical Affairs Law. The application must contain data from the vaccine which is produced with the potential pandemic influenza strain. Approval of vaccines against novel human influenza viruses, intended to be used for both periods (of pre-pandemic and pandemic influenza), is given based on the quality, nonclinical and clinical data on the potential pandemic vaccine. In the pandemic phase, vaccine is manufactured by the approved procedure using the pandemic influenza strain. Once a vaccine against a new influenza subtype has been approved, further clinical data on a variant of that subtype circulating during the pandemic period would probably not be needed for approval.

Special requirements regarding quality and manufacturing data

As for all vaccines, detailed information on formulation, vaccine production and control, standards of final product and in-process samples, excipients including adjuvant, and stability testing and stability protocol will be required.

Special requirements regarding clinical data

The special requirements regarding data on the clinical evaluation of influenza vaccines include:

- immunogenicity studies in animal models including challenge tests;
- nonclinical safety;
- clinical data from trials in healthy male adults stating the appropriate dose and schedules;
clinical data from trials in healthy adults aged under 65 years would be considered as confirmatory trials;
clinical safety data including clinical laboratory tests, description of signs and symptoms, and physical check-up;
estimation of effectiveness including serum HI antibody, NT antibody; and
post-licensure studies in children which include estimation of cross-reactivity.

Accelerated approval options and emergency use provisions
Vaccines against novel human influenza viruses can be granted priority review according to the “priority review provision” of the Pharmaceutical Affairs Law. In an emergency, provided that the pre-pandemic and/or the pandemic vaccine are being developed, the MHLW will grant conditional emergency approval, depending on the extent of the data available at the time of declaration of emergency.

United States of America
Regulatory authority
Influenza vaccines are regulated by the Food and Drug Administration, the Center for Biologics Evaluation and Research, and the Office of Vaccines Research and Review (OVRR) pursuant to Section 351 of the US Public Health Service Act and specific sections of the US Federal Food, Drug and Cosmetic Act.

Submission type and application
The licensing of new biological products, including vaccines, requires the filing of a Biologics license application (BLA) and approval is granted only when the review of the BLA shows the product to be “safe, pure and potent”. The word potency is interpreted to include effectiveness as demonstrated by adequate and well-controlled clinical studies unless the potency requirement is waived as being inapplicable to the biological product or when an alternative method is adequate to substantiate effectiveness.

Licensure of annual influenza vaccine
Each year, any of the three vaccine virus strains included in the trivalent seasonal influenza vaccines may be replaced with a new strain. Strain changes are based on evaluation of circulating wild-type strains. Any changes to the virus strains in the vaccine will require the submission and approval of supportive data as
a prior approval supplement to the existing manufacturer’s BLA. The US FDA does not require clinical data for approval of these annual supplements from licensed manufacturers of inactivated influenza vaccine.

**Timelines**

BLA standard review: 10-month review (priority 6 months); Chemistry, Manufacturing, and Controls (CMC) supplement 4-month review.

**Proposed pandemic regulatory pathway**

Currently in the United States all submissions for the initial licensure of vaccine for novel influenza viruses or a pandemic influenza vaccine would be submitted as a BLA, which allows for separate trade names and segregation of adverse event reporting from that for seasonal influenza vaccines. The amount of data a manufacturer would be required to submit with its BLA for a pandemic influenza vaccine will depend on whether the manufacturer already has a licensed influenza vaccine, and if so, whether the manufacturer intends to use the same manufacturing process for its pandemic vaccine.

