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Proposed Guidelines:

Regulatory Preparedness for Human Pandemic Influenza Vaccines

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

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Part A. Introduction

A.1 General considerations

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 strategy is to promote convergence between National Regulatory Authorities (NRA) 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 representation of NRAs from a broad range of countries, including vaccine producing countries and also countries that have indicated an interest to explore 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 the three workshop discussions 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 at the following link: 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 for a resolution on pandemic influenza preparedness 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, the WHO is investigating different mechanisms to facilitate this process.

A.2 Objectives

The guidelines are intended to provide, both NRAs and vaccine manufacturers, state-of-the art 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 post-marketing surveillance of pandemic influenza vaccines.

A.3 Scope of the guidelines

These guidelines are intended to cover the following scenarios:

(1) Vaccines that are developed during the inter-pandemic period in anticipation of an influenza pandemic. These vaccines contain an influenza A virus sub-type not currently circulating in humans. Throughout the 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.

(2) 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 pandemic influenza preparedness plans. Where applicable, special considerations for candidate vaccines intended for stockpiling are provided within the guideline.

(3) 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 compared to intended use after a pandemic is declared, special regulatory provisions are outlined in the document. 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 document will also apply to novel production systems for influenza vaccines currently under development, such as vaccines comprised of influenza proteins expressed in various genetically-engineered constructs. However, there may be additional quality control and regulatory considerations that must be taken into account for such vaccine candidates.

A.4 Terminology

A.4.1. Definitions

For clarity and consistency of the guidelines, the following human influenza vaccine terminology has been used:

Candidate vaccine: A prospective influenza A virus vaccine which is in 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 and one influenza B virus strains 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 a threat to infect people and a potential cause of a pandemic. The term "novel" refers to the human influenza A virus. An H5N1 vaccine is one specific example of vaccines 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 where 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 programs. WHO prequalification provides a single standard against which products from manufacturers can be assessed and so provides a basis by 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[1], and processes are being developed for vaccines against novel human influenza viruses and pandemic influenza vaccines.

A.4.2. Acronyms

AEFI	Adverse Event Following Immunization
CBER	Center for Biologics Evaluation and Research
EMEA	European Medicines Agency
EU	European Union
GBS	Guillain-Barre Syndrome
GISN	Global Influenza Surveillance Network
GMP	Good Manufacturing Practices
GMT	Geometric Mean Titre
HA	Haemagglutinin
HI	Haemagglutination Inhibition
ICH	International Conference on Harmonization
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 Assay

[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

USA	United States of America
US-FDA	United States Food and Drug Administration
WHO	World Health Organization

A.5 Background on vaccines against novel human influenza viruses

A vaccine for 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 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 vaccine demand and supply during an influenza pandemic. The plan proposes to increase pandemic influenza vaccine production capacity 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 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 pandemic influenza preparedness 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 seasonal influenza vaccine production. Some countries are potentially considering the use of veterinary vaccine production facilities during a pandemic to address their shortage of human influenza vaccine supply. These new approaches may expedite vaccine production at a larger scale in a pandemic situation, making vaccine potentially available weeks before conventional manufacture (*1*).

At a WHO meeting in 2007 (*2*), 16 manufacturers from 10 countries reported to be 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 ongoing. After completing safety analyses in adults, some manufacturers had initiated clinical trials in the elderly and children. All vaccines tested to date were safe and well tolerated in all age groups. Most of the data were

obtained on 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. Alum adjuvanted split vaccines, in striking contrast to some of the more promising alum adjuvanted whole virion vaccines, 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 likely allow dose sparing. Some studies demonstrate 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 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 allowing for faster (but not infinite) scale-up. Provided that 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 currently needed to determine whether the recombinant DNA approach to influenza vaccine production 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 due to the recombinant nature of these vaccine candidates may arise.

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

However, it should be noted that unresolved potential public and animal health concerns 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.6. 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 (inactivated) (*3*), are currently available or have extensively been used:

- a suspension of whole virus particles inactivated by a suitable method;
- a suspension treated so 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.

Whole virion inactivated adjuvanted seasonal influenza vaccine is used in at least one country (*4*); however, most countries use split virion or subunit non-adjuvanted inactivated vaccines. While being in general less reactogenic, purified influenza virus surface antigens are less immunogenic than purified whole virion vaccines in immunologically naïve individuals (e.g. small children and persons with no contact to 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 on an annual basis 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 ug 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. Currently used continuous cell lines include Vero cells which are widely used in the manufacture of other vaccines, the MDCK cell line and others which are less extensively used as a human vaccine substrate.

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 un-adjuvanted and inactivated seasonal influenza vaccines. LAIV have been shown to be more effective in immunologically naïve individuals, i.e. children below two 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 inactivated seasonal influenza vaccines in this age category (*6*). Further studies on protection against heterologous virus and minor variants as well as evidence of herd immunity induction through childhood vaccination are required. A review of the safety of LAIV in high-risk patients (such as those with asthma, immunocompromised, the very young or elderly people) 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 NRAs in licensing vaccines against novel human influenza viruses and for licensing pandemic influenza vaccines,
- identifies existing regulatory methods in the licensing process of 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 United States were analyzed in detail. These NRAs 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 NRAs is presented in Appendix IA. This will aid NRAs 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 Reg ulatory Authority pathways

The five NRAs studied have the following in common, or near in common, 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 inspectorate qualified to conduct Good Manufacturing Practices (GMP) inspections, most using the Pharmaceutical Inspection Cooperation Scheme (PIC/S) (The United States 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 post-marketing surveillance studies if needed;
- All have proposed a flexible approach to the receipt and review of information as part of pandemic influenza vaccine licensure;

- 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 effectiveness and seek post-market confirmatory efficacy evaluations;
- All agree that wherever possible, the manufacturing, safety, quality, and immunogenicity of pandemic vaccines should be evaluated as fully as possible prior to 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 human influenza vaccine regulatory pathways are presented in this document to provide information to NRAs and manufacturers and should not be considered as WHO endorsement of any specific regulatory pathway.

Europe, the United States, Australia and Japan plan to license inactivated vaccines against novel human influenza viruses. Canada has no current plans to license such vaccines; however, data from a vaccine against novel human influenza virus will be required to support licensure of a pandemic influenza vaccine. Options around the mechanism of licensure for a vaccine against novel human influenza virus are being investigated 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. In one pathway, the vaccine against a novel human influenza A virus although licensed, is not intended to be used or marketed before the pandemic is announced. The matching pandemic influenza A virus strain would have to be introduced into the authorization via a fast track type two variation. In 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 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 (Released for consultation July 2006). EMEA guidance regarding licensure of vaccines for novel human influenza viruses is limited to inactivated vaccines. No guidance exists for LAIV.

In the United States, all submissions for initial licensure of a vaccine against novel human influenza viruses or a pandemic influenza vaccine would be submitted as a Biologics License Application (BLA). This allows for separation of trade names and segregation of adverse event reporting from those of seasonal influenza vaccines. The amount of data required by FDA from the manufacturer to submit with its pandemic influenza vaccine license application, would depend on whether the manufacturer has already a licensed influenza vaccine and it 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 for both inter-pandemic and pandemic phases, is given based on the quality, non-clinical and clinical data of the potential pandemic influenza vaccine. The application must contain data from 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. Australia, Japan, USA, and the EMEA's regulatory preparedness are based on multiple 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. Refer to Appendix IV for an inventory of guidance documents from selected NRAs and the WHO.

B.3 Towards a harmonized regulatory pathway

A harmonized regulatory process would facilitate, but is not a pre-requisite to:

- the availability of pandemic influenza vaccine in a timely manner at 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 NRAs 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 to implement their own national pandemic influenza preparedness plans. All countries will be constrained somewhat by the existing laws and regulations concerning vaccine licensure and use 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 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

Recommendations pertaining to core quality, nonclinical, clinical, and post-marketing 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. NRAs are encouraged to limit requests for additional data to those which 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 and this knowledge would undoubtedly assist in the evaluation of vaccines against novel human influenza viruses and 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 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".[2]

Additionally to aiding developing countries with pandemic preparedness, prequalification would help NRAs acquiring alternate non-domestic influenza vaccines in the event of a vaccine supply shortage. 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 not manufactured for domestic use, would meet acceptable quality as defined by WHO.

Upon a pandemic declaration, there will be a lag time until any vaccine becomes available. Vaccines against novel human influenza viruses could be the only vaccines available to developing countries, particularly those most affected during early stages of the pandemic. With various manufacturers proceeding to developing vaccines against novel human influenza viruses with H5N1 strains, potential vaccine uses must be maximized in the early stages of a pandemic. Stockpiling vaccines against novel human influenza viruses is an option for pandemic influenza preparedness; this approach is under pursue or 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 post identification of the pandemic virus strain.

- Information Sharing

It is imperative that mechanisms be in place for NRAs and vaccine manufacturers to share data from clinical trials with different vaccine types (e.g. whole virion, split antigen or subunit vaccines, cell culture derived), 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, priming vaccination, 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 pandemic influenza vaccine manufacturing (without an inter-pandemic step), information sharing between NRAs and developing

[2] http://www.who.int/immunization_standards/vaccine_quality/final_expedited_procedure_flu_240207.pdf

countries is essential to maximize successful vaccine production to achieve to the greatest extent 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, NRAs, NCLs, public health authorities), the key areas to share data could be identified in advance. For example, in a pandemic situation the key strengths would be production capacity, production speed, fast 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 NRAs 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 pandemic influenza vaccine authorization can be developed and is provided as Appendix II to this document. Not all steps within 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 much data as possible should be obtained in the inter-pandemic period with the goal to license candidate pandemic influenza vaccines. Since the likelihood, timing and spreading speed 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.

While 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 NRAs may have a range of regulatory options for emergency use, other countries may be restricted in this area. It is recommended that countries carefully review their available options and implement any needed corrective measures as soon as possible.

Secondly, once the need to invoke emergency options is determined, the choice of usable options will depend on availability of vaccine data, if any, and the extent of vaccine distribution under such 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 data criteria for using an emergency option, it is the available data what dictates which emergency use option is most suitable.

In case of unavailability of pandemic vaccines and upon a pandemic declaration, 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

prequalified influenza vaccine manufacturers 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. national disaster and after approval by the Ministry of Health, when a specific pandemic vaccine, produced via the same manufacturing process as seasonal influenza vaccines, is not available.

Regulatory pathways for human pandemic influenza vaccines are outlined in Appendix II. A proposed standard process to guide jurisdictions on the use of an emergency option is provided as Appendix III to this document.

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

C.1 Quality/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 manufacturing stages 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 in compliance with the appropriate biosafety standard is also required. The responsiblity for assessing compliance may differ among jursidictions. Where applicable, the NRA and the agency responsible for biosafety inspections should work together.