**Special requirements regarding quality and manufacturing data**

The special requirements regarding data on the quality and manufacturing of influenza vaccines include:

- description and characterization of drug substance and drug product;
- information regarding methods of manufacturing, including animal sources, virus sources, cellular sources, microbial cells and animal cells (to assess for adventitious agents);
- assay development and validation;
- process controls, especially for safety processes, such as sterilization and virus clearance;
- manufacturing consistency, including reference standards and release testing;
- drug substance specifications;
- reprocessing;
- container and closure system;
- stability studies;
- composition and characterization of final drug product, including excipients, adjuvants and preservatives; and
- specifications and analytical methods for drug product ingredients.
Special requirements regarding clinical data

If the original BLA comes from a manufacturer already licensed by the FDA for the production of annual influenza vaccine where the process for manufacturing the pandemic influenza vaccine is the same, the following are required:

- clinical trials to support the appropriate dose and regimen of the pandemic vaccine (based on evaluation of immune response) (immunogenicity);
- assay performance data;
- safety data on well-defined local and systemic reactogenicity events;
- safety data from 6-month post-vaccination evaluation (submitted when available).

If the original BLA comes from a manufacturer whose pandemic influenza vaccine is manufactured by a process not already licensed by the FDA for the production of annual influenza vaccine the following are required:

- data from adequate and well-controlled clinical trials establishing a vaccine effect on surrogate end-points likely to predict clinical benefit based on epidemiological, therapeutic, pathophysiological or other evidence. Immune response may serve as a surrogate end-point;
- study with adequate power to assess co-primary end-points, geometric mean titre (GMT) and seroconversion;
- assay performance data;
- protocols for postmarketing studies;
- safety data as for supplement, described above;
- after approval, requirement to study the product further to verify and describe its clinical benefit.

Accelerated approval and emergency use provisions

Accelerated approval of new biological products for serious or life-threatening illnesses

Accelerated approval allows products used to treat serious or life-threatening illnesses to be approved if they successfully achieve an end-point that is reasonably likely to predict ultimate clinical benefit, usually one that can be studied more rapidly than showing protection against disease. Products eligible for accelerated approval should provide meaningful therapeutic benefit to patients over that provided by existing treatments (e.g. ability to treat patients unresponsive to or intolerant of, available therapy, or able to show improved patient response
over available therapy). The US FDA interprets the regulation (21 CFR 601.40) as allowing accelerated approval of an influenza vaccine during a shortage because influenza is a serious and sometimes life-threatening illness. Providing vaccine to those who would not otherwise be immunized during a shortage provides a meaningful benefit over existing treatments which are in short supply. Confirmatory postmarketing studies are required.

**Emergency use authorization**

Upon determination and declaration by the Secretary of the Department of Health and Human Services that a public health emergency (or the potential for one) that affects, or has the significant potential to affect national security, exists, the Secretary can authorize the use of a product:

- for a serious or life-threatening disease or condition;
- where it is reasonable to believe that the product may be effective in diagnosing, treating or preventing the serious life-threatening disease or condition;
- where there is no adequate, approved, available alternative; and
- where the known and potential benefits outweigh the known and potential risks.

If during the course of development it appears that an unapproved product or an unapproved use of an approved product might be suitable for use under an emergency use authorization (EUA) if a declared emergency occurs before its development process is complete and alternatives are lacking, and in particular if the product appears sufficiently promising that the Strategic National Stockpile might consider acquiring it for emergency use, appropriate government agencies and sponsors should focus on ensuring that complete data are provided to the US FDA. Data can be provided through pre-IND or IND submissions and discussion of current and future development plans, as far in advance of need as possible. This would be characterized as a pre-EUA. The US FDA would then assess the ability of the data to potentially support an EUA, and provide advice on additional studies and data that may be desirable both for further development and to support emergency use as warranted. The amount of data and information needed to support an EUA will depend on the nature of the product, the completed studies and the nature of the emergency. The use of a product under an EUA is limited to the duration of a declared emergency (and allows patients to finish treatment courses they started during an emergency), after which investigational product regulations would apply. Analysis of whether the available data and information support issuing an EUA if
requested for temporary use in a declared emergency, and the timeframe within which this could be done, may depend on various factors such as the adequacy of data provided in advance, the nature of the emergency, and the suitability and availability of approved alternatives. Therefore, advance submission and discussion of information from completed studies and proposals for additional studies will be critical to minimizing the time required for additional evaluation after onset of an emergency. The final determination of whether the criteria for issuance of an EUA are met can only be made after an emergency is declared.

Under the EUA, specific Conditions of Authorization are applied, which may include the requirement to inform health care workers or recipients, if feasible, of the EUA status of the product, to identify and communicate information on significant known and potential risks and benefits of the product and to provide the option to accept or refuse the product.

**Investigational new drug use**

In accordance with the US Department of Health and Human Services Pandemic Influenza Plan, Supplement 6 Vaccine Distribution and Use, in the event that the spread of a pandemic is rapid and vaccine is needed before the completion of the licensure process, state and local health departments should be prepared to distribute unlicensed vaccines under the investigational new drug (IND) provisions of the US FDA. IND provisions require strict inventory control and record-keeping, completion of a signed consent form from each vaccinee, and mandatory reporting of specified types of adverse events. IND provisions also require approval from institutional review boards in hospitals, health departments, and other vaccine-distribution venues. The FDA regulations permit the use of a national or “central” institutional review board.
Table A.2
Overview of five selected national regulatory authority pathways

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<tr>
<th>National regulatory agency</th>
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<th>Canada</th>
<th>European Union</th>
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<tr>
<td><strong>Regulatory authority</strong></td>
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<td><strong>Submission type</strong></td>
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<tr>
<td>Australia</td>
<td>Category 3 application</td>
<td>New drug submission (NDS); including an on-site evaluation</td>
<td>Centralized procedure (CP) Mutual recognition procedure (MRP)</td>
<td>New drug application</td>
<td>Biologics License Application (BLA)</td>
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<td>United States of America</td>
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<tr>
<td><strong>Timelines</strong></td>
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<tr>
<td>Australia</td>
<td>Category 3 application – 45 days after receipt of application</td>
<td>NDS – 300 days standard 180 days for priority</td>
<td>CP – 210 days; EC timeline for evaluation of application – 30 days MRP – 210 days (initial national authorization) + 90 days (mutual recognition)</td>
<td>12 months for regulatory timeline (6 months for priority review)</td>
<td>BLA standard review – 10 months, priority – 6 months, CMC supplement – 4 months</td>
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<th>National regulatory agency</th>
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<th>European Union</th>
<th>Japan</th>
<th>United States of America</th>
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<tr>
<td><strong>Annual influenza vaccine licensure</strong></td>
<td>Full submission required, including quality, preclinical and clinical data (in accordance with general Committee for Proprietary Medicinal Products (CPMP) guidance for new vaccines)</td>
<td>Filing of an amendment to the existing licence, in which manufacturers submit for review their revised labelling material. Any Chemistry, Manufacturing and Control (CMC) updates pertaining to the new strain and limited clinical data to support tolerability and immunogenicity</td>
<td>A special fast-track type II variation procedure is applicable for annual variation in human influenza vaccines</td>
<td>Manufacturers would submit for review their revised labelling material for the new yearly strain. National control laboratory (NCL) reviews the strain change data</td>
<td>Submission of a prior approval supplement to the existing manufacturer’s BLA is required for strain changes (chosen yearly, based on circulating wild-type strains)</td>
</tr>
<tr>
<td><strong>Proposed pandemic regulatory pathway</strong></td>
<td>Therapeutic Goods Administration (TGA) accepts EMEA guidelines on pandemic vaccine licensing</td>
<td>Submission of an NDS and not an amendment to an existing annual influenza licence</td>
<td>Submission and approval of the pre-pandemic Core Dossier during the inter-pandemic period for evaluation. Once a pandemic is declared a variation to the core pandemic dossier for fast-track approval will be submitted</td>
<td>Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) request a manufacturer who is producing vaccine for novel human influenza viruses (pre-pandemic and pandemic type) to file NDA pursuant to PAL.</td>
<td>Submissions for the initial licensure of a pandemic influenza vaccine would be submitted as a BLA, which provides for separate trade names and segregation of adverse event reporting.</td>
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Proposed pandemic regulatory pathway