- Quality specifications for production and control of egg- 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 those specifications for pandemic influenza vaccine should be met. However, if indicated by a risk-benefit analysis of a clinical development program, some specifications may be modificed. For example, the total protein content specification allowes up to 100 ug of total protein per virus strain per human dose (*3*). If unusually high 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, such vaccine virus may require further purification and more stringent specifications.

- If a cell line is used for influenza vaccine manufacturing, 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 vaccine packaging and labelling requirements contained in the WHO Good Manufacturing Practices for biological products (7) should apply to establishments manufacturing vaccines against novel human influenza viruses. Specific WHO information requirements on a standardized label for stockpiled vaccine or surplus vaccines released to international markets are not currently available. NRAs should require that any manufacturer producing vaccines under contract to them would 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 influenza vaccine manufacturing, 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 such vaccine candidates 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 were 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; residual DNA removal, host cell protein, detergents, and other trace residuals
- Quality control procedures: determine glycosylation patterns, purity, amino acid analysis, and recombinant protein molecular size
- Specifications for purity of recombinant HA which may be expected to be ≥ 95%
- Adaptation of tests such as Single Radial Immunodiffusion (SRID) assay to determine the specific antigen concentration in the vaccine derived from novel technology.

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

Independent from virus growth substrate and vaccine production method, storage periods assigned to vaccine intermediates and products should be justified by real time condition data as well as stability data under elevated temperatures. Applicable WHO and 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/immunogenicity studies and safety testing using appropriate animal models prior to testing the vaccine in human trials. Nonclinical evaluation refers to all *in vivo* and *in vitro* testing performed before and during the vaccine clinical development.

Guidance to NRAs 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 NRAs and manufacturers is also provided in the WHO 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 have been 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 bibliographic data, this literature should be provided and its relevance to the pandemic influenza vaccine candidate should be discussed.

In line with WHO policy on multidose presentations, an effective antimicrobial preservative may be used. The risk of possible microbial contamination during in-use shelf life 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.

Immunogenicity data from an accepted animal model that responds well to human influenza vaccines (e.g. ferrets) may be useful 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 for the first three batches should be presented to document consistency of production. The choice of immunogenicity assay(s) needs to be approved by the NRA; assays need to be appropriately standardized and validated to enable data comparison 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 relevant 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 endpoints 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 from 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 (*15*) and national/regional requirements.

Dose changes of whole virion, split or subunit pandemic influenza vaccines derived from a licensed process may not require repeating the nonclinical safety testing provided that the total HA content per dose does not exceed an amount agreed by the national control 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 single and repeated dose administration may be required. Local tolerance may be investigated when the vaccination schedule consists of multiple vaccine doses with total HA antigen content higher than the agreed on by the national control authority. In view of the possible use of vaccines against novel human influenza viruses in pregnant women, animal reproductive toxicity studies should be performed.

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

Enhancing vaccine antigen immunogenicity 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 by 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 non-human primate studies with other whole-virion adjuvanted vaccines (Respiratory Syncytial Virus, Measles, SARS). In these cases,

internal proteins e.g. nuclear proteins, are most likely 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 additional specifications, compared to WHO, in 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 in accordance with the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (*16*) and relevant national or regional recommendations regarding vaccine clinical development. In the clinical development phase, the applicants are encouraged to present and discuss with the NRAs 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 immuno-competence) 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[3], the serological criteria for assessment of seasonal influenza vaccines include:
(a) number of seroconversions or significant increase in antihaemagglutinin antibody titre >40%,
(b) increase in geometric mean titre (GMT) >2.5, and
(c) the proportion of subjects achieving an HI titre $\geq$40 or SRH titre >25 mm^2 should be 70%.

These three parameters are evaluated yearly in human clinical trials due to the annual update of seasonal influenza vaccine strain composition[3]. 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.

Failing to meet the three serological criteria may happen if a given study population have a very high residual immunity from pre-vaccination that can not be further boosted by the

[3] CPMP/BWP/214/96; http://www.emea.europa.eu/pdfs/human/bwp/021496en.pdf

candidate influenza vaccine. Seroconversion (increased HI titre >40% post vaccination) is assumed to correlate with protection as it has been associated with 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 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 factors above into account, vaccines against novel human influenza viruses should induce high GMTs and seroconversion rates, most preferably after only two doses. Ideally, the three serological criteria for assessment of seasonal influenza vaccines as defined in guideline CPMP/BWP/214/96[3] should be exceeded in the target population, with the proportion of subjects achieving HI titre $\geq$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 lesser levels of antibody would produce significantly less benefits. Based on results from animal and human studies with seasonal influenza vaccines, it cannot be excluded that there would be limited 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 fulfill all serological criteria specified above. High quality data from immunization/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 neutralising 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 assessment 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.

In order 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). It would be expected that applicants 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. There should also be prepared plans to assess vaccine efficacy after exposure to circulating influenza A viruses of pandemic potential (refer to Part G). 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 of 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 worth public health benefit. Because of the uncertainties, a priming schedule with two (or even more) vaccine doses may be preferential 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 short duration regimen would be needed to urgently achieve seroprotection in people who might come in contact with the virus e.g. poultry workers, veterinarians, animal caretakers, human health care providers.

In order to identify vaccine formulations (e.g. antigen dose and, if needed, adjuvant amount) 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, sample size is recommended to be at least 50[5].

Once the applicant considers that appropriate vaccine formulation and schedule have been identified for healthy adults aged 18-60 years, the safety and immunogenicity of chosen vaccine candidate should be evaluated in a larger sample size of similar age population. 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, data sub-stratification 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 NRA. 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.

The safety database size for each vaccine would be different depending on the population studied (Table 1). Follow-up of clinical trial study participants for the evaluation of safety should be at least six months and should include specified parameters of adverse event

causality, seriousness, expectedness and severity[4]. These data should be submitted as part of the license 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 clinical trial context. If the vaccine against novel human influenza virus contains thiomersal as a preservative, relevant WHO and national or regional guidance should be followed.

Table 1: Size of the safety database required to detect Adverse Events Following Immunization (AEFIs) at stated frequency[5]

Age group	AEFI frequency and sample size
Adults from 18 to 60 years	≤ one in one thousand persons vaccinated (i.e. rare AEFIs) (e.g. a database of approximately 3000 subjects might be sufficient)
Specified age groups (e.g. infants, children, adolescents, adults over 60 years of age)	≤ one in one hundred (i.e. uncommon AEFIs) (e.g. a database of approximately 300 subjects from each specified age group might be sufficient)
Specified risk groups (e.g. immune compromised individuals, chronically ill patients)	≤ one in one hundred (i.e. uncommon AEFIs) (e.g. a database of approximately 300 subjects from each specified risk group might be sufficient)

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

As 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 could occur:

[4] Defined in guideline CPMP/BWP/2490/00 at www.emea.europa.eu/pdfs/human/bwp/249000en.pdf and CHMP/VWP/164653/2005 at www.emea.europw.eu/pdfs/human/vwp/16465305en.pdf

[5] Applicants are encouraged to discuss the proposed safety database size with the NRA during the clinical development programme

a. 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).
b. 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.
- 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 were 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 NRA 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 NRA 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 from more advanced technologies may differ to the traditional inactivated influenza vaccines (via HA and HI assays). Ideally, the efficacy of a new technology-derived vaccine would be established initially against seasonal influenza through clinical trials. Preclinical efficacy data of such a vaccine in appropriate animal studies may provide useful supporting data for the acceptability of a new technology-derived candidate pandemic influenza vaccine.

For inactivated vaccines administered intramuscularly, serological markers such as functional anti haemagglutinin antibody titre and trend have widely been accepted as correlates of protection. For LAIV administered via 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 from infection by circulating wild-type human influenza viruses. Therefore, using similar immunogenicity parameters as applied to inactivated influenza vaccines may mislead 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 development program for 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 can not be administered concomitantly with neuraminidase inhibitors and/or other antivirals because these drugs would most likely abolish vaccine efficacy.

C.3.2 Pediatric studies

Pediatric data 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 issues for children, e.g. for adjuvanted influenza vaccines, or for vaccines that are intended for intranasal administration; and
- 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 (*18*) definitions, 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 vaccine clinical development program is generally done in a stepwise fashion, from adults to children. Over the past decade, this development pathway led to licensure of numerous pediatric vaccines including whooping cough, chickenpox, hepatitis A, pneumococcus, influenza, and meningococcus. It is very important to have safety and immunogenicity data in adults prior to initiating pediatric clinical studies of a vaccine against a novel human influenza virus.

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

Evaluation of immunogenicity and safety in children and adolescents should only be initiated after acceptable data is available from studies in healthy adults. Studies in infants and toddlers should only be initiated when data from older children and adolescents is 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 seek advice from the relevant NRA.

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 to have children participate in clinical trials with vaccines against novel human influenza viruses as proxy to pandemic influenza vaccine candidates, may be difficult to predict; especially in geographic areas with no circulating avian influenza viruses. It is of major importance to balance the safety benefits with the potential risks. In the recent Southeast Asian experience with avian influenza A (H5N1), the most affected were the young causing high mortality in infants and children (*20*). However, the epidemiology of a true pandemic strain may differ from a strain with very limited ability for person-to-person transmission.

C.3.2.1 Timing of pediatric studies

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

The ethical principles described below (Section C.3.2.2) should carefully be considered in decision making for pediatric 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 extensiveness of pediatric trials thus would 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 benefit/risk assessments;
- Immunological characterizations; and,
- Opportunity of obtaining efficacy/effectiveness data.

In general, the timing of pediatric studies depends upon factors[6] including:

- Extrapolation of immunogenicity data from adults into children or seek identical indication for all age bands;
- Trial information on relevant clinical outcomes, e.g. efficacy or immunogenicity, comparability of side effects, long term safety;
- Nature of disease e.g. serious and/or life-threatening, urgency for treatment and/or prophylaxis;
- Clinical findings in adult populations, e.g. major safety problem identified in adults; and
- Availability and/or necessity of a pediatric formulation.

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

[6] Mentioned in the ICH E11 Guidelines on Clinical Investigation of Medicinal Products in the Pediatric Population (http://www.ich.org/cache/compo/276-254-1.html

There may be national or regional differences with regard to the anticipated timing of pediatric studies with vaccines against novel human influenza viruses. In one country, for example, the law outlines that all sponsors have obligations to study pediatric populations, as appropriate.[7] Some countries with influenza (human and animal) outbreaks have indicated a special interest in conducting pediatric studies with vaccines against novel human influenza viruses. For example, studies with vaccines against novel human influenza viruses might be conducted in children who are 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 pediatric trials will be conducted before a pandemic. Consequently, bridging adult and/or foreign pediatric data may be critical for regulatory decision making.

In general, pediatric clinical data from seasonal influenza vaccines would be useful for planning pediatric pandemic influenza vaccine studies. 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 characterisation via standardized methods i.e. serological assays which must be in place prior to initiating pediatric studies.
- Safety e.g. a system of recording and analysing information on AEFIs (*21*).