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<th>National regulatory agency</th>
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<tr>
<td><strong>Inter-pandemic vaccine</strong></td>
<td>Licensure is based on approval of a core dossier for a pre-pandemic vaccine with quality, safety and efficacy data provided and authorized during inter-pandemic period. Pre-pandemic vaccine development: • quality data, • clinical trial applications (CTAs) Inter-pandemic – CTA for pandemic trial protocols (some as pre-pandemic data)</td>
<td><a href="http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf">http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf</a></td>
<td></td>
<td>Approval is given, based on dossier with data demonstrating quality, safety and efficacy during interpandemic period. Testing protocols and data requirements are addressed in the consultation process of the review agency in collaboration with NCL.</td>
<td>See above</td>
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</tbody>
</table>

The amount of data a manufacturer would be required to submit with its pandemic influenza vaccine BLA will depend on whether the manufacturer already has a licensed influenza vaccine, and if so, intends to use the same manufacturing process for its pandemic vaccine.
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<tbody>
<tr>
<td><strong>Inter-pandemic uses</strong></td>
<td>Same as Europe</td>
<td>Health Canada (HC) must be able to validate production process, test production capacity and establish minimum standards and requirements for safety and efficacy</td>
<td>The core dossier is not be used outside the pandemic context. For vaccines containing avian strains with pandemic potential (such as H5N1), the Committee for Medicinal Products for Human Use (CHMP) has adopted a draft Explanatory note, identifying dossier requirements. Such avian influenza vaccines for human use must be based (entirely) on the circulating influenza strain against which protection is claimed</td>
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</table>
| **Quality and manufacturing requirements** | Data obtained in interpandemic period Same for all uses | • production and testing of vaccine seed lot manufacturing process and validation | • vaccine reference virus development and testing  
• vaccine seed lots production process etc. | Controls and characterization for seed lots and vaccines:  
• process controls  
• tests for bulk materials | With adequate controls and characterization, US FDA permits use of recombinant or cell-culture based technologies in strain production. |
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<td><strong>Quality and manufacturing requirements</strong></td>
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<td>• specifications</td>
<td>• formulation</td>
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<td>Either a reassortment or wild-type virus</td>
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<td>• information on adjuvant, excipient, container and preservative</td>
<td>• vaccine standardization</td>
<td>• stability studies</td>
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<td>• batch analysis</td>
<td>• adjuvant</td>
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<td>• reference standards</td>
<td>• stability data and protocol</td>
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<td>• stability information</td>
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<td>• product-specific facility information</td>
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<td>• information on viral safety</td>
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<td><strong>Clinical data requirements</strong></td>
<td>Data obtained in interpandemic period</td>
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<td>Differ depending on use:</td>
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<td>• stockpiling for use at beginning of the pandemic</td>
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<td>• use for people at high risk (poultry workers)</td>
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<td>• for priming and boosting the population at large</td>
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<td>• local tolerance studies</td>
<td>• nonclinical safety</td>
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<td>• clinical (immunogenicity) studies on healthy adults</td>
<td>• novel adjuvant</td>
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<td>• targeted studies on the vulnerable</td>
<td>• challenge experiments</td>
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<tr>
<td>• protocols for postmarket studies, including any necessary informed consent document</td>
<td>• human clinical data</td>
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<td>• formulation</td>
<td>• formulation</td>
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<td>• all criteria for annual influenza vaccines</td>
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<td>• post-authorization commitments</td>
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<tbody>
<tr>
<td><strong>Clinical data requirements</strong></td>
<td>Human immunogenicity and safety studies</td>
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<td>Dependent upon whether manufacturer currently produces annual influenza vaccine using an FDA-licensed process and uses same process for the pandemic vaccine</td>
</tr>
</tbody>
</table>
| **Accelerated approval and emergency use provisions** | If a pandemic is declared – Core Pandemic Dossier using the actual pandemic strain and submission of quality and technical data in parallel with product as a pandemic variation to TGA for rapid approval and release | Licensure of a pandemic vaccine will follow the filing of an NDS containing composite information on the pre-pandemic vaccine supplemented with additional information on the actual pandemic vaccine | Emergency authorization:  
- accelerated review process (max. ± 150 days)  
- conditional marketing authorizations in case of public health crisis | | • Accelerated Approval of New Biologic Products for Serious or Life-threatening Illnesses  
• Emergency Use Authorization (EUA)  
• Investigational New Drug (IND) Use |

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<th>United States of America</th>
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</table>
| **Emergency use – additional requirements** | • expedited review  
• notice of compliance with conditions  
• Special Access Programme (SAP)  
• interim orders  
• clinical trials | In the case that a pandemic occurs before a core dossier is approved: emergency authorization to be used, relying on close interaction between the manufacturer and the EMEA using a process of rolling review of data packages before the submission of a formal application | • Accelerated approval of new biological products for serious or life-threatening illnesses  
• Emergency Use Authorization (EUA)  
• Investigational New Drug (IND) Use |
| **Guidance published** | No | No | Yes | No | Yes |

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Appendix 2

Regulatory pathways for human pandemic influenza vaccine

1. Manufacturing of vaccine against novel human influenza virus
   - harmonized GMP and parameters
   - shared facility inspection reports
   - advance agreement on acceptable conditions for alternative (e.g., veterinary) facilities
   - harmonized plans to expedite switch from seasonal to pandemic production

2. Nonclinical and human clinical trials with vaccine against novel human influenza virus
   - agreement on harmonized requirements for testing
   - exchange of non-proprietary data and information on strain choice
   - testing of vaccine against novel human influenza virus
   - identify early safety/effectiveness issues
   - reduce duplication in testing
   - provide information to jurisdictions whose manufacturers may not have time or resources to conduct testing
   - early harmonization of vaccine formulations (antigen content, adjuvant, immunogenicity and dose schedule)

3. Application for licensure of vaccine against novel human influenza virus
   - Standards for Core Dossier
   - Licensed vaccine against novel human influenza virus available for stockpiling and use

4. WHO Prequalification

   • Pandemic vaccine manufacturing initiated
     - Rapid availability of reagents/strain
     - Submission of quality information in parallel with manufacturing
     - Accelerated licensure of pandemic vaccine
     - Early assessment of capacity to determine possibility of supplying non-domestic markets

   • Nonclinical and human clinical trials with pandemic vaccine
     - agreement on harmonized requirements for nonclinical and clinical testing
     - exchange of nonproprietary data and information
     - testing of pandemic vaccines according to established regulatory procedures

5. Application for licensure of pandemic vaccine
   - Submission of a new drug/supplemental or variant application for pandemic vaccine
   - Manufacturer’s agreement to post-market commitments and monitoring
   - Vaccine licensure through accelerated approval

6. Sale and use of vaccine for immunization
   - Post-marketing:
     - surveillance
     - pharmacovigilance
     - lot release
     - filing of supplements to licensure

Declaration of pandemic and strain identification
For developing countries, pathway may be initiated at this stage
Appendix 3

Emergency use pathways for human pandemic influenza vaccine

**Manufacturing of vaccine against novel human influenza virus**

- **Declaration of pandemic**
  - No data available
  
**Nonclinical and human clinical trials with vaccine against novel human influenza viruses**

- **Declaration of pandemic**
  - Limited pre-pandemic data available

**Application for licensure of vaccine against novel human influenza viruses**

- **Declaration of pandemic**
  - Extensive inter-pandemic data available

**Manufacturing of pandemic vaccine initiated**

- **Pandemic spreading quickly/Vaccine needed**
  - No data on pandemic vaccine available