An improved understanding of seasonal influenza vaccine efficacy in pediatric populations would be particularly valuable. Available data indicate that the efficacy of inactivated seasonal influenza vaccines in pediatric populations less than two 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 programs would also be useful.

C.3.2.2 Ethical considerations of conducting pediatric 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 pediatric development plans to the NRAs as early as possible in the vaccine development process.

Since clinical trial data must support the use of a vaccine against novel human influenza virus in children, the following considerations[8] 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 pediatric studies must address issues of human subject protection particularly relevant to pediatric populations, in compliance with applicable national or

[7] Pediatric Research Equity Act of 2003, U.S. Public Law 108-155, http://www.fda.gov/opacom/laws/default.html
[8] Described in the EU/2001/20 directive: www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf

regional regulations. Decisions on pediatric clinical investigations should follow the framework of Institutional Review Boards or equivalent ethical oversight groups. Ethics committees should take considerable care when reviewing pediatric protocols. Appropriate provisions should be made for soliciting permission from parents or guardians and for obtaining assent from children participating in clinical studies. Ethical consideration at each step include (See the ICH E11 guidelines for additional guidance (*18*):

- The trial should be explained to the child as his or her age/maturity allows, and assent obtained when this is considered reasonable by consensus between the researchers and parent(s) or guardian(s).
- Risk should be minimised by using trained staff, appropriate study design, and rapid termination, if necessary.
- Distress should be minimised by appropriate measures.
- Financial or other incentives should not be given. Covering reasonable expenses such as travel are 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 the elderly. Careful study designs are also required to adapt dose and vaccination schedules from healthy adults to individual age categories in the elderly. This approach is necessary to reduce potential vaccination risks and optimize its benefits. Other risk categories such as 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 significantly increased risk of morbidity and mortality post exposure to a novel human influenza virus, the goal of clinical studies with the elderly and chronically ill people is to maximize vaccine efficacy (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 pediatric 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 ederly is provided (Table 1) but details on clinical design studies to be performed in specific risk populations are not covered in these guidelines. Due to the potential complexity such trial design should be discussed with the relevant NRA.

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[9].

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 defined stability testing program to justify the selected stockpile design 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 program should be approved by the relevant NRA and should include an agreed upon set of stability indicating parameters, procedures for the ongoing collection and sharing of stability data, and criteria to reject 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 about 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 is 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 for 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 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/Manufacturing

The general manufacturing requirements presented in section C.1 apply to the manufacture of pandemic influenza vaccines.

[9] http://who.int/vaccine_research/diseases/influenza/meeting_stockpile_181007/en/index.html

E.2.1 Stability criteria

It is anticipated that real time stability data would unlikely 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 prior to use of a pandemic vaccine.

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 pandemic strain antigen as quickly as possible. In these special circumstances it is anticipated that limited, 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. At minimum, data of the approved quality control (QC) release tests related to potency and safety should be available. Such a situation would be more likely to be acceptable if there had been accumulated experience with vaccines against novel human influenza viruses from the particular manufacturer.

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 seasonal 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, NRAs, and Indsutry). Refer to Section G for additional guidance.

E.4.1 Pediatric studies during an influenza pandemic

After a pandemic is declared, pediatric dose and schedule recommendations would be immediately needed, 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 likely be needed (*23-25*). Similarly to adults, it is anticipated that not previously vaccinated children will require at least two doses with one month interval between doses. In the case of seasonal influenza vaccines, seroconversion rates seem to increase with age from <50% in those <6 years to >80% in those >10 years, which likely 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 with 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 into the younger group as an emergency measure.

Clinical safety and immunogenicity data should be obtained for infants and toddlers. However, early in a pandemic, it may be necessary to extrapolate the adult pandemic vaccine and pediatric seasonal vaccine dose recommendations. This implies that seasonal influenza vaccine pediatric dose recommendations need to be well substantiated. Depending on legal constrains, data from pediatric 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 in a step wise approach (e.g. 6-12 months, 13-36 months, 3-6 years, 6-12 years, >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 pediatric clinical trial might be envisaged. It is recommended to seek advice from the NRA.

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

Pediatric safety studies should only be initiated after sufficient clinical data with the vaccine against novel influenza virus formulation is generated and acceptable proof of principle of safety and efficacy i.e. immunogenicity are obtained in healthy adults.

Since an indication for pediatric use would most likely be sought after initial licensure, pediatric safety and immunogenicity data may be submitted as a license 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 pediatric studies.

The general protocols and plans for pediatric 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 estimated of the feasibility of conducting pediatric studies during a pandemic.

- Choice of schedule: one important issue is whether pediatric 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 (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 many different schedules for different subpopulations may create problems for mass vaccination campaigns.

- Safety assessment: another issue is how much 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: there could be value to having early studies in place to address the vaccine impact on infectivity.

- Efficacy assessment: documenting clinical outcomes in a prespecified manner is important. For example, the vaccine efficacy in children may differ significantly from the inter-pandemic situation or may differ from 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 (QC) of pandemic influenza vaccines will be based on the processes and policies for seasonal influenza vaccines. Seasonal influenza vaccines should be produced under GMP conditions, tested for quality and safety by the vaccine manufacturer, and usually, subjected to independent QC testing by a National Control Laboratory (NCL). The vaccine may be used only when it has passed the tests at the NCL and has been released by the NCL. In a pandemic situation, vaccine QC performed by manufacturers and independent assessment by an NCL will also be required. In a pandemic situation, tests would be done in a high pressure environment with a much higher throughput than normal and where technical problems connected with the novelty of pandemic vaccines could interfere with efficient testing. In an inter-pandemic situation, vaccine QC will not be conducted 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 an NCL 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 LAL tests).

It is expected that NCLs normally engaged in seasonal influenza vaccine batch release, will also perform pandemic vaccine batch release. 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 pandemic vaccine QC, well before a pandemic starts and for NCLs to share their experience in order to minimize disruptions in vaccine supply. Some NCLs have already developed pandemic vaccine batch release procedures, others have not. Countries where such plans are not in place are strongly encouraged to develop plans 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 QC 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 QC testing of LAIV.

F.2 Quality control testing by vaccine manufacturers

F.2.1 Inactivated vaccines

Current experience with development inactivated H5N1 influenza vaccines suggests that a pandemic vaccine is likely to contain a reverse genetics-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 vaccine will be enormous. Nevertheless, all the normal QC 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 QC 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. Appendix V summarises the production and control of seasonal inactivated influenza vaccines according to WHO recommendations[2]. NCLs 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 (required by the European Pharmacopeia) protein 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 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 an NCL 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.

- Adventitious agent testing of cell culture-derived vaccines

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 that a comparison of in vivo and validated PCR tests are performed to substantiate the approach.

- Vaccine potency test

Vaccine potency is normally assessed by Single Radial Immunodiffusion (SRID) test. This test requires strain-specific antigen and antiserum reagents which normally require three

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 QC testing. Second, these reagents may be available, but they may not be useful to test final product due to 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 anti-serum, the use of alternative potency tests such as protein and/or SDS PAGE assays or mouse immunogenicity tests are 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 NCLs and acceptance criteria be defined prior to the pandemic.

When SRID reagents are available, they should be used to test bulk vaccine (also named monovalent pooled harvest[10] in one region of the world). Blending of vaccine into final formulation should be based on a potency agreed between the manufacturer and the NCL.

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 endotoxin test for batch release (required by the European Phamacopeia), the LAL assay should be evaluated by manufacturers and NCLs for possible interference by the adjuvant. If interference is likely, the LAL test should be done on the bulk vaccine before adding adjuvant.

F.2.2 Live attenuated influenza vaccines

In the event that a LAIV is used as pandemic vaccines, there would be similar concerns on rapid vaccine production and testing as 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 non-pathogenic 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 NCL.

[10] 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.

- Testing 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 NCL.

F.3 National Control Laboratory batch release procedures

F.3.1 Flexibility in National Control Laboratories batch release testing

Batch release of influenza vaccines by NCLs is essentially repetition of the important QC tests performed by a vaccine manufacturer. In a pandemic emergency, each NCL should agree on procedures to provide confidence in 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 NCL testing could be reduced to only key tests (refer to F.3.2) and/or testing could be done co-jointly between the vaccine manufacturer and NCL.

F.3.2 Batch release procedures for inactivated influenza vaccines

There are technical and logistic issues for pandemic influenza vaccines which could affect the NCL batch release process. Although there are significant differences between batch release procedures around the world, there is consensus on the key issues in NCL vaccine testing 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. The first priority should be given to review of the manufacturers' protocols and should always be part of the NCL batch release.

1. First priority: Protocol review

A protocol summarizing a manufacturer's QC test results shall be submitted to the NCL, preferably by electronic submission. The protocol should be based on the model supplied by WHO (*3*) but should also comply with national regulations.

2. Second priority, if time and resources allow, will be protocol review plus the following tests/activities:

   i. Vaccine potency test

   Where done, the NCLs should perform potency tests on bulk vaccine (before adding adjuvant) in parallel with manufacturers' tests to release batches. Alternative, validated potency test shall be performed on adjuvanted final product.

   The NCL 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, NCLs will not perform potency tests on final product. Manufacturers should formulate vaccine based on a potency agreed between the manufacturer and the NCL. This is done to enable

formulation from the bulk vaccine potency result with the required degree of confidence.

If tests on final product are required by an NCL (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, LAL test should be evaluated by vaccine manufacturers and NCLs for possible interference from adjuvant. If interference is determined, the LAL test would be done on the bulk vaccine before the adding adjuvant.

iii. Trend analysis

In extreme urgency in vaccine production and QC testing, there is scope for mistakes, which could affect vaccine safety and/or efficacy. Particular consideration should be given to monitoring the manufacturers' and/or NCL's QC 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 NCL and the national inspectorate to ensure compliance with GMPs 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 country of origin to another country, it is proposed that both countries NCLs work towards recognizing mutual batch release. This would avoid duplication of same batch release process by two or more NCLs. It is recognized that NCLs will require time, evidence and support to develop mutual confidence in the results of another NCL. 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 NCL to estimate their 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 on the likely number of pandemic vaccine batches and on the number of SRID tests required. This information should be provided to the relevant NCL 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 three months. In a pandemic, these procedures may not be adequate to ensure a speedy and adequate supply of reagents.

- International collaboration

In an emergency, there may be transport and import restrictions. The afore-mentioned 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 to perform calibration of new pandemic vaccine viruses either alone or using locally-developed networks which may include vaccine manufacturers and/or other NCLs.

- 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. NRLs and manufacturers should ensure that there are secured contractual arrangements in place (preferably with a back-up) for supply of antigen for QC 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 three 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, H9). National reference laboratories and manufacturers should ensure that the reagents from a library are acceptable for QC 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 pose any interference with the LAL test. During development of pandemic influenza vaccines, there should be an evaluation of interference in key QC tests. Methods to elute vaccine antigen from alum or other adjuvants should be evaluated and information shared between vaccine manufacturers and NCLs. 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 NCL in preparation for batch release testing.

F.3.8 Risk assessment

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

i. Are there sufficient personnel trained in influenza vaccine batch release to cope with the increased amount of testing? Should staff be required to work in shifts? Backup staff should be trained if necessary.
ii. Is there need for a back-up NCL?
iii. 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.
iv. Will the NCL's essential services be maintained during a pandemic when there may be high staff absences? This could include utilities (e.g. gas, electricity, and water), information technology and communications support, laboratory supplies and essential vaccine testing programmes.
v. 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.
vi. Will there be transport restrictions (including import/export) on SRID reagents and vaccines? A mechanism is needed to avoid such restrictions.
vii. 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 (i) large scale supply of antigen, (ii) availability of freeze drying facilities, (iii) availability of sheep, (iv) ordering and shipment of reagents, and (v) information exchange to other collaborating centres and vaccine manufacturers.
viii. Are there adequate storage facilities at the NCLs to handle the anticipated surge in samples for testing?

Part G. Post-marketing surveillance

G.1 General remarks

It is quite likely that limited immunogenicity and safety data, and no efficacy data would 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 the one 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 sub-groups, or potential vaccine-drug interactions. Safety experience with seasonal influenza vaccines may have only limited relevance due to changes in vaccine strain composition and manufacturing procedures to produce pandemic influenza vaccines. In consequence, the risks and benefits of pandemic influenza vaccines will need to be studied post-marketing.

Because of the likely extreme conditions of a pandemic, clear post-marketing surveillance objectives to evaluate effectiveness and safety of a pandemic influenza vaccine need to be agreed upon beforehand. Protocols should be developed to ensure that effectiveness and safety of the pandemic vaccine are adequately documented, analyzed and assessed during use in the field. Post-marketing surveillance preparedness plans should enable authorities to quickly and adequately assess vaccine safety, immunogenicity and effectiveness, thereby making evidence-based decisions concerning any necessary changes in vaccination programs (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 NRAs (if necessary) in advance. A need for flexibility, constant real-time review, and adaptability to changing plans and study designs of post-marketing surveillance will arise. Therefore, it is important to determine feasible and realistic conditions of post-marketing surveillance in different scenarios.

Setting up a post-marketing surveillance plan to respond to an influenza pandemic would facilitate adequate response to public concerns and maintain the public confidence in the vaccination programme. The sharing of post-market information (e.g. safety signals) is important, especially for those countries that do not conduct routine post-market surveillance. Such post-marketing preparedness requires collaboration between all stakeholders, WHO, Public Health Authorities, NRAs, and industry.

G.2 Post-marketing considerations for vaccines against novel human influenza viruses

With limited knowledge on immunogenicity and safety, and no knowledge on efficacy regarding cross-protection with a pandemic strain, some governments might plan to stockpile vaccines against novel human influenza viruses and immunize certain 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 safety and immunogenicity data. 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 pre-requisite, 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 post-marketing 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 prior to the pandemic in all age groups, pregnant women and representative numbers of patients with co-morbidities is highly unlikely, even unfeasible.

When feasible, the following parameters may be considered:

<u>Immunogenicity:</u>

- 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. Sufficient serum volume 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 in contact with an avian (i.e. non-pandemic) influenza virus (e.g. poultry workers, cullers, veterinarians, 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 among countries. In general principle, follow-up strategies should be based on the best available information and requires collaboration of all stakeholders (i.e. NRAs, health authorities, vaccine manufacturers, 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 such opportunity will not longer be available once the 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 population fractions with vaccines against novel human influenza viruses within a short time period, 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. Ad-hoc additional safety reports may be of importance. The format and periodicity of reporting may be the same as for pandemic vaccines. If a safety signal would arise, reactive hypothesis testing studies might be warranted.

G.3 Post-marketing considerations for pandemic influenza vaccines

G.3.1 Implementation of post-marketing surveillance

Pharmacovigilance and epidemiological surveillance systems will most probably be weakened during a pandemic possibly resulting in limited 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 overly time-consuming and non urgent activities. In order to avoid duplication of work, stakeholders should clarify responsibilities beforehand.

Some countries already have in place or are in the process of establishing or enhancing surveillance systems for seasonal influenza vaccines. Some systems may also meet the post-marketing 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 program ensuring that pandemic vaccine post-marketing surveillance systems provide robust and reliable information. Therefore, critical assessment of the strengths and limitations of the post-marketing systems would facilitate meeting the public health needs in 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, elderly) as pandemic influenza vaccines might target the whole population.

Data sharing with regard to effectiveness/efficacy and safety of seasonal influenza vaccines among different countries should be used as a pilot to test 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, specific risk groups) and follow up approach
- Differences in vaccine distribution and immunization setting e.g. workplace, community centres, general practitioners
- Different type of vaccines used in different countries (safety and effectiveness information should be available on all vaccines)
- Differences of health system organization
- Availability of data sources and surveillance in place for seasonal influenza illness and seasonal influenza vaccine (safety and effectiveness/efficacy)
- Study protocols already in place for investigating pandemic influenza vaccine safety in some countries
- Availability of large electronic databases and pre-existing data collection methods.

It is unlikely that a single post-marketing surveillance method will fit 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 effectiveness and safety data as a basis for operational decisions and model predictions
- Comprehensive analysis of safety and efficacy data by sub-groups, e.g. children stratified by age categories, adults, elderly, pregnant women, patients with chronic disease and immuno-compromised patients
- Post-marketing surveillance protocols and detailed work plans 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 to influenza vaccine and those associated to 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 influenza vaccine safety and effectiveness information. Furthermore, provision should be made for the international exchange of such data and the associated risk-benefit assessments.

National public health authorities, WHO, NRAs and vaccine manufacturers need to assess their capacities in anticipation of a pandemic crisis. The probability to handle large data sets within a short period of time is high in pandemic. Resource issues in the case of a pandemic should be critically evaluated. Provisions should be made to provide necessary resources in terms of personnel, technical equipment and tools to properly collect, manage and assess data to respond to public needs.

G.3.2. Pharmacovigilance Activities

The safety data available for 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, probably, not relevant in a pandemic. Post-pandemic evaluation for delayed adverse events, using routine pharmacovigilance (i.e spontaneous reporting of AEFIs, Periodic Safety Reports (PSR)) may be supplemented, if necessary, by ad hoc epidemiological studies. Therefore, preparedness considerations are required for:

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

G.3.2.1 Routine Pharmacovigilance

Spontaneous reporting

The potential postal service disruption and limited availability of health care professionals in a pandemic require the development and/or strengthening of alternative channels of reporting adverse reactions i.e. via fax, telephone or electronic transmission. The functionality and validity of these systems should be tested before the pandemic. Due to postal back logs, consideration should be given to discourage 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 or/and electronic transmission fail, telephone might work).

Simplified reporting forms for health care professionals and consumers should be developed to enhance compliance in a crisis situation. 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, Bells 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, EMEA EudraVigilance). These events should ideally be reported within less 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 a national license for the WHO Vigibase are advised to contact directly the Uppsala Data Monitoring Centre (WHO Programme for International Drug Monitoring and the Uppsala Data Monitoring Centre) via the following weblink: http://www.who-umc.org/DynPage.aspx . In absence of a national pharmacovigilance centre, expanded programs on immunization are also encouraged to submit AEFIs data.

As a minimum requirement, frequent exchanges (e.g. every 2-3 days within the first few weeks post-vaccination, weekly thereafter) of line-listings (according to the relevant Council for International Organizations of Medical Sciences format http://www.cioms.ch/cioms.pdf) might be acceptable where no AEFIs database 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/arthralgia), Case definitions may be developed (e.g. for each high priority- reaction should be developed with corresponding Standard MedDRA Queries. 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 GBS. Harmonized reporting rules, language and dictionaries across countries may be considered. Vaccine failure should not be prioritized,

as there will likely 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 many vary among different batches, therefore retrieval for different batches is necessary. Rapid transmission of safety information is essential. AEFIs should be communicated by vaccine manufacturers to NRAs ideally within 15 days. NRAs may consider working with the media and using it in information campaigns to educate the public on identifying reportable adverse reactions.

Periodic Safety Reports

Periodic safety reports (PSR) by manufacturers may provide an opportunity for aggregated summary safety data. These reports should be product-specific, simple to prepare and assess. The periodic safety reports should be more than a duplication of AEFIs case data 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 four to six weeks after start of vaccination and less frequent thereafter. The PSR may contain the number of all AEFIs in the reporting period , fatal AEFIs, life-threatening AEFIs, AEFIs of interest (e.g. allergic reactions requiring immediate resuscitation, 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 disproportionality 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. Vaccine distribution data 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 NRA s to compare between vaccines for possible differences in safety profiles.

Signal detection

The generation of a large amount of safety information is expected to arise 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 adverse event signal detection.

Already existing tools should be used and ideally adapted for influenza vaccine issues. 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 conducted 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/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 strengths and limitations of the method and avoiding possible misinterpretations or false alarms.

Programmatic errors

Improper handling of vaccines prior to, or during, immunization sessions may lead to infections, bacterial contamination and abscess formation, especially if multidose container vaccines without preservative are used. General guidance of the WHO (*15*) should be followed in this respect.

G.3.3 Additional pharmacovigilance activities

Post-marketing surveillance should address safety issues specific for 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, 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, adjuvanted vaccines).

G.3.3.1 Methodological considerations

Post-marketing safety study protocols should be developed beforehand. Key issues to be addressed are:

- target population to be studied,
- sample size,
- outcomes to be studied,
- analysis and control groups,

- data sharing, and
- post signal detection follow up.

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 immunised 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 an ongoing basis (e.g. through web-based system). Automated procedures to detect predefined adverse events may help to identify potential safety issues as soon as possible. Statistical analysis may be performed at defined time periods or based on some triggering events. Ideally, decision rules 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 pandemic vaccine safety profile compares to the historic data from inter-pandemic vaccines, or
- whether it is comparable with the clinical phase I-III data of a vaccine against a novel human influenza virus.

Possible methods to analyse influenza vaccine safety data include:

- relative risk (and confidence intervals) with stratification by age and other relevant risk factors,
- historical comparison, and
- observed versus expected analyses.

Pooling of data might increase the power of statistical analyses especially for risk-subgroup-level analysis.

G.3.3.3. Target population

The target population for a post-marketing study should include groups not covered in clinical trials conducted in the inter-pandemic phase. Subgroups (e.g. first responders such as health care professionals and their family members) likely receiving early vaccination may be selected for participation in post-marketing studies. Other groups that might be vulnerable to influenza and vaccine adverse events (e.g. elderly, children, pregnant women) need to be included in post-marketing surveillance. Studies might also be conducted in children's homes, kindergarten and schools. Adequate sample size for important subgroup analyses should be justified and documented by power calculations.