**Non-clinical and human clinical trials with pandemic vaccine**

- **Pandemic spreading quickly/Vaccine needed**
  - Some data available

**Application for licensure of pandemic vaccine**

- **Sale and use of vaccine for immunization**

**Sale/Use of Vaccine for immunization**

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*Contingency needed in the event that the actual pandemic strain differs significantly from the strain in vaccine against novel human influenza virus. Data determined from strain in vaccine against novel human influenza virus may be of unsuitable for extrapolation to use with pandemic strain.*
Appendix 4

Inventory of guidance documents from selected national regulatory authorities, and the World Health Organization

Australia

Official Control Authority Batch Release of Influenza Vaccines Adopted by the Therapeutic Goods Administration (TGA) with the following notation:

“Sponsors should note that Section 2 of this guideline (which refers to mandatory testing) is not adopted, however the TGA reserves the discretionary right to take samples and test. Sponsors should also note in respect of Section 4 (which relates to certification that materials derived from ruminants are compliant with Directive 1999/82/EC), that the ‘TGA Approach to Minimising the Risk of Exposure to Transmissible Spongiform Encephalopathies (TSEs) Through Medicines’ is relevant to assessment in Australia.” Effective February 7, 2003 http://www.tga.gov.au/docs/pdf/euguide/edqm/ocabr26.pdf


Canada

Good manufacturing practices guidelines, 2002 edition, version 2

Emergency interim orders

Administrative policy: management of biologics submissions for public health need
Available upon request

Guidance for sponsors-lot release program for Schedule D (Biologic) Drugs (2005)

Guidance document: pandemic influenza vaccine, manufacturing & clinical information review & regulatory authorization
Available on Request

**European Union**


Harmonization of requirements for influenza vaccines CPMP/BWP/214/96


Cell culture inactivated influenza vaccines (CPMP/BWP/2490/00) – Annex to note for guidance on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96)
Committee for Proprietary Medicinal Products – Guideline on core dossier structure and content for pandemic influenza vaccine marketing authorization application

Committee for Proprietary Medicinal Products – Guideline on submission of marketing authorization applications for pandemic influenza vaccines through the centralized procedure

EMEA pandemic influenza preparedness

Core summary of product characteristics for pandemic influenza vaccines, adopted June 2005

Guideline on dossier structure and content of marketing authorization applications for influenza vaccines derived from strains with a pandemic potential for use outside of the core dossier context

Guideline on summary of product characteristics, published by the European Commission—December 1999

Guideline on pharmaceutical aspects of the product information for human vaccines

Guideline on adjuvants in vaccines for human use (2005)

Cell culture inactivated influenza vaccines

Japan

Regulatory preparedness for human pandemic influenza vaccines

Guideline on manufacturing, use and post-marketing surveillance of H5N1 vaccine (after pandemic is declared) [in Japanese]
United States Food and Drug Administration

Guidance for industry: Clinical data needed to support the licensure of pandemic influenza vaccines

Guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm

Draft guidance for industry: Characterization and qualification of cell substrates and other biological starting materials used in the production of viral vaccines for the prevention and treatment of infectious diseases
http://www.fda.gov/cber/gdlns/vaccsubstrates.pdf

Guidance for industry: Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074827.htm

Draft guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials
http://www.fda.gov/cber/gdlns/toxvac.pdf

Draft guidance for industry: Considerations for plasmid DNA vaccines for infectious disease indications
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074770.htm

Guidance for industry: How to comply with the pediatric research equity act

Draft guidance: Emergency use authorization of medical products
http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm

Guidance for industry: Fast track drug development programs – designation, development, and application review
Guidance for industry: Content and format of chemistry, manufacturing and controls information for a vaccine or related product


World Health Organization


WHO Programme for International Drug Monitoring and the Uppsala Data Monitoring Centre

http://www.who.int/biologicals/publications/Influenza%20inactivated%20recommendations%20annex%203.pdf