G.3.3.4. Randomized clinical trial

As randomized clinical trials provide the highest level of evidence, such 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 allocated for late vaccination) to both the vaccine-receiving and non-receiving groups. If there is insufficient vaccine for all eligible people, it might be ethically acceptable to randomize them also. Effectiveness and immunogenicity of pandemic-specific strains may also be addressed 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 for some countries to assess risks associated with the use of pandemic vaccines in a pandemic. It might be possible to identify a cohort who will receive vaccination very early (e.g. high risk group, first responders) and an unvaccinated cohort who will receive vaccination later.

The same holds true for situations where the strain in a vaccine against a novel human influenza virus is close enough to the pandemic strain and vaccine stockpiles will be used in certain target groups in the very early pandemic phase when pandemic vaccine would not be available yet.

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

Observational studies provide simple methodology to demonstrate that the safety profile of the pandemic vaccine is acceptable under real life conditions. The pandemic vaccine safety would be investigated in a predefined number (e.g. few thousands) of vaccinees 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 vaccine reactions and may be useful in 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 do not probably exist in many countries include the electronic network and legal framework to extract patient-based information from electronic systems to be used by health care professionals. If such systems exist or are currently developed, testing of these systems in the inter-pandemic period might

be useful. These databases might also be useful for evaluation of delayed AEFIs and effectiveness of pandemic-specific strains.

G.3.4 Immunogenicity and efficacy/effectiveness

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

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 analyze 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. Methods to use will depend on 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 pre-vaccination person-time could be useful). The analysis of data from electronic registries or highly linked databases may only be feasible 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 vaccine introduction 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 with pre-defined allocation for vaccination might also be conducted, especially to prioritize the target population for vaccination. If plans to prioritize vaccination in the first wave (e.g. first responders will receive vaccination early) exist, identification of the cohorts and detailed study plan should be possible in the inter-pandemic phase.

Continuous assessment of vaccine effectiveness during the whole pandemic is essential to detect possible virus drift and to enable Public Health Authorities to modify, if necessary, the vaccination program. The extension of the follow-up period into a subset of the cohort population 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. This objective may also be addressed via sentinel reporting of clinical disease during the whole pandemic. Clinical data should be linked with laboratory surveillance data.

Some countries might choose a stepped wedge design for post-marketing surveillance of the effectiveness of a vaccination program. 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 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 NRA's and/or Public Health Authorities. Any hold-up in this process may cause serious decision making delays with serious public health implications.

G.3.5.1 Endpoints

Laboratory confirmation of influenza virus may not be feasible as the primary endpoint for post-marketing surveillance of effectiveness in the entire population, but only for a population subset to be defined. 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 that the primary analysis should focus on overall mortality of pneumonia and influenza clinical mortality. 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 should be provided regardless of time in relation to vaccine doses. All vaccine failures (as defined) and any other breakthrough cases should be investigated in detail.

Case definitions should be used for diagnosis of primary endpoint(s) (e.g. WHO definition of clinical disease, definition for need for hospitalization, 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 critically important that the individuals to most likely initiate possible case detection have clear instructions related to criteria for stimulating contact with designated healthcare professionals, telephone contacts, initial and further investigations once a case is confirmed.

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

G.3.6 Post-marketing 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. Post-marketing surveillance of safety and effectiveness in particular target groups is recommended to enable NRAs and health authorities to review the adequacy 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 in infants and adults. These age differences in immune response might translate into differences of efficacy and safety of

certain types of pandemic influenza vaccines. Targeted surveillance of effectiveness and safety in different age categories is thus warranted.

G.3.6.2 Pregnant women

Based on seasonal influenza morbidity pregnant women are considered to constitute a risk group for influenza-related complications and public health authorities might therefore recommend vaccination in pregnant women. On the other hand, pregnant women will most likely not 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 pandemic influenza vaccines (as they will be new vaccines perhaps in new formulations) in humans will be limited.

Live attenuated influenza vaccines are usually not recommended during pregnancy, but there might be circumstances where these 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 unknown 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 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 with seasonal influenza vaccines. In this respect, capability of already existing pregnancy registries or currently running epidemiological studies should be evaluated. Studies with pandemic human influenza vaccines 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 as risk benefit balance might deviate from 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, subunit vaccines with and without adjuvants, preservatives and excipients) have to be considered. Safety concerns associated to different types of vaccines should be addressed in the post-marketing 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 compared to the naturally infected. However, some LAIV are very rarely linked to 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 during a time 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 to properly assess these cases.

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

G.3.7.2 Immunological adjuvants

Post-marketing surveillance will depend on the type of adjuvant and the results of the non-clinical 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 post-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 drugs 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 to the benefit. As a rapid health benefit is expected to become evident for the individual vaccinee, certain probability of adverse event(s) might be acceptable for the individual, even if the incidence of adverse event 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 benefit risk assessment may differ in different target populations.

The benefit of a pandemic influenza vaccine may decline for an individual as vaccine coverage rises, the disease incidence decreases, and herd immunity occurs. 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 rate 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 post-marketing surveillance include:

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

Depending on 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 vaccine safety information exchange during a pandemic. All 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 case, vaccine manufacturers may not be requested to repeat adequate 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 initiative should meet the needs of interested stakeholders including lawyers, 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 critically important, is 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 outstanding data without causing panic. An essential part of the latter would be giving clear instructions for reporting suspected vaccine adverse events.

Communication might differ depending on the vaccine type (e.g. whole virion, cell culture, 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 information exchange of serious concerns regarding pandemic influenza vaccine safety and effectiveness with possible public health impact. This may include any measures that lead to a change of vaccination strategies.

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

Post-marketing surveillance data should be made available to WHO in order to contribute to strategic decisions about global influenza control.

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APPENDICES

NOTE: the information presented in the appendices is current as of (26 November 2007). Please refer to the respective National Regulatory Authority (NRA) websites for the most up-to-date information. The website links are provided below.

Country	NRA	Website
Australia	Therapeutic Goods Administration	www.tga.gov.au
Canada	Health Canada	www.hc-sc.gc.ca
European Union	European Medicines Agency	www.emea.europa.eu
Japan	The Ministry of Health, Labour and Welfare	www.mhlw.go.jp
United States of America	U.S. Food and Drug Administration	www.fda.gov

Appendix IA: Overview of five selected National Regulatory Authority Pathways to Pandemic Influenza Vaccine Licensure

See Appendix IB 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. The 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 flu vaccine, TGA require a full submission including quality data, preclinical data and clinical data. Data expectations would accord with general CPMP guidance for 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 there are changes to strains 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 EMEA guidelines 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 authorised during interpandemic period.

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

The TGA and 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:
For pre-pandemic vaccine:
Products containing ingredients of human or animal origin evaluated for TSE safety

Special Clinical Data Requirements:
For pre-pandemic vaccine:
human immunogenicity and safety studies including all age groups (especially children) and patients with some disease states, (to give confidence in the registration decision)

Canada

Regulatory Authority: Influenza vaccines are regulated by Health Canada/Health Products and Food Branch/Biologics and Genetic Therapies Directorate (BGTD) pursuant various provisions of the *Food and Drugs Act & 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 data set in support of the safety, efficacy and qualify of the vaccine as well as product-specific facility information that outlines the method of manufacture of the vaccine in significant detail. Further, an on-site evaluation is completed to assess the production process and the facility as it impacts 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 pre-dates some of the regulations being applied to new vaccines. Additionally 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 approved via the filing of an amendment to the existing license, 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 vaccine with the new strains.

During the 2000-2001 flu season, an increased number of influenza vaccine associated adverse events 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 are required to submit clinical trial data for their products, to assess the tolerance and efficacy of the vaccine in two groups of health volunteers, aged between 18 and 60 and over 60, as per the CPMP guidelines.

Consequently influenza vaccines for annual administration require an initial NDS authorization, with yearly updates of annual strain variation information. 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:

a. data to support the quality of production of the vaccine, as it relates to the new strain, plus any improvements/alterations to the production process;
b. data from two small clinical studies (generally ~ 50 patients each, in 18 - 60 yr old and > 60 yr old patient groups), to assess the tolerability and immunogenicity of the vaccine; and,
c. 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 have many have significant differences from a seasonal influenza vaccine. Therefore the regulatory process for a pandemic vaccine, while in many respects similar to that of the seasonal influenza vaccine, will accommodate these factors and assumptions. The regulatory process for approval of a pandemic vaccine will be that of an NDS and not of an amendment to an existing license 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 via clinical trials of a pre-pandemic vaccine. 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 they become available. It is anticipated that the majority of substantive information will be provided for the pre-pandemic vaccine, which will be considered representative of both the type and manufacturing for the pandemic influenza vaccine, and of some comparative utility for the safety, and efficacy / immunogenicity determinants. 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 programs.

In advance of an actual pandemic, protocols must be in place to both 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 post-market conditions.

Clinical Trial Applications 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 based on 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 carried out by studying pre-determined target populations during the pandemic. These should be addressed as part of the NDS filing, as conditional post marketing studies.

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 pandemic influenza vaccine, in order to protect the health, safety and security of all persons resident in Canada. In December 2006 Health Canada issued specific guidance to the contract manufacturing on the manufacturing and clinical information required to support licensure, as well and 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 for 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 adequate specification controls and limits, and specific batch information, are expected to be provided for the manufactured lots of:
    - the inter-pandemic vaccine used in clinical trials
    - the pandemic vaccine clinical trial material
    - 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, shall 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 shall be required;
- stability data and protocol for stability testing of pandemic vaccine
- viral safety data

Special Requirements regarding Clinical Data:

- pre-clinical and clinical safety and immunogenicity data 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 pre-clinical and clinical results derived with the inter-pandemic vaccine(s) should aid in determination of the
    - safety of the adjuvant used in the vaccine's formulation;
    - formulation of a vaccine appropriate for immunization of a naive population;
    - clinical trial requirements to assess the safety and efficacy of the pandemic vaccine
- a complete clinical safety and efficacy trial plan, including anticipated time lines, to generate the necessary data during the pandemic period, and to provide it for regulatory review (prepared during the inter-pandemic period)
- any available clinical safety and efficacy data for the pandemic vaccine.

Accelerated Approval Options/Emergency Use Provisions:

An NOC shall be issued only if complete quality, safety and efficacy /effectiveness data are provided, and an acceptable risk-benefit profile, in full compliance with the *FDA &R* can be demonstrated. If sufficient data for the pandemic influenza vaccine(s) is not provided, or not

available for evaluation at 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 EUND is a drug that would be used to treat, mitigate or prevent a life threatening or serious health condition in humans which result 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 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, and in cases such as pandemic influenza, time lines do not allow for full clinical testing of vaccines against the virus causing the pandemic. Under the current regulations, the absence of safety and clinical efficacy data limits that 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 human clinical safety and efficacy data, if it becomes available, or to conduct post-market 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, adverse drug reaction reporting, recall, 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 (SAP)

The 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 where Canada has a public health crisis and does not have approved product. Release would be to Surgeon General of the Department of National Defence, the F/P/T senior medical officer or medial officer designated by the Surgeon General.

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 immunize certain risk groups while, at the same time, accumulating clinical data to support approval and broader use of the vaccine.

European Union

Regulatory Authority: Directive 2001/83/EC, as amended, and Regulation (EC) No. 726/2004 of the European Parliament and Council, specifies the procedure for submissions to EU member states (decentralized and mutual recognition procedure) and to the EMEA (via the centralized route) respectively. Article 8 of Directive 2001/83/EC specifies the requirements for marketing authorization applications in Europe.

Submission Type and Application: The marketing authorisation for a new medicinal product is granted through three procedures: centralised, decentralised and mutual recognition procedure. 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 centralised 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 auto-immune disease and other auto-immune disorders and viral disease.

Other medicinal products containing a new active substance, or for which the applicant shows that it 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 optimal (on 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) who makes a final decision in granting of the European Community marketing authorisation. A European Community authorisation is valid throughout the whole of the European Union and is usually given for five years. Once renewed, the marketing authorisation 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 six months before this five-year period expire.

Under the Mutual Recognition Procedure, the applicants seek to have an existing authorisation recognised 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 Reference Member State (RMS) and it should notify this decision to the other Member States. This procedure is completed within 90 days. In case of a new product, the applicant has first to submit his application in one of the EU member states for authorisation. This member state will become the Reference Member State. Only afterwards, the 90-day mutual recognition procedure can start.

Annual Influenza Vaccine Licensure: Currently, all seasonal influenza vaccines in Europe as authorized via 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 part concerns the assessment of the administrative/quality data (Summary of product characteristics (SPC), patient leaflet, labelling and the chemical, pharmaceutical and biological documentation). The second part concerns the assessment of the clinical data. Results of clinical studies are required according to the *Guideline Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/ 214/96). A similar fast-track variation procedure exists in the centralised 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, non-clinical 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" authorisation of pandemic influenza vaccines as new (full) marketing authorisations, not variation to seasonal vaccine. Most scientific aspects as well as product information (doctor / patient leaflets) can be considered before a pandemic and can be approved in interpandemic period.

In 2005, EMEA published the guidance *Core Summary of Product Characteristics (SPC) for Pandemic Influenza Vaccines.* The aim of this guideline is to standardize SPCs for all inactivated pandemic influenza vaccines, thereby facilitating the submission of core dossiers. Under this guideline, product information will be approved as part of the core dossier authorization and minimal changes only needed as part of the pandemic variation approval (only information related to pandemic strain). The pre-pandemic vaccine will be produced (ideally) in same way as intended for 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:

- vaccine reference virus (development, testing)
- vaccine seed lots (production process, testing, extraneous agents)
- vaccine production: Production process
- Formulation (multidose: test for antimicrobial preservative)

- Vaccine standardisation (development of alternative tests to standardise the vaccine)
- Adjuvant
- Stability data and protocol for stability testing of pandemic vaccine

Special Requirements regarding Clinical Data:

- Immunogenicity (chicken, mice, ferrets)
- Non-clinical safety: the extent of the programme depending on composition of pandemic vaccine if entirely new production process: complete programme
- Novel adjuvants (no experience in humans): safety profile to be investigated separately & in combination with influenza virus antigen
- Challenge experiments in mice, ferrets, other animals should be performed unless the applicant provides justification (for not performing such experiments)
- Data from healthy adults of various age groups; data from children to be gathered post-authorisation
- No protective efficacy trials → characterisation of immunological response to pre-pandemic vaccine
- All criteria for annual influenza vaccines to be met
- Neutralising antibodies to be studied
- Formulation – dose finding – vaccination schedules
- Safety and immunogenicity study
    - Larger study, based on the results of dose finding study
    - Establish safety database (size of study should be sufficient to detect adverse events at a frequency of 1%)
    - Safety follow-up at least 6 months
- Post-authorisation commitments
    - Protocol for evaluation of immunogenicity, effectiveness and safety of pandemic vaccine
    - Data in children

Accelerated Approval/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 (on manufacturing, on testing, any preclinical data, relevant clinical data form pandemic-like strains etc). 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 license).

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 basis of a very limited data package and very short after the vaccines becoming available :

- Accelerated review process (max 150 days, can be shortened on agreement of the CHMP; art 14(9) of Regulation (EC) No 726/20004)
- Conditional marketing authorizations (Commission Regulation (EC) No 507/2006), which allow, in case of medicinal products to be used in emergency situations in response to public health threats, for authorization on basis of a limited data package. In emergency situations,

such a conditional marketing authorization may be granted even if comprehensive clinical, non-clinical and quality date are not available at the time of submission. Such marketing authorizations are linked to strict commitments to provide the missing clinical and non-clinical information within a defined timeframe.

Japan

Regulatory Authority: The Pharmaceuticals and Medical Devices Agency (PMDA) reviews pharmaceuticals and medical devices, based on the Pharmaceutical Affairs Law (PAL) (Law 145, 1960 revised 2002). The Ministry of Health, Labour and Welfare (MHLW) has the authority of approval upon the output of PMDA's review. PMDA also gives guidance and advice concerning clinical trials. The 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 a New Drug Application (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 NDA review process, based on demonstrated quality, safety and effectiveness of the product reviewed through PMDA's scientific review process.

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

Timelines: NDA standard review period: 12 months, priority review for 6 months

***Proposed Pandemic Regulatory Pathway**:* MHLW and PMDA request a manufacturer who is producing vaccine against novel human influenza viruses (pre-pandemic and pandemic type) to file NDA pursuant to PAL. 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 phases of pre-pandemic and pandemic influenza, is given based on the quality, non-clinical and clinical data of the potential pandemic vaccine. In pandemic phase, vaccine is manufactured by the approved procedure using pandemic influenza strain. Once a vaccine against a new influenza subtype has been approved, further clinical data with a variant of that subtype which is circulating in the pandemic period would likely not be needed for approval.

Special Requirements regarding Quality and Manufacturing data: As for all vaccines the requirements of formulation, vaccine production and production control; standards of final and in processing; excipients including adjuvant; stability and stability protocol will be required.

Special Requirements regarding Clinical Data:

- Immunogenicity in animal including challenge tests
- Non-clinical safety
- Clinical data from healthy male adults (appropriate dose and schedules)
- Clinical data from healthy adults (confirmatory trials from age group under 65)
- Safety; clinical laboratory tests, signs and symptoms and physical checkup

- Effectiveness: serum HI antibody, NT antibody
- Post licensure studies: Children, Cross-reactivity.

Accelerated Approval Options/Emergency Use Provisions: Vaccines against novel human influenza viruses can be designated to priority review, according to the priority review provision of the PAL. In an emergency, provided that the pre-pandemic/pandemic vaccine is being developed, MHLW will be granting conditional emergency approval, depending on the extent of the data available at that point.

United States of America

Regulatory Authority: Influenza vaccines are regulated by the Food and Drug Administration/Center for Biologics Evaluation and Research/Office of Vaccines Research and Review (OVRR) pursuant to Section 351 of the U.S. Public Health Service Act and specific sections of the U.S. 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 issued 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 waived as not applicable to the biological product or when an alternative method is adequate to substantiate effectiveness.

Annual Influenza Vaccine Licensure: Each year, any of the previous three vaccine strains may be replaced with a new strain. Strain changes are based on evaluation of circulating wild-type strains. Submission of a prior approval manufacturing supplement to an existing BLA is required for strain changes. FDA does not require clinical data for approval of these annual supplements for licensed manufacturers of inactivated flu vaccine

Timelines: BLA Standard Review: 10 month review (Priority 6 months); 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 seasonal influenza vaccines. 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.

Special Requirements regarding Quality and Manufacturing data:

- 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/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
- Specifications and analytical methods for drug product ingredients

Special Requirements regarding Clinical Data:
Original BLA of 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:

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

Original BLA of a manufacturer whose pandemic influenza vaccine is manufactured by a process not already licensed by the FDA for the production of annual influenza vaccine:

- data from adequate and well-controlled clinical trials establishing a vaccine effect on surrogate endpoints likely to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic or other evidence. Immune response may serve as surrogate endpoint.
- study with adequate power to assess co-primary endpoints-GMT and seroconversion
- assay performance data
- protocols for post-marketing 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/ Emergency Use Provisions:

Accelerated Approval of New Biologic Products for Serious or Life-Threatening Illnesses:
Accelerated approval allows products that treat serious or life-threatening illnesses to be approved based on successfully achieving an endpoint 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 existing treatments (e.g., ability to treat patients unresponsive to or intolerant of, available therapy, or improved patient response over available therapy). 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 the then-existing treatments, in short supply. Confirmatory post-marketing studies are required.

Emergency Use Authorization (EUA):

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;
- 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 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 FDA. Data can be provided through pre-IND or IND submissions and discussion of ongoing and future development plans, as far in advance of need as possible. This would be characterized as a Pre-EUA. 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 and completed studies and the nature of the emergency. EUA use of a product 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 in which this could be done, may depend on multiple factors such as the adequacy of data provided in advance, the nature of the emergency, and the adequacy 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 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 significant known and potential risks and benefits from the product and to provide the option to accept or refuse the product.

Investigational New Drug (IND) 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 pandemic spread is rapid and vaccine is needed prior to the completion of the licensure process, state and local health departments should be prepared to distribute unlicensed vaccines under FDA's IND provisions. 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 (IRBs) in hospitals, health departments, and other vaccine-distribution venues. The FDA regulations permit the use of a national or "central" IRB.

Appendix IB: Overview of five selected National Regulatory Authority pathways

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Regulatory Authority	Therapeutic Goods Act, 1989 and Therapeutic Goods Regulations, 1990, Trade Practices Act, 1974 Quarantine Act of 1908	Food and Drugs Act and Regulations Public Safety Act	Directive 2001/83/EC, Article 8 – marketing and authorization application, Regulation (EEC) 726/2004 – submission to the EMEA through centralized procedure.	Pharmaceutical Affairs Law (PAL) (Law 145, 1960 revised 2005) Infectious Diseases Law (revised name 1998)	Section 351 of Public Health Service Act Food, Drug and Cosmetic Act
Submission Type	Category 3 Application	New Drug Submission (NDS): including an On-Site Evaluation	Centralized Procedure (CP) Mutual Recognition Procedure (MRP)	New Drug Application	Biologics License Application (BLA)
Timelines	Category 3 Application = 45 days after receipt of application	NDS – 300 days standard 180 days for priority	CP – 210 days + EC 30 days, MRP – 210 days (initial national authorization) + 90 days (mutual recognition)	12 months for regulatory timeline (6 months for priority review)	BLA standard review – 10 months, Priority 6 months, CMC Supplement 4 months

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Annual Influenza Vaccine Licensure	Full submission required, including quality, pre-clinical and clinical data (in accordance with general CPMP guidance for new vaccines)	Filing of an amendment to the existing license, in which manufacturers submit for review their revised labeling material , any CMC updates pertaining to the new strain and limited clinical data to support tolerablility and immunogenicity	A special Fast Track Type II variation procedure is applicable for annual variation human influenza vaccines.	Manufacturers would submit for review their revised labeling material for the new yearly strain. NCL review the strain changing data.	Submission of a prior approval manufacturing supplement to an existing BLA is required for strain changes (chosen yearly, based on circulating wild-type strains)
Proposed Pandemic Regulatory Pathway	TGA accepts EMEA guidelines on pandemic vaccine licensing.	Submission of an NDS and not an amendment to an existing annual influenza license.	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.	MHLW and PMDA request a manufacturer who is producing vaccine for novel human influenza viruses (pre-pandemic and pandemic type) to file NDA pursuant to PAL.	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. The amount of data a manufacturer would be required to submit with its pandemic influenza vaccine BLA will depend on whether

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
					the manufacturer already has a licensed influenza vaccine, and if so, intends to use the same manufacturing process for its pandemic vaccine.
Inter-Pandemic Vaccine	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)	http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf http://www.emea.eu.int/pdfs/human/vwp/498603en.pdf	Approval is given, based on dossier demonstrating quality, safety and efficacy data during interpandemic period. Testing protocols and data requirements are addressed in the consultation process of the review agency in collaboration with NCL	See above

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Inter-Pandemic Uses	*Same as Europe*	HC must be able to validate productions process, test production capacity and establish minimum standards and requirements for safety and efficacy.	The core dossier is not be used out of the pandemic context. For vaccines containing avian strains with pandemic potential (such as H5N1), CHMP has adopted a draft Explanatory note, identifying dossier requirements. Such avian influenza vaccines for human use must be based (entirely) on the circulation influenza strain against which protection is claimed.		
Quality and manufacturing requirements	Data obtained in interpandemic period. Same for all uses.	• production and testing of vaccine seed lot manufacturing process and validation • specifications • adjuvant, excipient, container and preservative information	• vaccine reference virus development and testing, • vaccine seedlots production process etc. • formulation • vaccine standardization • adjuvant • stability data and	Controls and characterization for seed lots and vaccines; • process controls • tests for bulk materials • formulation • stability studies	With adequate controls and characterization, FDA permits use of recombinant or cell culture based technologies in strain production. Either a reassortment or wild type virus.

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
		• batch analysis • reference standards • stability information • product specific facility information • viral safety info	protocol		
Clinical data requirements	Data obtained in interpandemic period Different depending on use; A. Stockpiling for use at beginning of the pandemic B. Use for people at high risk (poultry workers) C. Use as prime and boost population at large Human immunogenicity and safety studies	• challenge studies in animals • local tolerance studies • clinical (immunogenicity) studies on healthy adults • targeted studies on vulnerable • protocols for post-market studies, including any necessary informed consent document	• immunogenicity & safety • non-clinical safety • novel adjuvant • challenge experiments • human clinical data • formulation • all criteria for annual influenza vaccines • post-authorization commitments	• immunogenicity and safety • comparative analysis • post-authorization commitments	Original BLA: See US FDA guidance: http://www.fda.gov/cber/gdlns/panfluvac.pdf Dependent upon whether manufacturer currently produces annual influenza vaccine using FDA licensed process and uses same process for the pandemic vaccine..

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Accelerated Approval/ Emergency Use Provisions	Pandemic Declared –Core Pandemic Dossier using the actual pandemic strain and submit quality/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.
Emergency Use Additional Requirements		• Expedited Review • Notice of Compliance with Conditions • Special Access Programme (SAP) • Interim Orders • Clinical Trials	In case a pandemic occurs before a core dossier is approved: Emergency authorization to be used, relying on very close interaction between the manufacturer and the EMEA using a rolling review process of data packages before the submission of a formal application.		• Accelerated approval of new biologic products for serious or life-threatening illnesses • Emergency Use Authorization (EUA) • Investigational New Drug (IND) Use
Guidance Published			Y		Y

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Regulatory Pandemic Plan WHO has issued a global influenza pandemic preparedness plan (http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5/en/).	http://www.health.gov.au/internet/wcms/publishing.nsf/Content/phd-pandemic-plan-5b.htm	http://hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/vac/pandemicvaccine_nov2005_e.html	EU Core Dossier http://www.emea.eu.int/pdfs/human/vwp/39740305en.pdf	http://www.mhlw.go.jp/english/topics/influenza/index.html page 13 and 17.	http://www.hhs.gov/pandemicflu/plan/ http://www.fda.gov/oc/op/pandemic/default.htm

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3167 **Appendix II: Regulatory Pathways for Human Pandemic Influenza Vaccine**

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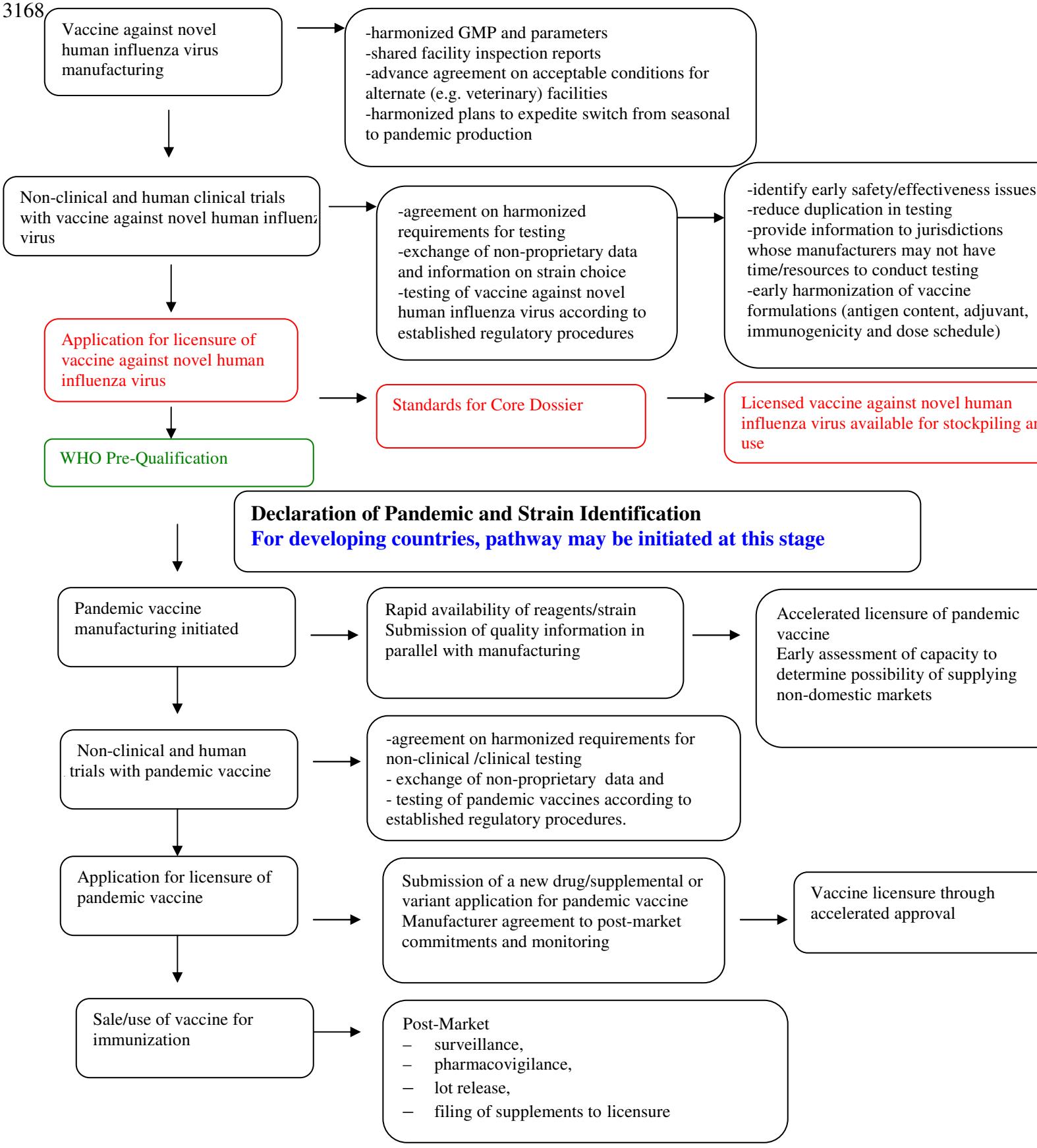
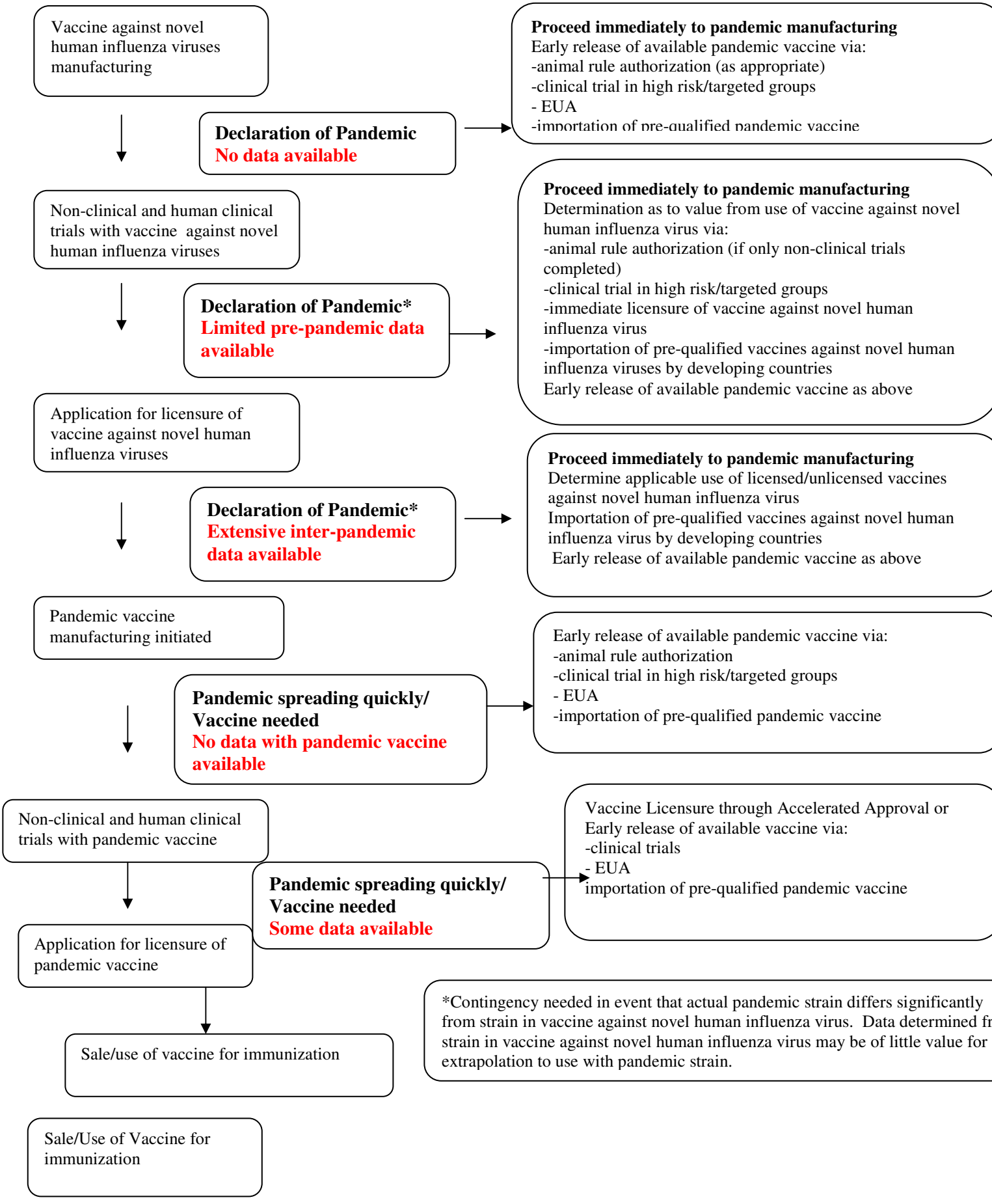


Appendix III: Emergency use pathways for human pandemic influenza vaccine



Appendix IV: 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 TGA with the following notation
Sponsors should note that Section 2 of this guideline (which refers to mandatory testing) is NOT adopted, however 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/EEC), 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

Harmonisation of Requirements for Influenza Vaccines Adopted by TGA July 1994
http://www.tga.gov.au/docs/pdf/euguide/vol3a/3ab14aen.pdf

Cell Culture Inactivated Influenza Vaccines - Annex to Note for Guidance on Harmonisation of Requirements for Influenza Vaccines CPMP/BWP/214/96 (EMEA Guidance)
Effective: 5 March 2003 http://www.tga.gov.au/docs/pdf/euguide/bwp/249000en.pdf

Guideline on the Scientific Data Requirements for a Vaccine Antigen Master File (VAMF) (EMEA Guidance) Published: TGA Internet Site Effective: 24 August 2004
http://www.tga.gov.au/docs/pdf/euguide/bwp/454803en.pdf

Guideline on Adjuvants in Vaccines for Human Use
http://www.tga.gov.au/docs/pdf/euguide/veg/134716en.pdf

Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application
http://www.tga.gov.au/docs/pdf/euguide/veg/471703en.pdf

Canada

Regulatory Preparedness for Pandemic Influenza Vaccines
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-nit/vac/pandemicvaccine_nov2005_e.html

Good Manufacturing Practices Guidelines, 2002 edition, Version 2
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/2002v2_e.pdf

Emergency interim orders
http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2002/2002_emergency-urgence_e.html

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)
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/gui_sponsors-dir_promoteurs_lot_program_e.pdf

Guidance Document: Pandemic Influenza Vaccine, Manufacturing & Clinical Information Review & Regulatory Authorization
Available on Request

European Union

EU/2001/20/EU of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States related to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf

Harmonization of requirements for influenza vaccines CPMP/BWP/214/96;
http://www.emea.europa.eu/pdfs/human/bwp/021496en.pdf

International Conference on Harmonisation. E11: Clinical Investigation of Medicinal Products in the Pediatric Population, July 2000 (http://www.ich.org/cache/compo/276-254-1.html;
http://www.emea.europa.eu/pdfs/human/ich/271199en.pdf

Cell culture inactivated influenza vaccines (Annex to note for on harmonization of requirements for influenza vaccines), CPMP/BWP/2490/00; www.emea.europa.eu/pdfs/human/bwp/249000en.pdf

Committee for Proprietary Medicinal Products—Guideline on Core Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application
http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf

Committee for Proprietary Medicinal Products—Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines Through the Centralised Procedure
http://www.emea.eu.int/pdfs/human/vwp/498603en.pdf

EMEA pandemic influenza preparedness
http://www.emea.europa.eu/htms/human/pandemicinfluenza/background.htm

Core Summary of Product Characteristics for Pandemic Influenza Vaccines, Adopted June 2005
http://www.emea.eu.int/pdfs/human/vwp/19303104en.pdf

Guideline on dossier structure and content of marketing authorisation applications for influenza vaccines derived from strains with a pandemic potential for use outside of the core dossier context
http://www.emea.europa.eu/pdfs/human/vwp/26349906en.pdf

Guideline on Summary of Product Characteristics, published by the European Commission—December 1999 http://pharmacos.eudra.org/F2/eudralex/vol-2/C/SPCGuidRev0-Dec99.pdf

Guideline on Pharmaceutical Aspects of the Product Information for Human Vaccines
http://www.emea.eu.int/pdfs/human/bwp/275802en.pdf

Guideline on Adjuvants in Vaccines for Human Use- 2005
http://www.emea.eu.int/pdfs/human/vwp/13471604en.pdf

Cell Culture Inactivated Influenza Vaccines
http://www.emea.eu.int/pdfs/human/bwp/249000en.pdf

Japan

Regulatory Preparedness for Pandemic Influenza Vaccines
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/pdf/03-03-02-en.pdf

Guideline on manufacturing, use and post-marketing surveillance of H5N1 vaccine (after pandemic is declared)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/pdf/09-09.pdf

United States Food and Drug Administration

Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines
http://www.fda.gov/cber/gdlns/panfluvac.pdf

Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
http://www.fda.gov/cber/gdlns/trifluvac.pdf

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/cber/gdlns/reprotox.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/cber/gdlns/plasdnavac.pdf

Guidance for Industry: How to Comply with the Pediatric Research Equity Act
http://www.fda.gov/cber/gdlns/pedreseq.pdf

Draft Guidance: Emergency Use Authorization of Medical Products
http://www.fda.gov/cber/gdlns/emeruse.pdf

Guidance for Industry: Fast Track Drug Development Programs —Designation, Development, and Application
http://www.fda.gov/cber/gdlns/fsttrk.pdf

Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information for a Vaccine or Related Product
http://www.fda.gov/cber/gdlns/cmcvacc.pdf

Pediatric Research Equity Act of 2003, U.S. Public Law 108-155
http://www.fda.gov/opacom/laws/default.html

World Health Organization

WHO Guidelines for good clinical practices (GCP) for trial on pharmaceutical products. World Health Organization Expert Committee on the use of essential drugs, Sixth report., 1995 Annex 3 (WHO Technical Report Series, No. 850)

WHO Programme for International Drug Monitoring and the Uppsala Data Monitoring Centre
http://www.who-umc.org/DynPage.aspx

WHO revised requirements for influenza vaccine (inactivated) and WHO requirements for influenza vaccine (live) World Health Organization, 1978, Annex 3 (WHO Technical Report Series, No. 638)
http://www.who.int/biologicals/publications/Influenza%20inactivated%20recommendations%20annex%203.pdf

WHO Good Manufacturing Practices for biological products, World Health Organization, 1991, Annex 1 (WHO Technical Report Series, No. 822)
http://www.who.int/biologicals/publications/trs/areas/biological_products/WHO_TRS_822_A1.pdf

WHO General requirements for the sterility of biological substances World Health Organization, 1998, Annex 3 (WHO Technical Report Series, No. 872)
http://www.who.int/biologicals/publications/trs/areas/biological_products/WHO_TRS_872_A3.pdf

WHO Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. World Health Organization, 1991, Annex 3 (WHO Technical Report Series, No. 814)
http://www.who.int/biologicals/publications/trs/areas/vaccines/rdna/WHO_TRS_814_A3.pdf

WHO guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. In WHO Expert Committee on Biological Standardization. Fifty-third report. Geneva, World Health Organization, 2004, Annex 4 (WHO Technical Report Series, No. 926)
http://www.who.int/biologicals/en/926-Inside%20page.pdf

WHO Regulation and licensing of biological products in countries with newly developing regulatory authorities. In WHO Expert Committee on Biological Standardization. Forty-fifth report. Geneva, World Health Organization, 1995, Annex 1 (WHO Technical Report Series, No. 858)
http://www.who.int/biologicals/publications/trs/areas/biological_products/WHO_TRS_858_A1.pdf

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Appendix V: WHO Recommendations on production and control of influenza vaccines (inactivated) – seasonal vaccines

WHO Expert Committee on Biological Standardization. Forty fourth report. Geneva, World Health Organization, 2005. (WHO Technical Report Series No. 927)

Summary of recommendations

1 Production control

- 1.1 Control of source material
  - 1.1.1 Eggs used for seed virus growth
  - 1.1.2 Eggs used for vaccine production
  - 1.1.3 Master cell bank and manufacture of working cell bank (cell-derived vaccine)
    - 1.1.3.1 Identity test
  - 1.1.4 Cell culture medium (cell-derived vaccine)
  - 1.1.5 Virus strains
  - 1.1.6 Seed lot system
    - 1.1.6.1 Identity of haemagglutinin and neuraminidase
  - 1.1.7 Tests on seed lots
    - 1.1.7.1 Extraneous agents
    - - either validation or testing
- 1.2 Production precautions
- 1.3 Production of monovalent virus pools
  - 1.3.1 Single harvests
  - 1.3.2 Inactivation procedure
  - 1.3.3 Testing of control cells (cell-derived vaccine)
- 1.4 Control of monovalent virus pools
  - 1.4.1 Effective inactivation
  - 1.4.2 Haemagglutinin content
  - 1.4.3 Presence of neuraminidase
  - 1.4.4 Virus disruption (split vaccine)
  - 1.4.5 Surface antigens (subunit vaccine)
  - 1.4.6 Identity
  - 1.4.7 Extraneous agents
  - 1.4.8 Purity of cell-derived vaccine
  - 1.4.9 Test for chemicals used in production
- 1.5 Control of final bulk
  - 1.5.1 Test for content of haemagglutinin antigen
  - 1.5.2 Sterility tests
  - 1.5.3 Total protein
  - 1.5.4 Ovalbumin (egg-derived vaccine)
  - 1.5.5 Adjuvant content

2 Filling and containers

3 Control tests on final lot

- 3.1 Identity test
- 3.2 Sterility test
- 3.3 Haemagglutinin content
- 3.4 General safety (innocuity) tests
- 3.5 Endotoxin
- 3.6 Inspection of final containers

4 Records

5 Retained samples

6 Labelling

7 Distribution and transport

8 Stability testing and expiry date

- 8.1 Stability tests
- 8.2 Storage conditions
- 8.3 Expiry date

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